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Weight gain following antiretroviral therapy (ART) initiation in ART-naïve people living with HIV in the current treatment era

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Abstract

Objectives—Evaluate differences in weight change by regimen among people living with HIV (PLWH) initiating antiretroviral therapy (ART) in the current era.

Methods—Between 2012–2019, 3232 ART-naïve PLWH initiated ≥3-drug ART regimens in eight Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) sites. We estimated weight change by regimen for 11 regimens in the immediate (first 6-months) and extended (all follow-up on initial regimen) periods using linear mixed models adjusted for time on regimen, interaction between time and regimen, age, sex, race/ethnicity, hepatitis B/C coinfection, nadir CD4, smoking, diabetes, antipsychotic medication, and site. We included more recently

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approved regimens (e.g. with tenofovir alafenamide fumarate (TAF)) only in the immediate period analyses to ensure comparable follow-up time.

Results—Mean follow-up was 1.9 years on initial ART regimen. In comparison to efavirenz/tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC), initiating bictegravir/TAF/FTC (3.9kg (95%CI:2.2–5.5)) and dolutegravir/TAF/FTC (4.4kg (95%CI:2.1–6.6)) were associated with the greatest weight gain in the immediate period, followed by darunavir/TDF/FTC (3.7kg (95%CI:2.1–5.2)) and dolutegravir/TDF/FTC (2.6kg (95%CI:1.3–3.9). In the extended period, compared with efavirenz/TDF/FTC, initiating darunavir/TDF/FTC was associated with a 1.0kg (95%CI:0.5–1.5) per 6-months greater weight gain, while dolutegravir/abacavir/FTC was associated with a 0.6kg (95%CI:0.3–0.9) and dolutegravir/TDF/FTC was associated with a 0.6kg (95%CI:0.1–1.1) per 6-months greater gain. Weight gain on dolutegravir/abacavir/FTC and darunavir/TDF/FTC was significantly greater than that for several integrase inhibitor-based regimens.

Conclusions—There is heterogeneity between regimens in weight gain following ART initiation among previously ART-naïve PLWH; we observed greater gain among PLWH taking newer INSTIs (DTG, BIC) and DRV-based regimens.

Keywords

HIV; weight; antiretroviral therapy; integrase strand transfer inhibitors; dolutegravir; bictegravir

Introduction

In the early HIV era, people living with HIV (PLWH) experienced severe wasting[1], which can be juxtaposed with the current era, when some PLWH are gaining weight after initiating antiretroviral therapy (ART)[2–4]. Wasting and subsequent metabolic disturbances among untreated PLWH have been well-documented[1], but the mechanisms associated with weight gain among treated PLWH have not been fully characterized. A link between ART initiation and a return to health effect, in part characterized by increasing CD4 count and weight gain, has been postulated[2, 5–8]. However, in more recent years, the prevalence of PLWH with obesity has continued to increase[3, 9], which warrants further investigation.

Regimens containing integrase strand transfer inhibitors (INSTIs), a relatively recent class of ART drugs including raltegravir (RAL), elvitegravir (EVG), dolutegravir (DTG), and bictegravir (BIC), demonstrated more rapid viral suppression compared to other ART classes, and are currently recommended as a component of initial HIV regimens[10–14]. Recent evidence has emerged documenting changes in body morphology in PLWH after initiating INSTIs[7, 15]. In particular, cases of atypical weight gain have occurred in some PLWH taking DTG[7, 16–19]. Excessive weight gain affects psychological[20] and social quality of life[21], as well as ART adherence[22], and can potentially lead to long-term adverse health outcomes[23–25] thus requiring monitoring of metabolic measures [25–27].

A potential association between INSTIs such as dolutegravir and weight gain has been suggested[7, 15–19, 28]. However, questions remain as prior studies have mainly been small[2, 16, 17], used historical rather than concurrent controls[17], did not include the most

recent INSTI drugs (e.g. BIC)[2, 9, 15, 28], did not account for other weight-impacting medications like antipsychotic medications[8, 9, 15, 17, 18], or were from trials that lack generalizability to the current diversity of PLWH in the United States[8, 17, 28]. In addition, many studies on weight change in PLWH on ART focused on ART class effects, thus were unable to compare individual agents[2, 9, 29]. Finally, many prior studies were not limited to PLWH initiating their first regimen, so they assessed outcomes after participants switched regimens, potentially allowing for carry-over effects from prior drugs[7, 9, 15, 28, 30]. To address these limitations, we conducted a large retrospective cohort study comparing weight gain in previously ART-naïve PLWH initiating various ART regimens in the current treatment era.

Methods

Overview and setting

The Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) is a dynamic cohort that includes >35,000 PLWH at eight academic clinical sites throughout the United States[31]. CNICS integrates verified clinical point-of-care data for its participants from outpatient and inpatient visits, including information on demographic characteristics, clinical and laboratory data and diagnoses, and medications.

Study cohort

We assessed body weight change in ART-naïve PLWH initiating one of the 11 most common ART regimens containing three or more drugs between January 1, 2012 and November 30, 2019 (Supplement Table 1). Regimens assessed were efavirenz (EFV), rilpivirine (RPV), ritonavir-boosted atazanavir (ATV), ritonavir-boosted darunavir (DRV), raltegravir (RAL), cobicistat-boosted elvitegravir (EVG), and dolutegravir (DTG), all with tenofovir disoproxil fumarate (TDF) and emtricitabine. In addition, we assessed DTG, bictegravir (BIC), and cobicistat-boosted EVG with tenofovir alafenamide fumarate (TAF) and emtricitabine. We also included DTG with abacavir (ABC) and emtricitabine. Emtricitabine and lamivudine were not distinguished for these analyses. We required regimens to have a minimum of 90 PLWH initiating them to be sufficient for evaluation. No two-drug regimen met sufficient numbers (≥90 PLWH) for inclusion. ART initiation date is hereinafter referred to as baseline and represents the start of follow-up. All PLWH were previously ART-naïve to eliminate impacts from prior regimens and maximize comparability among PLWH across regimens of interest. Follow-up for each PLWH ended when their initial ART regimen changed, ART was stopped, loss to follow-up or death, or the end of clinical data (varies somewhat by site, approximately 11/2019), whichever was earliest.

Analysis

We conducted descriptive analyses of demographic and clinical characteristics of PLWH by regimen and assessed differences between regimens with t-tests for continuous variables and chi-squared tests for categorical variables. The main outcome, body weight change, was calculated as the difference in weight between a follow-up visit and baseline weight (measured at or immediately before baseline). We estimated body weight change by ART regimen using linear mixed models with exchangeable correlation matrices and robust

standard errors to account for within-subject correlations, random intercepts, and random slopes for time on ART[32]. We examined weight change in the immediate period (first 6 months) after ART initiation. All models were adjusted for age, sex, race/ethnicity, hepatitis C virus (HCV) (defined as positive detection of hepatitis C antibodies or RNA) and/or hepatitis B virus (HBV) coinfection (defined as positive test for hepatitis B surface antigen), nadir CD4 count (cells/mm^3), diabetes mellitus (defined as a patient having a diabetes specific medication, a diabetes related medication with diabetes diagnosis, or a hemoglobin A1C value ≥6.5), smoking status, time-updated antipsychotic medication use (antipsychotic or antipsychotic plus antidepressant medication), clinical site, time on ART, and the interaction of time on ART and regimen.

Differences in body weight change between regimens were evaluated using Wald tests. As we were using linear mixed models, body weight change was evaluated using generalized additive models (GAM) to assess linearity and patterns of weight change over time to ensure parametric assumptions were met. Additional weight change sensitivity analyses incorporated extended follow-up time (excluded recently-approved regimens including TAF), time-updated CD4 count, stratification by baseline BMI (≥25 kg/m^2 vs <25 kg/m^2) to assess the potential for a return to health effect, and exclusion of PLWH with a weight change in the top or bottom five percent of all observed weight changes to ensure the observed differences were not due to influential outliers.

Results

We observed 3232 previously treatment-naïve PLWH in the CNICS cohort who initiated one of 11 ART regimens. Demographic and clinical characteristics of the study cohort by regimen are presented in Table 1. The EVG/TDF/FTC regimen had the most participants (24% of cohort), and the ATV/TDF/FTC (3%) and RAL/TDF/FTC (3%) regimens had the fewest. Overall average follow-up time on initial ART regimen was 1.9 years (Interquartile Range (IQR): 0.6–2.9). The mean age was 37 years and PLWH were predominantly male (84%). Overall, 35% of PLWH were white, 45% were black, and 13% were Hispanic. Hepatitis C coinfection was 9% on average, with a higher rate of coinfection among those on RAL/TDF/FTC (22%) and ATV/TDF/FTC (16%). Average nadir CD4 count among PLWH by regimen was between 295 and 432 cells/mm^3 (overall mean=381 cells/mm^3). Average baseline weight was 79 kg (IQR: 67–89) and baseline BMI was 26 kg/m^2 (IQR: 22–28) for the entire cohort.

On average, the entire study cohort gained weight after ART initiation (Table 2). In the immediate period after ART initiation (N=3186), DRV/TDF/FTC was associated with a 3.7 kg (95% CI: 2.1–5.2) per 6 months greater weight gain, DTG/TAF/FTC was associated with a 4.4 kg (95% CI: 2.1–6.6) per 6 months greater gain, and BIC/TAF was associated with a 3.9 kg (95% CI: 2.2–5.5) per 6 months greater gain compared with EFV/TDF/FTC (Table 2). We assessed differences in weight gain directly between regimens. Weight gain on DTG/TAF/FTC and BIC/TAF/FTC were statistically significantly greater ($p<0.05$) than EFV/TDF/FTC, RPV/TDF/FTC, EVG/TDF/FTC, and EVG/TAF/FTC regimens, but not statistically significantly greater than DTG/ABC/FTC (p=0.08 vs. DTG/TAF/FTC; p=0.06

vs. BIC/TAF/FTC) (Table 2). GAM plots restricted to the first 6 months after ART initiation suggest linear increases in weight during this period (Supplement Figure 1).

We conducted several sensitivity analyses of the extended period on the initial ART regimen. Among 2646 PLWH, average follow-up time was 2.1 years. PLWH taking DRV/TDF/FTC experienced the most weight gain, followed by those taking DTG/TDF/FTC and DTG/ABC/FTC, per 6 months compared to EFV/TDF/FTC (Supplement Table 2). The overall pattern of weight change by regimen did not differ when also adjusting for time-updated CD4 count. We stratified participants by baseline BMI (<25 kg/m^2 vs ≥25 kg/m^2, Supplement Table 3), and weight change was similar between most strata of baseline BMI with a few small differences (e.g. more weight gain on ATV in lower vs. higher BMI group) (Supplement Table 4). PLWH with an observed weight change in the top or bottom five percent of all weight changes were evenly distributed across all regimens. The results after excluding these PLWH were generally similar to the analysis of the entire study cohort with greater weight gain among those on DRV/TDF/FTC and DTG-based regimens (Supplement Table 5).

Discussion

Among PLWH initiating their first ART regimen in the current treatment era (2012–2019), we observed weight gain across all regimens. Weight gain was most rapid early after ART initiation. We found that in the immediate period (first 6 months) after ART initiation, weight gain was greatest for several recently approved regimens that, to-date, have limited data from real-world clinical settings. Specifically, we found more weight gain among PLWH initiating BIC/TAF/FTC and DTG/TAF/FTC compared to some other regimens. When we examined extended follow-up time, we found greater weight gain in INSTI- and DRV-based regimens compared to those on EFV/TDF/FTC. In particular, those taking DTG experienced more weight gain than PLWH who initiated EVG, a commonly used first-generation INSTI.

These observed differences in weight gain between regimens highlight differences between some new INSTIs and older regimens. In contrast to previous trials on drug efficacy, this study provides insight as to weight gain among PLWH in routine clinical care, [12, 33, 34]. We were also able to compare differences between TDF and TAF between regimens with the same core drug in PLWH in clinical care and found slightly greater weight gain in PLWH on the TAF-based regimens, as was noted in a large clinical trial in South Africa[28].

Return to health, characterized by an overall improvement in well-being, including increasing CD4 cell count and some weight gain, may occur following ART initiation in PLWH with poor health status who may have experienced wasting[2, 5]. An association between higher BMI and higher CD4 cell count among PLWH initiating their first ART regimen has been observed, but lacks causality and impact on other indicators of long-term health[35]. Return to health has been proposed as a possible mechanism to investigate weight gain after ART initiation, and superior virologic benefits of INSTIs could be a factor in a faster presentation of return to health. However, current recommendations for treatment advise beginning ART immediately, making this less salient [14]. In our study, the amount of weight gained on DTG and BIC regimens was greater than weight gained on some other

INSTIs, indicating that return to health does not explain the whole association between DTG and weight gain.

The strengths of this study include the comprehensive clinical data, antipsychotic mediation use[36–38] and large, diverse sample size of PLWH in CNICS. CNICS also does frequent data updates and ongoing data quality control to ensure timely data. The strict inclusion criteria regarding regimen composition and duration of follow-up (i.e. ART-naïve at study start, follow-up ends when original regimen is switched or ended) eliminated possible carryover effects from other ART drugs or classes that other studies have not been able to avoid[7, 18].

This study also has limitations worth noting. There were variable lengths of follow-up time between PLWH on different regimens, particularly for newer regimens. Our primary analysis focused on the immediate (6-month) period after ART initiation to allow comparable follow-up time across regimens in the window when weight gain was most likely related to the drugs. We assessed each regimen individually, rather than by class, so there were some regimens with small sample sizes, such as ATV and RAL, limiting power and our ability to compare these regimens with others. As an observational study, unmeasured confounding is a limitation. Finally, while CNICS is a large, diverse cohort, our study population was mostly male, and recent findings suggest that women may be more likely to experience treatment-related weight gain[39].

Conclusion

This study found more weight gain among previously ART-naïve PLWH on newer INSTIs (DTG and BIC) and DRV-based regimens in the current ART treatment era, although weight gain appeared to plateau over time. Longer-term observation of PLWH taking INSTIs is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Demographic and clinical characteristics of people living with HIV from CNICS sites across the United States who initiated their first antiretroviral therapy regimen between 2012–2019.

N (%) or Mean (SD)[a]	Everyone	EFV	RPV	ATV	DRV	RAL	EVG/TDF	EVG/TAF	DTG/TDF	DTG/TAF	DTG/ABC	BIC
N	3232 (100)	427 (13)	347 (11)	97 (3)	263 (8)	99 (3)	787 (24)	289 (9)	237 (7)	127 (4)	389 (12)	170 (5)
Age (years)	37 (12)	37 (11)	35 (11)	35 (11)	38 (11)	43 (12)	35 (11)	35 (12)	39 (13)	39 (13)	38 (13)	35 (11)
Female (N (%))	505 (16)	34 (8)	61 (18)	32 (33)	47 (18)	22 (22)	103 (13)	35 (12)	44 (19)	22 (17)	80 (21)	25 (15)
Race/ethnicity												
White (N (%))	1136 (35)	185 (43)	102 (29)	41 (42)	99 (38)	56 (57)	273 (35)	87 (30)	100 (42)	43 (34)	108 (28)	42 (25)
Black (N (%))	1463 (45)	149 (35)	165 (48)	46 (47)	103 (39)	27 (27)	374 (48)	136 (47)	87 (37)	60 (47)	211 (54)	105 (62)
Hispanic (N (%))	402 (13)	67 (16)	52 (15)	6 (6)	44 (17)	9 (9)	86 (11)	43 (15)	29 (12)	13 (10)	43 (11)	10 (6)
Other (N (%))	231 (7)	26 (6)	28 (8)	4 (4)	17 (6)	7 (7)	54 (7)	23 (8)	21 (9)	11 (9)	27 (7)	13 (8)
HCV (N (%))	298 (9)	32 (7)	25 (7)	16 (16)	33 (13)	22 (22)	51 (6)	33 (11)	26 (11)	14 (11)	30 (8)	16 (9)
HBV (N (%))	84 (3)	5 (1)	10 (3)	3 (3)	7 (3)	3 (3)	29 (4)	7 (2)	10 (4)	3 (2)	3 (1)	4 (2)
Nadir CD4 (cells/mm^3)	381 (249)	400 (245)	432 (201)	373 (220)	295 (232)	375 (252)	378 (253)	425 (273)	325 (228)	372 (272)	388 (255)	379 (270)
Smoker (N (%))	633 (20)	79 (19)	67 (19)	28 (29)	63 (24)	23 (23)	139 (18)	52 (18)	59 (25)	41 (32)	53 (14)	29 (17)
Diabetes (N (%))	152 (5)	19 (4)	16 (5)	2 (2)	11 (4)	5 (5)	26 (3)	11 (4)	19 (8)	5 (4)	30 (8)	8 (5)
Baseline weight (kg)	79 (19)	80 (17)	81 (19)	80 (18)	77 (17)	80 (18)	79 (18)	79 (21)	75 (16)	80 (18)	82 (21)	80 (20)
Baseline BMI (kg/m^2)	26 (6)	26 (5)	27 (6)	26 (6)	25 (5)	26 (5)	26 (6)	26 (7)	25 (5)	26 (6)	27 (7)	26 (6)
Years on regimen (years)	1.9 (1.6)	2.2 (1.9)	2.6 (2.0)	1.8 (1.8)	1.9 (1.6)	2.2 (1.8)	2.2 (1.6)	1.6 (1.0)	1.3 (1.2)	1.1 (0.8)	2.1 (1.4)	0.5 (0.3)

Definitions: EFV (Efavirenz®), RPV (Edurant®, Complera®, Odefsey®), ATV (Atazanavir®), DRV (Prezista®, Prezcobix®), RAL (Isentress®, Isentress HD®), EVG (Vitekta®, Stribild®, Genvoya®), DTG (Tivicay®, Triumeq®), BIC (Biktarvy®), ABC (abacavir), TDF (tenofovir disoproxil fumarate), TAF (tenofovir alafenamide fumarate)

Abbreviations: HCV: hepatitis C virus; HBV: hepatitis B virus; BMI: body mass index; CNICS: Centers for AIDS Research Network of Integrated Clinical Systems

[a]All tests for differences between regimens tested significant at $p<0.05$, except HBV ($p=0.13$)

Table 2.

Weight change (Δ kg/6 months) in the immediate period (first 6-months) among people living with HIV from CNICS sites across the United States who initiated their first antiretroviral therapy regimen between 2012–2019 (n=3186) in adjusted[a] analyses (linear mixed models)

	Δ kg/6 months	95% CI		P-value
Time on regimen (EFV reference)	0.71	−0.12	1.53	0.09
Reg type x Time on regimen				
1: RPV	−0.36	−1.62	0.90	0.58
2: ATV	2.15	−0.01	4.30	0.051
3: DRV	3.68	2.13	5.22	<0.001
4: RAL	2.06	0.11	4.01	0.04
5: EVG/TDF	1.81	0.72	2.90	<0.01
6: EVG/TAF	1.88	0.61	3.16	<0.01
7: DTG/TDF	2.61	1.29	3.92	<0.001
8: DTG/TAF[b]	4.37	2.10	6.64	<0.001
9: DTG/ABC	2.28	1.06	3.49	<0.001
10: BIC[c]	3.86	2.24	5.48	<0.001

Abbreviations: CNICS: Centers for AIDS Research Network of Integrated Clinical Systems, EFV: efavirenz, RPV: rilpivirine, ATV: atazanavir, DRV; darunavir, RAL: raltegravir, EVG: elvitegravir, DTG: dolutegravir, BIC: bictegravir, TDF: tenofovir disoproxil fumarate, TAF: tenofovir alafenamide fumarate, ABC: abacavir

[a]Model adjusted for time on regimen, regimen, age, sex, race/ethnicity, Hepatitis C, Hepatitis B, nadir CD4, smoking, diabetes, site, and antipsychotic medication use (time-updated)

[b]DTG/TAF tested different using a Wald test vs EFV, RPV, EVG/TDF, EVG/TAF; DTG/ABC: p=0.08

[c]BIC tested different using a Wald test vs EFV, RPV, EVG/TDF, EVG/TAF; DTG/ABC: p=0.06