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ORIGINAL RESEARCH

Weight and BMI Changes Following Initiation of Emtricitabine/Tenofovir Alafenamide Co-Formulated with Darunavir or Co-Administered with Dolutegravir in Overweight or Obese, ART-Naïve People Living with HIV-1

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Introduction: Integrase strand transfer inhibitor-based regimens (eg, containing dolutegravir [DTG]) are associated with weight/body mass index (BMI) increases among people living with HIV-1 (PLWH). Assessing antiretroviral therapy (ART)-related weight/BMI changes is challenging, as PLWH may experience return-to-health weight gain as a result of viral suppression. This retrospective, longitudinal real-world study compared weight/BMI outcomes among overweight/obese (BMI ≥25 kg/m^2; thus excluding return-to-health weight/BMI changes), treatment-naïve PLWH who initiated darunavir (DRV)/cobicistat (c)/emtricitabine (FTC)/tenofovir alafenamide (TAF) or DTG + FTC/TAF.

Methods: Treatment-naïve PLWH with BMI ≥25 kg/m^2 who initiated DRV/c/FTC/TAF or DTG + FTC/TAF (index date) had ≥12 months of baseline observation and ≥1 weight/BMI measurement in baseline and post-index periods in the Symphony Health IDV® database (07/17/2017–12/31/2021) were included. Inverse probability of treatment weighting (IPTW) was used to balance differences in baseline characteristics between cohorts. On-treatment time-to-weight/BMI increases ≥5% were compared between cohorts using weighted adjusted Cox models.

Results: Post-IPTW, 76 overweight/obese DRV/c/FTC/TAF-treated (mean age = 51.2 years, 30.7% female, 35.6% Black, mean baseline BMI = 33.2 kg/m^2) and 88 overweight/obese DTG + FTC/TAF-treated PLWH (mean age = 51.5 years, 31.4% female, 31.4% Black, mean baseline BMI = 32.7 kg/m^2) were included. The median [interquartile range] time from ART initiation to weight/BMI increase ≥5% was shorter for the DTG + FTC/TAF cohort (21.8 [9.9, 32.3] months) than the DRV/c/FTC/TAF cohort (median and interquartile times not reached; Kaplan–Meier rate at 21.8 months = 20.8%). Over the entire follow-up, overweight/obese PLWH initiating DTG + FTC/TAF had a more than twofold greater risk of experiencing weight/BMI increase ≥5% compared to those initiating DRV/c/FTC/TAF (hazard ratio [95% confidence interval] =2.43 [1.02; 7.04]; p = 0.036).

Conclusion: Overweight/obese PLWH who initiated DTG + FTC/TAF had significantly greater risk of weight/BMI increase ≥5% compared to similar PLWH who initiated DRV/c/FTC/TAF and had shorter time-to-weight/BMI increase ≥5%, suggesting a need for additional monitoring to assess the risk of weight gain-related cardiometabolic disease.

Keywords: human immunodeficiency virus, weight gain, BMI, darunavir, dolutegravir, observational study

Introduction

The emergence of antiretroviral therapy (ART) to treat people living with HIV-1 (PLWH) has resulted in marked improvements in life expectancy, clinical outcomes, and quality of life.[1–4] However, the longer life expectancy reported among PLWH in United States (US)[5] has also led to an increase in the prevalence of chronic cardiometabolic disease and

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other aging-related comorbidities for PLWH treated with ART.[6,7] As the prevalence of obesity has also increased among ART initiators (from 9% in 1998 to 18% in 2010),[8] weight gain has emerged as an important clinical consideration among PLWH and a risk factor for cardiometabolic disease for those treated with ART.[9]

The US Department of Health and Human Services (DHHS) guidelines generally recommend ART regimens containing either dolutegravir (DTG) or bictegravir (BIC), both integrase strand transfer inhibitors (INSTIs), for the majority of newly diagnosed PLWH initiating treatment who do not have a history of using long-acting injectable pre-exposure prophylaxis.[10] Pharmacokinetic-enhanced protease inhibitors (PIs), including darunavir (DRV), are also specifically recommended among PLWH who have yet to receive baseline laboratory and resistance testing results but need to initiate treatment rapidly or among those who are at risk of non-adherence.[10] Of note, despite INSTIs being recommended for most PLWH, the US DHHS guidelines also highlight the greater risk of weight gain for INSTI-based regimens relative to other approved ART regimens. INSTI-related weight gain has been further confirmed in a recent systematic literature review of previously published real-world studies that showed that PLWH treated with an agent from the INSTI class experienced greater weight gain or body mass index (BMI) increase than with agents from other ART classes.[11]

Specifically, when compared to PIs, INSTI-based ART has been associated with greater weight and BMI increase after initiation in both treatment-naïve and treatment-experienced PLWH.[12,13] DTG, in particular, has been noted in multiple settings to lead to a greater weight increase in treatment-naïve PLWH relative to other INSTIs and other ART classes.[14–16] Furthermore, beyond INSTIs, and potentially compounding the effect on weight outcomes, tenofovir alafenamide (TAF), a backbone agent used in many ART regimens, has been associated with greater weight increases than other backbone agents (eg, tenofovir disoproxil fumarate or abacavir/lamivudine).[17–22] Assessing the impact of ART on weight or BMI change among PLWH in the real-world has been challenging, given that many PLWH who initially lost weight after HIV infection may experience a return-to-health following treatment initiation and achieving viral suppression.[23,24] One strategy to capture weight or BMI changes beyond the return-to-health phenomenon would be to evaluate ART-related weight/BMI changes among PLWH who are overweight or obese. The Centers for Disease Control and Prevention considers adults with a BMI ≥25 and <30 kg/m^2 as overweight, whereas those with a BMI ≥30 kg/m^2 are considered obese; it further subdivides obesity into the following categories: Class 1 (BMI of 30 to <35 kg/m^2), Class 2 (BMI of 35 to <40 kg/m^2), and 3 (BMI ≥40 kg/m^2).[25] However, there are limited data on weight/BMI changes among treatment-naïve PLWH who are overweight or obese, who may be at a greater risk of experiencing longer-term cardiovascular or metabolic outcomes, after initiating ART.[26] To help separate the impact of treatment on ART-related weight gain relative to return-to-health weight gain, the objective of this study was to describe and compare real-world weight and BMI changes in treatment-naïve PLWH who are overweight or obese (ie, BMI ≥25 kg/m^2; thus excluding weight/BMI changes occurring due to return-to-health phenomenon) and who initiated either DRV/cobicistat (c)/emtricitabine (FTC)/TAF or DTG + FTC/TAF in the US.

Materials and Methods

Data Source

To identify the study population and conduct the analysis, this study used nationwide US electronic medical records (EMR) data from the Symphony Health, an ICON plc company, IDV® database from 07/17/2017 to 12/31/2021. Historical clinical information such as clinical diagnoses, weight and BMI measurements, medications prescribed and administered, vitals, and lab results are included as part of this provider-based EMR database. The data contains de-identified information and is compliant with the patient requirements of the Health Insurance Portability and Accountability Act (HIPAA).

Study Design

This study used a retrospective longitudinal cohort study design. Adult (≥18 years old), PLWH with BMI ≥25 kg/m^2 initiated on DRV/c/FTC/TAF or DTG + FTC/TAF between 07/17/2018 and 08/31/2021 were included. The same backbone agents (ie, FTC/TAF) were required for all PLWH, to isolate the effect that the third agent (ie, DRV/c or

DTG) has on weight/BMI changes. Mutually exclusive DRV/c/FTC/TAF or DTG + FTC/TAF cohorts were created based on the first observed prescription for DRV/c/FTC/TAF or DTG (index date), with no previous ART prescriptions observed in the 12-month period prior to the index date, to ascertain that these were treatment-naïve cohorts. PLWH were considered for inclusion in the DTG + FTC/TAF cohort if FTC/TAF was received within 14 days before or after the first DTG prescription date.

The baseline period, during which patients were required to have a weight or BMI measurement, was defined as the 12-month period before the index date. For PLWH without a weight/BMI measurement during the baseline period, weight/BMI was further assessed up until 30 days post-index, given weight/BMI changes during this period are likely unrelated to the index ART.[8] An on-treatment approach was used to define the follow-up period, which spanned from 30 days after the index date until the earliest of initiation of a new ART regimen, end of continuous clinical activity, or end of data availability (ie, 12/31/2021).

Study Population

Adult PLWH were included in this study if they initiated DRV/c/FTC/TAF or DTG + FTC/TAF between 07/17/2018 and 08/31/2021 (to allow sufficient potential follow-up before the end of data to observe ≥1 weight or BMI measurement starting 30 days post-index), had ≥1 diagnosis code for HIV-1 on or prior to the index date (International Classification of Disease, Ninth Revision, Clinical Modification [ICD-9-CM]: 042, 795.71 and V08; International Classification of Disease, Tenth Revision, Clinical Modification [ICD-10-CM] codes: B20, R75, and Z21), had ≥12 months of clinical activity prior to the index date (ie, baseline period), were ≥18 years old on the index date, had ≥1 weight measurement in both the baseline (including the first 30 days after baseline) and follow-up periods or ≥1 BMI measurement in both the baseline (including the first 30 days after baseline) and follow-up periods, and had their most recent baseline BMI measurement ≥25 kg/m^2.

PLWH were excluded if they had ≥1 prescription for ART during the baseline period (excluding prescriptions for FTC/TAF in the 14 days preceding the index date for the DTG + FTC/TAF cohort); had ≥1 diagnosis code for HIV-2 during the baseline period, had ≥1 diagnosis code for cirrhosis or hepatitis during the baseline period; had ≥1 diagnosis code for stage V chronic kidney disease or end-stage renal disease, or creatine clearance <15 mL/min during the baseline period; had ≥1 diagnosis code for pregnancy during the baseline period or on the index date; had ≥1 diagnosis code for cancer, except for resected non-invasive cutaneous squamous carcinoma, basal cell carcinoma, or cutaneous Kaposi's sarcoma during the baseline period; or had a prescription for both DRV/c/FTC/TAF and DTG on the index date.

Study Measures

A description of the demographic and clinical characteristics during the baseline period was performed for the DRV/c/FTC/TAF or DTG + FTC/TAF cohorts. The baseline weight/BMI measurement was the measurement closest to the index date in the baseline period, or within 30 days post-index if no baseline measurements were available.

Time to weight or BMI increase of ≥5% or ≥10% above the baseline weight/BMI measurement was evaluated over the entire follow-up period and compared between the DRV/c/FTC/TAF and DTG + FTC/TAF cohorts. Change in BMI categories between the baseline and follow-up (ie, on-treatment measurement furthest from the index date) periods was described for the two cohorts separately. In addition, mean differences, as well as percentage increases (ie, >0% increase, ≥5% increase, and ≥10% increase) in weight and BMI between the baseline and follow-up periods were explored at 3-, 6-, 9-, and 12-month time points during the follow-up period and described in the DRV/c/FTC/TAF and DTG + FTC/TAF cohorts. Mean follow-up weight/BMI measurements for each time point were based on all weight/BMI measurements observed during the specific 3-month interval of interest.

Statistical Analysis

Baseline characteristics were balanced between PLWH in the DRV/c/FTC/TAF and DTG + FTC/TAF cohorts using inverse probability treatment weighting (IPTW). Weights were calculated based on propensity scores (PSs) obtained from a logistic regression model that included the following independent variables: age, sex at birth, race, geographic region, insurance plan type, year of the index date, Quan-Charlson Comorbidity index (Quan-CCI) excluding HIV-1 symptoms,

hypertension, baseline BMI, use of medications associated with weight gain, and use of antihypertensives. For each individual, the IPTW-derived weight was calculated as 1/PS for PLWH in the DRV/c/FTC/TAF cohort and 1/(1-PS) for PLWH in the DTG + FTC/TAF cohort. In addition, IPTW-derived weights were normalized by the mean treatment weight. In the resulting IPTW-weighted sample, each individual's contribution was based on their reweighted representation, and the IPTW-weighted sample size for each cohort was calculated as the sum of the IPTW-derived weight for each individual in that cohort. Therefore, even though the same individuals were included in the analysis before and after weighting, the IPTW-weighted sample size was different from the sample size before applying IPTW.[27] Based on the calculations above, the average treatment effect was obtained from the comparison of weight/BMI changes between the IPTW-weighted DRV/c/FTC/TAF and DTG + FTC/TAF cohorts.

Comparison of baseline characteristics after applying IPTW was made using standardized differences, with differences of <10% being considered balanced.[28] The time to weight or BMI increase ≥5% or ≥10% was described for the DRV/c/FTC/TAF and DTG + FTC/TAF cohorts using weighted Kaplan–Meier (KM) analysis. In addition, hazard ratios (HRs) estimated based on weighted Cox proportional hazard models were used to compare the time to weight or BMI increase of ≥5% or ≥10% between cohorts. Mean differences estimated based on weighted ordinary least squares regression models were used to compare the mean change in weight/BMI from the baseline period to each follow-up time point between the DRV/c/FTC/TAF and DTG + FTC/TAF cohorts. The proportion of PLWH with >0% increase, ≥5% increase, or ≥10% increase in weight or BMI between the baseline and each follow-up time point was also described between cohorts. Remaining imbalances in baseline characteristics (after applying IPTW) were adjusted for in all IPTW-weighted regression models to obtain doubly robust estimates. The following baseline variables were adjusted for: race, geographic region, insurance plan type, and dyslipidemia/hyperlipidemia during baseline. All 95% confidence intervals (CIs) and p-values were calculated using non-parametric bootstrap procedures with 500 iterations.

Results

Patient Characteristics

A total of 164 PLWH who were overweight or obese were eligible for analysis, of which 51 were included in the DRV/c/FTC/TAF cohort and 113 were included in the DTG + FTC/TAF cohort (Figure 1). After IPTW, the weighted sample size yielded 76 PLWH in the DRV/c/FTC/TAF cohort (mean age: 51.2 years, 30.7% female, 35.6% Black, 71.1% resided in the South) and 88 PLWH in the DTG + FTC/TAF cohort (mean age: 51.5 years, 31.4% female, 31.4% Black, 63.9% resided in the South; Table 1). The mean (standard deviation [SD]) baseline BMI was 33.2 (6.5) kg/m^2 in the DRV/c/FTC/TAF cohort and 32.7 (6.0) kg/m^2 in the DTG + FTC/TAF cohort. The mean (SD) baseline weight was 99.4 (20.6) kg [219.1 lbs] in the DRV/c/FTC/TAF cohort and 98.0 (18.7) kg [216.1 lbs] in the DTG + FTC/TAF cohort, and the mean (SD) follow-up period was 16.6 (9.7) months in the DRV/c/FTC/TAF cohort and 15.5 (9.7) months in the DTG + FTC/TAF cohort.

Time to Weight or BMI Increase ≥5% or ≥10%

The DTG + FTC/TAF cohort had a shorter median [interquartile range (IQR)] time from ART initiation to weight gain ≥5% (21.8 [9.9, 32.3] months) than the DRV/c/FTC/TAF cohort (median and interquartile times not reached; Figure 2a). At 24 months, descriptively higher rates of weight increase ≥5% based on KM analyses were observed among PLWH in the DTG + FTC/TAF cohort (KM rate [95% CI] = 50.6% [34.6%; 69.0%]; n = 6 remaining at risk, ie, PLWH who did not have weight increase ≥5%, but who are still observable at 24 months) than PLWH in the DRV/c/FTC/TAF cohort (KM rate [95% CI] = 20.8% [9.1%; 43.6%]; n = 14 remaining at risk). Similarly, at 24 months, PLWH in the DTG + FTC/TAF (n = 10 remaining at risk) cohort had descriptively higher rates of weight increase ≥10% (KM rate [95% CI] = 21.7% [12.4%; 36.4%]; median [IQR] time not reached [25.0 months, not reached]) than PLWH in the DRV/c/FTC/TAF cohort (KM rate [95% CI] = 5.3% [0.7%; 33.4%]; n = 17 remaining at risk; median and interquartile times not reached; Figure 2b).

Similar trends were observed for BMI increases ≥5% and ≥10% (Figures 2c and d). Over the entire follow-up period, PLWH who were overweight or obese and initiated DTG + FTC/TAF had a more than twofold greater risk of experiencing a weight or BMI increase ≥5% as compared to PLWH who were overweight or obese and initiated

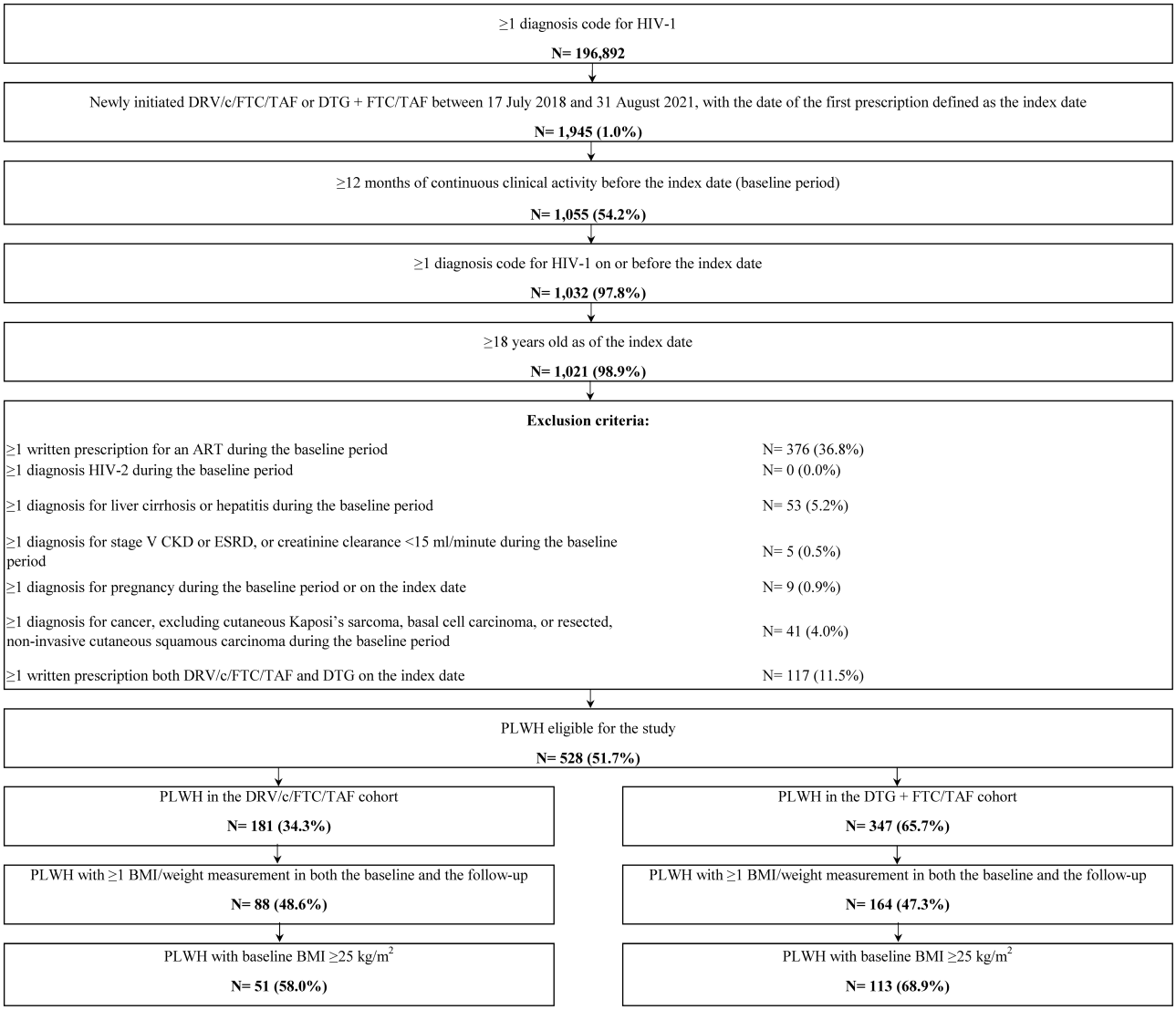


Figure 1 Identification of the study population.
Abbreviations: ART, antiretroviral therapy; BMI, body mass index; c, cobicistat; CKD, chronic kidney disease; DRV, darunavir; DTG, dolutegravir; ESRD, end-stage renal disease; FTC, emtricitabine; PLWH, people living with HIV-1; TAF, tenofovir alafenamide.

DRV/c/FTC/TAF (HR [95% CI] = 2.43 [1.02; 7.04]; p = 0.036; Figure 3). The comparative analysis for weight/BMI increase ≥10% did not converge, given the small number of events. Nevertheless, over the entire follow-up, the proportion of patients with weight/BMI increase ≥10% was descriptively higher for the DTG + FTC/TAF (14.9%) than for the DRV/c/FTC/TAF cohort (6.9%).

Change Between Baseline and Latest Follow-Up BMI Category

During follow-up, 26.3% (20/76) of PLWH in the DRV/c/FTC/TAF cohort and 31.8% (28/88) of PLWH in the DTG + FTC/TAF cohort experienced a change in BMI category between the baseline and follow-up periods (Table 2). More specifically, 17.0% (15/88) of DTG + FTC/TAF initiators increased one BMI category relative to 14.4% (11/76) of DRV/c/FTC/TAF initiators. A descriptively higher proportion of Class 3 obese DRV/c/FTC/TAF PLWH moved to Class 2 obesity (26.4%) than Class 3 obesity (10.1%). A descriptively higher proportion of Class 1 obese DTG + FTC/TAF PLWH progressed to Class 2 obesity (15.7%) than Class 1 obesity (0.0%).

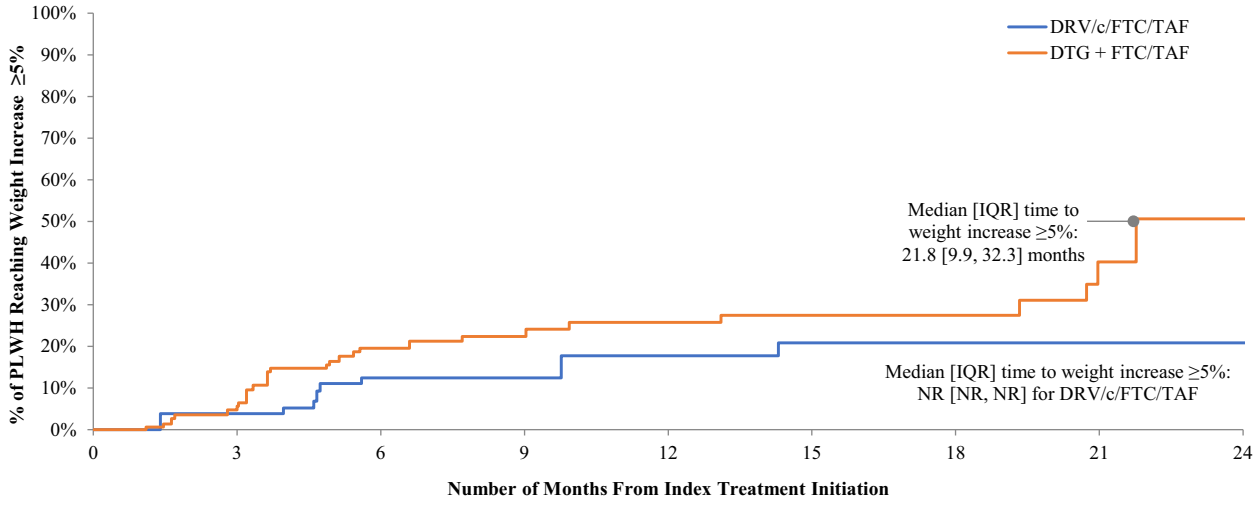
Table 1 Baseline Demographics and Clinical Characteristics

	Weighted Population[a]		
	DRV/c/FTC/TAF Cohort N= 76	**DTG + FTC/TAF Cohort N= 88**	**Standardized Difference[b]**
Demographic characteristics			
Age at the index date (years), mean ± SD [median]	51.2 ± 11.7 [55.0]	51.5 ± 12.6 [54.0]	2.8%
Female sex at birth, n (%)	23 (30.7)	28 (31.4)	1.6%
Race, n (%)			
Black	27 (35.6)	28 (31.4)	8.8%
White	26 (33.8)	36 (41.5)	16.1%
Other/Unknown	23 (30.7)	24 (27.0)	8.0%
Unknown	15 (19.0)	20 (22.9)	9.4%
Hispanic	6 (8.1)	3 (3.3)	20.7%
Other	3 (3.5)	1 (0.9)	18.2%
US geographic region, n (%)			
South	54 (71.1)	56 (63.9)	15.4%
West	11 (14.6)	15 (17.6)	8.3%
Midwest	6 (7.7)	5 (5.3)	9.7%
Northeast	5 (6.7)	12 (13.2)	22.0%
Insurance plan type, n (%)			
Insurance plan information available (in claims)	72 (94.7)	87 (98.7)	22.7%
Commercial	55 (71.4)	60 (68.3)	6.8%
Medicaid	9 (12.2)	12 (13.3)	3.2%
Medicare	8 (11.1)	12 (13.5)	7.4%
Other/Unknown	0 (0.0)	3 (3.6)	27.4%
Year of the index date, n (%)			
2018–2019	46 (60.4)	56 (63.3)	6.0%
2020–2021	30 (39.6)	32 (36.7)	6.0%
Clinical characteristics			
Quan-CCI (excluding HIV-1 symptoms), mean ± SD [median]	0.3 ± 0.6 [0.0]	0.3 ± 0.7 [0.0]	3.8%
Other physical comorbidities, n (%)			
Hypertension	13 (16.5)	13 (14.3)	6.0%
Dyslipidemia/hyperlipidemia	11 (14.1)	7 (7.8)	20.5%
Obesity	6 (8.0)	6 (6.9)	4.0%
Type II diabetes mellitus	4 (4.9)	6 (6.7)	7.9%
Prediabetes	2 (3.0)	3 (3.7)	3.9%
BMI (kg/m^2), mean ± SD [median]	33.2 ± 6.5 [31.9]	32.7 ± 6.0 [31.2]	6.8%
Weight (kg), mean ± SD [median]	99.4 ± 20.6 [98.4]	98.0 ± 18.7 [94.4]	6.9%
Antihypertensives, n (%)	17 (22.3)	18 (20.1)	5.3%
Medications associated with weight gain,[c] n (%)	12 (16.2)	17 (19.7)	9.1%
Medications associated with weight loss,[d] n (%)	6 (7.8)	7 (8.0)	0.5%

Notes: [a]Of note, the number of PLWH reported in this weighted population represents the sum of weights for the corresponding PLWH, rounded to the nearest integer. The proportions displayed were calculated prior to the rounding and may be slightly different than if they were calculated based on rounded numbers. [b]For continuous variables, the standardized difference is calculated by dividing the absolute difference in means of the DRV/c/FTC/TAF cohort and the DTG + FTC/TAF cohort by the pooled standard deviation of both groups. The pooled standard deviation is the square root of the average of the squared standard deviations. For categorical variables with two levels, the standardized difference is calculated using the following equation where P is the respective proportion of participants in each group: $(P_{DTG + FTC/TAF}\text{-}P_{DRV/c/FTC/TAF})/\sqrt{([p1 + p2]/2)}$, where $p1=P_{DTG + FTC/TAF}(1\text{-}P_{DTG + FTC/TAF})$ and $p2=P_{DRV/c/FTC/TAF}(1\text{-}P_{DRV/c/FTC/TAF})$. [c]Medications associated with weight gain included anticonvulsants (divalproex, pregabalin, perampanel), antidepressants (escitalopram, citalopram, tricyclic antidepressants, mirtazapine, paroxetine, monoamine oxidase inhibitors), antidiabetic medications (insulins, sulfonylureas, thiazolidinediones, meglitinides), antipsychotics (quetiapine, olanzapine, risperidone, clozapine, thioridazine), corticosteroids, antihistamines (cyproheptadine), beta blockers, alpha blockers, hormonal therapy, and appetite stimulants. [d]Medications associated with weight loss included anticonvulsants (topiramate, lamotrigine, zonisamide, felbamate, stiripentol), antidepressants (bupropion, venlafaxine, desvenlafaxine), antidiabetic medications (sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide-1 agonists, pramlintide), antipsychotics (ziprasidone), growth hormone releasing hormone (tesamorelin, ipamorelin, sermorelin), ADHD medications, appetite suppressants, and anti-obesity medications.

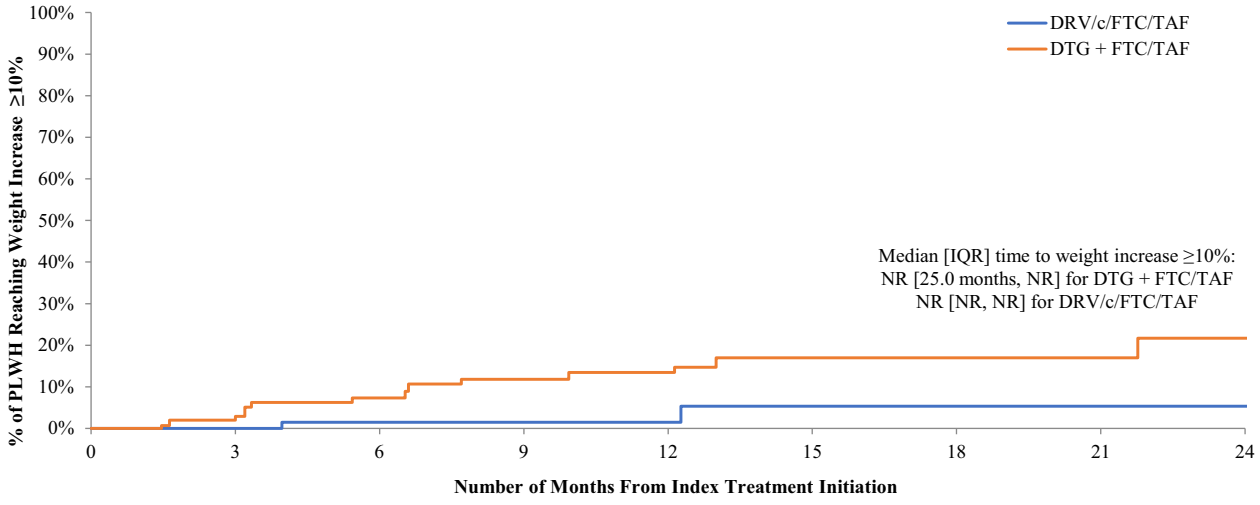
Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index; c, cobicistat; DRV, darunavir; DTG, dolutegravir; FTC, emtricitabine; PLWH, people living with HIV-1; SD, standard deviation; TAF, tenofovir alafenamide; US, United States.

A)



	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months
PLWH at risk[a,b], n (%)						
DRV/c/FTC/TAF	68 (88.8)	50 (65.5)	47 (61.3)	34 (44.1)	23 (30.2)	14 (18.2)
DTG + FTC/TAF	73 (83.3)	52 (58.8)	41 (47.1)	33 (37.5)	16 (18.2)	6 (6.8)
Kaplan Meier rates (95% CI)						
DRV/c/FTC/TAF	3.8% (0.8; 18.0)	12.4% (4.7; 30.4)	12.4% (4.7; 30.4)	17.8% (7.7; 38.0)	20.8% (9.1; 43.6)	20.8% (9.1; 43.6)
DTG + FTC/TAF	5.7% (2.4; 12.9)	19.5% (12.6; 29.6)	22.3% (14.8; 32.8)	25.8% (17.6; 36.8)	27.4% (18.9; 38.8)	50.6% (34.6; 69.0)

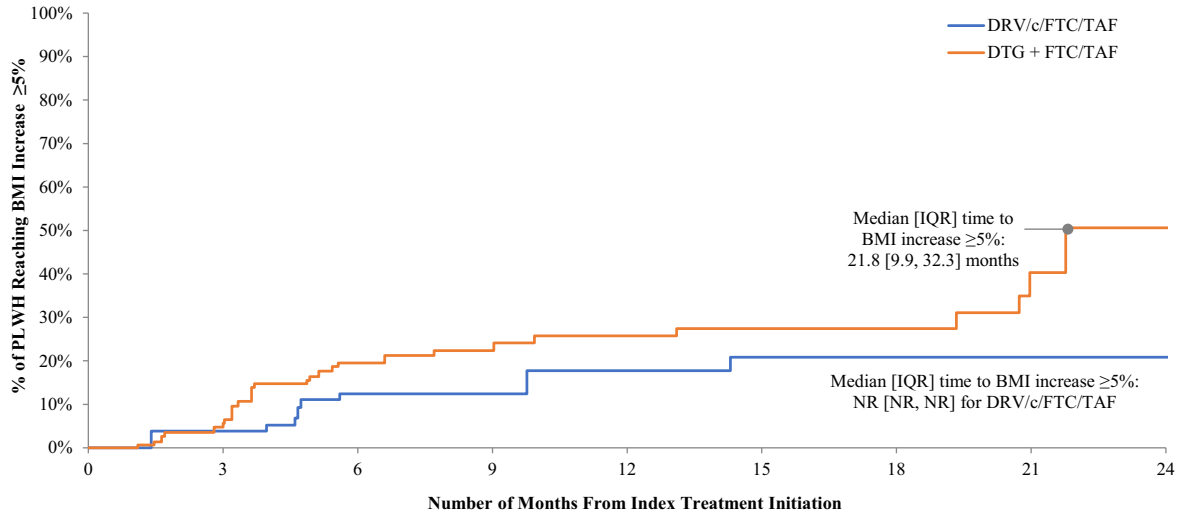
B)



	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months
PLWH at risk[a,b], n (%)						
DRV/c/FTC/TAF	68 (88.8)	54 (70.2)	48 (63.3)	38 (49.8)	26 (33.9)	17 (21.9)
DTG + FTC/TAF	75 (85.0)	57 (65.5)	46 (52.7)	38 (43.5)	19 (21.8)	10 (11.2)
Kaplan Meier rates (95% CI)						
DRV/c/FTC/TAF	0.0% (0.0; 0.0)	1.5% (0.1; 23.6)	1.5% (0.1; 23.6)	1.5% (0.1; 23.6)	5.3% (0.7; 33.4)	5.3% (0.7; 33.4)
DTG + FTC/TAF	2.9% (0.9; 9.4)	7.3% (3.4; 15.3)	11.8% (6.4; 21.1)	13.5% (7.6; 23.2)	17.0% (10.1; 27.9)	21.7% (12.4; 36.4)

Figure 2 Continued.

C)



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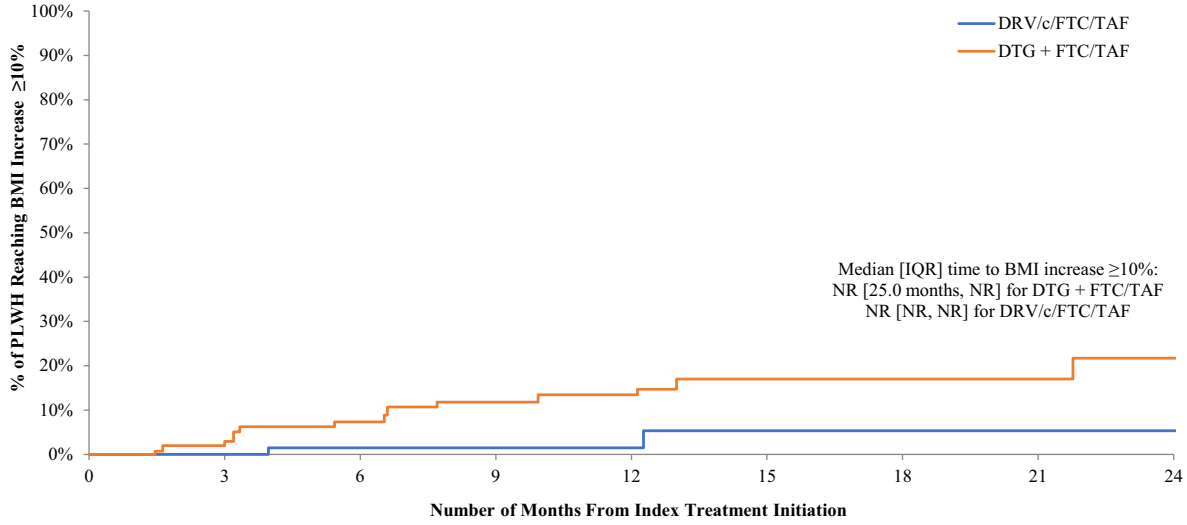
DTG + FTC/TAF	5.7% (2.4; 12.9)	19.5% (12.6; 29.6)	22.3% (14.8; 32.8)	25.8% (17.6; 36.8)	27.4% (18.9; 38.8)	50.6% (34.6; 69.0)

D)

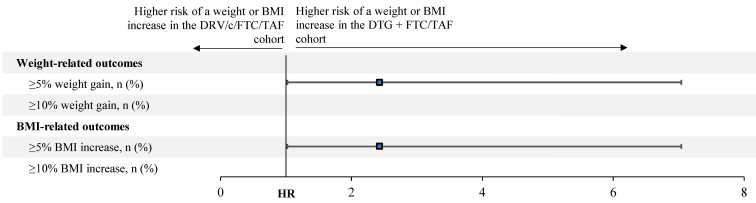


	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months
PLWH at risk[a,b], n (%)						
DRV/c/FTC/TAF	68 (88.8)	54 (70.2)	48 (63.3)	38 (49.8)	26 (33.9)	17 (21.9)
DTG + FTC/TAF	75 (85.0)	57 (65.5)	46 (52.7)	38 (43.5)	19 (21.8)	10 (11.2)
Kaplan Meier rates (95% CI)						
DRV/c/FTC/TAF	0.0% (0.0; 0.0)	1.5% (0.1; 23.6)	1.5% (0.1; 23.6)	1.5% (0.1; 23.6)	5.3% (0.7; 33.4)	5.3% (0.7; 33.4)
DTG + FTC/TAF	2.9% (0.9; 9.4)	7.3% (3.4; 15.3)	11.8% (6.4; 21.1)	13.5% (7.6; 23.2)	17.0% (10.1; 27.9)	21.7% (12.4; 36.4)

Figure 2 Kaplan Meier curves of time to weight/BMI increase above threshold. (**a**) Time to weight increase ≥5%. (**b**) Time to weight increase ≥10%. (**c**) Time to BMI increase ≥5%. (**d**) Time to BMI increase ≥10%.

Notes: (**a**) Of note, the number of PLWH reported in this weighted population represents the sum of weights for the corresponding PLWH, rounded to the nearest integer. The proportions displayed were calculated prior to the rounding and may be slightly different than if they were calculated based on rounded numbers. (**b**) Refers to the population at risk of having the event at that point in time (ie, PLWH who have not had the event and have not been lost to follow-up).

Abbreviations: BMI, body mass index; c, cobicistat; CI, confidence interval; DRV, darunavir; DTG, dolutegravir; FTC, emtricitabine; IQR, interquartile range; NR, not reached; PLWH, people living with HIV-1; TAF, tenofovir alafenamide.



	Weighted population[a]		Weighted Adjusted Hazard Ratio[b] (95% CI)[c]	P-value[c]
	DRV/c/FTC/TAF cohort	DTG + FTC/TAF cohort		
Weight-related outcomes	N=76	N=88		
≥5% weight gain, n (%)	12 (15.9)	24 (27.6)	2.43 (1.02; 7.04)	0.036*
≥10% weight gain, n (%)	5 (6.9)	13 (14.9)	--[d]	--[d]
BMI-related outcomes	N=76	N=88		
≥5% BMI increase, n (%)	12 (15.9)	24 (27.6)	2.43 (1.02; 7.04)	0.036*
≥10% BMI increase, n (%)	5 (6.9)	13 (14.9)	--[d]	--[d]

Figure 3 Comparison of time to weight or BMI increase outcome.
Notes: *Significant at the 5% level. (a) Of note, the number of PLWH reported in this weighted population represents the sum of weights for the corresponding PLWH, rounded to the nearest integer. The proportions displayed were calculated prior to the rounding and may be slightly different than if they were calculated based on rounded numbers. (b) A hazard ratio >1 indicates that the DTG + FTC/TAF cohort had a higher risk of a weight or BMI increase than the DRV/c/FTC/TAF cohort. (c) Non-parametric 95% bootstrap CIs and p-values were obtained from 500 bootstrap resamples. At each bootstrap resample, the inverse probability of treatment weights were re-estimated. (d) Data not available, given that the Cox proportional hazard models for these outcomes did not converge.
Abbreviations: BMI, body mass index; c, cobicistat; CI, confidence interval; DRV, darunavir; DTG, dolutegravir; FTC, emtricitabine; HR, hazard ratio; PLWH, people living with HIV-1; TAF, tenofovir alafenamide.

Comparison of Weight and BMI Change at Specific Time Points

PLWH in the DTG + FTC/TAF cohort experienced descriptively greater absolute weight or BMI increases than PLWH in the DRV/c/FTC/TAF cohort, with results reaching statistical significance at 12 months (Supplementary Figure 1). Weighted doubly robust mean differences in weight ranged from 1.36 kg [3.00 lbs] at 3 months (increase for DTG + FTC/TAF cohort: $\Delta_{3\ months}$= +0.49 kg [+1.08 lbs]; decrease for DRV/c/FTC/TAF cohort: $\Delta_{3\ months}$= −0.67 kg [−1.48 lbs]; p = 0.18) to 4.08 kg [8.99 lbs] at 12 months (increase for DTG + FTC/TAF cohort: $\Delta_{12\ months}$= +0.49 kg [+1.08 lbs]; decrease for DRV/c/FTC/TAF cohort: $\Delta_{12\ months}$= −2.14 kg [−4.72 lbs]; p = 0.024). At each time point, PLWH in the

Table 2 Baseline BMI Category and Proportion of PLWH with BMI Category Shifts[a] During Follow-Up

Baseline BMI Category	DRV/c/FTC/TAF Cohort (N=76)[b]					
	Follow-Up BMI Category[c]					
	BMI <25 kg/m^2	BMI 25–29 kg/m^2	BMI 30–34 kg/m^2	BMI 35–39 kg/m^2	BMI ≥40 kg/m^2	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n
BMI 25–29 kg/m^2 (overweight)	1 (2.7)	23 (69.0)	10 (28.3)			34
BMI 30–34 kg/m^2 (class 1 obesity)		2 (16.3)	13 (83.7)			15
BMI 35–39 kg/m^2 (class 2 obesity)			2 (20.2)	9 (71.8)	1 (8.0)	12
BMI ≥40 kg/m^2 (class 3 obesity)				4 (26.4)	11 (73.6)	15
Baseline BMI Category	**DTG + FTC/TAF Cohort (N=88)[b]**					
	Follow-Up BMI Category[c]					
	BMI <25 kg/m^2	BMI 25–29 kg/m^2	BMI 30–34 kg/m^2	BMI 35–39 kg/m^2	BMI ≥40 kg/m^2	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n
BMI 25–29 kg/m^2 (overweight)	3 (8.4)	24 (70.8)	7 (20.8)			34
BMI 30–34 kg/m^2 (class 1 obesity)		6 (19.3)	17 (59.5)	4 (15.7)	2 (5.5)	29
BMI 35–39 kg/m^2 (class 2 obesity)		1 (9.2)	2 (15.9)	9 (61.5)	2 (13.4)	14
BMI ≥40 kg/m^2 (class 3 obesity)				1 (10.1)	10 (89.9)	11

Notes: [a]Blue shading indicates patients who had a decrease between the baseline and latest follow-up BMI category. Green shading indicates patients who had no change between the baseline and latest follow-up BMI category. Yellow shading indicates patients who had an increase between the baseline and latest follow-up BMI category. Dark grey shading indicates that no patients were observed experiencing these increases between the baseline and latest follow-up BMI category. [b]Of note, the number of PLWH reported in this weighted population represents the sum of weights for the corresponding PLWH, rounded to the nearest integer. The proportions displayed were calculated prior to the rounding and may be slightly different than if they were calculated based on rounded numbers. [c]Evaluated based on the on-treatment measurement furthest from the index date.
Abbreviations: BMI, body mass index; c, cobicistat; DRV, darunavir; DTG, dolutegravir; FTC, emtricitabine; PLWH, people living with HIV-1; TAF, tenofovir alafenamide.

DRV/c/FTC/TAF cohort experienced an overall mean decrease in weight post-index, while PLWH in the DTG + FTC/TAF cohort experienced an overall mean increase in weight post-index. Results were consistent for the comparison of mean BMI differences between the DRV/c/FTC/TAF and DTG + FTC/TAF cohorts, with results reaching statistical significance at 12 months (Supplementary Figure 1). The proportion of PLWH who were overweight or obese that experienced ≥5% or ≥10% weight/BMI increase was numerically higher in the DTG + FTC/TAF cohort compared to the DRV/c/FTC/TAF cohort at each time point (Supplementary Table 1).

Discussion

To the authors' knowledge, this real-world study is the first to compare changes in weight or BMI between PLWH who were overweight or obese and initiated a DRV/c-based regimen compared with PLWH who initiated a DTG-based regimen that included the same FTC/TAF nucleoside reverse transcriptase inhibitor backbone. In PLWH, it can be difficult to separate the effect of individual medications in an ART regimen on weight gain from the return-to-health phenomenon observed when PLWH begin ART.[24] Furthermore, the most recent US DHHS HIV treatment guidelines specifically call out the concern for excess weight gain associated with INSTI-based regimens that include DTG or bictegravir compared to non-nucleoside reverse transcriptase inhibitor (NNRTI)- or PI-based regimens.[10] Thus, addressing the question of the impact of different ART regimens on weight change among PLWH who were initially overweight or obese is important as there has already been an observed increase in the prevalence of obesity among PLWH initiating ART.[8] Hence, the current study focused on an understudied population, ie, PLWH who were already overweight or obese (BMI ≥25 kg/m^2) at baseline prior to ART initiation, in an effort to exclude PLWH experiencing the return-to-health phenomenon and better ascertain the effect of specific ART regimens on weight gain.

Based on this study design, it was found that PLWH treated with DTG + FTC/TAF experienced a more than twofold (HR = 2.43) greater risk of weight/BMI increase ≥5% while on treatment compared to DRV/c/FTC/TAF. The DTG + FTC/TAF cohort also had a shorter median time to weight gain related to the DRV/c/FTC/TAF cohort, such that 51% of the overweight or obese DTG + FTC/TAF cohort (vs 21% in DRV/c/FTC/TAF cohort) experienced the ≥5% weight/BMI outcome within 2 years of starting treatment, with differences between the two cohorts starting to appear as early as after 3 months of follow-up. In addition, PLWH treated with DTG + FTC/TAF experienced an increase in mean weight gain/BMI increase at each time point up to 12 months post-treatment initiation, whereas PLWH who initiated DRV/c/FTC/TAF experienced a decrease in mean weight gain/BMI at each time point over the same period.

Findings of the current study are consistent with several previous real-world analyses, which have demonstrated increased weight gain associated with initiating therapy with an INSTI-based regimen relative to other types of regimens, such as those that are PI-based.[12,29,30] In a large retrospective real-world study of 20,367 PLWH in the US, those who initiated a new PI were 39% less likely to experience ≥5% weight gain ($p = 0.014$) and 49% less likely to experience a ≥5% BMI gain ($p < 0.001$) than PLWH who initiated a new INSTI.[12] Similar associations have been observed for INSTI-based regimens compared to NNRTI-based regimens.[16,31,32] A retrospective longitudinal study of 22,972 PLWH from the North American AIDS Cohort Collaboration on Research and Design found that after 5 years of ART, PLWH who initiated an INSTI-based regimen experienced mean weight gain of 5.9 kg [13.0 lbs], compared to 3.7 kg [8.2 lbs] for NNRTI-based regimens.[16]

Within the INSTI class of ART, DTG has been linked to a higher risk of weight gain and an increase in BMI, relative to other INSTI drugs or NNRTI-based regimens.[15,33,34] In one study of 1152 treatment-naive PLWH from the Vanderbilt Comprehensive Care Clinic cohort, the adjusted average weight gains for PLWH treated with DTG at 18 months were significantly higher compared to gains for NNRTIs or elvitegravir (6.0 kg [13.2 lbs] vs 2.6 kg [5.7 lbs] and 0.5 kg [1.1 lbs], respectively; both $p < 0.05$).[15] These findings are also supported by a recent systematic literature review and network meta-analysis of 73 studies spanning approximately 10 years (2011 to September 13, 2021), which found that DTG-based regimens can result in significantly higher average weight gains relative to other ART regimens, including NNRTIs and elvitegravir/c.[34]

Weight change in PLWH remains an important topic in patients initiating an ART regimen, as there are potential implications on downstream clinical outcomes. For instance, various studies have shown an increase in the risk of type II diabetes mellitus among obese PLWH.[9,24,35–38] In a study that analyzed data of 9193 PLWH from the Data Collection on

Adverse Events of Anti-HIV Drugs (D:A:D) study, adjusted models reported an incidence rate ratio for the risk of diabetes mellitus of 1.12 (95% CI: 1.04, 1.22; p = 0.005) for every unit gain in BMI after 1 year of ART therapy.[35] A separate retrospective longitudinal real-world study of treatment-naïve adult female, Black, or Hispanic PLWH who initiated ART found that PLWH who experienced a ≥ 5% weight/BMI gain (n = 620) after initiating ART were significantly more likely (HR = 2.19; p = 0.044) to be diagnosed with type 2 diabetes mellitus during a mean 2-year follow-up period.[9] While additional research is warranted, these findings suggest that ART regimens may play a role in the increased risk of additional comorbidities among PLWH. For PLWH, who are already overweight or obese, ART-associated weight gain may further compound the risk of chronic cardiometabolic disease and other aging-related comorbidities. Future studies are warranted to evaluate consequences of ART-related weight gain in PLWH.

Limitations

Some limitations apply to the data used and analyses conducted as part of the current study. First, EMR data may contain inaccuracies or omissions in diagnoses, medication use, and other variables. Second, it was assumed that the prescribed ART medication was taken as indicated. Third, the provider-based data source used in this study does not capture the services PLWH may have received from providers outside of the network. Fourth, since this study population included treatment-naïve PLWH, results may not be generalizable to treatment-experienced PLWH. Similarly, given that only PLWH who are overweight/obese were included in the present study, findings may not be generalizable to the population of PLWH who are not overweight or obese. Fifth, despite using IPTW and adjusting for many variables available in the data, unmeasured confounders associated with weight/BMI changes (eg, lifestyle changes, diet, physical activity, contraceptive methods) may remain; however, it is not possible to determine what impact these unmeasured confounders may have on the results, as these are not observable in the data. Sixth, variables such as waist circumference and laboratory results (eg, HIV viral load and CD4+ cell count), which may be associated with weight change, could not be included in the PS model for balancing, as they were unavailable for the majority of PLWH in the sample. In addition, use of pre-exposure prophylaxis was not measured in the period prior to the 12-month baseline period; however, there is no reason to indicate that this would differ between the two cohorts, so it is thus likely not a confounder for this study. Finally, while results consistently showed greater weight/BMI increases for DTG + FTC/TAF relative to DRV/c/FTC/TAF, the ability to detect statistically significant results for the comparison of weight and BMI change at specific time points was limited by small sample size.

Conclusions

Treatment-naïve PLWH who were overweight or obese and initiated ART with DTG + FTC/TAF were at significantly greater risk of experiencing weight or BMI increase ≥5% compared to PLWH who were overweight or obese and initiated DRV/c/FTC/TAF. Based on these findings, it may be important for PLWH who are at greater risk of developing cardiovascular and metabolic conditions associated with obesity to carefully select their initial ART regimen. Future studies with larger sample sizes and additional follow-up are needed to confirm these findings, particularly among PLWH using newer ART formulations of DTG (ie, DTG/lamivudine).

Data Sharing Statement

The data that support the findings of this study are available from Symphony Health, an ICON plc Company. Restrictions apply to the availability of these data, which were used under license for this study.

Ethics Statement

Data were de-identified and comply with the patient requirements of the Health Insurance Portability and Accountability Act (HIPAA) of 1996; therefore, no review by an institutional review board was required per Title 45 of CFR, Part 46.101(b)(4) (https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/#46.101).

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Author Contributions

All authors have made substantial contributions to the conception or design of the study, or the acquisition, analysis, or interpretation of data, drafting the manuscript and revising it critically for important intellectual content, and have provided final approval of this version to be published and agree to be accountable for all aspects of the work. All authors reviewed and approved the final content of this manuscript and agreed to submit the manuscript to ClinicoEconomics and Outcomes Research.

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Disclosure

Prina Donga, Brahim K. Bookhart, and Johnnie Lee are employees of Janssen Scientific Affairs, LLC and are stockholders of Johnson & Johnson. Bruno Emond, Carmine Rossi, Gabrielle Caron-Lapointe, Fangzhou Wei, and Marie-Hélène Lafeuille are employees of Analysis Group, Inc., a consulting company that provided paid consulting services to Janssen Scientific Affairs, LLC. The authors report no other conflicts of interest in this work.

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