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BRIEF REPORT

"Weight and See": Initial Weight Gain After Starting Antiretroviral Therapy Is Not Associated With Antiretroviral Regimen Type and Does Not Predict Subsequent Weight Trajectory

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In a Canadian cohort with HIV, 61% gained weight, 26% lost weight, and 12% remained stable in the first year of antiretroviral therapy. Weight gain was not associated with regimen type and slowed in years 2 to 3, with 44%, 34%, and 23% experiencing increasing, decreasing, and stable trajectories. Although 23% had significant weight gain year 1, many subsequently lost weight despite continuing antiretroviral therapy.

Keywords. antiretroviral; HIV; integrase inhibitor; tenofovir alafenamide; weight gain.

Weight gain beyond "return to health" [1, 2] has been associated with antiretroviral therapy (ART) based on integrase strand transfer inhibitor (INSTI) and/or tenofovir alafenamide (TAF) [3–5]. Black race, female sex, lower CD4, higher viral load, and higher body mass index are inconsistently associated with weight gain [4–6] and observations beyond 1 year less frequent [7]. We aimed to identify the amount, trajectory, and associated factors for weight change over a 3-year period in a diverse population initiating ART at a Canadian tertiary care HIV clinic.

METHODS

This single-center retrospective cohort study consisted of adults initiating first ART between 1 January 2010 and 30 September 2022. Weight was recorded every 3 to 6 months at clinic visits. Participant data were collected for 3 years, until the first ART switch, loss to follow-up, or 30 September 2022.

The longitudinal outcome was weight. The index date was the first ART prescription. In the primary analysis of weight change over time, all participants with at least 2 weight measurements were included (supplementary methods). The main exposure of interest was ART class, with 3 a priori comparisons: TAF vs tenofovir disoproxil fumarate (TDF) vs other nucleoside reverse transcriptase inhibitor (NRTI) backbones, second-generation INSTI vs other regimens, and second-generation INSTI plus TAF vs other regimens. Other covariates included age, sex, race and ethnicity, and baseline CD4 and viral load. In the secondary analysis of significant weight increases (≥10% gain/y), participant-level weight slope values were used. For descriptive purposes, weight trajectories in the 2 time segments (year 1 and years 2–3) were categorized as increasing (>1% gain/y), decreasing (>1% loss/y), or stable (±1% change/y).

RESULTS

Of 930 potentially eligible participants, 399 were included in the analysis (Supplementary Table 1) after exclusions due to insufficient/missing data (Supplementary Figure 1). Median length of ART was 4.0 years (IQR, 2.1–5.7) and included a median 9 weight measurements per participant. At study end, 39% remained with the initial ART, and 93% had HIV RNA <50 copies/mL.

Participant-level slopes showed a mean increase of 3.2 kg per 4.6% over the first year (n = 391) with high interparticipant variation (SD, 7.6 kg/10.0%). In year 1, 91 (23%) participants experienced significant weight gain (mean, +13.2 kg/18.4%; SD, 5.6 kg/7.6%). In years 2 to 3 (n = 271), the mean weight increase was lower (0.4 kg/0.5%/y), although the SD remained high (4.1 kg/5.1%); 4% experienced significant weight gain of at least 10% per year during this observation period. Of those with a significant weight increase in year 1, 3% experienced further significant weight increases in years 2 to 3 (Table 1).

In year 1, 61% gained, 26% lost, and 12% had stable weight, as opposed to 44%, 34%, and 23% in years 2 to 3, respectively (Figure 1, Tables 1 and 2). Of those who gained weight in year 1, 37% continued to gain it, 42% lost it, and 21% remained stable in years 2 to 3. Of those who lost weight in year 1, 16% continued to lose it, 56% gained it, and 28% remained stable in years 2 to 3. Of participants with significant weight gain in 1 year, 32% continued to increase (mean, 5.0 kg/y), 46% declined (mean, −4.8 kg/y), and 22% were stable in years 2 to 3 while continuing initial ART. The year 2–3 trajectories in those

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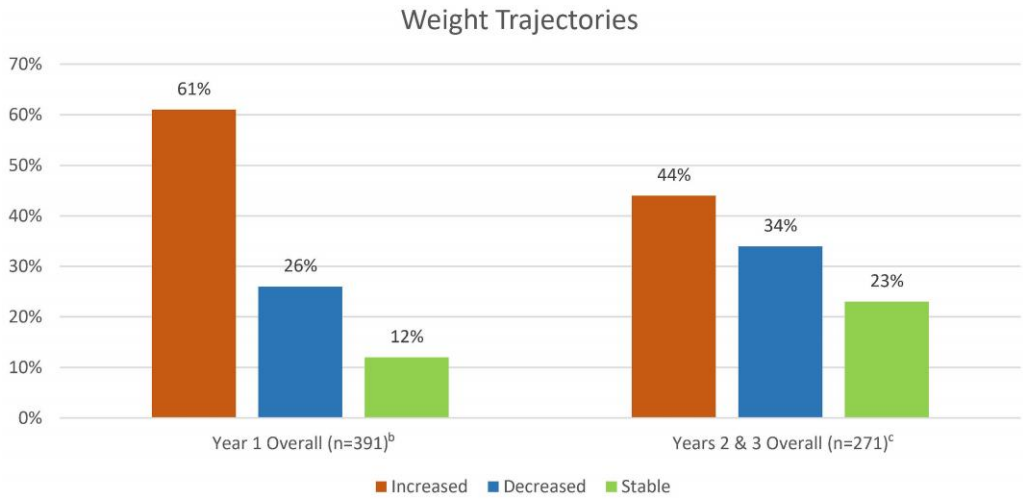

Figure 1. Weight trajectories in the first year vs the second and third years of antiretroviral therapy. Weight Trajectories[a]; [a]Weight change categories: increased weight, >1% weight gain per year; decreased weight, >1% weight loss per year; stable weight, ±1% weight change per year. [b]Participants who did not have sufficient data in year 1 to determine an average weight change, n = 8. [c]Participants who did not have sufficient data after year 1 to determine an average weight change; n = 128.

Table 1. Weight Change to Year 1 and in Years 2–3 After Antiretroviral Therapy Initiation

	Weight Change per Year			Weight Change per Year by Category [a]					
				Increased		Decreased		Stable	
	kg	%	≥10%	kg	%	kg	%	kg	%
Year 1[b] (n = 391)			91 (23)	240 (61)		103 (26)		48 (12)	
Mean ± SD	3.2 ± 7.6	4.6 ± 10.0		7.4 ± 5.9	10 ± 8.3	−5.1 ± 4.6	−6.1 ± 5.4	0.1 ± 0.5	0.2 ± 0.6
Years 2–3[c] (n = 271)			10 (4)	118 (44)		92 (34)		61 (23)	
Mean ± SD	0.4 ± 4.1	0.5 ± 5.1		3.8 ± 2.8	4.6 ± 3.4	−3.6 ± 2.9	−4.5 ± 3.7	0.1 ± 0.5	0.1 ± 0.6
Gained ≥10% by year 1 (n = 59)			3%	19 (32)		27 (46)		13 (22)	
Mean ± SD	−0.5 ± 5.3	−0.8 ± 6.2		5 ± 3.7	5.6 ± 4.5	−4.8 ± 3.4	−5.8 ± 4.0	0.2 ± 0.6	0.1 ± 0.6
Did not gain ≥10% by year 1 (n = 212)			4%	99 (47)		65 (30)		48 (23)	
Mean ± SD	0.7 ± 3.7	0.9 ± 4.7		3.5 ± 2.6	4.4 ± 3.2	−3.2 ± 2.6	−4.0 ± 3.5	0.1 ± 0.5	0.1 ± 0.6

Data are presented as No. (%) unless noted otherwise.

[a]Weight change categories: increased, >1% weight gain per year; decreased, >1% weight loss per year; stable, ±1% weight change per year.

[b]Participants who did not have sufficient data up to year 1 to determine an average weight change: n = 8.

[c]Participants who did not have sufficient data after year 1 to determine an average weight change: n = 128.

without significant weight gain in year 1 were similar, with 47% increased (mean, 3.5 kg/y), 31% declined (mean, −3.2 kg/y), and 23% stable (unadjusted $P = .069$; Supplementary Figure 2).

In the primary analysis, conducted by linear mixed effects models, no significant differences were observed in longitudinal weight according to gender (Supplementary Figure 3), between NRTI backbones, between second-generation INSTI and others, or between second-generation INSTI with TAF and others (Supplementary Figure 4). In the secondary analysis of significant weight gain during year 1, baseline CD4 <200 cells/mm^3 and viral load >100 000 copies/mL were significantly associated with significant weight gain in year 1 (logistic regression); participants with significant weight gain had lower baseline weight and remained under initial ART for a shorter duration. NRTI backbone was not associated (Supplementary Table 2); adjusted models replacing the NRTI backbone with second-generation INSTI or second-generation INSTI and TAF also showed no association (model results not shown).

DISCUSSION

We provide insight into the nature of weight changes over 3 years after starting ART. Although weight gain was observed in 61% of participants, one-quarter lost weight in the first year of ART. Those with significant weight gain (>10%) had lower

Table 2. Weight Trajectory in Years 2–3 According to Weight Change in Year 1 After Antiretroviral Therapy Initiation

	Weight Change in Years 2–3, No. (%) [a]			
Year 1 (n = 271) [b]	Increased	Decreased	Stable	*P* Value
Weight change				.003
Increased (n = 164)	61 (37)	69 (42)	34 (21)	
Decreased (n = 71)	40 (56)	11 (16)	20 (28)	
Stable (n = 36)	17 (47)	12 (33)	7 (19)	
Gained ≥10%				.069
Yes (n = 59)	19 (32)	27 (46)	13 (22)	
No (n = 212)	99 (47)	65 (31)	48 (23)	

Data are presented as No. (%) of row totals.

[a]Weight change categories: increased, >1% weight gain per year; decreased, >1% weight loss per year; stable, ±1% weight change per year.

[b]Participants who did not have sufficient data in years 2 to 3 to determine an average weight change: n = 128.

baseline weight, yet only 2% were underweight, suggesting that etiologies other than return to health are at play. The weight gain trajectory during the first year was numerically higher, but not statistically significant, in people taking a second-generation INSTI, TAF, or both relative to other regimens.

Our results are similar to those reported in other naive cohorts. In a longitudinal analysis of 2624 treatment-naive participants enrolled in randomized trials, average weight gain at week 48 was 3.6 kg, with 22% gaining ≥10% body weight from baseline [8]. In a cohort of patients initiating ART between 2008 and 2022, a median increase in body mass index of 5.4 kg per 7.4% was observed by year 3, with 41% experiencing a ≥10% increase from baseline [9]. These increases are higher than those reported in a pooled analysis of 8 randomized trials in treatment-naive individuals [4], where a median weight gain of 2.0 kg at 96 weeks was observed, with 12.8% and 17.3% experiencing a ≥10% increase from baseline by 48 and 96 weeks, respectively. Of note, the pooled analysis included a higher proportion of males, a lower proportion of Black participants, and a higher CD4 count at baseline, as compared with our cohort and others.

The overall weight trajectory over years 2 to 3 in our cohort continued to increase but at a slower rate. Others also report weight gain trajectories steepest in the first 6 to 12 months, which then stabilized or continued at a slower rate of increase over 1.5 to 2 years [4, 6]

Importantly, not all participants in our cohort experienced weight gain after starting ART: 26% experienced weight loss in the first year and 34% in years 2 to 3, similar to a pooled analysis where 30.2% of participants lost weight through week 96 [4]. In our cohort, two-thirds who gained weight in year 1 subsequently experienced weight loss or stable weight, while over half the participants who initially lost weight in year 1 subsequently gained weight. In the subgroup who experienced ≥10% weight gain in year 1, 46% decreased, 32% increased, and 22% were stable in years 2 to 3. This reinforces the concept that weight gain with ART is not universal, and gaining significant weight in the first year of therapy does not imply continued weight gain in subsequent years.

In our study, weight gain did not strongly correlate with second-generation INSTIs and TAF, consistent with a recent review of major clinical trials suggesting that they are weight neutral [10]. We did not observe a significant difference in the weight gain trajectory in both periods according to NRTI backbone. Others have attributed weight-attenuating effects to TDF, particularly when combined with efavirenz [10]. In the pooled analysis of treatment-naive individuals, weight gain was observed at 96 weeks with all modern nucleosides, including TDF [4]. Combined with our data, this suggests that weight effects of TDF are variable and may depend on other accompanying agents.

Our study has many strengths. Our cohort was older, with a higher baseline CD4 count and lower viral load than prior reports, and included persons who may not qualify for clinical trials. Over half were born outside of Canada, with more Asian/southeast Asian and Indigenous participants, thereby providing information on underrepresented populations. We captured a median 9 weights per person over 4 years.

A limitation of our study was that more than half our potential sample was excluded for lack of adequate baseline or follow-up weights. Besides having implications for statistical power and inflating the type II error rate, this may have resulted in selection bias. While the procedure for weight measurement was relatively consistent, recording was by different clinic staff, and patient seasonal outerwear and footwear varied significantly. ART adherence was not formally measured, and we cannot be certain to the trajectory in those who elected to change ART. Our data may also be subject to confounding bias—for example, we did not assess the potential influence of other medications or unobserved biological or behavioral factors that influence weight. Notably, during the COVID-19 pandemic, in-person visits were limited for the most urgent. With virtual visits, weight measurements were either self-reported by non-standardized weight-measuring equipment or not reported. Many people experienced drastic changes in activity levels and dietary patterns due to restricted access to recreational facilities, social isolation, and change in financial status. These circumstances and behaviors may have played an outsized role on people's weight over this period. The generalizability of our findings may also be limited by the fact that the majority of our patients are male, and gender may play a role in weight gain experiences.

We emphasize that our findings are associative rather than causal, and we recommend that weight be measured at each care visit with appropriate counseling on lifestyle changes and metabolic laboratory monitoring so that sudden or significant changes in weight may be addressed.

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.

Notes

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