Weight Gain Following Initiation of Antiretroviral Therapy: Risk Factors in Randomized Comparative Clinical Trials

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Summary: In this report, we use pooled data from randomized clinical trials to identify demographic-, HIV disease-, and antiretroviral therapy (ART)-related risk factors for weight gain after the initiation of ART, highlighting the multifactorial nature of ART-associated weight gain.

Abstract

Background: Initiation of antiretroviral therapy (ART) often leads to weight gain. While some of this weight gain may be an appropriate return-to-health effect, excessive increases in weight may lead to obesity. We sought to explore factors associated with weight gain in several randomized comparative clinical trials of ART initiation.

Methods: We performed a pooled analysis of weight gain in 8 randomized controlled clinical trials of treatment-naïve people with HIV (PWH) initiating ART between 2003-2015, comprising over 5,000 participants and 10,000 person-years of follow-up. We used multivariate modeling to explore relationships between demographic factors, HIV disease characteristics, and ART components and weight change following ART initiation.

Findings: Weight gain was greater in more recent trials and with the use of newer ART regimens. Pooled analysis revealed baseline demographic factors associated with weight gain including lower CD4, higher HIV-1 RNA, no injection drug use, female sex and black race. Integrase strand transfer inhibitors (INSTIs) were associated with more weight gain than protease inhibitors or non-nucleoside reverse transcriptase inhibitors (NNRTI), with dolutegravir and bictegravir associated with more weight gain than elvitegravir/cobicistat. Among the NNRTIs, rilpivirine was associated with more weight gain than efavirenz. Among nucleoside/nucleotide reverse transcriptase inhibitors, tenofovir alafenamide was associated with more weight gain than tenofovir disoproxil fumarate, abacavir, or zidovudine.

Interpretation: Weight gain is ubiquitous in clinical trials of ART initiation, and is multifactorial in nature, with demographic factors, HIV-related factors, and the composition of ART regimens contributing. The mechanisms by which certain ART agents differentially contribute to weight gain are unknown.

Keywords: HIV, weight gain, obesity, antiretroviral therapy

Introduction

Excess weight and obesity are an escalating global health concern, affecting an estimated 600 million adults and contributing to substantial morbidity and mortality through an increased risk of cardiovascular disease, diabetes, chronic kidney disease, non-alcoholic steatohepatitis (NASH), and cancer. An Increasing prevalence of overweight and obesity has also been reported in people with HIV (PWH), among whom initiation of antiretroviral therapy (ART) often leads to weight gain.[1-7] While this weight gain may be a positive prognostic indicator in PWH who are underweight at the time of ART initiation,[6,8,9] among those in normal or overweight categories weight gain may increase the risk of cardiovascular and metabolic diseases.[7,10,11]

Possible mechanisms for ART-associated weight gain include a return-to-health phenomenon, especially in those with advanced HIV disease, with weight returning to a pre-illness baseline. The mechanism underlying the return-to-health phenomenon is incompletely understood, but likely results from the alleviation of HIV-associated inflammation and accelerated catabolism.[12] Treatment of HIV may also hasten resolution of opportunistic infections and gastrointestinal dysfunction that could adversely affect appetite and nutrient absorption. Additional factors associated with weight gain among PWH include both demographic and HIV-specific characteristics, with greater weight gain observed in black people, women, and in those with high pre-treatment HIV RNA or low CD4 cell counts.[2,4-6,13-15] Specific ART regimens or drug classes have also been implicated in weight gain, with integrase strand transfer inhibitors (INSTIs) cited in two randomized studies[15,16] and several retrospective cohort studies.[2,17,18] In order to further explore the demographic-, HIV-, and treatment-related contributors to weight gain, we conducted a pooled analysis of eight randomized comparative clinical trials of initial ART. We also explored whether weight changes were associated with adverse metabolic effects.

Methods

Study design and participants

Pooled analyses included eight Gilead-sponsored trials of participants initiating ART 2003-2015 that satisfied the selection criteria of phase 3 stage, active-controlled design, enrollment of treatment-naïve participants, and follow-up duration of at least 96 weeks; the trial designs, treatment arms, and dates are provided in Supplementary Table 1. One additional trial (99-903) was included in individual trial analyses (Figure 1A and 1B) but was excluded from all pooled analyses due to inadequate frequency of weight monitoring. All participants provided informed consent and trials were undertaken in accordance with the Declaration of Helsinki and approved by central or site-specific review boards or ethics committees.

Procedures

All studies included a baseline visit and follow-up visits every 12 weeks through week 96. Height was collected at baseline; body weight and body mass index calculation (BMI; weight in kilograms divided by height in meters, squared) were performed at each visit. Analyses included only weights that were obtained while the participant was on randomized therapy. Laboratory evaluation including CD4 cell count and HIV-1 RNA were performed at each study visit. Serum glucose and lipid measurements were performed after an 8 hour fast. All laboratory evaluations were performed by Covance Laboratories, Indianapolis, IN, USA.

Adverse events (AEs) were reported by the site investigators and were coded using the Medical Dictionary for Regulatory Activities (MedDRA); version varied depending on clinical trial. Diabetes-related treatment-emergent AEs reported by the study site investigators were identified by querying MedDRA terms found in the “hyperglycemia/new-onset diabetes mellitus (SMQ)” class (Supplementary Table 2 and Supplementary Methods).

Statistical analyses

Statistical testing, multivariate models and linear mixed effect models were performed as described in the Supplemental Methods section. All analyses were performed using SAS v9.4 (SAS Institute, Cary, NC, USA).

Results

Population, demographics, and baseline disease characteristics

In the pooled analyses of eight Phase III trials (Supplementary Table 1), 5680 treatment-naïve participants initiated ART. At ART initiation, median BMI was 24.8 kg/m^2; 16.3% were obese (BMI ≥30 kg/m^2), 31.4% were overweight (BMI 25-29.9 kg/m^2), and 52.2% were normal or underweight. Additional baseline weight and demographic data are summarized in Table 1, and baseline disease characteristics are summarized in Table 2.

Baseline weight was higher in the more recent trials, as was baseline CD4 count (**Error! Reference source not found.**1A). Weight gain occurred in all study arms. The magnitude of weight gain was larger in the more recent trials, and the investigational regimen was consistently associated with more weight gain than the comparator (**Error! Reference source not found.**1B). The international composition of the trials can be found in Supplementary Figure 1.

Weight gain in participants initiating ART

In pooled analyses, the 96-week median weight gain was 2.0 kg (IQR -1.0, 5.8), with the greatest rate of weight gain occurring during the initial 48 weeks (Figure 1C). Through 96 weeks, 48.6%, 36.6% and 17.3% of participants had at least 3%, 5%, and 10% weight increase from baseline, respectively. Weight gain was not observed in all participants; 30.2% lost weight. The proportion of participants in overweight and obese BMI categories increased over time

(Figure 1D).

Risk factors for any weight gain in participants initiating ART

Baseline CD4 count had the strongest association with weight gain in multivariate models; participants with a baseline CD4 count of <200/μL gained on average 2.97 kg more than participants with baseline CD4 ≥200/μL (95% CI 2.81-3.13, p <0.001)(Table 3). Furthermore, increases in CD4 count and weight over time were closely correlated (Supplementary Figure 3). Higher baseline HIV RNA (>100,000 c/mL) was associated with a mean 0.96 kg greater weight gain (95% CI 0.84-1.08, p<0.001); participants with symptomatic HIV or AIDS gained 0.51 kg more than those with asymptomatic HIV (95% CI 0.36 – 0.65, p<0.001). Participants who did not inject drugs at baseline gained 1.41 kg more than those who did (95% CI 0.97-1.85, p<0.001). Black race was associated with weight gain, with a mean 0.99 kg greater weight gain compared to non-black participants (95% CI 0.87-1.11, p<0.001). Female sex, age <50 years and persons with baseline obesity had smaller but statistically significant correlations with weight gain (Table 3).

We further explored these findings by using longitudinal models to study the relationship between sex, race, and weight gain. Female participants gained more weight than male participants, and black participants gained significantly more weight than non-black participants (Figure 2A-B and Supplementary Table 3). Stratification by both sex and race revealed the greatest weight gain among black female participants, followed by black male participants (96-week difference between black females and black males 1.12 kg 95% CI 0.25-1.99, p=0.011; Figure 2C and Supplementary Table 3).

Association of antiretroviral regimen components with any weight gain

Longitudinal modeling of weight gain and ART third agent class (INSTI, NNRTI or PI) revealed weight gain in all three classes (96-week least squares [LS] mean weight gain: INSTI, 3.24 kg

[95% CI 3.02-3.46]; NNRTI, 1.93 kg [95% CI 1.58-2.28]; PI, 1.72 kg [95% CI 1.01-2.43]) (**Error! Reference source not found.**3A). Participants taking INSTIs experienced the most weight gain (Figure 3A and Supplementary Table 4). Weight gain was similar between the NNRTI and PI treatment groups. Absolute weight followed a similar trend (Figure 3B and Supplementary Table 4).

We next assessed the association between weight gain and the specific INSTI used. Participants taking bictegravir (BIC) or dolutegravir (DTG) demonstrated similar weight gain, both greater than that in PWH taking cobicistat-boosted elvitegravir (EVG/c) (96-week LS mean weight gain: BIC, 4.24 kg [95% CI 3.71-4.78]; DTG, 4.07 kg [95% CI 3.51-4.62]; EVG/c, 2.72 kg [95% CI 2.45-3.0]). We observed a similar trend when the analysis was performed using absolute weight (Figure 3C-D and Supplementary Table 4).

Among participants taking NNRTI-containing regimens, those taking rilpivirine (RPV) gained more weight compared to those taking efavirenz (EFV) (96-week LS mean weight gain: RPV, 3.01 kg [95% CI 2.35-3.68]; EFV, 1.7 kg [95% CI 1.31-2.09]). Absolute weights were similar after an initial rapid increase in participants taking RPV (Figure 3E-F and Supplementary Table 4).

Finally, we assessed whether specific NRTIs were differentially associated with weight gain, using zidovudine (AZT) as a reference. At 96 weeks, mean weight gains by NRTI are: tenofovir alafenamide (TAF), 4.25 kg [95% CI 3.94-4.56]; abacavir (ABC), 3.08 kg [95% CI 2.36-3.81]; tenofovir disoproxil fumarate (TDF), 2.07 kg [95% CI 1.84-2.30]), as compared to AZT 0.39 kg [95%CI -0.57-1.34]. Absolute weight followed a similar trend (Figure 3G-H and Supplementary Table 4).

Risk factors for ≥10% weight increase in participants initiating ART

To understand factors associated with more extreme weight gain, we stratified the pooled trial data into individuals who gained ≥10% body weight over 48 weeks (12.8% of participants) versus those who did not. Individuals with ≥10% weight gain were more likely to be female or black, have a lower baseline weight or BMI, have lower baseline CD4 count, and higher baseline HIV-1 RNA (Table 4).

In multivariate regression models (Table 5), lower CD4 count and higher HIV-1 RNA were associated with greater odds of ≥10% weight gain (OR 4.4; 95% CI 3.60-5.27, p<0.001, and OR 2.0; 95% CI 1.65-2.37, p<0.001, respectively). Normal baseline BMI was associated with ≥10% weight gain when compared to individuals with overweight or obese baseline BMIs (normal vs. overweight OR 1.54 [95% CI 1.27-1.87 p<0.001], normal vs. obese OR 1.66 [95% CI 1.29-2.15]). Female sex and black race were associated with ≥10% weight gain (female vs. male OR 1.54 [95% CI 1.21-1.96, p<0.001], and black vs. non-black OR 1.32 [95% CI 1.10-1.59, p = 0.003]). More black women experienced ≥10% weight gain than non-black women (19.7% vs 12.4%, p<0.001).

We assessed the association between the specific third agent drug and ≥10% weight gain (Table 5). Compared to EFV, the initiation of BIC or DTG (OR 1.82, 95% CI 1.24-2.66, p=0.002), EVG/c (OR 1.36, 95% CI 1.04-1.78, p=0.026), RPV (OR 1.51, 95% CI 1.03-2.20, p=0.035), but not ATV/r, were associated with an increased risk of ≥10% weight gain. Among the NRTIs, TAF (OR 1.75, 95% CI 1.04-2.95, p=0.034), but not ABC or TDF, were associated with increased risk for ≥10% weight gain compared to AZT. TAF was also associated with an increased risk of ≥10% weight gain compared to ABC (OR 1.90, 95% CI 1.25-2.88, p = 0.003) and TDF (OR 1.47, 95% CI 1.14-1.90, p = 0.003).

Metabolic impacts of significant weight increase

Next, we evaluated whether ≥10% weight gain was associated with subsequent changes in fasting glucose or the incidence of treatment-emergent AEs related to diabetes or hyperglycemia. We found no significant difference in fasting glucose change between participants with ≥10% or <10% weight gain (96-week mean fasting glucose change for both groups was 3 mg/dL, 95% CI 1.01-4.99 mg/dL and 2.39-3.61 mg/dL respectively, Supplementary Figure 2A). The incidence rate of diabetes-/hyperglycemia-related AEs was higher in individuals with ≥10% weight gain versus those without, although this difference was not statistically significant (1.01 per 100 person-years [PY] [95% CI 0.59, 1.74] and 0.67 per 100 PY [95% CI 0.53, 0.85] respectively, p = 0.18). LDL and triglycerides had similar small increases in both groups, whereas HDL had a small but significant increase in participants with <10% weight increase compared to those with ≥10% weight increase (Supplementary Figure 2B-D). Total cholesterol-to-HDL ratio was slightly higher in the ≥10% weight gain group (week 96 median [IQR] 3.7 [2.9, 4.6] vs 3.5 [2.9, 4.4] p = 0.027). Blood pressure data are available for three trials (264-0110, 380-1489, and 380-1490); no clinically significant changes were observed (week 96 weighted mean change from baseline in systolic and diastolic blood pressure are 2.2 and 1.5 mmHg respectively).

Discussion

In our pooled analysis of eight ART-naïve randomized clinical trials ranging from 2003 to 2019, we found that PWH are initiating ART at higher baseline weight and many gain significant amounts of weight during the first two years of therapy. A mix of demographic, HIV disease-specific, and ART-specific factors were associated with weight increase from baseline and with more extreme (≥10%) weight gain.

Similar to other reports, we observed higher baseline weight in more recent ART-naïve studies, with median baseline BMIs at or near the overweight category.[1-4] Weight gain was common following ART initiation: about half of participants gained at least 3% body weight with a median weight gain of 2.0 kg over nearly 2 years of follow-up. This degree of weight gain mirrors the obesity trend observed in the NHANES CARDIA study, where the average American aged 20-40 gained nearly one kilogram per year.[19] Accordingly, the distribution of BMI classes in trial participants shifted toward overweight and obese categories by trial conclusion, approaching the distribution seen in recent HIV cohort studies and in the general population (approximately 1/3 overweight, 1/3 obese).[4,5,19-21]

We did not observe a clinically significant metabolic impact of weight gain in our trials as measured by fasting glucose and investigator reported AEs, however this analysis is limited by duration of follow-up, a relatively small number of reported AEs, and the absence of more sensitive markers of glucose tolerance.

Black race and female sex were associated with weight gain, consistent with other studies.[2,5-6,13,15] This association was particularly notable among black females, who gained approximately twice as much weight as non-black women. The mechanism underlying this observation is unknown, but it mirrors the disproportionately high prevalence of obesity in black women in the

US,[22] and both may be affected by similar factors. These findings are similar to prior studies reporting a concurrence of HIV and obesity risk in the black population[23], and highlight the need for increased obesity awareness, monitoring and clinical intervention in this high-risk population.

We observed strong associations between weight gain and HIV disease characteristics. Disease stage, as reflected by low baseline CD4 count, and high baseline HIV RNA correlated with weight gain in our models of any weight gain and ≥10% weight gain, similar to other reports.[2,4-6,15] These findings support a contribution of the return-to-health phenomenon to weight gain in PWH initiating ART. This effect may be desirable in some individuals, but could also contribute to excess weight gain in individuals with early stage HIV disease and those with normal or above-normal BMI.

Our analyses revealed several important associations between weight gain and ART at the class and drug level. Examining the clinical trials individually, we observe greater weight gain in newer investigational regimens relative to the comparator, consistent with the findings reported by others.[2,24] In our pooled analyses, INSTI-containing regimens were associated with more weight gain than NNRTI or PI-based regimens, with DTG and BIC associated with more weight gain than EVG/c. Among NNRTIs, RPV was associated with more weight gain than EFV. Among NRTI pairs, TAF/emtricitabine (FTC) was associated with the most weight gain, ABC/lamivudine (3TC) and TDF/FTC with slightly less weight gain, and AZT/3TC with weight stability. These findings are similar to the ADVANCE trial, in which DTG and TAF were associated with treatment-emergent obesity, while TDF/FTC/EFV was associated with treatment-emergent underweight status and a higher rate of treatment discontinuation.[25] Altogether, these findings establish a pattern of more weight gain with newer ART regimens, possibly reflecting better tolerated, easier to take regimens.[26]

The hypothesis that improved tolerability may contribute to weight gain in PWH initiating ART is supported by clinical trial data comparing the gastrointestinal (GI) tolerability of HIV regimens. INSTIs such as DTG, BIC, and RAL do not require boosting with cobicistat, which has been associated with nausea and diarrhea.[27] Among NNRTIs, RPV is better tolerated than EFV, and should be taken with food which may result in higher caloric intake.[28] In the case of NRTIs, early trials demonstrated more GI toxicity with AZT compared to newer NRTIs, including ABC and TDF.[29] There is also evidence that TAF may be associated with better GI tolerability than ABC; in a study comparing BIC/FTC/TAF vs. ABC/DTG/3TC, there was a lower incidence of nausea in the TAF-containing arm, a difference not observed in a study comparing BIC with DTG, both with TAF/FTC.[30-31]

If individual agents contribute to weight gain aside from tolerability, the mechanisms by which they do so is not known. For treatment-naïve PWH, some of the association between weight gain and INSTI-containing regimens could be their faster virologic control compared to older regimens.[32] Another explanation for drug-specific effects on weight could be off-target biological interactions. One such example is the observed interaction between DTG and melanocortin 4 receptor (MC4R), a receptor involved in the regulation of caloric intake by modulating leptin signaling in the central nervous system.[33-34] This finding is intriguing since mutations in MC4R are associated with heritable obesity.[34] This potential mechanism requires further validation, and it remains unknown whether other INSTIs interact similarly.

Evaluating the effect of ART drugs on weight gain is confounded by HIV disease factors such as return-to-health; some of these limitations may be avoided by studying weight changes in pre-exposure prophylaxis (PrEP) trials. In the iPrEx study comparing TDF/FTC to placebo, the TDF/FTC arm gained less weight than placebo, suggesting TDF/FTC may have a mild weight suppressive effect.[35] In the DISCOVER trial of TDF/FTC vs. TAF/FTC for PrEP, weight gain at week 48 was 1.1 kg in the TAF/FTC arm with no change in the TDF/FTC arm.[36] Finally, in a

phase 2 placebo controlled trial of cabotegravir for PrEP, both arms experienced about 1kg of weight gain over 41 weeks, with no significant difference between arms.[37] Together these findings suggest that heathy participants taking TAF or an INSTI likely experience weight gain much like the general population, which contrasts with the weight-suppressive effect of TDF.

There are several limitations to our analyses. We do not have body composition data, so we cannot determine the anatomical distribution of the observed weight gain. However, data from recent studies suggest that ART-associated weight gain is generalized, with increases in subcutaneous fat, visceral fat, and lean mass.[38] Additionally, our assessment of GI tolerability relied solely on investigator-reported AEs, as more detailed and sensitive participant-reported outcome data are only available in more recent trials.[30-31] Our analyses did not evaluate other potential contributors to weight gain such as psychiatric comorbidities, concomitant medications, diet, physical activity, or smoking. In the included trials, newer third agents were generally co-administered with newer NRTIs, making it challenging to completely disentangle the independent associations of individual agents with weight gain, and thus these associations should be interpreted with some caution. Finally, while we report two-year data, the duration of follow-up may not be long enough to capture longer-term metabolic consequences of weight gain.

Collectively our results suggest that there are demographic-, HIV- and treatment-related contributors to weight gain in PWH. Our findings raise the possibility that modern ART regimens with improved tolerability and potency may lead to weight gain in some PWH, necessitating increased clinical attention to the maintenance of healthy body weight, lifestyle modification, and exercise at ART initiation.[39-40] Ongoing studies including the analysis of weight gain in ART switch trials may provide important insights by avoiding the contribution of return-to-health effects. Additional important areas for investigation include the magnitude, clinical significance, and biologic mechanisms of ART-related weight gain.

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Potential Conflicts of Interest

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41. Figure Captions

42. Figure 1. Weight trends in participants initiating antiretroviral therapy. A. Baseline median CD4 count and median weight in the indicated clinical trials, which are ordered by date of trial initiation. Error bars represent the 1st through 3rd quartile. B. Mean weight change observed at the 48 week time point for the indicated trials, which are organized by date of initiation. Red bars are the investigational regimen and grey bars are the comparator. Asterisk indicates $p<0.05$ by ANOVA. C. Median weight (red) and median weight change (blue) over time in eight pooled clinical trials. D. BMI category distributions over time in eight pooled clinical trials.
43. Figure 2. Effect of sex and race on weight change in individuals initiating antiretroviral therapy. A. Least squares mean (LSM) weight change over time stratified by sex. B. LSM weight change over time, stratified by race (black vs. non-black). C. LSM weight change over time stratified by both sex and race. For panels A and B, asterisks indicate $p<0.05$ versus the comparator. For panel C, single asterisks indicate $p<0.05$ for black females vs. non-black females, and double asterisks indicate $p<0.05$ for black females vs. non-black females and for black females vs. black males. P values for these comparisons are found in Supplementary Table 3.
44. Figure 3. Weight change and absolute weight in participants initiating antiretroviral therapy. A & B: Least squares (LS) mean weight change (A) and absolute weight (B) over time in all participants, stratified by third antiretroviral agent. C & D: LS mean weight change (C) and absolute weight (D) in participants taking INSTIs, stratified by INSTI used. E & F: LS mean weight change (E) and absolute weight (F) in all participants taking NNRTI, stratified by NNRTI used. G & H: LS mean weight change (G) and absolute weight (H) in participants taking an NRTI, stratified by NRTI used. Error bars depict the 95% CI. Asterisks are color-coded to match the respective comparator, and denote $p\leq0.05$ compared to NNRTI (panels

A and B), EVG/c (panels C and D), EFV (panels E and F), or AZT (panels G and H). P values for these comparisons are found in Supplementary Table 3.

Tables

Table 1: Demographics and Baseline Characteristics by Study.

Clinical Trials	Combined	**934** EFV+FTC/TDF vs. EFV+AZT/3TC	**236-0102** E/C/F/TDF vs. EFV/FTC/TDF	**236-0103** E/C/F/TDF vs. ATV/r+F/TDF	**264-0110** RPV/FTC/TDF vs. EFV/FTC/TDF	**292-0104, 292-0111** E/C/F/TAF vs. E/C/F/TDF	**380-1489** B/F/TAF vs. ABC/DTG/3TC	**380-1490** B/F/TAF vs. DTG+F/TAF
Year first participant screened	-	2003	2010	2010	2011	2012	2015	2015
N	5680	501	698	704	781	1728	629	639
Age (years)								
Mean (SD)	37 (10.7)	38 (9.5)	38 (10.5)	38 (10.2)	37 (10.7)	36 (10.6)	34 (10.8)	37 (11.9)
Median (Q1,3)	35 (28, 44)	37 (32, 42)	37 (29, 45)	38 (30, 45)	36 (28, 45)	34 (27, 43)	32 (25, 41)	34 (27, 45)
Sex at Birth								
Male	5018 (88.3%)	434 (86.6%)	621 (89.0%)	637 (90.5%)	725 (92.8%)	1469 (85.0%)	567 (90.1%)	565 (88.4%)
Female	662 (11.7%)	67 (13.4%)	77 (11.0%)	67 (9.5%)	56 (7.2%)	259 (15.0%)	62 (9.9%)	74 (11.6%)
Race								
Asian	290 (5.1%)	6 (1.2%)	16 (2.3%)	34 (4.8%)	21 (2.7%)	180 (10.4%)	16 (2.6%)	17 (2.7%)
Black	1471 (25.9%)	113 (22.6%)	197 (28.2%)	118 (16.8%)	191 (24.5%)	432 (25.0%)	226 (36.0%)	194 (30.4%)
White	3499 (61.6%)	296 (59.2%)	439 (62.9%)	524 (74.4%)	524 (67.3%)	982 (56.8%)	359 (57.3%)	375 (58.7%)
Other	415 (7.3%)	85 (17.0%)	46 (6.6%)	28 (4.0%)	43 (5.5%)	134 (7.8%)	26 (4.1%)	53 (8.3%)
Unknown*	4 (0.1%)	1	0	0	1	0	2	0
Sex and race								
Male, black	1161 (20.4%)	80 (16.0%)	155 (22.2%)	88 (12.5%)	156 (20.0%)	341 (19.7%)	184 (29.3%)	157 (24.6%)
Male, non-black	3853 (67.8%)	354 (70.7%)	466 (66.8%)	549 (78.0%)	567 (72.6%)	1128 (65.3%)	381 (60.6%)	408 (63.8%)
Female, black	310 (5.5%)	33 (6.6%)	42 (6.0%)	30 (4.3%)	35 (4.5%)	91 (5.3%)	42 (6.7%)	37 (5.8%)
Female, non-black	351 (6.2%)	33 (6.6%)	35 (5.0%)	37 (5.3%)	21 (2.7%)	168 (9.7%)	20 (3.2%)	37 (5.8%)
Ethnicity								
Hispanic or Latino	1119 (19.7%)	78 (15.6%)	166 (23.8%)	109 (15.8%)	132 (17.0%)	334 (19.4%)	137 (21.9%)	163 (25.5%)
Not Hispanic or Latino	4535 (79.8%)	423 (84.4%)	532 (76.2%)	581 (84.2%)	643 (83.0%)	1391 (80.6%)	489 (78.1%)	476 (74.5%)
Unknown*	24 (0.4%)	0	0	14 (2.0%)	5 (0.6%)	2 (0.1%)	3 (0.5%)	0
Baseline weight (kg)								
N	5680	501	698	704	781	1728	629	639
Mean (SD)	78.9 (17.25)	76.5 (14.93)	81.3 (17.75)	79.3 (16.57)	79.2 (16.39)	77.4 (17.09)	80.2 (18.03)	79.8 (19.18)
Median (Q1, Q3)	76.2 (67.1, 87.5)	74.8 (65.8, 85.4)	78.5 (69.8, 90.2)	77.1 (68.0, 87.5)	76.2 (68.0, 88.0)	75 (65.3, 86.6)	77.4 (68.0, 88.8)	76.1 (67.7, 88.4)
Baseline BMI (kg/m^2)								

N	5674	496	698	704	780	1728	629	639
Mean (SD)	25.7 (5.20)	25.0 (4.55)	26.4 (5.58)	25.6 (4.95)	25.6 (4.70)	25.5 (5.18)	26.0 (5.53)	26.0 (5.66)
Median (Q1, Q3)	24.8 (22.2, 28.1)	24.3 (22.0, 27.4)	25.2 (22.7, 28.6)	24.8 (22.2, 27.8)	24.8 (22.4, 28.1)	24.5 (21.8, 28.0)	25 (22.4, 28.8)	24.8 (22.2, 28.1)
Baseline BMI Categories (kg/m²)								
Underweight: <18.5	136 (2.4%)	18 (3.6%)	13 (1.9%)	15 (2.1%)	16 (2.1%)	41 (2.4%)	21 (3.3%)	12 (1.9%)
Normal: ≥18.5 - < 25	2829 (50.0%)	266 (53.6%)	318 (45.6%)	355 (50.4%)	390 (50.0%)	891 (51.6%)	292 (46.4%)	317 (49.6%)
Overweight: ≥ 25 - < 30	1785 (31.4%)	154 (31.0%)	236 (33.8%)	236 (33.5%)	248 (31.8%)	527 (30.5%)	197 (31.3%)	187 (29.3%)
Obese: ≥ 30	924 (16.3%)	58 (11.7%)	131 (18.8%)	98 (13.9%)	126 (16.2%)	269 (15.6%)	119 (18.9%)	123 (19.2%)

* Inquiry regarding race and ethnicity were not permitted at some study sites

One participant with missing race and two participants with missing ethnicity were excluded from the race, combination of sex and race, and ethnicity summary.

Table 2. Baseline Disease Characteristics by Study.

Clinical Trials	Combined	**934** EFV+FTC/TDF vs. EFV+AZT/3TC	**236-0102** E/C/F/TDF vs. EFV/FTC/TDF	**236-0103** E/C/F/TDF vs. ATV/r+F/TDF	**264-0110** RPV/FTC/TDF vs. EFV/FTC/TDF	**292-0104, 292-0111** E/C/F/TAF vs. E/C/F/TDF	**380-1489** B/F/TAF vs. ABC/DTG/3TC	**380-1490** B/F/TAF vs. DTG+F/TAF
HIV-1 RNA (Log10 c/mL)								
N	5680	501	698	704	781	1728	629	639
Mean (SD)	4.65 (0.667)	5.01 (0.538)	4.75 (0.583)	4.81 (0.614)	4.79 (0.629)	4.53 (0.674)	4.42 (0.665)	4.41 (0.698)
Median (Q1, Q3)	4.69 (4.23, 5.08)	5.04 (4.63, 5.36)	4.76 (4.34, 5.15)	4.87 (4.37, 5.19)	4.79 (4.36, 5.22)	4.58 (4.14, 4.96)	4.47 (4.04, 4.87)	4.44 (4.00, 4.87)
HIV-1 RNA Categories								
≤100,000 c/mL	4020 (70.8%)	246 (49.1%)	466 (66.8%)	415 (58.9%)	508 (65.0%)	1338 (77.4%)	526 (83.6%)	521 (81.5%)
>100,000 c/mL	1660 (29.2%)	255 (50.9%)	232 (33.2%)	289 (41.1%)	273 (35.0%)	390 (22.6%)	103 (16.4%)	118 (18.5%)
CD4 (cells/µL)								
N	5679	501	698	704	781	1727	629	639
Mean (SD)	401 (211.4)	242 (163.9)	386 (179.7)	370 (170.1)	391 (182.8)	428 (217.7)	464 (226.3)	456 (244.4)
Median (Q1, Q3)	382 (264, 513)	229 (123, 322)	380 (271,484)	359 (270, 460)	375 (284, 490)	406 (288, 549)	444 (307, 598)	442 (291, 597)
CD4 (categories)								
<200 cells/µL	871 (15.3%)	209 (41.7%)	94 (13.5%)	91 (12.9%)	103 (13.2%)	228 (13.2%)	68 (10.8%)	78 (12.2%)
≥200 cells/µL	4808 (84.7%)	292 (58.3%)	604 (86.5%)	613 (87.1%)	678 (86.8%)	1499 (86.8%)	561 (89.2%)	561 (87.8%)
IV drug use								
Yes	87 (1.5%)	14 (2.8%)	22 (3.2%)	12 (1.7%)	10 (1.3%)	11 (0.6%)	9 (1.4%)	9 (1.4%)
No	5593 (98.5%)	487 (97.2%)	676 (98.8%)	692 (98.3%)	771 (98.7%)	1717 (99.4%)	620 (98.6%)	630 (98.6%)
HIV disease status								
Asymptomatic	4590 (80.8%)	57 (11.4%)	583 (83.5%)	576 (81.8%)	660 (84.6%)	1574 (91.5%)	572 (90.9%)	568 (88.9%)
Symptomatic*	599 (10.5%)	241 (48.1%)	63 (9.0%)	73 (10.4%)	84 (10.8%)	87 (5.1%)	30 (4.8%)	21 (3.3%)
AIDS	483 (8.5%)	203 (40.5%)	52 (7.4%)	55 (7.8%)	36 (4.6%)	60 (3.5%)	27 (4.3%)	50 (7.8%)
Unknown	8 (0.1%)	0	0	0	1 (0.1%)	7 (0.4%)	0	0

* Defined as any participant with symptoms attributable to HIV infection but without AIDS defining criteria, as determined by the study site investigator.

Table 3. Risk factors for any weight gain in individuals initiating ART.

Variable	Difference (kg)	95% CI	p value
CD4 (<200 vs. ≥200/μL)	2.97	2.81, 3.13	**<0.001**
IV drug use (no vs. yes)	1.41	0.97, 1.85	**<0.001**
Race (black vs. non-black)	0.99	0.87, 1.11	**<0.001**
HIV RNA (>100k vs. ≤100k c/mL)	0.96	0.84, 1.08	**<0.001**
Symptomatic HIV (yes vs. no)	0.51	0.36, 0.65	**<0.001**
Sex (female vs. male)	0.23	0.07, 0.4	**0.006**
Age (<50 vs. ≥50 years)	0.22	0.07, 0.37	**0.004**
BMI (obese vs. normal)	0.21	0.06, 0.36	**0.005**
BMI (overweight vs. normal)	-0.24	-0.36, -0.13	**<0.001**

Stepwise model selection was used to identify baseline risk factors associated with weight gain in individuals initiating ART, resulting in the inclusion of the above eight baseline risk factors in the mixed effexts model. Difference, 95% CI, and p values were determined from the mixed effect model including these eight baseline risk factors and visit as fixed effects and participants as a random effect.

Table 4: Demographics, baseline weight characteristics and baseline disease characteristics by weight gain category (≥10% or <10% weight increase through 48 weeks).

Weight gain category	Weight increase ≥10%	Weight increase <10%	p value
N (for demographics)	728	4952	
Age (years)			0.59
Mean (SD)	36 (10.8)	37 (10.7)	
Median (Q1, Q3)	35 (28, 44)	35 (28, 44)	
Sex at Birth			<0.001
Male	613 (84.2%)	4405 (89%)	
Female	115 (15.8%)	547 (11%)	
Race			<0.001
Asian	29 (4.0%)	261 (5.3%)	
Black	239 (32.8%)	1232 (24.9%)	
White	406 (55.8%)	3093 (62.5%)	
Other	52 (7.1%)	363 (7.3%)	
Unknown*	2 (0.3%)	2 (0.1%)	
Sex and race			
Male			<0.001
Black	178 (24.5%)	983 (19.9%)	
Non-black	433 (59.5%)	3420 (69.1%)	
Female			0.15
Black	61 (8.4%)	249 (5.0%)	
Non-black	54 (7.4%)	297 (6.0%)	
Ethnicity			0.58
Hispanic or Latino	138 (19%)	981 (19.8%)	
Not Hispanic or Latino	587 (80.6%)	3948 (79.8%)	
Unknown*	3 (0.4%)	21 (0.4%)	
Baseline weight (kg)			<0.001
N	728	4952	
Mean (SD)	75.2 (17.3)	79.4 (17.2)	
Median (Q1, Q3)	72 (63.5, 83.7)	77 (67.9, 88.0)	
Baseline BMI (kg/m^2)			<0.001
N	728	4946	
Mean (SD)	24.6 (5.1)	25.9 (5.9)	
Median (Q1, Q3)	23.4 (21.2, 26.6)	24.9 (22.4, 28.3)	
Baseline BMI Categories (kg/m^2)			<0.001
Underweight: <18.5	34 (4.7%)	102 (2.1%)	
Normal: ≥18.5 - < 25	426 (58.5%)	2403 (50.6%)	
Overweight: ≥ 25 - < 30	176 (24.2%)	1609 (32.5%)	
Obese: ≥ 30	92 (12.6%)	832 (16.8%)	

HIV-1 RNA (Log10 c/mL)			<0.001
N	727	4952	
Mean (SD)	4.97 (0.7)	4.6 (0.65)	
Median (Q1, Q3)	4.98 (4.54, 5.46)	4.65 (4.19, 5.03)	
HIV-1 RNA Categories			<0.001
≤100,000 c/mL	380 (52.2%)	3640 (73.5%)	
>100,000 c/mL	348 (47.8%)	1312 (26.5%)	
CD4 cells/µL			<0.001
N	728	4952	
Mean (SD)	291 (220.9)	417 (205.0)	
Median (Q1, Q3)	270 (99, 432)	393 (284, 523)	
CD4 cells/µL categories			<0.001
<200 cells/mL	296 (40.7%)	575 (11.6%)	
≥200 cells/mL	431 (59.2%)	4377 (88.4%)	
IV drug use			NS
Yes	9 (1.2%)	78 (1.6%)	
No	719 (98.8%)	4874 (98.4%)	
HIV disease status			<0.001
Asymptomatic	475 (65.2%)	4115 (83.1%)	
Symptomatic	93 (12.8%)	506 (10.2%)	
AIDS	160 (22%)	323 (6.5%)	
Unknown	0	8 (0.2%)	

* Inquiry regarding race and ethnicity were not permitted at some study sites.

For categorical data, p-value was from the CMH test (general association statistic was used for nominal data, row mean scores differ statistic was used for ordinal data). For continuous data, p-value was from the 2-sided Wilcoxon rank sum test.

Table 5. Risk factors for significant (≥10%) weight gain in individuals initiating ART.

Variable	OR	95% CI	p value
CD4 (<200 vs. ≥200/μL)	4.36	3.6, 5.27	**<0.001**
HIV RNA (>100k vs. ≤100k c/mL)	1.98	1.65, 2.37	**<0.001**
BMI (normal vs. overweight	1.54	1.27, 1.87	**<0.001**
BMI (normal vs. obese)	1.66	1.29, 2.15	**<0.001**
Sex (female vs. male)	1.54	1.21, 1.96	**<0.001**
Race (black vs. non-black)	1.32	1.1, 1.59	**0.003**
Third agent (BIC/DTG vs. EFV)	1.82	1.24, 2.66	**0.002**
Third agent (EVG/c vs. EFV)	1.36	1.04, 1.78	**0.026**
Third agent (RPV vs. EFV)	1.51	1.03, 2.2	**0.035**
Third agent (ATV/r vs. EFV)	0.92	0.59, 1.45	0.73
NRTI (TAF vs. AZT)	1.75	1.04, 2.95	**0.034**
NRTI (TDF vs. AZT)	1.19	0.76, 1.87	0.44
NRTI (ABC vs. AZT)	0.93	0.47, 1.8	0.82
NRTI (TAF vs. ABC)	1.9	1.25, 2.88	**0.003**
NRTI (TDF vs. ABC)	1.29	0.79, 2.11	0.31
NRTI (TAF vs. TDF)	1.47	1.14, 1.9	**0.003**

Stepwise model selection was used to identify which baseline risk factors were associated with significant (≥10%) weight gain in individuals initiating ART. As a result, CD4, HIV RNA, BMI, Sex, and Race were selected. Odds Ratio and its 95% CI, p-values were from the logistic regression model including baseline categories of CD4, HIV-1 RNA, BMI, Sex, and Race as risk factors; third agent and NRTIs as fixed effects.

Figure 1

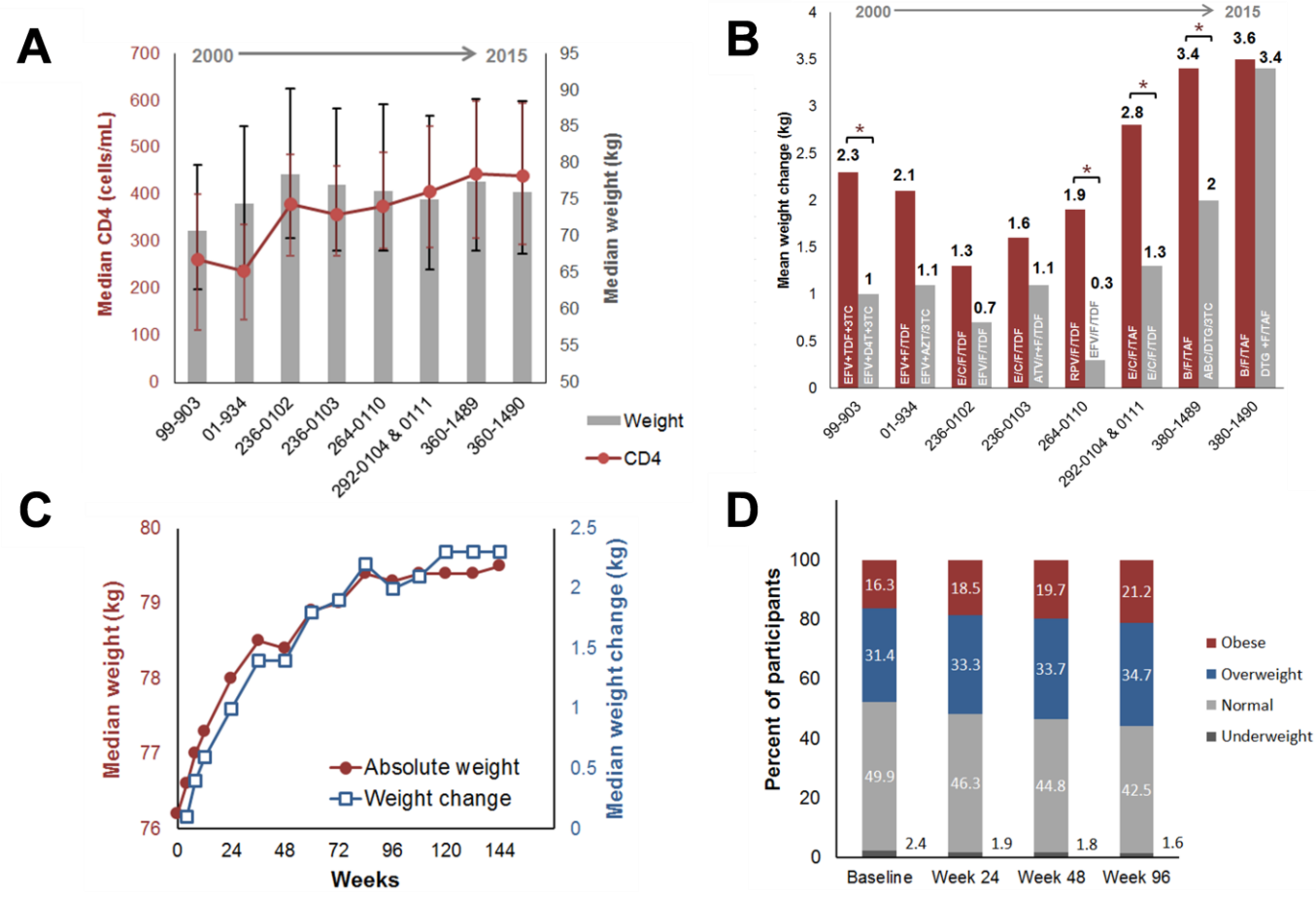

Figure 2

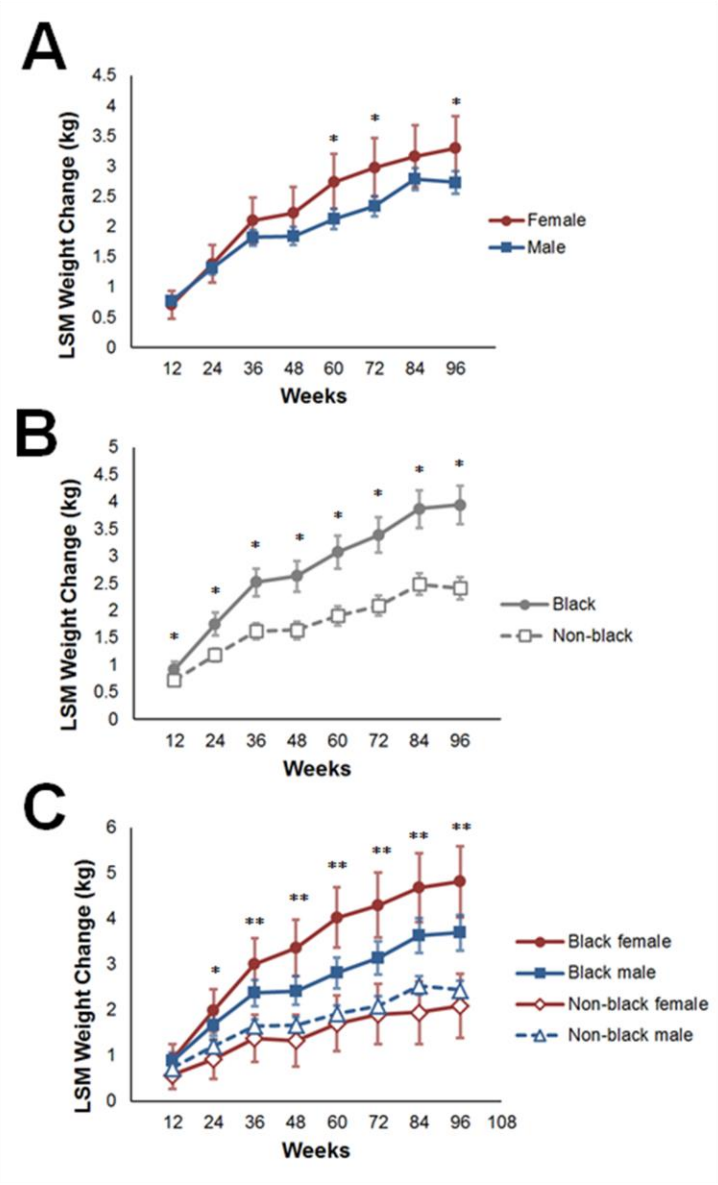

Figure 3