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Integrase Strand Transfer Inhibitors Play the Main Role in Greater Weight Gain Among Men With Acute and Early HIV Infection

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Background. The predictors of weight gain remain unclear in people with acute and early HIV infection (AEH).

Methods. Eligible antiretroviral-naïve men diagnosed with AEH from January 1, 2000, to December 31, 2019, were enrolled in an observational cohort study at the University California, San Diego. The study used multivariable mixed-effect linear regression models to analyze differences in the rate of weight gain over time between participants receiving early vs deferred antiretroviral therapy (ART) treatment, low vs high baseline CD4 count and HIV RNA, and different classes of ART.

Results. A total of 463 participants were identified, with mean CD4 cell count of 507 cells/μL and log HIV RNA of 5.0 copies/mL at study entry. There was no difference in the rate of weight gain between participants who did and did not receive ART within 96 weeks of incident HIV infection. Neither a baseline CD4 count of <350 cells/μL nor a baseline HIV RNA of >100 000 copies/mL was a predictor of weight gain. Compared with persons taking non-nucleoside reverse transcriptase inhibitor–based regimens, those who received integrase strand transfer inhibitor (INSTI)–based regimens showed greater weight gain over time.

Conclusions. Neither baseline CD4 count and HIV RNA nor early ART was associated with weight change in the first 96 weeks following incident HIV infection. Use of INSTI-based regimens represented a major driver of weight gain in men who initiated ART with relatively higher CD4 cell counts.

Keywords. acute and early HIV; antiretroviral therapy; HIV; integrase strand transfer inhibitor; weight gain.

The factors associated with weight change in people with HIV (PWH) have been thoroughly investigated [1–6]. Even without effective antiretroviral therapy (ART), PWH still show gradually increasing weight until late-stage disease [7, 8]. Once ART was initiated, weight gain among PWH was almost ubiquitous [1–4]. Factors associated with greater weight gain have included (1) a low CD4 count and high HIV RNA at ART initiation, (2) use of integrase strand transfer inhibitor (INSTI) and (3) tenofovir alafenamide (TAF), (4) Black race, and (5) female sex [1, 9–16]. However, the majority of participants in published studies have been people with chronic HIV infection. The trajectory of weight change and the factors that may influence weight gain remain unknown in people with acute and early HIV infection (AEH).

After ART initiation, the weight increase was once undoubtedly welcome because it represented a sign of recovery and was linked to lower mortality among people whose body mass index (BMI) was normal or below normal [17]. Independent of ART, rates of obesity have increased among PWH [2, 5, 18], with greater weight gain potentially contributing to undesirable metabolic and cardiovascular disorders [19–21].

The mechanisms of weight gain on ART are not fully understood. Some experts have considered the return-to-health phenomenon as a major driver, a process by which individuals with reduced weight recover to their pre-illness weight (ie, healthy weight) following ART initiation [22]. Several studies support the return-to-health phenomenon, including the finding that people with lower CD4 counts and higher HIV RNA levels had more significant weight gain after treatment [1, 12]; more weight gain was observed in the first year after ART initiation [4, 15]; and weight change in PWH approached HIV-uninfected comparators after 3 years of ART [2].

People with AEH have a shorter duration of infection than persons with chronic infection and may therefore demonstrate different weight trajectories with and without ART. By including AEH individuals who received early ART, we can

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analyze the effect of ART on weight change in the earliest stage of HIV disease we can ever acquire at this time. This approach may also help minimize confounders caused by prolonged HIV infection. To better understand weight changes in people with AEH and identify potential factors associated with greater weight gain, we conducted a retrospective analysis of longitudinal weight data from an observational database.

METHODS

Study Design and Participants

Participants with AEH were identified at HIV screening programs of the Primary Infection Resource Consortium (PIRC) at the University of California San Diego (UCSD). Participants newly diagnosed with HIV infection were enrolled between January 1, 2000, and December 31, 2019. An estimated date of infection was calculated using serologic and virologic data, as previously described [23]. The current analysis was limited to adults (age ≥18 years) who were assigned male at birth. We chose not to include the individuals assigned female at birth because this population accounted for only 1.9% of all participants, which might prevent drawing any definite conclusion. Participants were followed according to the observational study schedule, and weight was measured each visit at the same clinic.

Data were collected from January 1, 2000, through July 31, 2020, and included baseline demographics (age, race, ethnicity), longitudinal clinical data (CD4 counts, HIV RNA, ART regimen, weight), and date of visit. An individual who had a follow-up period of <24 weeks or lacked a weight record at either study enrollment or 24 weeks after enrollment was excluded. If the weight record on a scheduled visit date was not available, we recorded the weight within the nearest 30 days before or after that date. The PIRC classified participants as having acute HIV infection when early antigen/nucleic acid positive and antibody negative/indeterminate (indexed to Fiebig stage classification I–II) and as having early HIV infection when the antibody was positive and the results of detuned assay were consistent with recent infection <170 days [23–25]. Viral suppression was defined as an HIV RNA of <200 copies/mL.

Patient Consent Statement

The UCSD Human Research Protections Program approved the study protocol. All participants provided written informed consent.

Study Process

For this analysis, we created 2 data sets, A and B (Figure 1). Data set A was built to describe the weight change and identify factors that may affect weight trajectory among people with AEH. Data set A recorded participants' weight at study enrollment and at 12, 24, 48, 72, and 96 weeks thereafter. As most participants were enrolled immediately after HIV diagnosis, the

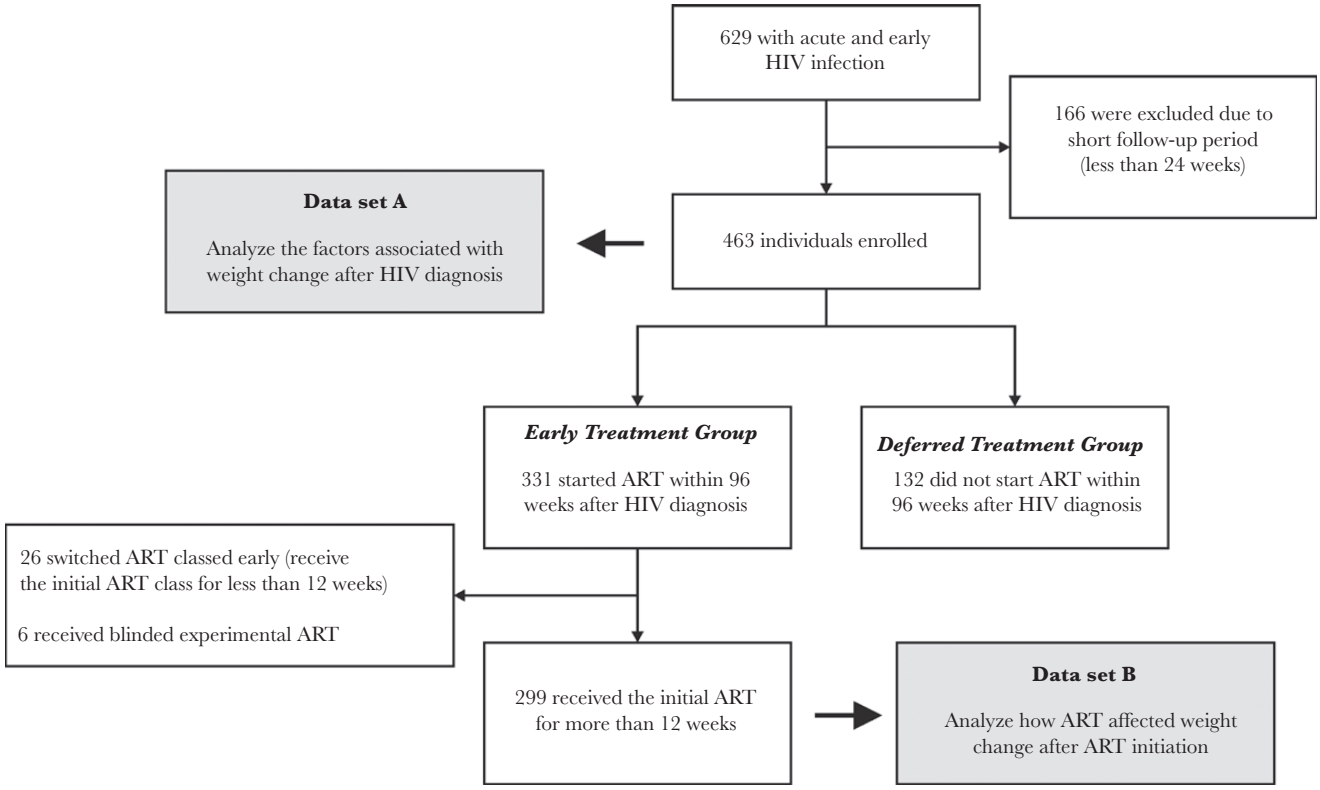

Figure 1. Study diagram. Abbreviation: ART, antiretroviral therapy.

time of enrollment was also considered the time of HIV diagnosis. Participants were further divided into an Early Treatment Group and Deferred Treatment Group according to whether they received ART within 96 weeks after HIV diagnosis. Both groups were censored either at 96 weeks or when the participant was lost to follow-up. We also used Data set A to identify potential variables associated with excessive weight gain, defined as a weight increase of ≥15% through 96 weeks after HIV diagnosis. A sensitivity analysis using different cutoff values for excessive weight gain of 18% and 12% was also performed.

Data set B included the participants in the Early Treatment Group and recorded weight since the time ART was initiated. The purpose of Data set B was to analyze the impact of antiretroviral agents on weight change. Data set B was censored either at 96 weeks after ART initiation or when participants switched ART classes (non-nucleoside reverse transcriptase inhibitor [NNRTI], protease inhibitor [PI], and INSTI), regardless of the nucleoside reverse transcriptase inhibitor (NRTI) components. The main NRTI components recorded in this study were primarily the initial NRTIs. If the initial NRTIs were taken for <24 weeks, then the NRTIs used for the longest time were considered the main NRTI components.

Statistical Analysis

In the descriptive analysis, the study used the chi-square or Fisher exact test for categorical variables, the Wilcoxon rank-sum test for continuous variables between 2 groups, and the Kruskal-Wallis test for continuous variables among ≥3 groups. For longitudinal data, we adopted multivariable mixed-effects linear regression models to compare differences in the slopes of weight gain over time between 2 specific groups of participants. Each comparison was performed using a separate model. Every participant's repeated measurements were treated as the random effect, consisting of a random intercept allowing for individuals' baseline differences and a random slope allowing for individuals' differences in weight change over time. Additionally, each comparison was adjusted for relevant factors, such as age, race, ethnicity, CD4 count, HIV RNA, and ART component. The study used the logistic regression model to identify variables associated with excessive weight gain in univariable and multivariable analyses. A *P* value of <.05 was considered statistically significant. Stata Statistical Software, version 15.1 (StataCorp LLC, College Station, TX, USA), was used for all study analyses.

RESULTS

Overview of Participants

A total of 463 men were included in the study analysis (Data set A), with a median age of 33.7 years, CD4 count of 507 cells/μL, and log HIV RNA of 5.0 copies/mL at enrollment. Overall, 331 participants received ART treatment within 96 weeks of HIV diagnosis, and 130 participants received ART ≥96 weeks after HIV diagnosis; these were classified as the Early and Deferred Treatment Groups, respectively (Table 1). A low CD4 count of <200 cells/μL at study entry was noted in 12 participants (2.6%) and was more likely to occur in acute HIV infection than in early HIV infection (7 vs 5; *P* = .044). Temporal trends in participants' age, baseline weight, HIV RNA, and CD4 count were not statistically different (Supplementary Figure 1). Individuals with acute HIV infection (n = 130, 28.1%) had a higher median log HIV RNA (5.7 vs 4.8 copies/mL; *P* < .001) and a lower median CD4 count (468 vs 523 cells/μL; *P* < .001) than those with early HIV infection (n = 333, 71.9%) (Supplementary Table 1).

Factors Associated With Weight Gain Over Time

The median weight gain among the 463 study participants (interquartile range [IQR]) was 1.8 (0.0 to 4.8) kg at 48 weeks and 2.7 (−0.5 to 5.9) kg at 96 weeks (Table 2). After adjusting for baseline demographics and clinical characteristics, there was no difference in the slope of weight gain over time between the Early and Deferred Treatment Groups, acute and early HIV infection, participants with study entry HIV RNA greater or less than 100 000 copies/mL, and participants with study entry CD4 counts greater or less than 350 cells/μL (Figure 2). There was also no difference in the slope of weight gain over time between persons in the Early Treatment Group and Deferred Treatment Group with baseline HIV RNA greater or less than 100 000 copies/mL, or baseline CD4 count greater or less than 350 cells/μL (Supplementary Figure 2). When the cutoff value for CD4 count was set to 200 cells/μL, more weight gain over time was observed in people with baseline CD4 counts <200 cells/μL than those with baseline CD4 counts ≥200 cells/μL (Supplementary Figure 3).

Factors Associated With Excessive Weight Increase

Excessive weight gain was observed in 71 (15.3%), 44 (9.5%), and 30 (6.5%) persons in Data set A using a definition of more than 12%, 15%, and 18% weight increase, respectively, from HIV diagnosis through 96 weeks. In the multivariable analysis, only INSTI-based ART (odds ratio, 1.87; 95% CI, 1.04–3.38; *P* = .037) was significantly associated with a weight gain of ≥12% through 96 weeks (Supplementary Tables 2 and 3). No variable was identified that was associated with a weight increase of more than 15% or 18% (Supplementary Tables 4 and 5).

How ART Regimens Affected Weight Gain

A total of 299 participants received ART within 96 weeks of study entry (median time from study entry to ART initiation, 3.9 weeks; ie, Early ART—Data set B), 72 with NNRTI-based (24.1%), 124 with PI-based (41.5%), and 95 with INSTI-based (31.8%) regimens (Table 3). The other 8 persons received triple-NRTI regimens without another agent. Efavirenz was the most commonly used NNRTI (67/72, 93.1%), and elvitegravir accounted for 77.9%

Table 1. Demographics, Clinical Characteristics, and Antiretroviral Therapy Regimens of Participants (Results From Data Set A)

	All (n = 463)	Early Treatment (n = 331)	Deferred Treatment (n = 132)	*P* Value
Age at HIV diagnosis, median (IQR), y	33.7 (26.9 to 41.5)	34.1 (27.0 to 41.8)	32.7 (26.6 to 39.8)	.236
Race				.316
White, No. (%)	387 (83.6)	273 (82.5)	114 (86.4)	
Black, No. (%)	25 (5.4)	17 (5.1)	8 (6.1)	
Hispanic ethnicity, No. (%)	142 (31.1)	106 (32.7)	36 (27.3)	.255
Year of HIV diagnosis, median (IQR)	2005 (2003 to 2012)	2006 (2003 to 2014)	2004 (2003 to 2008)	<.001
Acute HIV infection, No. (%)	130 (28.1)	100 (30.2)	30 (22.7)	.106
Time from HIV diagnosis to enrollment, median (IQR), wk	0 (0 to 1.4)	0 (0 to 1.1)	0 (0 to 2.1)	.074
Time from enrollment to initial ART, median (IQR), wk	7.8 (2.1 to 37.6)	4.9 (2.1 to 22.0)	155.1 (118.7 to 233.0)	<.001
Overall follow-up time, median (IQR), wk	121.4 (71.6 to 203.9)	112.7 (71.0 to 194.9)	143.3 (77.9 to 246.4)	.009
Baseline weight, median (IQR), kg	75.8 (68.0 to 84.4)	75.3 (67.6 to 85.3)	76.2 (69.9 to 83.0)	.704
Baseline CD4 count, median (IQR), cells/μL	507 (390 to 649)	490 (351 to 621)	545 (463 to 750)	<.001
<350 cells/μL, No. (%)	90 (19.4)	82 (24.8)	8 (6.1)	<.001
<200 cells/μL, No. (%)	12 (2.6)	12 (3.6)	0 (0.0)	.023
CD4 count at 24 wk after HIV diagnosis, median (IQR), cells/μL	639 (474 to 809)	657 (482 to 850)	583 (467 to 738)	.033
Baseline log HIV RNA, median (IQR), copies/mL	5.0 (4.2 to 5.7)	5.2 (4.6 to 5.9)	4.4 (3.6 to 5.1)	<.001
HIV RNA ≥100 000 copies/mL, No. (%)	232 (50.1)	194 (58.6)	37 (28.0)	<.001
Log HIV RNA at 24 wk after HIV diagnosis, median (IQR), copies/mL	2.1 (1.6 to 4.4)	1.7 (1.3 to 2.5)	4.3 (3.3 to 4.9)	<.001
Viral suppressed at 24 wk after HIV diagnosis, No. (%)	251 (54.2)	237 (71.6)	14 (10.6)	<.001
Initial ART class[a]				
NNRTI-based, No. (%)	84 (18.1)	84 (25.4)	-	
PI-based, No. (%)	134 (28.9)	134 (40.5)	-	
INSTI-based, No. (%)	96 (20.7)	96 (29.0)	-	
Other, No. (%)	17 (3.7)	17 (5.1)	-	
Main NRTI component[a]				
TDF	200 (43.2)	200 (60.4)	-	
TAF	49 (10.6)	49 (14.8)	-	
Other	70 (15.1)	70 (21.1)	-	

Abbreviations: ART, antiretroviral therapy; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

[a]ART initiated within 96 weeks after HIV diagnosis.

(74/95) of INSTI. Among participants taking a PI, 48 received lopinavir (38.7%) and 41 received atazanavir (33.1%). A detailed distribution of ART regimens is listed in Supplementary Table 6. The proportions of participants with viral suppression 24 weeks after treatment were not different by ART class (NNRTI, 95.8%; PI, 96.0%; INSTI, 97.9%; $P = .567$). As for the NRTI component, the numbers of participants receiving tenofovir disoproxil fumarate (TDF), TAF, and other NRTIs were 178 (59.5%), 49 (16.4%), and 72 (24.1%), respectively (Table 3). The median length of time on ART was shorter for participants in the TAF group vs the non-TAF group (70.1 vs 89.4 weeks; $P = .004$).

The median percent weight change at 96 weeks after ART initiation among NNRTI-, PI-, INSTI-based regimen users was 0.9%, 4.3%, and 4.9%, respectively (Table 4). After adjusting for baseline demographics and HIV clinical characteristics, weight gain over time was significantly greater among participants receiving INSTI-based regimens compared with NNRTI-based regimens ($P = .012$) (Figure 3A). The slope of weight gain over time was not different between participants receiving INSTI vs PI, NNRTI vs PI, and TAF vs non-TAF regimens ($P = .080$, .168, and .105, respectively) (Figure 3B, C, D).

Table 2. Median Percent Weight Change and Interquartile Range After HIV Diagnosis (Results From Data Set A)

Time of visit	All (n = 463)	Early Treatment (n = 331)	Deferred Treatment (n = 132)	*P* Value
Week 12 (n = 439)	1.5 (–0.6 to 3.8)	1.5 (–0.6 to 3.9)	1.5 (–0.7 to 3.5)	.528
Week 24 (n = 434)	2.0 (–0.6 to 4.8)	2.0 (–0.6 to 5.1)	2.0 (–1.1 to 4.5)	.664
Week 48 (n = 369)	2.8 (0.0 to 6.3)	3.0 (0.0 to 6.9)	2.1 (–0.5 to 6.0)	.314
Week 72 (n = 296)	3.2 (0.0 to 7.9)	3.4 (0.0 to 7.9)	2.8 (0.0 to 7.9)	.690
Week 96 (n = 267)	3.8 (–0.6 to 8.1)	4.3 (0.0 to 8.4)	3.1 (–1.1 to 6.5)	.148

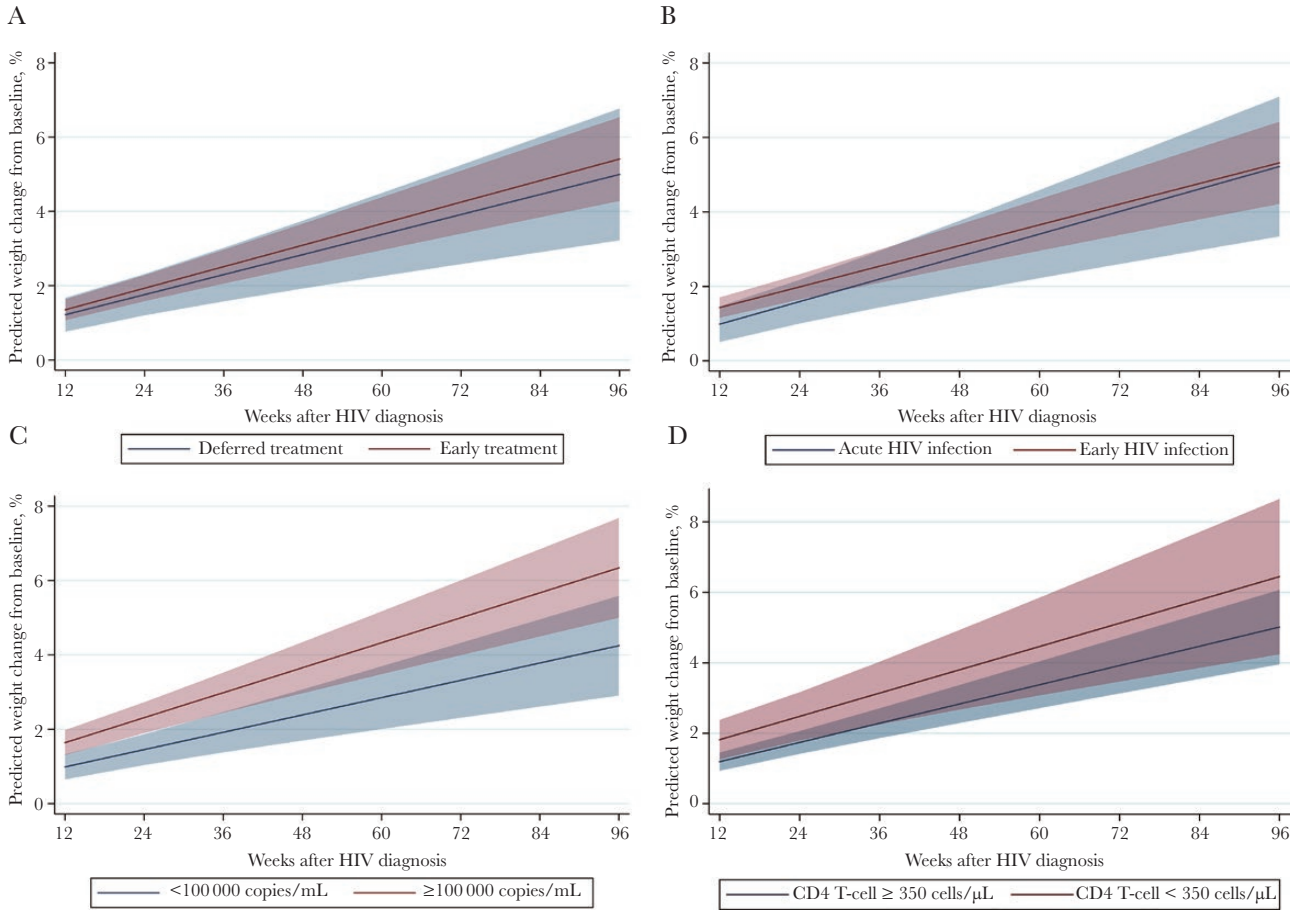

Figure 2. Predicted weight change from baseline between individuals with different variables, adjusted for age, race, ethnicity, baseline CD4 count, baseline HIV RNA, baseline weight, receiving antiretroviral therapy or not, and year of HIV diagnosis as adequate (results from Data set A). A, Early treatment vs deferred treatment (difference between slopes, $P = .773$). B, Early HIV infection vs acute HIV infection (difference between slopes, $P = .733$). C, Baseline HIV RNA ≥100 000 copies/mL vs <100 000 copies/mL (difference between slopes, $P = .101$). D, Baseline CD4 count <350 cells/μL vs ≥350 cells/μL (difference between slopes, $P = .477$).

Table 3. Demographics and HIV-Related Clinical Characteristics of Participants Receiving Early Treatment by ART Class (Results From Data Set B)

	All (n = 299)	NNRTI (n = 72)	PI (n = 124)	INSTI (n = 95)	*P* Value[a]
Age at ART initiation, median (IQR), y	34.6 (27.7 to 42.0)	34.4 (28.3 to 42.9)	36.1 (28.8 to 41.9)	31.8 (26.3 to 40.8)	.152
Race					.032
White, No. (%)	249 (83.3)	64 (88.9)	108 (87.1)	69 (72.6)	
Black, No. (%)	16 (5.4)	3 (4.2)	6 (4.8)	7 (7.4)	
Hispanic ethnicity, No. (%)	95 (31.8)	19 (26.4)	22 (17.7)	51 (53.7)	<.001
Year of ART initiation, median (IQR)	2005 (2003 to 2014)	2003 (2002 to 2005)	2004 (2002 to 2010)	2016 (2015 to 2017)	<.001
Weight at ART initiation, median (IQR), kg	76.2 (68.0 to 86.0)	76.2 (68.5 to 84.6)	76.0 (68.9 to 84.1)	74.4 (66.7 to 88.8)	.939
CD4 count at ART initiation, median (IQR), cells/μL	499 (366 to 674)	492 (359 to 674)	489 (355 to 619)	541 (404 to 682)	.109
CD4 count at 24 wk after ART initiation, median (IQR), cells/μL	696 (525 to 865)	574 (470 to 752)	709 (549 to 862)	753 (610 to 916)	<.001
Log HIV RNA at ART initiation, median (IQR), copies/mL	5.0 (4.5 to 5.6)	4.8 (4.5 to 5.3)	5.1 (4.7 to 5.8)	5.0 (4.3 to 5.8)	.014
Viral suppressed at 24 wk after ART initiation, No. (%)	281 (96.3)	69 (95.8)	119 (96.0)	93 (97.9)	.567
Time from enrollment to ART initiation, median (IQR), wk	3.9 (2.1 to 13.7)	14.5 (7.1 to 32.1)	3.4 (2.1 to 10.9)	2.1 (2.0 to 4.0)	<.001
Time of initial ART use, median (IQR), wk	84.1 (48.6 to 126.0)	91.3 (54.6 to 146.2)	78.1 (48.9 to 106.3)	86.6 (45.7 to 136.4)	.192
Main NRTI component					<.001
TDF, No. (%)	178 (59.5)	51 (70.8)	78 (62.9)	43 (45.3)	
TAF, No. (%)	49 (16.4)	0 (0.0)	0 (0.0)	49 (51.6)	
Other NRTI, No. (%)	72 (24.1)	21 (29.2)	46 (37.1)	3 (3.2)	

Abbreviations: ART, antiretroviral therapy; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

[a]Eight individuals who received NRTI only were not included for analysis.

Table 4. Median Percent Weight Change and Interquartile Range After ART Initiation (Results From Data Set B)

Time of Visit	All (n = 299)	NNRTI (n = 72)	PI (n = 124)	INSTI (n = 95)	*P* Value[a]
Week 12 (n = 281)	1.3 (–0.7 to 3.3)	0.0 (–1.0 to 2.8)	1.3 (–0.9 to 3.3)	1.5 (–0.3 to 3.9)	.284
Week 24 (n = 267)	1.3 (–1.0 to 4.0)	0.6 (–1.4 to 3.1)	1.0 (–1.3 to 3.3)	2.1 (–0.7 to 5.1)	.082
Week 48 (n = 232)	2.1 (–1.0 to 5.8)	1.0 (–2.4 to 5.2)	2.6 (–1.0 to 5.4)	2.2 (0.4 to 7.3)	.102
Week 72 (n = 168)	2.6 (–0.9 to 6.9)	1.0 (–0.6 to 3.0)	2.6 (–1.3 to 6.6)	4.6 (–0.2 to 10.6)	.018
Week 96 (n = 149)	3.6 (0.0 to 7.9)	0.9 (–3.6 to 5.8)	4.3 (1.5 to 7.8)	4.9 (–0.3 to 10.4)	.016

Abbreviations: ART, antiretroviral therapy; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

[a]Eight individuals who received NRTI only were not included for analysis.

DISCUSSION

This study demonstrated that the baseline HIV-related clinical characteristics, primarily the HIV RNA and CD4 count, were not significantly associated with weight gain among most men (>95%) with AEH. Neither an HIV RNA >100 000 copies/mL nor a CD4 count <350 cells/μL was associated with a higher rate of weight gain among participants overall, or for those either on or off ART. Only among the 2.6% of participants with CD4 counts <200 cells/μL at HIV diagnosis was weight gain greater than that observed among the comparators. Additionally, the Early Treatment Group participants did not gain more weight than those in the Deferred Treatment Group. These results suggest that, when initiating in the early stage of HIV disease, ART is not a significant contributor to greater weight gain.

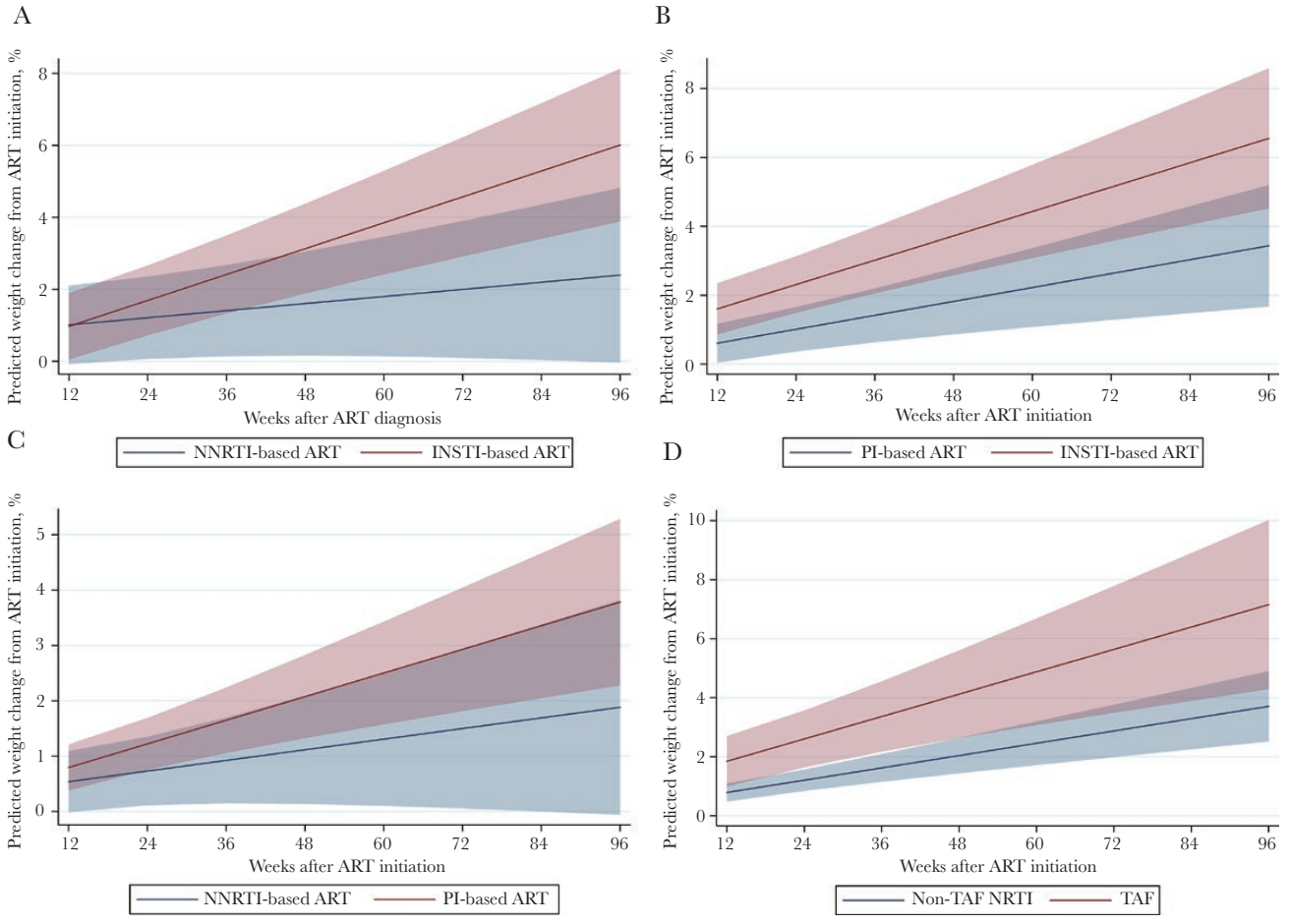

Figure 3. Predicted weight change from ART initiation between individuals receiving different ART components, adjusted for age, race, ethnicity, CD4 T-cell count at ART initiation, HIV RNA at ART initiation, weight at ART initiation, year of HIV diagnosis, main NRTI component, and ART class (results from Data set B). A, INSTI-based vs NNRTI-based ART (difference between slopes, $P = .012$). B, INSTI-based vs PI-based ART (difference between slopes, $P = .080$). C, PI-based vs NNRTI-based ART (difference between slopes, $P = .168$). D, TAF-containing vs non-TAF-NRTI-containing ART (difference between slopes, $P = .105$). Abbreviations: ART, antiretroviral therapy; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TAF, tenofovir alafenamide.

HIV RNA and CD4 count have been identified as strong predictors of weight change in previous reports [1, 5, 6, 12, 15]. There are 2 possible explanations of why we did not observe similar findings. First, weight is less influenced by HIV infection in AEH than in chronic HIV infection; the duration of infection may not be sufficient for these clinical characteristics to influence weight. Second, CD4 count and HIV RNA dynamics are unique in AEH. In AEH, Le and colleagues observed a spontaneous restoration of CD4 counts in the initial 4-month window after HIV infection, followed by a progressive decline [23]. Another study revealed that peak and nadir viremia occurred at a median of 13 and 31 days after HIV RNA being detected, respectively [26]. The nonlinear nature of CD4 counts and HIV RNA during AEH may weaken their associations with weight change.

Taking an INSTI-based regimen was the single most sensitive predictor for an excessive weight increase in this study. Besides, similar to several previous reports [1, 4, 9, 12], our findings show that INSTI users had greater weight gain than NNRTI users, even though the most prevalent INSTI in our study was elvitegravir, which was associated with less weight gain than dolutegravir or bictegravir [1, 9]. These findings may partly be explained by the effect of efavirenz on weight suppression as efavirenz accounted for 93% of NNRTIs in this study [27, 28]. Our results did not, however, support the hypothesis that the greater weight gain caused by INSTI was due to a more rapid return-to-health effect. The proportions of participants with viral suppression at 24 weeks after treatment were similar by ART class. The greater CD4 count increase among INSTI users was most likely due to the shorter duration from HIV diagnosis to ART initiation, which was associated with an enhanced CD4 count recovery [23]. In previous reports without a noticeable return-to-health effect, such as regimen-switching studies among virally suppressed populations [29, 30], INSTI users still had a greater weight gain than NNRTI users. Further research is needed to clarify the mechanism underlying INSTI-based weight gain.

TAF use compared with non-TAF use demonstrated only a trend toward greater weight gain in this study population. This observation is in contrast to previous reports showing that TAF use was associated with greater weight gain than non-TAF NRTI use [31–33]. Several reasons may explain the discrepancy. First, we censored our weight record in Data set B only when participants switched ART classes, not when they switched NRTI components. Therefore, participants who initially started TDF-containing regimens and then switched to TAF-containing regimens were still categorized in the TDF group. Second, the median length of time on ART was significantly shorter for participants in the TAF group vs the non-TAF group. Third, all TAF users took INSTIs at the same time, and INSTIs were associated with excessive weight gain in this study. The effect of INSTIs on weight change may also influence the results of the analysis between the TAF and non-TAF groups. Finally, only 16.4% of the study participants received TAF. Collectively, these explanations suggest that the power to discriminate between the TAF and non-TAF groups may be limited. Thus, our results cannot confidently conclude that weight gain over time did not differ between TAF users and non-TAF-NRTI users.

There were several limitations to this study. First, participants were mainly white men. The results may not be generalizable to women and Blacks. Second, baseline height was available in only a small proportion of participants. Therefore, we cannot calculate BMI for better categorization and adjustment. Instead of BMI or absolute weight change, the percentage of weight change was used in most of our analyses. Third, our study did not include other factors that may influence weight change, such as dietary habits, physical activity, concomitant disease and medications, and smoking. In addition, ~78% of the INSTI use was elvitegravir, which has been associated with less weight gain [1, 9], so our findings may not be representative of dolutegravir or bictegravir use. Last, all TAF users took INSTIs simultaneously, and about half of INSTI users took TAF at the same time. Therefore, even after statistical adjustment, we may not be able to separate the effects of TAF and INSTI on weight gain completely.

To conclude, the influence of the ART regimen outweighed that of HIV-related clinical characteristics on weight gain in the acute and early stages of HIV infection. As more PWH were diagnosed at an earlier stage of HIV infection and INSTI-based regimens are almost universally recommended as initial ART [34], the role of ART regimen on weight gain will become even more crucial.

Supplementary Data

Supplementary materials are available at *Open Forum 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.

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