SYMTUZA® (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide)
SYMTUZA - Effect on Weight

Clinical Data with D/C/F/TAF

Treatment-Naïve

- Results from 2 **phase 3** clinical trials:

Clinical Trial	Median Change in Body Weight, kg	
	D/C/F/TAF vs Baseline	Control vs Last Value Before Switch
AMBER (week 96)[a]	2.0 (IQR, -0.3 to 5.0)	1.0 (IQR, 0 to 2.9)
DIAMOND (week 48)[b]	2.9 (95% bootstrap CI, 1.5-4.1)	

- In a **real-world, retrospective study**,[c] greater weight and BMI increases were observed between the pre- and post-index periods among patiēnts in the TAF 25 mg cohort compared with those in the TAF 10 mg (which included patients on D/C/F/TAF), TDF, and non-TAF/TDF cohorts at 12 months.
- In a **retrospective cohort study**,[d] overweight/obese PLWH who initiated DTG+FTC/TAF had a more than twofold greater risk of experiencing weight/BMI increase ≥5% compared to those who initiated D/C/F/TAF.
- In a **retrospective cohort study**,[e] treatment-naïve female, Black or Hispanic PLWH who were overweight or obese at baseline and were initiated on BIC/FTC/TAF had larger increases in weight/BMI at 24 months than those who were initiated on D/C/F/TAF.

Treatment-Experienced

- Results from a **phase 3** clinical trial:

Clinical Trial	Median Change in Body Weight, kg	
	D/C/F/TAF vs Baseline	Late Switch vs Last Value Before Switch
EMERALD (week 96)[d]	1.8 (IQR, -0.8 to 4.6)	1.6 (IQR, -0.4 to 3.5)

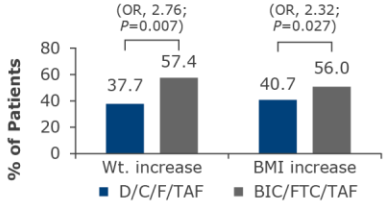
- Results from a **phase 4** clinical trial:

Clinical Trial	Percent Change in Body Weight From Baseline to Week 24		
	D/C/F/TAF	INSTI +TAF/FTC	*P* Value
DEFINE (week 24)[g]	0.63 (95% CI, -0.44 to 1.70)	-0.24 (95% CI, -1.35 to 0.87	0.2394

Treatment-Naïve and Treatment-Experienced

- In a **retrospective study**,[h] greater weight and BMI increases between the pre- and post-index periods were observed in the BIC/FTC/TAF cohort than in the D/C/F/TAF cohort with a statistically significant difference at 9 months.

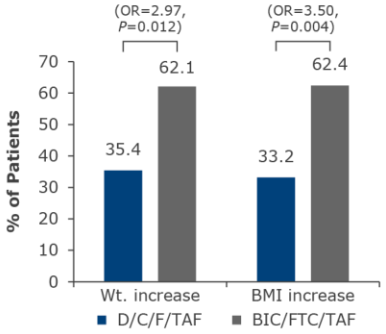
Proportion of Patients With Weight and BMI Increases at 9 Months Post-index



- Female gender was a common predictor of weight or BMI increase ≥5% in both cohorts (D/C/F/TAF: OR, 5.92; *P*=0.014; BIC/FTC/TAF: OR, 2.00; *P*<0.001).

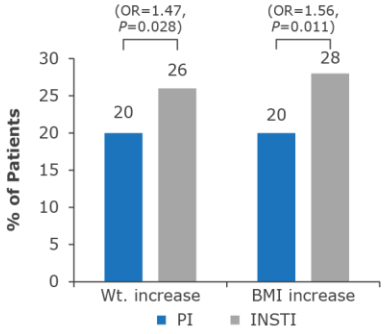
- In a **retrospective study**,[i] greater weight and BMI increases were observed in the BIC/FTC/TAF cohort than in the D/C/F/TAF cohort between the pre- and post-index periods, with a statistically significant difference at 12 months.

Proportion of Patients With Weight and BMI Increases at 12 Months Post-index



- In a **retrospective study**,[g] weight and BMI increases ≥5% between the pre- and post-index periods were more likely with a new INSTI-based regimen compared with a new PI-based regimen.

Proportion of Patients With ≥5% Weight or BMI Increases



Header sections within the image contain hyperlinks to related sections within the document.

Abbreviations: BIC, bictegravir; BMI, body mass index; CI, confidence interval; D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; FTC, emtricitabine; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; ITT, intention-to-treat; LS, least squares; NR, not reached; OR, odds ratio; PI, protease inhibitor; PLWH, people living with HIV-1; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; wt, weight.

[a]Orkin (2020).[1] [b]Huhn (2020).[2] [c]Emond (2022).[3] [d]Donga (2023).[4] [e]Donga (2023).[5] [f]Eron (2019).[6] [g]Short (2023).[7] [h]Emond (2021).[8] [i]Emond (2022).[9] [j]Chow (2020).[10]

SUMMARY

- In the AMBER study, median (interquartile range [IQR]) change in body weight at week 96 was 2.0 (-0.3 to 5.0) kg in the SYMTUZA arm vs baseline and 1.0 (0 to 2.9) kg in the control arm vs last value before switch.[1]
- In the DIAMOND study, the median change (95% bootstrap confidence interval [CI]) in body weight from baseline was 2.9 (1.5-4.1) kg at week 48 in the SYMTUZA study population.[2]
- In a real-world, retrospective, longitudinal study, greater weight and body mass index (BMI) increases were observed between the pre- and post-index periods among patients in the tenofovir alafenamide (TAF) 25 mg cohort compared with those in the TAF 10 mg (which included patients on SYMTUZA), tenofovir disoproxil fumarate (TDF), and non-TAF/TDF cohorts at 12 months.[3]
- In a retrospective cohort study, overweight/obese people living with human immunodeficiency virus (HIV-1) (PLWH) who initiated dolutegravir (DTG)/emtricitabine (FTC)/TAF had a more than twofold greater risk of experiencing weight/BMI increase ≥5% compared to those who initiated SYMTUZA.[4]
- In a retrospective, longitudinal cohort study, treatment naïve female, Black, or Hispanic PLWH who were overweight or obese at baseline and were initiated on bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) had larger increases in weight or BMI at 24 months than those initiated on SYMTUZA.[5]
- In the EMERALD study, median (IQR) change in body weight at week 96 was 1.8 (-0.8 to 4.6) kg vs baseline in the SYMTUZA arm and 1.6 (-0.4 to 3.5) kg vs the value prior to switching in the late switch arm.[6]
- In the DEFINE study, there was no significant difference in percent change in body weight from baseline between participants in the SYMTUZA arm (0.63 [-0.44, 1.70]) and control arm (-0.24 [-1.35, 0.87]) at week 24.[7]
- In a retrospective longitudinal study, greater weight and BMI increases between the pre- and post-index periods were observed in the BIC/FTC/TAF cohort than in the SYMTUZA cohort; a statistically significant difference between cohorts was only seen at 9-months post-index. Female gender was a common predictor of weight or BMI increase ≥5% in both cohorts.[8]
- In a retrospective longitudinal study, significantly greater weight and BMI increases were observed between the pre- and post-index periods among patients in the BIC/FTC/TAF cohort compared with the SYMTUZA cohort at 12 months.[9]
- In a retrospective longitudinal study, patients initiating a new integrase strand transfer inhibitor (INSTI)-based regimen were more likely to experience weight and BMI increases ≥5% between the pre- and post-index periods relative to patients initiating a new protease inhibitor (PI)-based regimen.[10]

BACKGROUND

The Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV developed by the U.S. Department of Health and Human Services (DHHS) Panel review data from studies showing increased weight gain associated with certain antiretroviral (ARV) medications. The guidelines may be accessed at: https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv.[11]

CLINICAL DATA WITH SYMTUZA

Treatment-Naïve Patients

AMBER

The AMBER study was a phase 3, randomized, active-controlled, double-blind, noninferiority study to evaluate efficacy and safety of SYMTUZA vs darunavir (DRV)/cobicistat (COBI) fixed dose combination (FDC) co-administered with FTC/TDF in ARV treatment-naïve HIV type 1 (HIV-1)-infected adults (N=725).[12]

Study Design/Methods

- Patients were stratified by screening viral load (VL; < / ≥100,000 copies/mL) and by screening cluster of differentiation 4 (CD4)+ cell counts (< / ≥200 cells/mm^3) and then randomized to a single-tablet regimen (STR) of SYMTUZA (DRV 800 mg/COBI 150 mg/FTC 200 mg/TAF 10 mg) with matching DRV/COBI + FTC/TDF placebo or the active-control regimen of DRV/COBI + FTC/TDF with a matching SYMTUZA placebo.
- After week 48, patients continued to take their blinded study drug until the last patient had reached week 48 and treatment assignments were unblinded.
- After unblinding, all patients entered the open-label, single-group treatment phase with continued SYMTUZA use in the SYMTUZA group and switch to SYMTUZA in the control group up to week 96.

Results

- The median (minimum; maximum) change from baseline in weight at week 48 was 1.5 (-8.4; 16.2) kg among 340 patients in the SYMTUZA arm and no change (-20.4; 19.4) among 330 patients in the control arm.[13]
- Median (IQR) change in body weight at week 96 was 2.0 (-0.3 to 5.0) kg in the SYMTUZA arm vs baseline (n=319) and 1.0 (0 to 2.9) kg in the control arm vs last value before switch (n=290).[1]
- Through week 96, weight gain was reported as an adverse event (AE) in 3 cases in the initial SYMTUZA arm and 10 cases in the control arm (8 prior to switch and 2 following switch to SYMTUZA); however, none occurring during treatment with SYMTUZA were thought to be drug-related.[13]
- There were no discontinuations due to weight gain.[1]

DIAMOND

The DIAMOND study was a phase 3, single-arm, open-label, multicenter study to evaluate the safety and efficacy of SYMTUZA in newly diagnosed, HIV-1 infected, treatment-naïve patients in a rapid initiation model of care over 48 weeks (N=109).[2]

Study Design/Methods

- Eligible patients were enrolled and started on SYMTUZA once daily (QD) as soon as within 24 hours of the screening/baseline visit and before results of the baseline safety and resistance laboratory tests were available.

Results

- The median change (95% bootstrap CI) in body weight from baseline was 2.9 (1.5-4.1) kg, with a mean change of 4.3 kg at week 48.
- There were no discontinuations due to weight gain.

Decision Resource Group

A real-world study was conducted to assess weight gain and BMI increase among adult patients with HIV-1 who were initiated on an ART regimen containing TAF 10 mg (including SYMTUZA), TAF 25 mg, TDF, or not containing TAF/TDF agents in the United States (US).[3]

Study Design/Methods

- A retrospective, longitudinal study was conducted using electronic medical record (EMR) data from the Decision Resources Group's (DRG) Real World Data Repository (part of Clarivate) from 7/17/2017-3/1/2020.
- Patients were included if they had ≥1 diagnosis of HIV-1 on or before the index date, had ≥12 months continuous clinical activity before the index date (baseline period), and ≥1 weight or BMI measurement in the baseline and follow-up periods.

- The index date was the date of initiation of a DHHS-recommended ART regimen containing TAF 10 mg (including SYMTUZA; TAF 10 mg cohort), TAF 25 mg (TAF 25 mg cohort), TDF (TDF cohort), or not containing TAF/TDF (non-TAF/TDF cohort) between 07/17/2018 and 10/15/2019.
- The follow-up period spanned from the index date until the initiation of a new ART regimen that would result in a change in treatment cohort, end of continuous clinical activity, or end of data availability (whichever was earlier).

- The pre-index weight or BMI measurement was defined as the measurement closest to the index date in the baseline period (or ≤30 days post-index if no pre-index measurements were available).
- The post-index weight or BMI measurement was defined as the measurement closest to the post-index time points (3, 6, 9, or 12 months; ≤45 days before or after the time point).
- The absolute and relative increases (any, ≥5%, and ≥10%) in weight and BMI between the post-index timepoint and the pre-index measurement were also assessed.
- The time to weight or BMI increase ≥5% or ≥10% was compared between the cohorts over the entire follow-up period.

Results

- Overall, 1652 patients were included (TAF 10 mg cohort, n=303; TAF 25 mg cohort, n=710; TDF cohort, n=219; non-TAF/TDF cohort, n=420).
- Baseline characteristics were generally similar between cohorts, with some differences between the TAF 25 mg cohort and other cohorts; see Table: Baseline Characteristics Prior to the Index Date.
- As a part of the index ART regimen, a majority of the patients were initiated on an INSTI-based regimen in the TAF 10 mg (87.1%), TAF 25 mg (83.2%), and non-TAF/TDF (99.5%) cohorts whereas a majority of the patients were initiated on an nonnucleoside reverse transcriptase inhibitor (NNRTI)-based regimen in the TDF cohort (50.7%).
- In the TAF 10 mg cohort, 12.9% of patients initiated SYMTUZA.
- In the TAF 25 mg cohort, 66.2% of patients initiated BIC/FTC/TAF and 14.4% initiated a DTG-based regimen.

Baseline Characteristics Prior to the Index Date[3]

	Cohorts				**Standardized difference vs TAF 25 mg, %**		
	TAF 10 mg (n=303)	**TAF 25 mg (n=710)**	**TDF (n=219)**	**Non-TAF/TDF (n=420)**	**TAF 10 mg**	**TDF**	**Non-TAF/ TDF**
Age, years, mean±SD	50.2±12.8	49.7±13.7	49.9±13.2	51.3±13.0	3.6	1.5	11.6
Female, n (%)	88 (29.0)	188 (26.5)	67 (30.6)	116 (27.6)	5.7	9.1	2.6
Race, n (%)							
White	101 (33.3)	279 (39.3)	73 (33.3)	148 (35.2)	12.4	12.4	8.4
Black	106 (35.0)	203 (28.6)	66 (30.1)	125 (29.8)	13.8	3.4	2.6
Hispanic	20 (6.6)	48 (6.8)	17 (7.8)	28 (6.7)	0.6	3.9	0.4
Other	4 (1.3)	20 (2.8)	6 (2.7)	8 (1.9)	10.5	0.5	6.0

	Cohorts				Standardized difference vs TAF 25 mg, %		
	TAF 10 mg (n=303)	TAF 25 mg (n=710)	TDF (n=219)	Non-TAF/TDF (n=420)	TAF 10 mg	TDF	Non-TAF/ TDF
Unknown	72 (23.8)	160 (22.5)	57 (26.0)	111 (26.4)	2.9	8.2	9.1
US geographic region, n (%)							
South	169 (55.8)	417 (58.7)	126 (57.5)	240 (57.1)	6.0	2.4	3.2
West	62 (20.5)	141 (19.9)	42 (19.2)	92 (21.9)	1.5	1.7	5.0
Northeast	39 (12.9)	82 (11.5)	28 (12.8)	48 (11.4)	4.0	3.8	0.4
Midwest	29 (9.6)	57 (8.0)	20 (9.1)	35 (8.3)	5.4	3.9	1.1
Unknown	4 (1.3)	13 (1.8)	3 (1.4)	5 (1.2)	4.1	3.7	5.3
Patients with BMI measurement, n (%)	299 (98.7)	703 (99.0)	217 (99.1)	411 (97.9)	3.1	0.7	9.3
BMI, kg/m^2, mean±SD	28.9±8.9	28.3±6.2	28.5±6.1	28.0±5.8	8.2	2.9	4.4
Patients with Wt. measurement, n (%)	303 (100.0)	710 (100.0)	219 (100.0)	420 (100.0)	-	-	-
Wt., kg, mean±SD	85.1±20.7	84.2±18.7	83.8±19.1	83.6±18.1	4.7	1.9	3.1
Index regimen, n (%)							
PI-based	39 (12.9)	27 (3.8)	9 (4.1)	7 (1.7)	33.3[a]	1.6	13.1 [a]
INSTI-based	264 (87.1)	591 (83.2)	99 (45.2)	418 (99.5)	11.0	86.4 [a]	60.6 [a]
NNRTI-based	0	92 (13.0)	111 (50.7)	82 (19.5)	-	88.6 [a]	17.9 [a]
Use of ≥1 medication associated with weight change, n (%)	97 (32.0)	229 (32.3)	59 (26.9)	128 (30.5)	0.5	11.7	3.8

Abbreviations: BMI, body mass index; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SD, standard deviation; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; US, United States; Wt., weight.
[a]*P*<0.05.

- Numerically greater weight and BMI increases were observed in the TAF 25 mg cohort compared with the TAF 10 mg, TDF and non-TAF/TDF cohorts:
  - At 12 months after index, in the TAF 10 mg vs TAF 25 mg cohort, numerically smaller increases in weight ($\Delta_{12\ months}$, 1.08 kg vs 1.72 kg; *P*=0.39) and BMI ($\Delta_{12\ months}$, -0.92 kg/m^2 vs 0.71 kg/m^2; *P*=0.006) were observed.
- Additionally, at 12 months after index, the proportion of patients experiencing any weight or BMI increase was higher among patients in the TAF 25 mg cohort (weight, 55.3%; BMI, 56.2%) compared with those in the TAF 10 mg (weight, 54.7%; BMI,

54.1%), TDF (weight, 47.3%; BMI, 47.3%), and non-TAF/TDF (weight, 56.5%; BMI, 55.2%) cohorts.

- Over the entire follow-up period, weight and BMI increases of ≥5% or ≥10% were less likely to be experienced by patients in the TAF 10 mg, TDF, and non-TAF/TDF cohorts compared with those in the TAF 25 mg cohort; see Table: Comparison of Time to Weight or BMI Increase of ≥5% or ≥10%.

Comparison of Time to Weight or BMI Increase of ≥5% or ≥10%[3]

	Adjusted Analyses vs TAF 25 mg, HR (95% CI)		
	TAF 10 mg	**TDF**	**Non-TAF/TDF**
Weight			
Weight increase ≥5%	0.87 (0.68-1.11) *P*=0.248	0.81 (0.60-1.08) *P*=0.154	0.77 (0.61-0.96) *P*=0.023
Weight increase ≥10%	0.96 (0.69-1.35) *P*=0.830	0.56 (0.34-0.94) *P*=0.027	0.62 (0.43-0.88) *P*=0.008
BMI			
BMI increase ≥5%	0.94 (0.73-1.23) *P*=0.672	0.85 (0.62-1.17) *P*=0.308	0.83 (0.66-1.05) *P*=0.121
BMI increase ≥10%	0.88 (0.62-1.26) *P*=0.492	0.61 (0.37-1.02) *P*=0.059	0.54 (0.37-0.77) *P*<0.001

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

- The median time from index treatment initiation to ≥5% increase in weight or BMI was shorter in the TAF 25 mg cohort than in the TAF 10 mg, TDF, and non-TAF/TDF cohorts and was NR in any cohort for the ≥10% threshold. See Table: Time From Index Treatment Initiation to ≥5% Increase in Weight or BMI.

Time From Index Treatment Initiation to ≥5% Increase in Weight or BMI[3]

	Cohorts			
	TAF 10 mg	**TAF 25 mg**	**TDF**	**Non-TAF/TDF**
Weight	n=303	n=707	n=217	n=418
Median time to weight increase ≥5%, months	17.8	16.5	18.2	18.5
Patients with weight increase ≥5%, n (%)	98 (32.3)	248 (35.1)	64 (29.5)	119 (28.5)
BMI	n=293	n=695	n=212	n=408
Median time to BMI increase ≥5%, months	NR	16.5	19.1	18.6
Patients with BMI increase ≥5%, n (%)	88 (30.0)	220 (31.7)	54 (25.5)	114 (27.9)

Abbreviations: BMI, body mass index; NR, not reached; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

EMR data from The Symphony Health, IDV® Database

Donga et al (2023)[4] conducted a real-world study to compare the weight or BMI changes among overweight or obese (BMI ≥25 kg/m^2), treatment-naïve adult PLWH who were initiated on SYMTUZA or DTG+FTC/TAF.

Study Design/Methods

- Retrospective, longitudinal cohort study using data from the Symphony Health Integrated Dataverse (IDV)® database (07/17/2018-08/31/2021).
- Patients were included if they had ≥1 diagnosis code for HIV-1 on or prior to the index date, ≥12 months of clinical activity prior to the index date (baseline), ≥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.
- Index date was defined as the patients' first prescription for SYMTUZA or DTG.
- Changes in weight and BMI from baseline were assessed at 3, 6, 9, and 12 months.
- Time to weight/BMI increase of ≥5% or ≥10% above the baseline weight or BMI measurement was evaluated over the entire follow-up period.
- To account for differences in baseline characteristics between treatment cohorts, the inverse probability of treatment weighting (IPTW) based on propensity scores was used.

Results

- Overall, 164 PLWH who were overweight or obese were included; 51 and 113 in the SYMTUZA and DTG/FTC/TAF cohorts, respectively.
- For baseline demographics and clinical characteristics, see Table: Baseline Characteristics

Baseline Characteristics[4]

Characteristics	Weighted Population	
	SYMTUZA Cohort (n=76)	DTG/FTC/TAF Cohort (n=88)
Age at the index date, mean±SD, years	51.2±11.7	51.5±12.6
Female, n (%)	23 (30.7)	28 (31.4)
Race, n (%)		
Black	27 (35.6)	28 (31.4)
White	26 (33.8)	36 (41.5)
Other/unknown	23 (30.7)	24 (27.0)
Unknown	15 (19.0)	20 (22.9)
Hispanic	6 (8.1)	3 (3.3)
Other	3 (3.5)	1 (0.9)
US geographic region, n (%)		
South	54 (71.1)	56 (63.9)
West	11 (14.6)	15 (17.6)
Midwest	6 (7.7)	5 (5.3)
Northeast	5 (6.7)	12 (13.2)
BMI, mean±SD (median), kg/m^2	33.2±6.5 (31.9)	32.7±6.0 (31.2)
Weight, mean±SD (median), kg	99.4±20.6 (98.4)	98.0±18.7 (94.4)
Medications associated with weight gain,[a] n (%)	12 (16.2)	17 (19.7)
Medications associated with weight loss,[b] n(%)	6 (7.8)	7 (8.0)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BMI, body mass index; DTG, dolutegravir; FTC, emtricitabine; SD, standard deviation; TAF, tenofovir alafenamide; US, United States.
[a]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.
[b]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.

- The DTG+FTC/TAF cohort had a shorter median (IQR) time from ART initiation to ≥5% weight gain (21.8 [9.9-32.3] months) and ≥10% weight gain (25 [not reached [NR]] months) than the SYMTUZA cohort (median/IQR, NR for either endpoint).
- Over the course of the follow-up period, PLWH who started DTG+FTC/TAF had a more than two-fold greater risk of experiencing a ≥ 5% weight or BMI increase compared with those who started SYMTUZA (hazard ratio [HR], 2.43; 95% CI, 1.02-7.04; *P*=0.036).
- In addition, the proportion of patients with ≥10% weight or BMI increase was descriptively higher in the DTG+FTC/TAF cohort (14.9%) than in the SYMTUZA cohort (6.9%), see Table: Comparison of Time to Weight or BMI Increase Outcomes

Comparison of Time to Weight or BMI Increase Outcomes[4]

	Weighted Population[a]		Weighted Adjusted HR[b] (95% CI)[c]	*P* Value[c]
	SYMTUZA Cohort, n (%) (n=76)	DTG/FTC/TAF Cohort, n (%) (n=88)		
Weight-related outcomes				
≥5% weight gain	12 (15.9)	24 (27.6)	2.43 (1.02-7.04)	0.036
≥10% weight gain	5 (6.9)	13 (14.9)	-[d]	-[d]
BMI-related outcomes				
≥5% BMI increase	12 (15.9)	24 (27.6)	2.43 (1.02-7.04)	0.036
≥10% BMI increase	5 (6.9)	13 (14.9)	-[d]	-[d]

Abbreviations: BMI, body mass index; CI, confidence interval; DTG, dolutegravir; FTC, emtricitabine; HIV, human immunodeficiency virus; HR, hazard ratio; PLWH, people living with HIV-1; TAF, tenofovir alafenamide.
[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]An HR >1 indicates that the DTG+FTC/TAF cohort had a higher risk of weight or BMI increase than the SYMTUZA cohort.
[c]Nonparametric 95% bootstrap CIs and *P* values were obtained from 500 bootstrap resamples. At each bootstrap resample, the inverse probability of treatment weights was reestimated.
[d]Data not available, given that the Cox proportional hazard models for these outcomes did not converge.

Donga et al (2023)[5] reported the results of a cohort study that described and compared real-world weight and BMI changes among female, Black (male or female), or Hispanic (male or female) treatment-naïve PLWH with BMI ≥25 kg/m^2 who were initiated on SYMTUZA or BIC/FTC/TAF.

Study Design/Methods

- Retrospective, longitudinal cohort study conducted with data from the Symphony Health IDV® database (07/17/2017-12/31/2021).
- Patients were included if they were treatment-naïve, ≥ 18 years old with ≥ 1 diagnosis code for HIV-1, ≥ 1 characteristic associated with a higher risk of BMI/weight gain: female, Black, or Hispanic, newly initiated on SYMTUZA or BIC/FTC/TAF between

07/17/2018 and 08/31/2021, ≥ 12 months of continuous clinical activity before the index date (baseline).
    - Index date was defined as the patients first prescription for SYMTUZA or BIC/FTC/TAF
- Changes in weight and BMI from baseline were assessed at 3, 6, 9, 12, 18, and 24 months.
- To account for differences in baseline characteristics between treatment cohorts, the IPTW based on propensity scores was used.

Results

- In the SYMTUZA cohort (N=260), the mean age was 51.9 years, 56.6% were female, 60.2% were Black, 15.9% were Hispanic, and 82.1% resided in the South.
- In the BIC/FTC/TAF cohort (N=324), the mean age was 50.6 years, 59.6% were female, 56.3% were Black, 14.6% were Hispanic, and 79.1% resided in the South.
- In the SYMTUZA cohort and the BIC/FTC/TAF cohort, the mean (standard deviation [SD]) baseline BMI was 32.8 (6.7) kg/m^2 and 33.3 (6.2) kg/m^2, respectively.
- In the SYMTUZA and the BIC/FTC/TAF cohorts, the mean (SD) follow-up period was 13.8 (8.7) and 16.3 (9.8) months, respectively.
- An increase in the BMI category occurred in 13.6% of BIC/FTC/TAF patients vs 8.1% in SYMTUZA patients.
- Patients in the SYMTUZA cohort had a higher proportion of overweight patients that became normal/underweight (n=15 (14.8%)) compared to the BIC/FTC/TAF cohort (n=9 (7.4%)).
- At all time points, increases in weight or BMI were seen in patients in the BIC/FTC/TAF cohort compared to the patients in the SYMTUZA cohort (statistically significant at 3, 6, and 9 months).
- At each time point, patients in the SYMTUZA cohort had an overall reduction in body weight compared to patients in the BIC/FTC/TAF cohort who had an overall increase in body weight.
- At 24 months, a sample of patients (n=77) had a mean (SD) difference in weight of 8.59 kg (increase of +2.63 kg in the BIC/FTC/TAF cohort; decrease of -2.10 kg in the SYMTUZA cohort; *P*=0.060).

Treatment-Experienced Patients

EMERALD

The EMERALD study was a phase 3, randomized, active-controlled, open-label noninferiority study to evaluate the efficacy, safety, and tolerability of switching to SYMTUZA vs continuing the current regimen consisting of a boosted PI (bPI) combined with FTC/TDF in virologically suppressed, HIV-1-infected adults (N=1141).[14]

Study Design/Methods

- Patients were stratified according to bPI (DRV/ritonavir [r] or DRV/COBI QD, atazanavir [ATV]/r or ATV/COBI QD, or lopinavir (LPV)/r twice daily [BID]) and then randomized 2:1 to switch to SYMTUZA or to continue their bPI regimen.
- At week 52, patients in the SYMTUZA arm could continue current therapy and patients in the control arm could switch to SYMTUZA in an extension phase until week 96.

Results

- The median (minimum; maximum) change from baseline in weight at week 48 was 1.3 (-25.6; 20.9) kg among 728 patients in the SYMTUZA arm and 0.50 (-23.3; 13.6) kg among 356 patients in the control arm.[15]

- Median (IQR) change in body weight at week 96 was 1.8 (-0.8 to 4.6) kg vs baseline in the SYMTUZA arm (n=701) and 1.6 (-0.4 to 3.5) kg vs the value prior to switching in the late switch arm (n=338).[6]
- Through week 96, there were 25 cases (3.3%) of weight gain reported as an AE in the SYMTUZA arm and 9 cases (2.4%) in the control arm. However only 5 cases (0.7%) in the SYMTUZA arm and 2 cases (0.6%) in the control arm (occurring after switch to SYMTUZA) were thought to be drug-related.[15]
- There were no discontinuations due to weight gain.[6]

DEFINE

The DEFINE study is a multicenter, randomized, open-label, parallel assignment phase 4 study conducted in virologically suppressed adults with HIV-1 who have experienced ≥10% increase in body weight within a 36-month period on an INSTI + TAF/FTC to determine if a switch to SYMTUZA results in a change in body weight (N=103).[7, 16]

Study Design/Methods

- Participants were randomized to switch immediately to SYMTUZA QD for 48 weeks or to remain on their current regimen for 24 weeks, after which they will switch to SYMTUZA for an additional 24 weeks.
- The primary endpoint was the percent change in body weight from baseline at week 24.

Results

- At week 24, in the intention to treat population, there was no significant difference in percent change in body weight from baseline between participants in the SYMTUZA arm (0.63 [-0.44, 1.70]) and control arm (-0.24 [-1.35, 0.87]).[7]
- At week 24, of the 49 participants in the SYMTUZA arm, 31 had body weight changes of ≤±3%.[7]
- Additionally, most participants remained within baseline BMI and waist circumference categories.[7]
- At week 24, percent change in body weight from baseline was consistent among various subgroups (BMI ≥30 kg/m^2, gender, and race).[7]

Treatment-Naïve and Treatment-Experienced Patients

The Symphony Health, IDV® Database

Emond et al (2021)[8] reported the results of a real-world study conducted to assess the weight change and predictors of weight change in patients with HIV-1 in the US treated with SYMTUZA or BIC/FTC/TAF.

Study Design/Methods

- Retrospective longitudinal study conducted with data from the Symphony Health IDV® database (07/17/2017-09/30/2019).
- Data included pharmacy claims, medical and hospital claims, and linked EMRs.
- Patients were included if they were treatment-naïve or treatment-experienced with ≥1 claim for an HIV-1 diagnosis on or before the index date, ≥12 months of continuous clinical activity before the index date, and ≥1 weight or BMI measurement at both baseline and follow-up periods.
    - The index date was date of initiation of SYMTUZA or BIC/FTC/TAF on or after 07/17/2018.
    - The baseline period was defined as the 12-month period of continuous clinical activity prior to the index date.
    - The follow-up period was from the index date until the end of continuous clinical activity or end of data availability.

- The population for predictors of weight or BMI increase included patients with ≥1 weight or BMI measurement in both the baseline and the follow-up periods.
- The population for the comparison of weight and BMI change included patients who initiated SYMTUZA and BIC/FTC/TAF who were allocated to only 1 cohort based on first observed regimen.
- A change in body weight or BMI was defined as the difference between the latest pre-index measurement and the post-index measurement at 3, 6, 9 and 12 months following the index date.
- Predicting factors of weight or BMI increase of ≥5% were evaluated at last measurement for each treatment cohort separately.
- To account for differences in baseline characteristics between treatment cohorts, the IPTW based on propensity scores was used.

Results

- In the comparative analysis, a total of 122 patients initiated SYMTUZA and 827 initiated BIC/FTC/TAF on the index date.
- Using the IPTW method, there were 452 weighted patients in the SYMTUZA cohort and 497 weighted patients in the BIC/FTC/TAF cohort.
- Greater weight and BMI increases between the pre- and post-index periods were observed in the BIC/FTC/TAF cohort than in the SYMTUZA cohort at all time points; a statistically significant difference between cohorts was only seen at 9-months post-index. See Table: Comparison of Weight and BMI Changes at 9 Months.
    - The 12-month post-index time point lacked power due to small sample sizes.
- At 9 months post-index, the proportion of patients who experienced any increase in weight or BMI was higher in patients who initiated BIC/FTC/TAF than in those who initiated SYMTUZA (weight increase, 57.4% and 37.7%, respectively; odds ratio [OR], 2.76; *P*=0.007; BMI increase: 56.0% and 40.7%, respectively; OR, 2.32; *P*=0.027). See Table: Proportion of Patients With Weight Gain or BMI Increase at 9 Months Post-Index.

Comparison of Weight and BMI Changes at 9 Months[8]

	SYMTUZA Cohort	**BIC/FTC/TAF Cohort**	**Weighted Mean Difference in Change From Post- to Preindex Periods Between BIC/FTC/TAF and SYMTUZA**
Weight at 9 months			
Patients with both baseline and follow-up measurements	n=102	n=123	-
Weight preindex, mean±SD, kg	92.57±24.54	89.15±23.59	2.5 kg *P*=0.005
Weight at 9 months postindex, mean±SD, kg	91.74±22.73	90.70±24.25	
BMI at 9 months			
Patients with both baseline and follow-up measurements	n=94	n=121	-
BMI preindex, mean±SD, kg/m^2	29.38±7.18	29.65±7.33	0.66 kg/m^2 *P*=0.027
BMI at 9 months postindex, mean±SD, kg/m^2	29.35±6.80	30.20±7.65	

Abbreviations: BIC, bictegravir; BMI, body mass index; FTC, emtricitabine; SD, standard deviation; TAF, tenofovir alafenamide.

Proportion of Patients With Weight Gain or BMI Increase at 9 Months Post-Index[8]

	SYMTUZA Cohort	BIC/FTC/TAF Cohort	Weighted OR (95% CI)	*P* Value
Weight at 9 months, %	n=102	n=123	-	-
Any weight gain	37.7	57.4	2.76 (1.33-5.74)	0.007
Weight gain ≥5%	20.8	22.5	2.21 (0.87-5.61)	0.094
Weight gain ≥10%	10.8	10.6	-	-
BMI at 9 months, %	n=94	n=121	-	-
Any BMI gain	40.7	56.0	2.32 (1.10-4.89)	0.027
BMI gain ≥5%	20.3	23.4	2.17 (0.85-5.52)	0.104
BMI gain ≥10%	11.7	11.2	1.57 (0.41-5.97)	0.507

Abbreviations: BIC, bictegravir; BMI, body mass index; CI, confidence interval; FTC, emtricitabine; OR, odds ratio; TAF, tenofovir alafenamide.

- In the predictive analysis (SYMTUZA, n=123; BIC/FTC/TAF, n=829), female gender was associated with a higher likelihood of weight or BMI increase ≥5% in both cohorts (SYMTUZA: OR, 5.92; *P*=0.014; BIC/FTC/TAF: OR, 2.00; *P*<0.001). Higher baseline BMI (≥25 kg/m^2) was associated with a lower likelihood of weight or BMI increase of ≥5% (OR, 0.27; *P*=0.028) in the SYMTUZA cohort.

Decision Resource Group

A real-world study was conducted to assess weight and BMI changes in adult patients with HIV-1 for up to 1 year following treatment initiation with SYMTUZA or BIC/FTC/TAF in the US.[9]

Study Design/Methods

- A retrospective, longitudinal study which included EMR data from the DRG Real World Data Repository (part of Clarivate) from 7/17/2017-3/1/2020.
- Patients were included if they were treatment-naïve or virologically suppressed with an HIV-1 diagnosis on or before the index date, had ≥12 months continuous clinical activity before the index date, and ≥1 weight or BMI measurement in the baseline and observation period.
    - The index date was the date of initiation of SYMTUZA or BIC/FTC/TAF on or after 07/17/2018.
    - The baseline period was defined as the 12-month period of continuous clinical activity before the index date.
    - The follow-up period started on the index date and ended at the end of continuous clinical activity or end of data availability (whichever was earlier).
    - Continuous clinical activity spanned the period from the first to the last record in the EMR database.
- IPTW was used to account for differences in baseline characteristics between the treatment cohorts.
- Mean weight and BMI changes were evaluated between weighted cohorts at each of the post-index timepoints (3-, 6-, 9-, and 12-months), and were defined as the mean difference between the post- and the pre-index measurement.
- The proportion of patients with weight and BMI increases (any, ≥5%, and ≥10%) from the pre-index period to each of the post-index timepoints was also compared.
- The time to weight or BMI increase ≥5% or ≥10% was compared between the cohorts over the entire follow-up period.

Results

- Overall, a total of 223 patients initiated SYMTUZA and 2027 patients initiated on BIC/FTC/TAF.
- Using the IPTW method, there were 1116 weighted patients in the SYMTUZA cohort and 1134 weighted patients in the BIC/FTC/TAF cohort.
- In the SYMTUZA cohort, the mean age was 49.2 years, 27.9% were female, 35.5% were Black, 7.4% were Hispanic, and 72.9% resided in the South.
    - Treatment-experienced, 61.4%; use of TAF in preindex period, 30.8%.
- In the BIC/FTC/TAF cohort, the mean age was 48.9 years, 28.6% were female, 38.1% were Black, 6.7% were Hispanic, and 71.9% resided in the South.
    - Treatment-experienced, 60.3%; use of TAF in preindex period, 29.7%.
- Compared to patients initiating SYMTUZA, significantly greater weight and BMI increases were experienced by patients initiating BIC/FTC/TAF at 12 months (mean difference [MD] in weight=2.84 kg [6.26 lbs], *P*=0.008; MD in BMI=1.23 kg/m^2, *P*<0.001).
- At 12 months post-index, the proportion of patients experiencing any weight or BMI increase was higher among patients initiated on BIC/FTC/TAF compared with those initiated on SYMTUZA (weight: 62.1% vs 35.4%, OR=2.97, *P*=0.012; BMI: 62.4% vs 33.2%, OR=3.50, *P*=0.004).
- Over the entire follow-up period, patients in the BIC/FTC/TAF cohort were significantly more likely to experience weight gain ≥5% (HR, 1.76; *P*=0.004) and ≥10% (HR, 2.01; *P*=0.020), as well as BMI increase ≥5% (HR, 1.77; *P*=0.004) and ≥10% (HR, 1.76; *P*=0.044), compared with patients in the SYMTUZA cohort.
- The median time from index treatment initiation to ≥5% increase in weight was shorter in the BIC/FTC/TAF cohort (12.9 months) than in the SYMTUZA cohort (14.5 months) and was NR in either cohort for the ≥10% threshold.

Chow et al (2020)[10] described real-world demographic, clinical characteristics, weight, and BMI changes following the initiation of a new PI or INSTI agent among adult patients with HIV-1 in the US insured through multiple payer channels.

Study Design/Methods

- Retrospective longitudinal study which included data from the DRG's Real World Data repository (7/17/2017-3/1/2020).
- Patients from all US states were included, and the data comprised open source claims from multiple electronic data interchanges and EMRs from a major vendor.
- Adult patients with HIV-1, with or without a prior history of ART and with ≥1 claim for a newly initiated PI or INSTI on or after 7/17/2018 (date of approval of SYMTUZA) were included.
- Patients were required to have both claims and EMR data, in addition to ≥1 weight or BMI measurement, during both the pre-and post-index periods.
    - The index date was defined as the date of the first claim for a newly initiated PI or INSTI on or after 7/17/2018; patients had to initiate the PI or INSTI agent as part of an ART regimen.
    - The pre-index period was defined as the 12-month period of continuous clinical activity before the index date.
    - The post-index period spanned from the index date until the end of continuous clinical activity (defined as a consecutive period of time when patients had ≥1 claim in each 3-month interval) or the end of data availability (ie, 3/1/2020), whichever was earliest.
- Pre-index characteristics between the PI and INSTI cohorts were balanced using IPTW, which was assessed using standardized differences.

Results

- Using the IPTW method, there were 373 and 385 weighted patients in the PI and INSTI cohorts, respectively.
- The majority of patients were treatment-experienced (73.5% PI, 70.7% INSTI).
- The majority of patients also received TAF (83.5% PI, 77.8% INSTI).
- Most patients in the PI cohort initiated a DRV-based regimen (89%; 64.7% SYMTUZA), and 24.0% of patients in the INSTI cohort initiated DTG.
- Comparisons of weight and BMI changes between the pre-and post-index periods are detailed in Table: Mean Change Between Pre-and Post-index Weight and BMI and Table: Proportions of Patients With ≥5% or ≥10% Weight or BMI Increase.
- Patients initiating an INSTI-based regimen were significantly more likely to experience ≥5% increase in weight and BMI than those initiating a PI-based regimen.

Mean Change Between Pre- and Postindex Weight and BMI[10]

	PI Cohort	INSTI Cohort	Weighted Mean Difference Between Pre-and Postindex Periods, PI vs INSTI Cohort
Weight			
Patients with both baseline and last follow-up weight measurement	n=372	n=383	-
Weight preindex, mean±SD, kg	86.55±20.21	86.00±20.52	-1.44 kg; *P*=0.006
Weight at the latest measurement postindex, mean±SD, kg	86.58±20.12	87.48±20.47	
BMI			
Patients with both baseline and last follow-up BMI measurement	n=373	n=370	-
BMI preindex, mean±SD, kg/m^2	29.14±6.68	29.29±6.50	-0.47 kg/m^2; *P*=0.007
BMI at the latest measurement postindex, mean±SD, kg/m^2	29.15±6.53	29.78±6.48	

Abbreviations: BMI, body mass index; INSTI, integrase strand transfer inhibitor; PI, protease inhibitor; SD, standard deviation.

Proportions of Patients With ≥5% or ≥10% Weight or BMI Increase[10]

	Proportion of Patients (PI; INSTI)	Weighted OR (95% CI); *P* Value
Weight		
≥5% weight gain	(20%; 26%)	1.47 (1.04-2.08); *P*=0.028
≥10% weight gain	(8%; 11%)	1.47 (0.90-2.38); *P*=0.125
BMI		
≥5% BMI increase	(20%; 28%)	1.56 (1.11-2.17); *P*=0.011
≥10% BMI increase	(11%; 12%)	1.19 (0.76-1.89); *P*=0.441

Abbreviations: BMI, body mass index; CI, confidence interval; INSTI, integrase strand transfer inhibitor; OR, odds ratio; PI, protease inhibitor.

LITERATURE SEARCH

A literature search of MEDLINE®, EMBASE®, BIOSIS Previews®, and DERWENT® (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 19 July 2023.

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