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

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Abstract

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Objectives

We evaluated weight change among people living with HIV (PLWH) initiating antiretroviral therapy (ART) in the current treatment era.

Methods

Between 2012-2019, in 8 Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) sites, we identified 3232 ART-naïve PLWH starting 3-drug ART, including efavirenz (EFV), rilpivirine (RPV), atazanavir (ATV), darunavir (DRV), raltegravir (RAL), elvitegravir (EVG), dolutegravir (DTG), or bictegravir (BIC), with tenofovir disoproxil fumarate (TDF), tenofovir alafenamide fumarate (TAF) or abacavir (ABC) and emtricitabine or lamivudine plus a booster if necessary. Weight change was estimated for short-term (6-month) and long-term (all) follow-up using linear mixed models adjusted for time on regimen, interaction between time and regimen, age, sex, race, hepatitis B or C coinfection, nadir CD4, smoking, diabetes, anti-psychotic medication use, and site.

Results

Mean follow-up was 1.9 years. In the long-term, compared with EFV/TDF, DRV/TDF was associated with a 1.0 kg (95%CI:0.5-1.5) per 6-months greater weight gain, while DTG/ABC was associated with a 0.6 kg (95%CI:0.3-0.9) and DTG/TDF was associated with a 0.6 kg (95%CI:0.1-1.1) per 6-months greater gain. Weight gain on DTG/ABC and DRV/TDF was significantly greater than EFV/TDF, RPV/TDF, and EVG/TDF. In the short-term, compared with EFV/TDF, BIC/TAF (3.9 kg

(95%CI:2.2-5.5)) and DTG/TAF (4.4 kg (95%CI:2.1-6.6)) were associated with the greatest weight gain per 6-months, followed by DRV/TDF (3.7 kg (95%CI:2.1-5.2)) and DTG/TDF (2.6 kg (95%CI:1.3-3.9).

Conclusions

DRV/TDF users showed the greatest weight gain in long-term analyses, that excluded TAF regimens, while DTG/TAF and BIC/TAF users showed the greatest gain in the first 6-months.

Introduction

In the early HIV era, people living with HIV (PLWH) experienced severe wasting[1], which can be juxtaposed with the current era, during which some PLWH are gaining weight after initiating antiretroviral therapy (ART), and concerns about excessive weight gain have been noted[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 has 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 into the mechanisms and consequences involved in excessive weight gain.

Regimens containing integrase strand transfer inhibitors (INSTIs), a relatively new 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 initial HIV therapy[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 occurred in PLWH taking DTG[7, 16-18]. Excessive weight gain affects psychological[19] and social quality of life[20], as well as ART adherence[21], and can potentially lead to long-term adverse health effects[22-24]. PLWH on ART require close attention to metabolic measures to prevent premature morbidity and mortality[24-26].

A potential association has been suggested between INSTIs such as dolutegravir and weight gain[7, 15-18, 27]. However, many 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, such as BIC[2, 9, 15, 27], 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, 27]. 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, 28]. Finally, 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, 27]. To address these prior limitations, we conducted a large retrospective observational 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 more than 35,000 PLWH at eight different academic clinical sites throughout the United States[29]. 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.

Participants

We assessed body weight change in ART-naïve PLWH initiating one of the eleven most common three or more drug ART regimens 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 or lamivudine. In addition, we assessed cobicistat-boosted EVG, DTG, and bictegravir (BIC) with tenofovir alafenamide fumarate (TAF) and emtricitabine or lamivudine. We also included DTG with abacavir (ABC) and emtricitabine or lamivudine. We required regimens to have

a minimum of 90 PLWH initiating them to ensure adequate numbers for statistical power. ART initiation date is hereinafter referred to as baseline and represents the start of follow-up. This analysis was limited to 2012 and later to focus on regimens relevant in the current clinical era and current population levels of adiposity[30]. All participants were ART-naïve and initiating their first ART regimen to eliminate impacts from prior regimens and maximize comparability among PLWH across regimens of interest. Follow-up for each participant ended when the initial ART regimen changed, ART was stopped, loss to follow-up or death, or November 30, 2019, whichever was earliest.

Analysis

We conducted descriptive analyses of demographic and clinical characteristics of participants 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[31]. We examined weight change in both a long-term model and a short-term model. The long-term model included all follow-up time and excluded regimens whose use started more recently, resulting in limited follow-up time, specifically those with TAF and BIC. The short-term model restricted follow-up to six months after ART initiation, allowing for more recently approved drugs, such as TAF and BIC, to be included with a comparable timeframe. The models were adjusted for age, sex, race, hepatitis C virus (HCV) (defined as positive detection of hepatitis C antibodies or RNA) and/or hepatitis B virus (HBV) coinfection (positive test for hepatitis B surface antigen), nadir CD4 count (cells/mm^3), diabetes mellitus (diabetes specific medication, diabetes related medication plus

diabetes diagnosis, or hemoglobin A1C ≥6.5), smoking status, time-updated antipsychotic medication use (anti-psychotic or anti-psychotic plus anti-depressant medication), clinical site, time on ART, and the interaction of time on ART and regimen. All covariates were identified *a priori* based on review of literature and clinical knowledge.

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 time-updated CD4 count, stratification by baseline BMI (≥25 kg/m$_2$ vs <25 kg/m$_2$), and exclusions of participants with extreme weight changes, defined as a weight change in the top or bottom five or one percent of all weight changes during follow-up. These sensitivity analyses were intended to highlight any potential effect of these factors on weight gain and assess the possibility of a return to health effect (e.g. if time-updated CD4 affects weight change there may be an effect of improving immune status).

Results

We observed 3232 previously treatment-naïve PLWH in the CNICS cohort who initiated one of the eleven ART regimens. Demographic and clinical characteristics of the study cohort by regimen are in Table 1. The EVG/TDF regimen had the most participants, representing 24% of study participants, and the ATV and RAL regimens had the fewest at 3% each. Overall average follow-up time on the initial ART regimen was 1.9 years (Interquartile Range (IQR): 0.6, 2.9). More recently-approved regimens, including those containing TAF, had shorter average follow-up (EVG/TAF: 1.6 years; DTG/TAF: 1.1 years; BIC: 0.5 years). The average age of the cohort was 37 years and participants were predominantly male (84%). Overall, 35% of participants 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 (22%) and ATV-based (16%) regimens. Average nadir CD4

count among the regimens 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 population gained weight after ART initiation (Table 2). The long-term analysis (N=2646) had an average follow-up time of 2.1 years. Compared with EFV, the reference regimen, DRV was associated with a 1.0 kg (95% CI: 0.5-1.5) per 6 months greater weight gain, DTG/TDF was associated with a 0.6 kg (95% CI: 0.1-1.1) per 6 months greater gain, and DTG/ABC was associated with a 0.6 kg (95% CI: 0.3-0.9) per 6 months greater gain. We assessed differences in weight gain directly between regimens using Wald tests. Weight gain on DTG/ABC and DRV were statistically significantly greater than EFV, RPV, and EVG/TDF-based regimens, while DTG/TDF was greater than EFV and RPV (Table 2). The RAL and ATV regimens had the fewest participants, so statistical comparisons to other regimens were underpowered. GAM plots suggested that most weight gain in this cohort occurred early after ART initiation, particularly in the first year, then began to plateau for most regimens, although this effect varied (Figure 1).

In the short-term analysis, with follow-up restricted to 6 months after ART initiation, (N=3186), DRV/TDF was associated with a 3.7 kg (95% CI: 2.1-5.2) per 6 months greater weight gain, DTG/TAF 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 (Table 3). Weight gain on DTG/TAF and BIC/TAF regimens were statistically significantly greater than EFV/TDF, RPV/TDF, EVG/TDF, and EVG/TAF regimens, but not statistically significantly greater than DTG/ABC (p=0.08 vs DTG/TAF; p=0.06 vs BIC/TAF) (Table 3). GAM plots restricted to the first 6 months after ART initiation suggest linear increases in weight during this period (Supplement Figure 1).

We also conducted several sensitivity analyses of the long-term model, which included all follow-up on the initial ART regimen. The overall pattern of weight changes by regimen did not

differ from the primary analysis when also adjusting for time-updated CD4 count. We also stratified participants by baseline BMI (<25 kg/m$_2$ vs ≥25 kg/m$_2$, Supplement Table 2), and weight change was mostly similar between strata of baseline BMI with a few small differences (e.g. more weight gain on ATV in lower vs higher BMI group) (Supplement Table 3). The proportion of participants excluded due to a weight change in the top or bottom five or one percent of all weight changes was similar across all regimens. The results after these exclusions were generally similar to the analysis of the entire study population with greater weight gain among those on DRV and DTG-based regimens (Supplement Table 4).

Discussion

Among PLWH initiating their first ART regimen in the current treatment era (2012-2019), we observed weight gain across all regimens, and greater weight gain in INSTI- and DRV-based regimens compared to those on EFV. In particular, those taking DTG experienced more weight gain than PLWH who initiated EVG, a commonly used first-generation INSTI. Weight gain after ART initiation was fastest early after ART initiation. We found that in the 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, in short-term analyses, we found more weight gain among PLWH initiating BIC/TAF and DTG/TAF compared to some other regimens.

These observed differences in weight gain between regimens highlight important distinguishing features between some new INSTIs and older regimens. DTG and BIC showed non-inferiority in viral suppression compared to other INSTIs in trials of ART-naïve patients; in addition, these agents have demonstrated higher barriers to resistance compared to RAL, and lack the need for a boosting agent compared with EVG[12, 32, 33]. These studies, however, included only PLWH willing to participate in trials, which may not generalize to routine clinical care populations of PLWH and leave many questions unaddressed regarding weight and other metabolic consequences in routine clinical care settings [12, 32, 33]. When deciding an ART regimen, side

effects such as weight gain can play an important role after prioritizing the benefits of virus control. The greater weight gain observed among participants taking newer INSTIs or DRV should be considered as a factor in long-term care as metabolic disturbances may affect risk of chronic diseases[22-25] in an already high-risk population[34, 35]. 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 on the TAF-based regimens, as was noted in a large clinical trial in South Africa[27]. However, our analysis of these drugs was only with six months of follow-up, thus longer-term studies are warranted to elucidate these differences and also provide additional information for newer INSTIs.

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[36]. 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, rather than historical recommendations to wait until more advanced disease; which decreases, but does not eliminate, the extent to which PLWH experience poor health status before ART initiation in the current treatment era[14]. The average nadir CD4 count (381 cells/mm^3; median: 364; IQR: 203, 531) at ART initiation for this study population highlights that some PLWH are initiating ART relatively late, but in general ART initiation is occurring earlier in the current treatment era than in the past, which may diminish the likelihood and impact of a return to health effect. Moreover, the baseline CD4 count of participants taking DTG was close to the overall average (DTG/TDF: 325 cells/mm^3, DTG/ABC: 388 cells/mm^3), while DRV, which showed the greatest weight gain in the long-term

model, had the lowest average nadir CD4 count of all regimens (295 cells/mm3), suggesting the additional weight gain observed in participants taking DRV may be influenced by return to health, but those taking DTG had higher baseline health status based on nadir CD4 count, thus less potential to return to better health status. Additionally, the amount of weight gained on DTG regimens was greater than weight gained on some other INSTIs, indicating that even if the return to health phenomenon is at play here, it does not explain the whole association between DTG and weight gain.

The strengths of this study include the larger sample size and geographic, demographic, and clinical diversity of PLWH in CNICS, which enhances generalizability of study findings compared to some earlier studies [17, 18]. Additionally, the comprehensive clinical data of CNICS provided the ability to address other important variables that may be contributing to weight gain. For example, PLWH are at a higher risk of a dual diagnosis with a mental illness compared to the general population[37]. We adjusted our analyses for use of antipsychotic medications, which is associated with weight gain[38, 39], providing a potentially less biased estimate of the true association compared to other studies that did not consider anti-psychotic medication use. CNICS also does frequent data updates and ongoing data quality control to ensure timely data without delays, which allowed us to include newer regimens, such as BIC, that other studies have not been able to assess. We included only PLWH who initiated ART in 2012 or after to ensure current relevance of findings. 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]. Our results further isolate weight gain due to specific ART medications, such as DTG and BIC, rather than focusing only on class effects such as all INSTIs. Chronic metabolic consequences, such as CVD and diabetes, are prevalent among PLWH[24-26], but the mechanisms

contributing to this elevated risk are not entirely understood, and this study helps support a strong association between ART regimen and weight gain.

This study also has limitations worth noting. There were variable lengths of follow-up time between PLWH on different regimens, particularly for newer regimens, which we addressed by using GAM plots to look at patterns over specific time periods where a large portion of participants were included and comparable. Despite this, neither the DTG/TAF or BIC regimens were included in any long-term analyses. Therefore, we also conducted analyses restricting follow-up time to six months to assess weight change in a timeframe where newer regimens could be analyzed. The use of linear mixed models further allowed for varied follow-up time between participants. While a strength of this study was focusing on PLWH initiating clinically relevant ART regimens in the current ART treatment era (2012 and after), this inevitably limited follow-up time. Finally, since this study assessed each regimen individually, rather than by class, there were some regimens with small sample sizes, such as ATV and RAL, limiting power and our ability to compare these regimens with others. A better understanding of the effects on metabolic measures and composition of weight gain, particularly the balance between gain of adipose tissue and lean mass and the impact on body morphology, could elucidate the specifics of the weight gain associated with long-term use of current ART regimens.

Conclusion

This study found more weight gain among previously ART-naïve PLWH on newer INSTIs (DTG and BIC; only short-term data available for BIC) and DRV-based regimens in the current ART treatment era, although weight gain appeared to plateau over time. We found that in the first 6 months after ART initiation, PLWH who initiated DTG/TAF and BIC/TAF-based regimens had the greatest weight gain, but more follow-up is needed. These findings suggest that the observed weight gain may not be exclusively a consequence of return to health, but also a drug-specific effect.

While many other factors, such as genetics and diet, also influence weight gain and the development of chronic diseases, ART regimen may play an important role. Longer-term observation of PLWH taking INSTIs is warranted to promote prolonged well-being.

Tables and Figures

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 – 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)
Hepatitis C (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)
Hepatitis B (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)

BMI: body mass index

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

Table 2. Weight change (Δ kg/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=2646) initiating an ART regimen in adjusted[a] analyses (linear mixed models)

	(Δ kg/6 months)	95% CI		P-value
Time on regimen (EFV reference)	0.45	0.26	0.64	0.00
Reg type x Time on regimen				
1: RPV	-0.14	-0.47	0.18	0.39
2: ATV	0.55	-0.24	1.34	0.17
3: DRV	0.99	0.51	1.48	0.00
4: RAL	0.50	-0.13	1.13	0.12
5: EVG/TDF	0.18	-0.09	0.44	0.19
7: DTG/TDF	0.59	0.12	1.06	0.02
9: DTG/ABC[b]	0.59	0.27	0.90	0.00

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

[b] DTG/ABC tested different using a Wald test vs EFV, RPV, EVG/TDF

Table 3. Weight change (Δ kg/6 months) among previously ART-naïve individuals (n=3186) in the first six months after initiating an ART regimen in adjusted[a] analyses (linear mixed models)

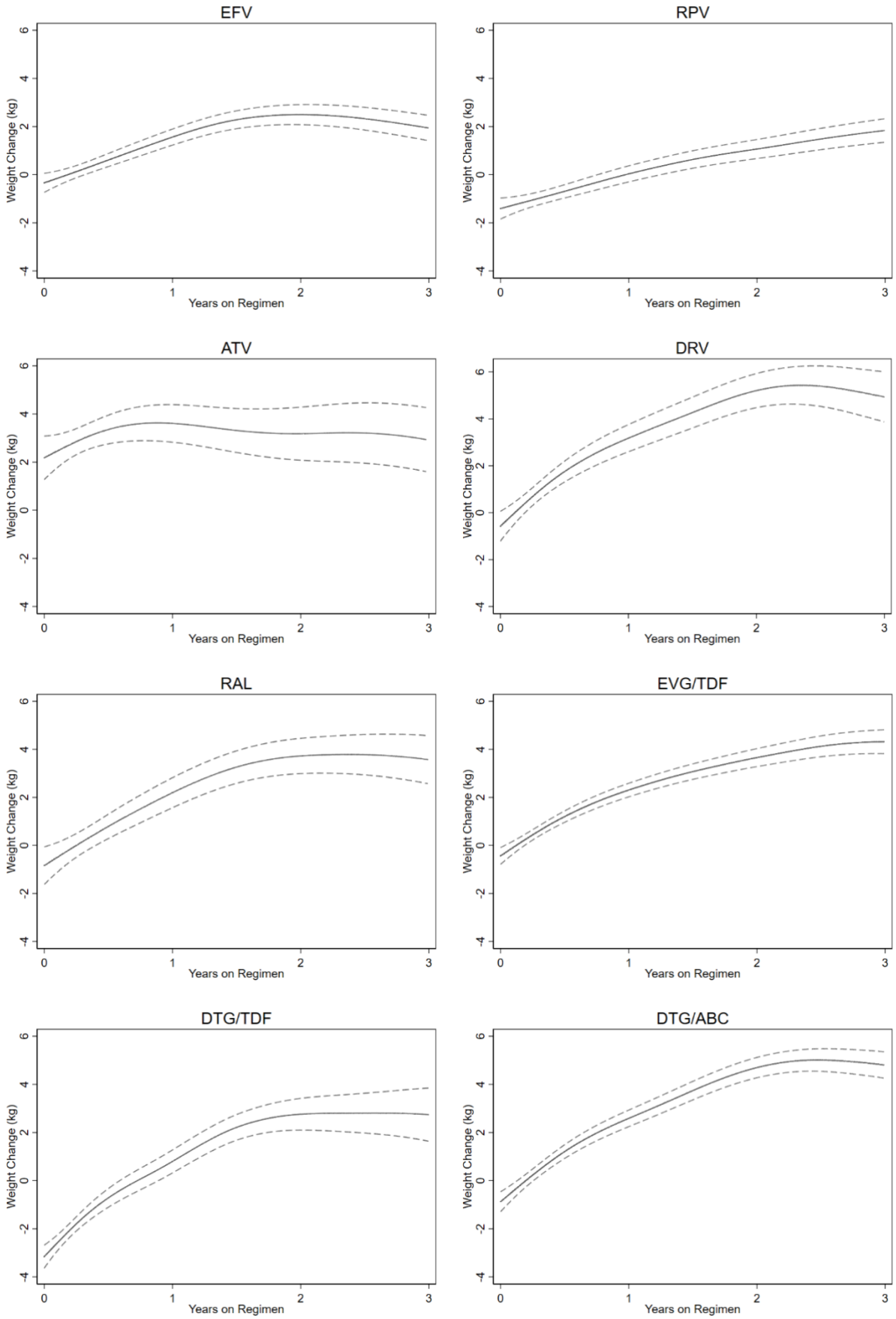
	(Δ kg/6 months	95% CI		P-value
Time on regimen (EFV reference)	0.71	-0.12	1.53	0.09
Reg type x Time on regimen				
1: RPV	-0.36	-1.62	0.90	0.58
2: ATV	2.15	-0.01	4.30	0.05
3: DRV	3.68	2.13	5.22	0.00
4: RAL	2.06	0.11	4.01	0.04
5: EVG/TDF	1.81	0.72	2.90	0.00
6: EVG/TAF	1.88	0.61	3.16	0.00
7: DTG/TDF	2.61	1.29	3.92	0.00
8: DTG/TAF[b]	4.37	2.10	6.64	0.00
9: DTG/ABC	2.28	1.06	3.49	0.00
10: BIC[c]	3.86	2.24	5.48	0.00

[a] Model adjusted for time on regimen, regimen, age, sex, race, Hepatitis C, Hepatitis B, nadir CD4, smoking, diabetes, site, and anti-psychotic 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

Figure 1. Generalized additive model plots of weight gain during the first 3 years after ART initiation among previously ART-naïve PLWH.



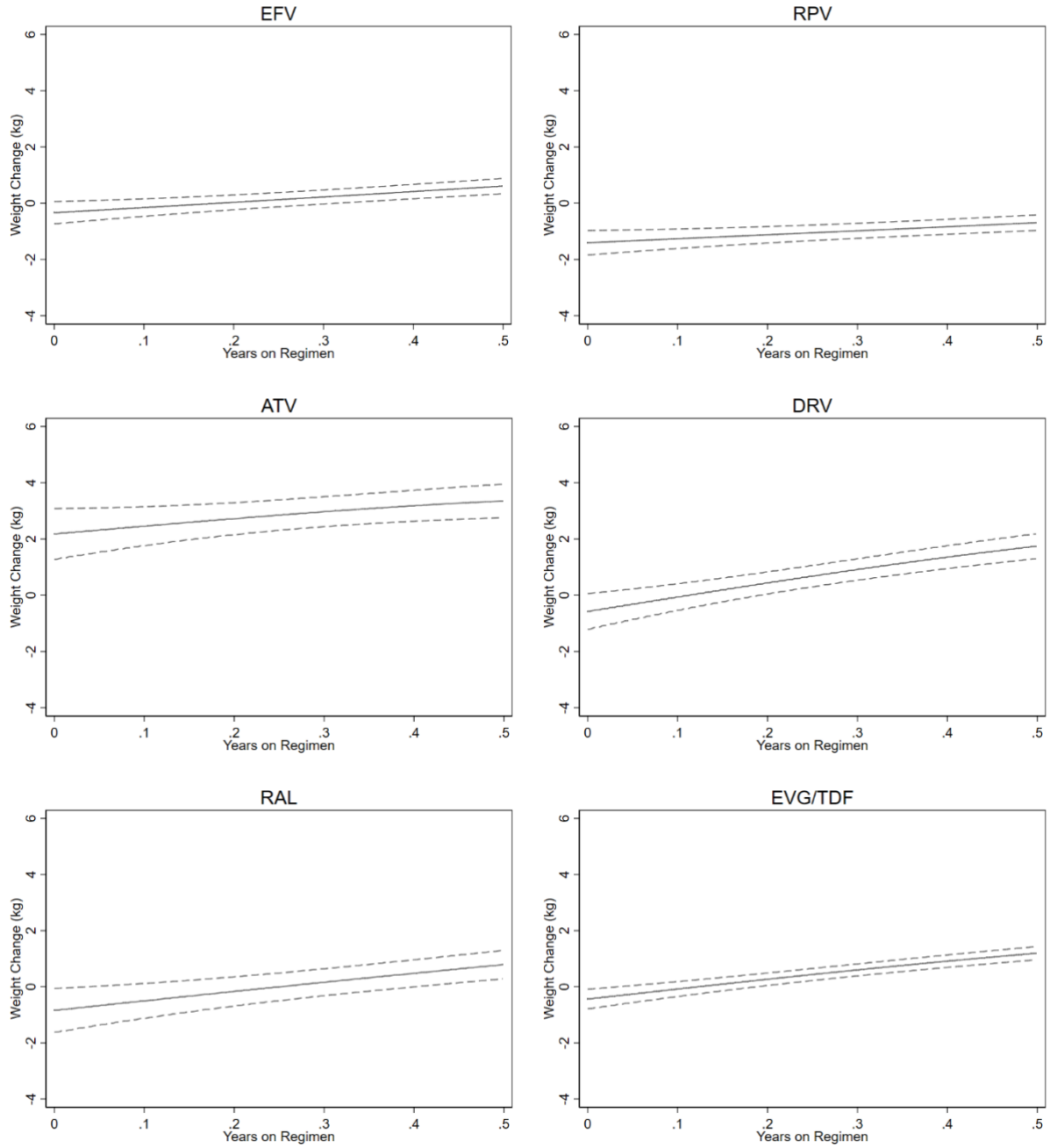
Supplement Tables

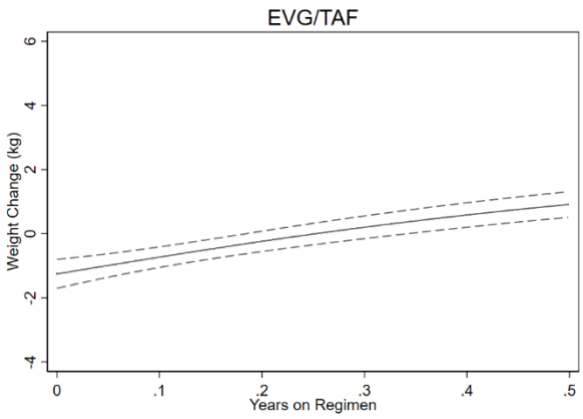
Supplement Table 1. Drugs included in each regimen

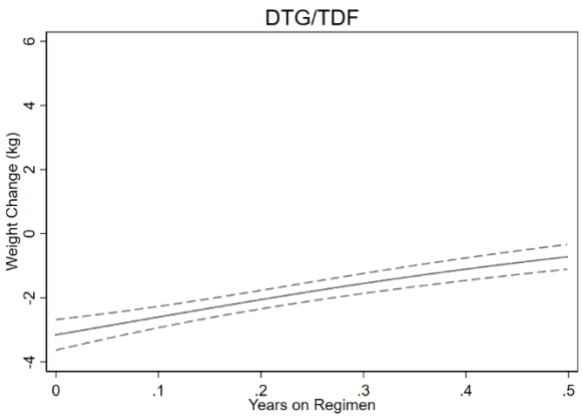
Regimen	Core Class	Drug 1	Drug 2	Drug 3	Booster
EFV	NNRTI	Efavirenz	Emtricitabine/Lamivudine	TDF	
RPV	NNRTI	Rilpivirine	Emtricitabine/Lamivudine	TDF	
ATV	PI	Atazanavir	Emtricitabine/Lamivudine	TDF	Ritonavir
DRV	PI	Darunavir	Emtricitabine/Lamivudine	TDF	Ritonavir
RAL	INSTI	Raltegravir	Emtricitabine/Lamivudine	TDF	
EVG/TDF	INSTI	Elvitegravir	Emtricitabine/Lamivudine	TDF	Cobicistat
EVG/TAF	INSTI	Elvitegravir	Emtricitabine/Lamivudine	TAF	Cobicistat
DTG/TDF	INSTI	Dolutegravir	Emtricitabine/Lamivudine	TDF	
DTG/TAF	INSTI	Dolutegravir	Emtricitabine/Lamivudine	TAF	
DTG/ABC	INSTI	Dolutegravir	Emtricitabine/Lamivudine	Abacavir	
BIC	INSTI	Bictegravir	Emtricitabine/Lamivudine	TAF	

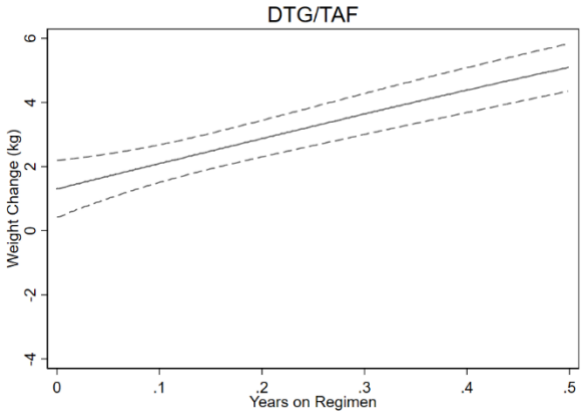
Definitions: NNRTI (non-nucleoside reverse transcriptase inhibitor), PI (protease inhibitor), INSTI (integrase strand transfer inhibitor), TDF (tenofovir disoproxil fumarate), TAF (tenofovir alafenamide fumarate)

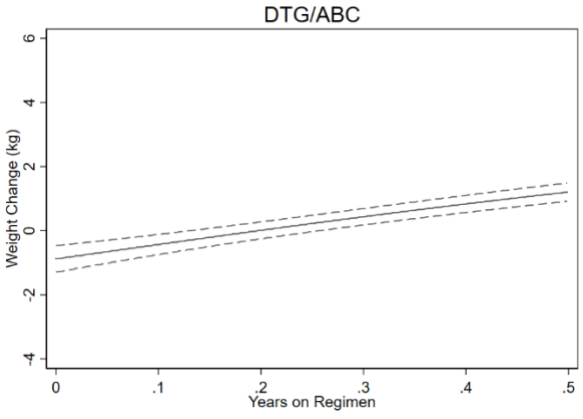
Supplement Figure 1. Generalized additive model plots of weight gain during the first 6 months after ART initiation among previously ART-naïve PLWH.

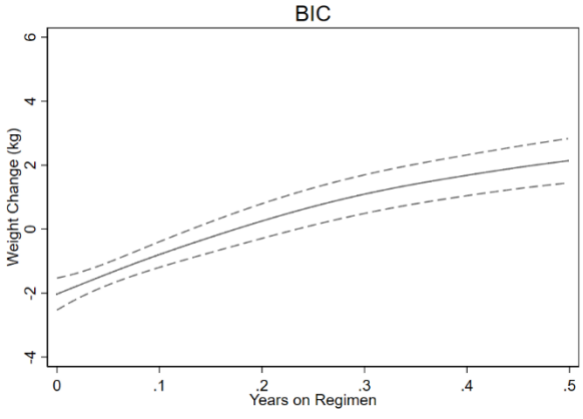



EVG/TAF
Weight Change (kg)
6
4
2
0
-2
-4
0
.1
.2
.3
.4
.5
Years on Regimen


DTG/TDF
Weight Change (kg)
6
4
2
0
-2
-4
0
.1
.2
.3
.4
.5
Years on Regimen


DTG/TAF
Weight Change (kg)
6
4
2
0
-2
-4
0
.1
.2
.3
.4
.5
Years on Regimen


DTG/ABC
Weight Change (kg)
6
4
2
0
-2
-4
0
.1
.2
.3
.4
.5
Years on Regimen


BIC
Weight Change (kg)
6
4
2
0
-2
-4
0
.1
.2
.3
.4
.5
Years on Regimen

Supplement Table 2. Description (n (%)) of baseline BMI of previously-ART naïve individuals by ART regimen.

BMI Categories	Everyone	EFV	RPV	ATV	DRV	RAL	EVG/TDF	DTG/TDF	DTG/ABC
<25	1353 (51)	217 (51)	160 (46)	51 (53)	144 (55)	43 (43)	427 (54)	140 (59)	170 (44)
≥25	1293 (49)	209 (49)	187 (54)	46 (47)	119 (45)	56 (57)	360 (46)	97 (41)	219 (56)
Total	2646	427	347	97	263	99	787	237	389

Supplement Table 3. Weight change (Δ kg/6 months) among previously ART-naïve individuals (n=2646) initiating an ART regimen in adjusted[a] analyses (linear mixed models), stratified by baseline BMI

	Baseline BMI <25 (n=1353)				Baseline BMI ≥25 (n=1293)			
	(Δ kg/6 months)	95% CI		P-value	(Δ kg/6 months)	95% CI		P-value
Time on regimen (EFV reference)	0.46	0.18	0.74	0.00	0.45	0.19	0.71	0.00
Reg type x Time on regimen								
1: RPV	0.09	-0.35	0.52	0.70	-0.32	-0.79	0.15	0.19
2: ATV	1.59	0.30	2.88	0.02	-0.41	-1.26	0.45	0.35
3: DRV	0.79	0.11	1.48	0.02	1.18	0.50	1.85	0.00
4: RAL	0.44	-0.53	1.41	0.37	0.55	-0.25	1.36	0.18
5: EVG/TDF	0.41	0.06	0.76	0.02	-0.09	-0.49	0.31	0.66
7: DTG/TDF	0.78	0.22	1.33	0.01	0.28	-0.56	1.11	0.52
9: DTG/ABC[b]	0.78	0.34	1.21	0.00	0.44	-0.01	0.88	0.05

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

[b] DTG/ABC tested different using a Wald test vs EFV, RPV, DRV (only for BMI≥25), and EVG/TDF (only for BMI≥25)

Supplement Table 4. Weight change (Δ kg/6 months) among previously ART-naïve individuals initiating an ART regimen in adjusted[a] analyses (linear mixed models), excluding the top and bottom 5% or 1% of weight changes

Excluding top/bottom:	5% (n=2061)				1% (n=2503)			
	(Δ kg/6 months)	95% CI		P-value	(Δ kg/6 months)	95% CI		P-value
Time on regimen (EFV reference)	0.57	0.40	0.75	0.00	0.48	0.30	0.67	0.00
Reg type x Time on regimen								
1: RPV	-0.08	-0.32	0.15	0.48	-0.11	-0.37	0.16	0.44
2: ATV	0.50	-0.15	1.15	0.13	0.24	-0.54	1.03	0.55
3: DRV	0.67	0.32	1.02	0.00	1.03	0.61	1.45	0.00
4: RAL	0.29	-0.20	0.78	0.24	0.59	-0.03	1.21	0.06
5: EVG/TDF	0.14	-0.08	0.36	0.21	0.23	-0.01	0.47	0.06
7: DTG/TDF	0.39	0.03	0.76	0.03	0.43	-0.001	0.86	0.05
9: DTG/ABC[b]	0.33	0.07	0.59	0.01	0.58	0.29	0.87	0.00

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

[b] DTG/ABC tested different using a Wald test vs EFV and RPV for 5% exclusion and vs EFV, RPV, DRV, and EVG/TDF for 1% exclusion

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