GILEAD | Medical Information

Biktarvy® (BIC/FTC/TAF) Weight Changes

This document is in response to your request for information regarding the use of Biktarvy® (bictegravir/emtricitabine/tenofovir alafenamide [BIC/FTC/TAF]) and weight changes. This response was developed according to principles of evidence-based medicine and includes data from Gilead phase 3 studies and large real-world cohorts.

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The full indication, important safety information, and boxed warnings are available at: www.gilead.com/-/media/files/pdfs/medicines/hiv/biktarvy/biktarvy_pi.

Summary

Background on BIC/FTC/TAF Use and Weight Changes

- The global obesity epidemic has grown steadily in both PWH and the general population.[1-3]
- Post marketing experience has led to an investigation of increased weight with BIC/FTC/TAF or TAF-containing products. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.[4]
- Findings from two phase 3, randomized, double-blind studies suggested a mild weight-suppressive effect with the use of TDF as a component of FTC/TDF for HIV PrEP.[5-7]

Clinical Data on BIC/FTC/TAF Use and Weight Changes in ARV-Naive Participants

In a pooled analysis of ARV-naive participants (N=5680) who initiated a variety of ART regimens between 2003 and 2015 yielded the following findings:[5]

- Median weight increases were observed in all study arms.[5]
- Participants treated with INSTIs experienced more weight gain from BL than did those treated with NNRTIs or PIs. Within INSTIs, greater weight gain was seen with BIC- and DTG-based regimens compared with EVG-based ones.[5]
- In participants treated with NRTIs, the most weight gain from BL was observed in those treated with TAF, followed by those treated with ABC and those treated with TDF.[5]
- Weight changes that occurred 96Weeks after ART initiation were not associated with impacts on metabolic parameters.[5]

Clinical Data on BIC/FTC/TAF Use and Weight Changes in TE Participants

A pooled analysis was conducted among virologically suppressed participants (N=7316) who switched to a variety of ARV regimens or SBR.[8]

- Weight increases were observed in both switch and SBR participants but were significantly greater in participants who switched their ART than in SBR participants, with most weight gain occurring ≤24 weeks after switch. Switch participants gained a median of 1.6 kg from BL to Week 48 and a median of 2 kg from BL to Week 96. SBR participants gained a median of 0.4 kg from BL to Week 48 and a median of 0.5 kg from BL to Week 96.[8]
- Younger age and lower BL BMI were associated with ≥10% weight gain.[8]
- BL ARV regimens were predictors of weight gain after switch. Switching from DTG to BIC was not associated with significantly different weight change, and switching from EVG/c to BIC was associated with a 0.7 kg greater weight gain at Week 48 compared with remaining on BL INSTI. Switching from TDF to TAF was associated with ≥10% weight gain compared with staying on TDF; switching from ABC to TAF was not.[8]
- Weight gain ≥10% at Week 48 in switch participants was not associated with impacts on metabolic parameters.[8]

Pooled Analyses of Studies on BIC/FTC/TAF Use and Weight Changes in Both ARV-Naive and TE Participants

In a pooled analysis of six phase 3 studies, there was no significant difference in weight change between participants aged <50 years and those aged ≥50 years from BL to Week 48 in virologically suppressed PWH and from BL to Week 240 in ARV-naive PWH.[9]

In a pooled analysis of five phase 2/3 studies in participants assigned female at birth, weight gain occurred in virologically suppressed and ARV-naive participants; however, weight gain or loss was an uncommon AE and occurred in 1.2% of BIC/FTC/TAF-treated participants and in <1% of comparator regimen-treated participants.[10]

Real-World Data on BIC/FTC/TAF Use and Weight Changes

BIC/FTC/TAF weight change data from real-world studies are available for BICSTaR and the Trio cohort.

Background on BIC/FTC/TAF Use and Weight Changes

Weight Changes in the General Population

The global obesity epidemic has grown steadily in both PWH and the general population.[1-3] In an analysis from 2003 using data from the NHANES and CARDIA studies, the average American aged 20 to 40 years gained nearly 1 kg/year.[11] Weight gain can be a positive outcome for patients who are underweight; however, excess weight can increase the risk of cardiovascular and metabolic conditions for patients who are of normal weight or overweight. The return-to-health phenomenon, which likely results from the reduction of HIV-associated inflammation and accelerated catabolism, is one of the possible mechanisms for ART-associated weight gain.[5]

Product Labeling[4]

Post marketing experience has led to an investigation of increased weight with BIC/FTC/TAF or TAF-containing products. Because these events are reported voluntarily

from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

TDF and Weight Loss

Weight decrease was an AE reported in >2% of individuals receiving FTC/TDF and was reported more frequently than in individuals receiving placebo among HIV-1–uninfected adults in PrEP trials.[12] Findings from two phase 3, randomized, double-blind studies suggested a mild weight-suppressive effect with the use of TDF as a component of FTC/TDF for HIV PrEP.[5-7] In a metabolic substudy of the iPrEx study, participants in the FTC/TDF arm gained less weight than those in the placebo arm. At Week 24, the median difference in net weight between the FTC/TDF and placebo arms was -0.8% (95% CI: -1.5% to -0.1%; *P*=0.02).[6]

Weight changes in individuals who did not have HIV and received TAF-containing regimens for HIV PrEP and HBV treatment were similar to those in the general population (+0.5 to 1 kg/year).[5,13,14] In the DISCOVER study, participants in the FTC/TAF arm had a median weight change of 1 kg at Week 48 and 1.7 kg at Week 96, whereas those in the FTC/TDF arm had a median weight change of 0 kg at Week 48 and 0.5 kg at Week 96.[15]

Clinical Data on BIC/FTC/TAF Use and Weight Changes in ARV-Naive Participants

Pooled Analysis: Weight Gain After Initiation of ART

Study design and demographics[5]

Pooled analyses were conducted with data from eight phase 3 studies to assess the association between BL demographics, HIV disease characteristics, and treatment-related contributors to weight gain in ARV-naive participants who initiated ART between 2003 and 2015 (Table 1). The association between weight changes and adverse metabolic effects was also analyzed. In all studies, participants were seen at BL and every 12 weeks for ≥96 weeks. BL weight and CD4 count values were higher in the more recent studies than in older studies.

Table 1. BL Demographics and Disease Characteristics of Participants Initiating ART (Sax et al)[5a]

Key Demographics and Characteristics		Pooled Population (N=5680)
Age, mean (SD), years		37 (10.7)
Male, n (%)		5018 (88.3)
Race, n (%)	White	3499 (61.6)
	Black	1471 (25.9)
	Asian	290 (5.1)
	Other	415 (7.3)
Weight, mean (SD), kg		78.9 (17.3)
BMI category,[b] n (%)	Underweight (BMI <18.5 kg/m^2)	136 (2.4)
	Normal (BMI ≥18.5 to <25 kg/m^2)	2829 (50)
	Overweight (BMI ≥25 to <30 kg/m^2)	1785 (31.4)
	Obese (BMI ≥30 kg/m^2)	924 (16.3)

Key Demographics and Characteristics		Pooled Population (N=5680)
HIV-1 VL	Mean (SD), log_{10} c/mL	4.65 (0.7)
	>100,000 c/mL, n (%)	1660 (29.2)
CD4	Mean (SD),[c] cells/mcL	401 (211.4)
	≥200 cells/mcL, n (%)	4808 (84.7)
HIV disease status, n (%)	Asymptomatic	4590 (80.8)
	Symptomatic	599 (10.5)
	AIDS	483 (8.5)
No use of IV drugs		5593 (98.5)

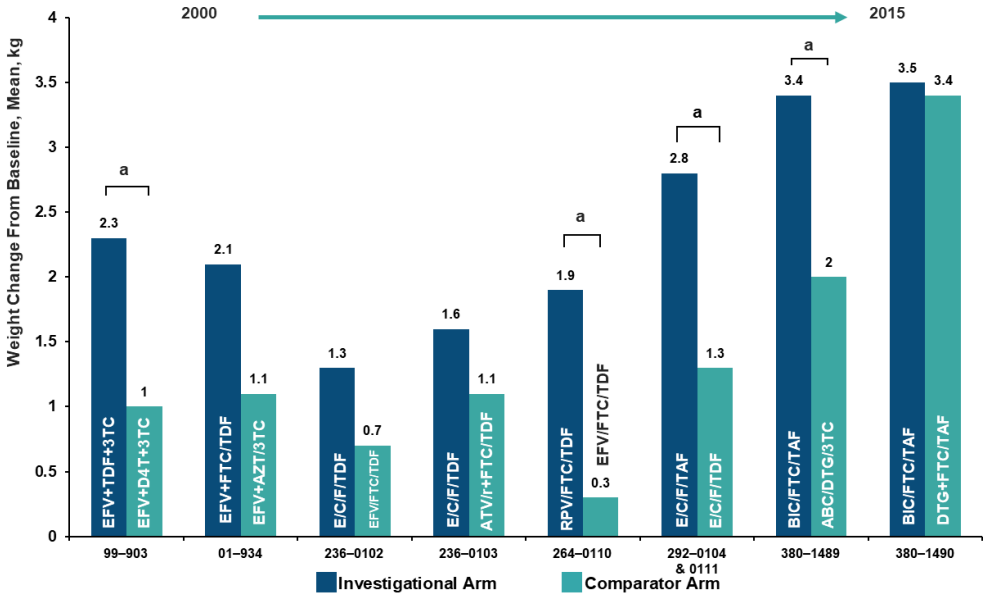
[a]ART from all eight studies included EFV + FTC/TDF vs EFV + AZT/3TC, E/C/F/TDF vs EFV/FTC/TDF, E/C/F/TDF vs ATV/r + FTC/TDF, FTC/RPV/TDF vs EFV/FTC/TDF, E/C/F/TAF vs E/C/FTC/TDF, BIC/FTC/TAF vs ABC/DTG/3TC, and BIC/FTC/TAF vs DTG + FTC/TAF.
[b]Calculated out of a total of 5674 participants with available data.
[c]Calculated out of a total of 5679 participants with available data.

Results

Weight change[5]

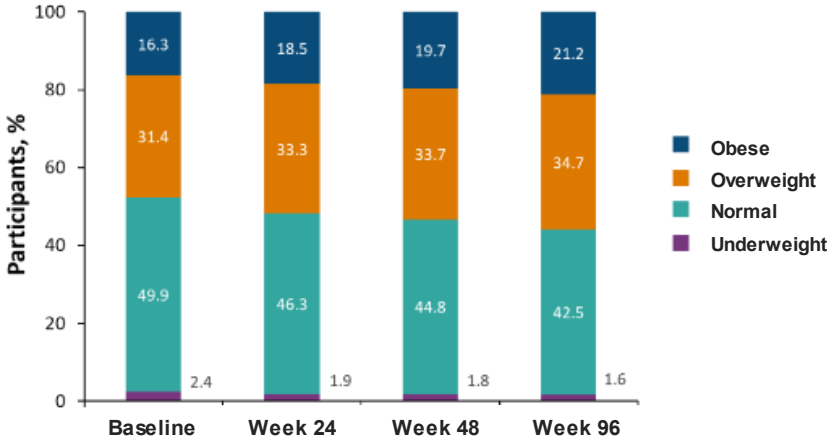
Median weight increases were observed in all study arms; however, the magnitude of weight gain was greater in the more recent studies than in the older studies (Figure 1). The investigational treatment arms were also associated with numerically higher weight gains than in the comparator arms. Weight gains were greatest during the first 48 weeks of treatment and then started to plateau from Weeks 72 to 144. At Week 96, the median (IQR) weight gain was 2 (-0.9 to 5.9) kg, and 17.3% of participants experienced weight increases of ≥10%. The proportion of participants in the overweight and obese BMI categories consistently increased through Week 96 (Figure 2). Weight gain was not universal across the studied population, as weight loss was reported in 30.2% of participants.

Figure 1. Mean Weight Change From BL to Week 48 (Sax et al)[5]



[a]*P*<0.05.

Figure 2. BMI Categories Through Week 96 (Sax et al)[5]



In multivariate models, BL CD4 count was the risk factor most strongly associated with weight gain. Participants with BL characteristics associated with advanced disease (CD4 counts <200 cells/mcL, HIV-1 VL >100,000 c/mL, and symptomatic HIV or AIDS) gained significantly more weight than their counterparts without these characteristics (Table 2). Other BL risk factors associated with weight gain included no IV drug use, Black race, female sex, age <50 years, and BMI ≥25 kg/m^2 (each, *P*<0.006).

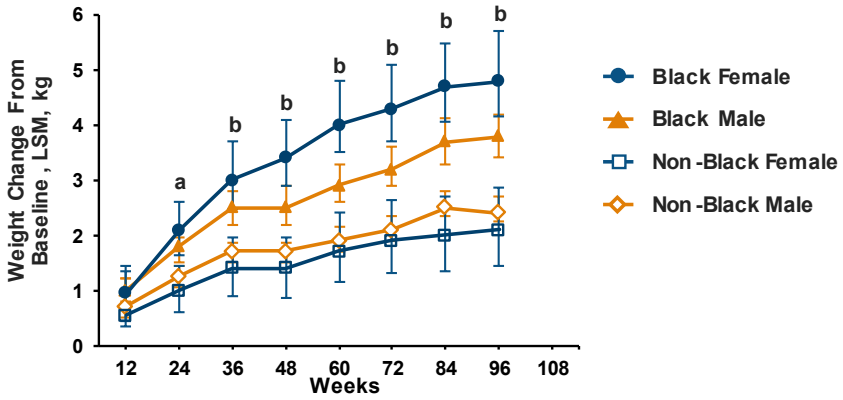
Table 2. Risk Factors Associated With ≥10% Weight Gain (Sax et al)[5]

Risk Factors		During ART	
		OR (95% CI)[a]	*P*-Value[a]
CD4 <200 vs ≥200 cells/mcL		4.36 (3.6–5.27)	<0.001
HIV VL >100,000 vs ≤100,000 c/mL		1.98 (1.65–2.37)	<0.001
BMI category	Normal vs overweight	1.54 (1.27–1.87)	<0.001
	Normal vs obese	1.66 (1.29–2.15)	<0.001
Female vs male sex		1.54 (1.21–1.96)	<0.001
Black vs non-Black race		1.32 (1.1–1.59)	0.003

[a]Values from logistic regression model.

In longitudinal models through Week 96, female participants gained more weight than male participants, and statistically significant differences were noted at Weeks 60, 72, and 96 (*P*<0.05 at each time point). A significantly greater increase in weight gain was also observed in Black participants than in non-Black participants at all time points through Week 96 (*P*<0.05). At Week 96, Black female participants gained 1.12 kg more than Black male participants did (95% CI: 0.25–1.99; *P*=0.011; Figure 3).

Figure 3. Weight Changes According to Sex and Race (Sax et al)[5]

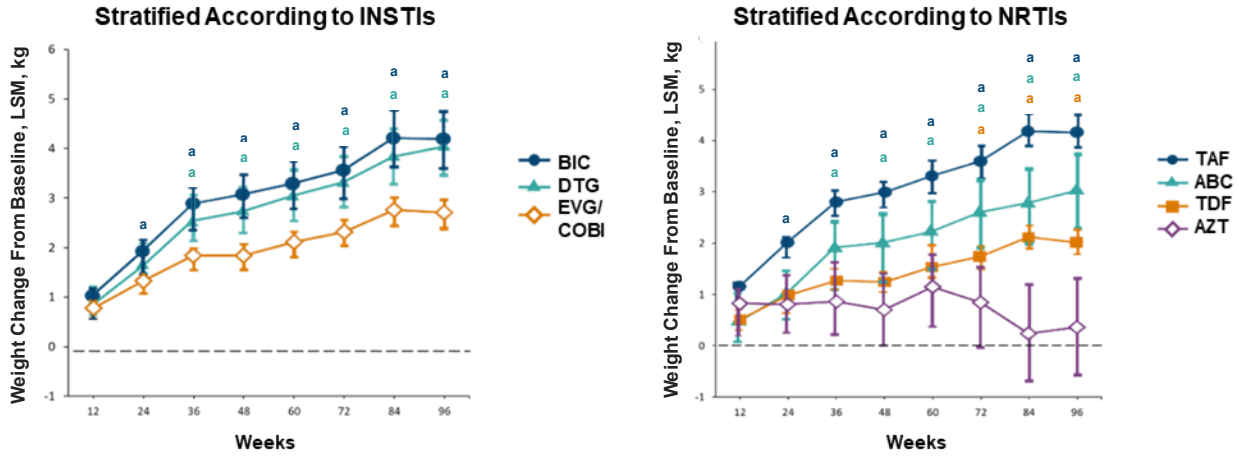


[a]*P*<0.05 for Black vs non-Black females only.
[b]*P*<0.05 for Black vs non-Black females and Black females vs Black males.
Note: Published peer-reviewed data were only available at Week 48.

Weight change and type of ART

When the effect of ART according to third agent was analyzed, it was noted that participants treated with INSTIs experienced greater weight gain than those treated with NNRTIs or PIs. Among those treated with INSTIs, significantly greater weight gain was observed at Week 96 in participants treated with BIC or DTG than in those treated with boosted EVG (LSM, +4.24 kg, +4.07 kg, and +2.72 kg, respectively; Figure 4). Among participants treated with NRTIs, the greatest increase in weight gain was observed in those treated with TAF (+4.25 kg), followed by ABC (+3.08 kg) and TDF (+2.07 kg).[5]

Figure 4. Weight Changes in ARV-Naive Participants From BL to Week 96 According to ART (Sax et al)[5]



[a]*P*≤0.05 (asterisks are color coded to match the respective comparator: EVG/c for INSTIs and AZT for NRTIs).

Effect of weight changes on metabolic outcomes

To determine the impact of weight gain on metabolic outcomes, differences in fasting glucose, lipid parameters, blood pressure, and investigator-reported AEs were evaluated. No significant difference in changes in fasting glucose from BL to Week 96 was observed in participants with ≥10% weight gain compared with those with <10% weight gain. A small but significant increase in HDL levels was observed in participants with <10% weight gain

compared with those with ≥10% weight gain. Small increases were seen in LDL and triglyceride levels for both groups; however, these small changes were not statistically significant.[16] The median ratio of total cholesterol to HDL at Week 96 was 3.7 for participants with ≥10% weight increase and 3.5 for participants with <10% weight increase (*P*=0.027).[5]

No significant differences in diabetes- or hyperglycemia-related AEs were reported between participants with ≥10% or <10% weight gain. No clinically significant changes were observed in blood pressure values that were available from three of the clinical trials. There was no clinically significant metabolic impact of weight gain observed in this pooled analysis, as measured by fasting glucose, lipids, blood pressure, or investigator-reported AEs.[5]

Studies 1489 and 1490 in ARV-Naive Participants

Study design and demographics

Studies 1489 and 1490 are phase 3, randomized, double-blind, active-controlled, non-inferiority clinical trials that compared BIC/FTC/TAF to DTG/ABC/3TC and DTG + FTC/TAF, respectively, in ARV-naive PWH.[17,18]

BL characteristics were similar between treatment arms in both studies (Table 3).

Table 3. Studies 1489 and 1490: BL Demographics and Disease Characteristics[17-19]

Key Demographics and Characteristics	Study 1489		Study 1490	
	BIC/FTC/TAF (n=314)	DTG/ABC/3TC (n=315)	BIC/FTC/TAF (n=320)	DTG + FTC/TAF (n=325)
Age, median (range), years	31 (18–71)	32 (18–68)	33 (18–71)	34 (18–77)
Male, n (%)	285 (91)	282 (90)	280 (88)	288 (89)
Black or African descent, n (%)	114 (36)	112 (36)	97 (30)	100 (31)
HIV-1 VL, median (IQR), log_{10} c/mL	4.42 (4.03–4.87)	4.51 (4.04–4.87)	4.43 (3.95–4.9)	4.45 (4.03–4.84)
HIV-1 VL >100,000 c/mL, n (%)	53 (17)	50 (16)	66 (21)	54 (17)
CD4 count, median (IQR), cells/mcL	443 (299–590)	450 (324–608)	440 (289–591)	441 (297–597)
CD4 count <200 cells/mcL, n (%)	36 (11)	32 (10)	44 (14)	34 (10)

Weight change through Week 144

Median changes in weight from BL to Week 144 were similar in all arms (Table 4).[19]

Table 4. Studies 1489 and1490: Weight Changes From BL to Week 144[19,20]

Parameter	Study 1489			Study 1490		
	BIC/FTC/TAF (n=314)	DTG/ABC/3TC (n=315)	*P*-Value	BIC/FTC/TAF (n=320)	DTG + FTC/TAF (n=325)	*P*-Value
Weight change from BL, median, kg	+4.1	+3.5	0.196	+4.4	+5	0.649
≥5% weight gain, %	52	48	–	53	55	–
≥10% weight gain, %	29	25	–	30	32	–
Weight loss or no change from BL, %	24	26	–	21	22	–

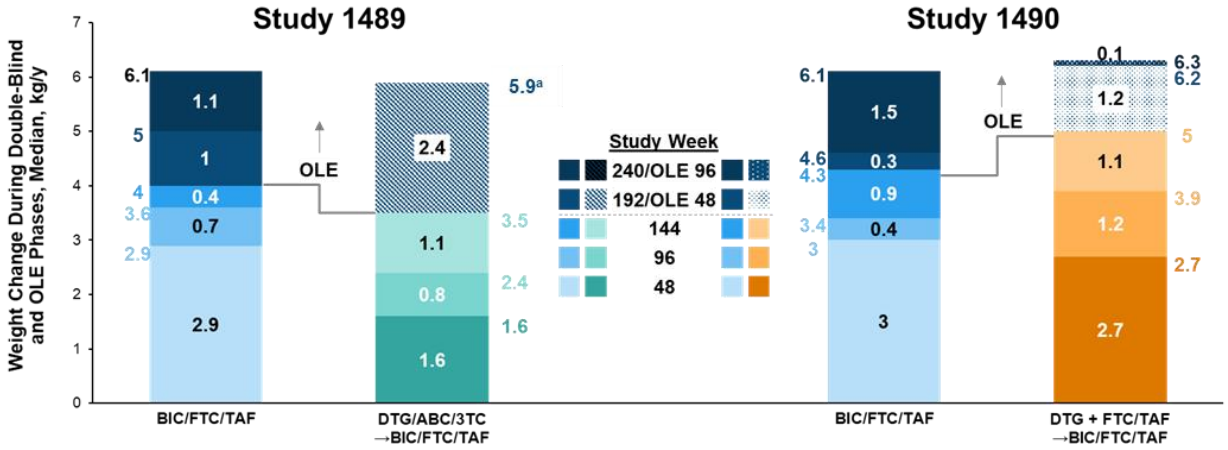
OLE through Week 240

At the Week 144 secondary endpoint, all participants were eligible to receive BIC/FTC/TAF in the OLE phase. In Study 1489, 254 participants who were receiving DTG/ABC/3TC switched to BIC/FTC/TAF in the OLE phase, and 221 completed Week 240 assessments. In Study 1490, 265 participants who were receiving DTG + FTC/TAF switched to BIC/FTC/TAF in the OLE phase, and 236 completed Week 240 assessments. A total of 506 participants who were initially randomly assigned to receive BIC/FTC/TAF in both studies continued to receive BIC/FTC/TAF during the OLE phase.[21]

In a pooled analysis of the 506 participants who were initially randomly assigned to receive BIC/FTC/TAF, a median cumulative weight gain of 6.1 kg was observed through Week 240; approximately 3 kg weight gain occurred in the first 48 weeks, with a weight gain of 1 kg/year thereafter. Median weight changes through Week 240 for each arm are shown in Figure 5.[5,22-27] One participant discontinued treatment due to a treatment-related AE of morbid obesity during Week 233.[27]

During the OLE, participants who switched to BIC/FTC/TAF from DTG/ABC/3TC had greater median weight gain between Weeks 144 and 240 than those who switched from DTG + FTC/TAF (2.4 vs 1.3 kg; *P*=0.01); however, cumulative weight changes were numerically similar across all treatment groups (Figure 5). One participant who was randomly assigned to DTG/ABC/3TC experienced treatment-related weight gain on Day 29 of the blinded phase, later switched to BIC/FTC/TAF, and discontinued at Week 228 in the OLE phase.[21]

Figure 5. Studies 1489 and1490: Changes in Weight Throughout the Study According to the DTG-Based Regimen Received During the Double-Blind Phase[21]



[a]This value represents the median cumulative change at Week 192; no changes in weight were observed from Week 192 to 240.

Note: The numbers within the bars represent the yearly weight changes (calculated as the median change from BL at the later time point minus the median change at the previous time point). The numbers to the left and right of each bar indicate the median cumulative weight changes at each time point.

Pooled subgroup analysis according to BL VL and CD4 counts through Week 240

Demographics and disposition by BL VL and CD4 counts[28]

A pooled subgroup analysis of Studies 1489 and 1490 was conducted according to BL VL and CD4 count in participants initially assigned to BIC/FTC/TAF.

At Week 48, BL VL ≥100,000 c/mL and CD4 <200 cells/mcL were associated with significantly greater median changes in weight from BL than were BL VL <100,000 c/mL and CD4 ≥200 cells/mcL (Table 5). At Week 240, the median weight change from BL was greater in participants who had ≥100,000 c/mL at BL than in those with a VL <100,000 c/mL (+9.9 kg vs +5.6 kg; *P*<0.001).

Table 5. Weight Changes in BIC/FTC/TAF-Treated Participants From BL at Week 240[a] According to BL Stratification Subgroups[28]

Change in Weight, Median, kg	BL VL <100,000 c/mL (n=353)	BL VL ≥100,000 c/mL (n=78)	BL CD4 ≥200 cells/mcL (n=381)	BL CD4 <200 cells/mcL (n=50)	BL VL ≥100,000 c/mL & CD4 <200 cells/mcL (n=21)
BL to Week 48	+3	+4.1	+2.7	+8.3	+9.7
	P<0.05		*P*<0.001		*P*<0.001[b]
Weeks 48 to 96	+0.3	+3.1	+0.6	+2.2	+1.2
Weeks 96 to 144	+0.9	+0.1	+0.8	-0.2	0
Weeks 144 to 192	+0.4	+1.9	+0.4	+2.4	+3.2
Weeks 192 to 240	+1	+0.7	+1.3	-0.6	-0.5

[a]Ns refer to participants who had weight data available at BL and at Week 240.
[b]*P*-value vs BL VL <100,000 c/mL.

The median actual weights at Week 240 were comparable across subgroups, despite BL values that were significantly lower in the VL ≥100,000 c/mL subgroup than in the VL <100,000 c/mL subgroup (72.8 kg vs 77.8 kg; *P*<0.01) and in the CD4 <200 cells/mcL subgroup than in the CD4 ≥200 cells/mcL subgroup (71.2 kg vs 77 kg; *P*<0.05).

Clinical Data on BIC/FTC/TAF Use and Weight Changes in TE Participants

Weight Change Following ARV Switch in Virologically Suppressed Participants[8]

Study design and demographics

Pooled analyses were conducted with data from 12 randomized, active-controlled studies to identify the factors associated with weight change following ART switch. Virologically suppressed participants (HIV-1 VL <50 c/mL for ≥3 months) were randomly assigned to switch their ART (n=4166) or SBR (n=3150). Body weight was measured at least every 12 weeks, and participants were followed for ≥48 weeks following ART switch. Overall, 1949 participants switched both their NRTIs and third agents, 1326 switched their NRTIs only, and 891 switched their third agent only (Table 6).

Table 6. Participants According to NRTI or Third Agent Switch or SBR (Erlandson et al)[8]

ARV	Participants, n
NRTI Switch	
FTC/TDF→FTC/TAF	2670
ABC/3TC→FTC/TAF	605
Third Agent Switch	
PI→EVG	696
DTG→BIC	566
EFV→EVG	515
EFV→RPV	437
PI→BIC	301
EVG→BIC	223
NVP→EVG	57
RPV→EVG	45

ARV	Participants, n
NRTI SBR	
FTC/TDF	2804
FTC/TAF	637
ABC/3TC	600
Third Agent SBR	
PI	1110
EFV	787
RPV	704
EVG	692
DTG	641
NVP	331
RAL	211

Abbreviation: NVP=nevirapine.

BL demographics were similar across 10 of the 12 studies: mean age was 40 to 50 years; 10% to 20% were female; 10% to 30% were of Black race; 5% to 25% were of Hispanic/Latinx ethnicity; and 15% to 30% had BMI values ≥30 (obese). Of the other two studies, one study (GS-US-380-1961) included only female participants and a larger proportion of Black participants, and one study (GS-US-292-1826) enrolled participants with a median age of 65 years, of whom <3% were of Black race.

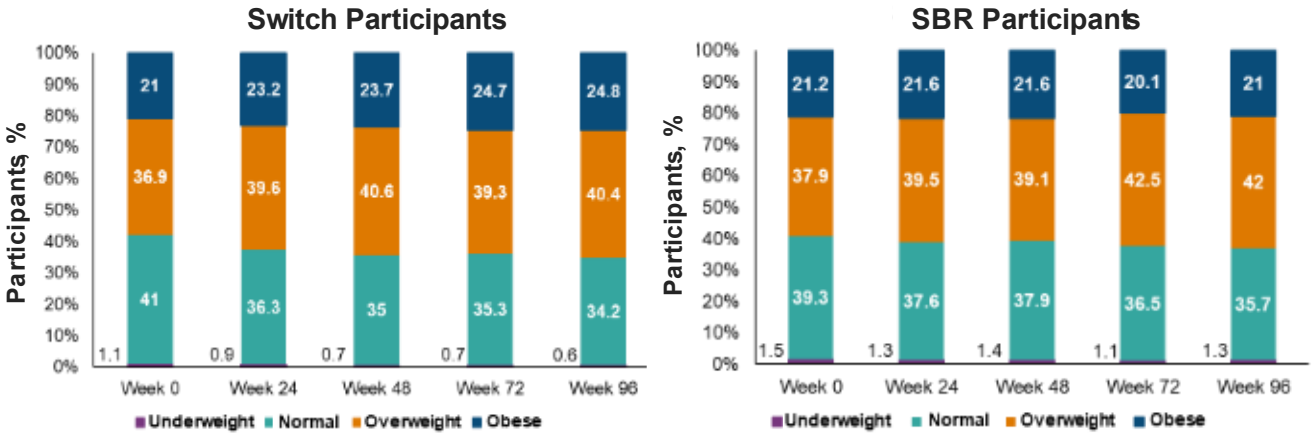
Results

Weight change

Weight increases were observed in both groups; however, the median increases from BL were significantly greater ($P<0.05$) in participants who switched their ART than in SBR participants at all assessed time points, including at Weeks 48 (1.6 kg vs 0.4 kg, respectively) and 96 (2 kg vs 0.5 kg; each, $P<0.0001$). From BL to Week 48, 6.4% of switch participants and 2.2% of SBR participants experienced ≥10% weight gain. There were outliers with more extreme weight gain in 2.6% of switch participants (n=102) and in 1.7% of SBR participants (n=49). Weight gain reached a plateau between Weeks 24 and 36 for most participants in the majority of the switch and SBR categories. From BL to Week 96, the proportion of participants in the obese BMI category increased from 21% to 24.8% among switch participants and remained stable (21%) in SBR participants (Figure 6).

Weight gain was not universal across the population, as weight loss was reported by 28% of switch participants and by 43% of SBR participants by Week 96.

Figure 6. BMI Categories From BL Through Week 96 for Switch and SBR Participants (Erlandson et al)[8]



Younger age and lower BMI at BL were risk factors for experiencing ≥10% weight gain (Table 7). Race, ethnicity, and sex were not significant predictors of ≥10% weight gain in this pooled analysis.

Table 7. Risk Factors Associated With a 10% Weight Gain From BL to Week 48 (Erlandson et al)[8,29]

Risk Factors		During ART	
		OR (95% CI)	*P*-Value
BMI category	Underweight/normal vs obese	2.42 (1.8–3.26)	<0.0001
	Underweight/normal vs overweight	1.67 (1.34–2.08)	<0.0001
Age ≤35 years vs >35 years		1.5 (1.2–1.87)	0.0003

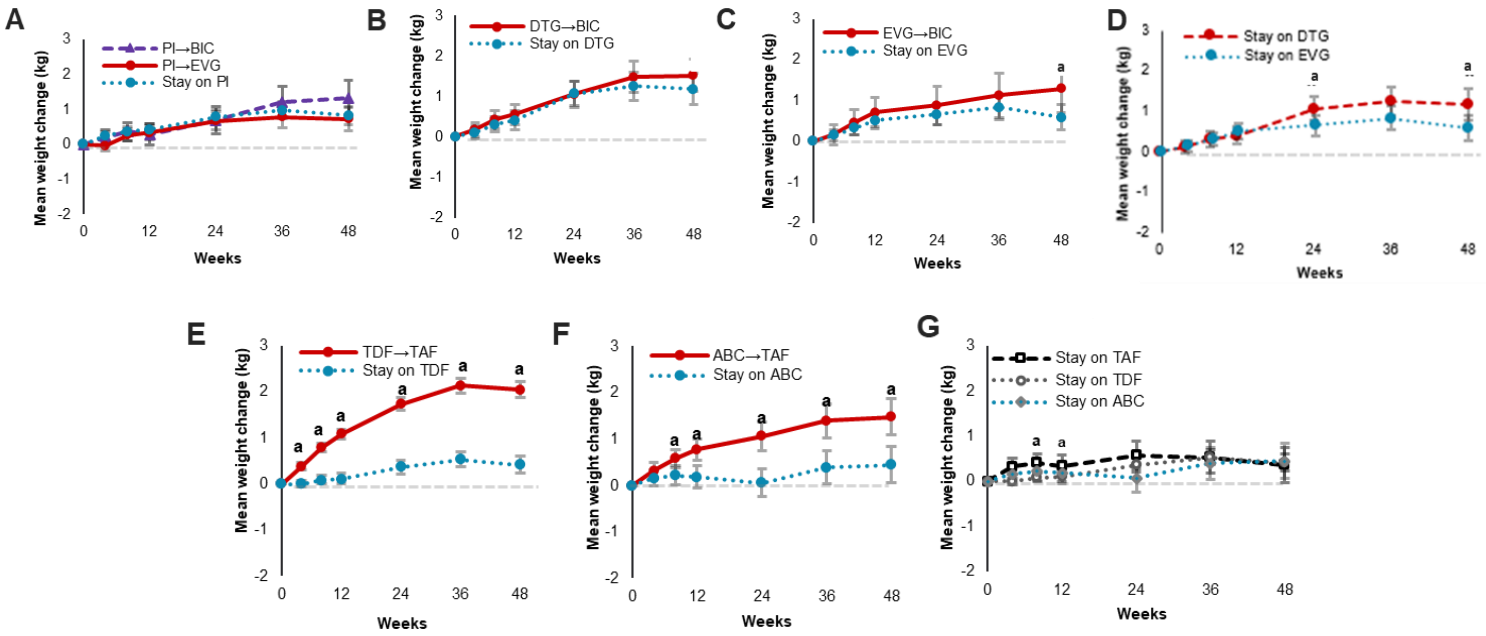
Note: *P*-values are derived from a logistic regression model that included BL BMI and age as risk factors.

In analyses of the associations of sex and race on weight gain at Week 48, female participants had a 0.3 kg greater weight gain than male participants (*P*=0.0046), Black male participants gained 0.3 kg more than non-Black male participants (*P*=0.41), and non-Black female participants had a 0.5 kg greater weight gain than non-Black male participants (*P*=0.013). There was no significant difference in weight gain between Black vs non-Black participants, Black male vs Black female participants, and female participants of all races.

Weight change and type of ART

Consistent with the suggested mild weight-suppressive effect with the use of TDF as a component of FTC/TDF for HIV PrEP,[5-7] switching from TDF to TAF was associated with ≥10% weight gain compared to staying on FTC/TDF (OR, 2.58; 95% CI: 1.94–3.43; *P*<0.0001); switching from ABC to TAF was not.

Figure 7. Weight Changes From BL to Week 48 by ART Switch (Erlandson)[8]



[a]*P*<0.05 compared to weight change in SBR participants.

- No significant difference in weight change was reported between groups that switched from a boosted PI to EVG/c or BIC (Figure 7A).
- The change in weight reported when switching from DTG to BIC was not significantly different from remaining on DTG (Figure 7B).
- Switching from EVG/c to BIC was associated with greater weight gain (0.7 kg) at Week 48 compared with remaining on EVG/c (*P*=0.034; Figure 7C).
- Remaining on DTG was associated with greater weight gain (0.6 kg) at Week 48 than staying on EVG/c (P=0.02; Figure 7D).
- Among participants who switched NRTIs, switching from TDF (+1.6 kg) or ABC to TAF resulted in significant weight gain (*P*<0.001; Figure 7E–F).
- Participants who stayed on TDF or ABC experienced similar weight changes compared to those who stayed on TAF (Figure 7G).

Effect of weight changes on metabolic outcomes

Among participants who experienced ≥10% weight gain, changes in lipid panel values and systolic blood pressure were similar between switch and SBR participants at Week 48. Small reductions in HDL were observed in participants with ≥10% weight gain; other metabolic parameters were mostly stable. Treatment-emergent AEs associated with hyperglycemia or diabetes were not significantly different between participants who experienced ≥10% and <10% weight gain.

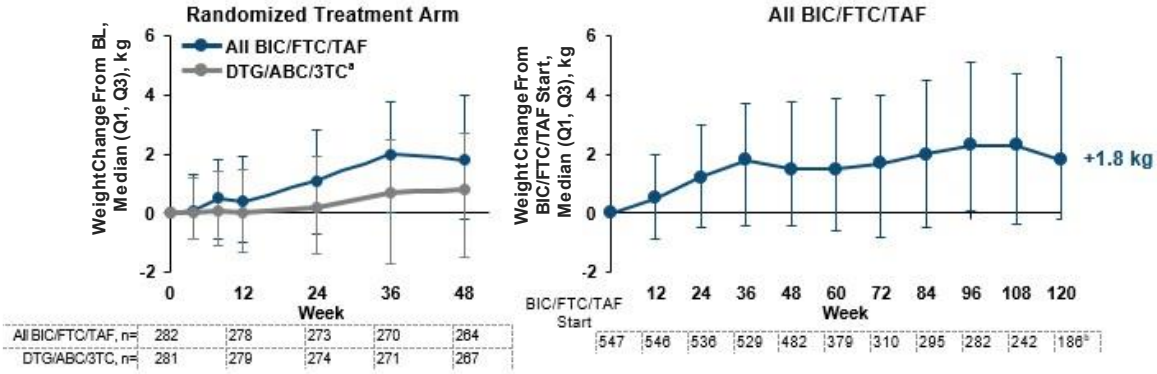
Study 1844 in Treatment-Experienced Participants

A phase 3, randomized, double-blind study evaluated the safety and efficacy of switching to BIC/FTC/TAF (n=282) vs staying on a BL regimen of DTG/ABC/3TC (n=281) in virologically suppressed PWH. After the Week 48 primary endpoint, participants were evaluated through Week 168 in an OLE phase. The all-BIC/FTC/TAF arm (N=547) consisted of participants who received ≥1 dose of BIC/FTC/TAF, including those who received BIC/FTC/TAF in the

OLE phase.[30] Most participants were White and male, and the median age was 47 years.[30,31]

The median weight change from BL to Week 120 was +1.8 kg among all BIC/FTC/TAF participants and was generally stable from Weeks 48 to 120 (Figure 8).[30]

Figure 8. Study 1844: Weight Changes From BL to Week 48 and Week 120[30]



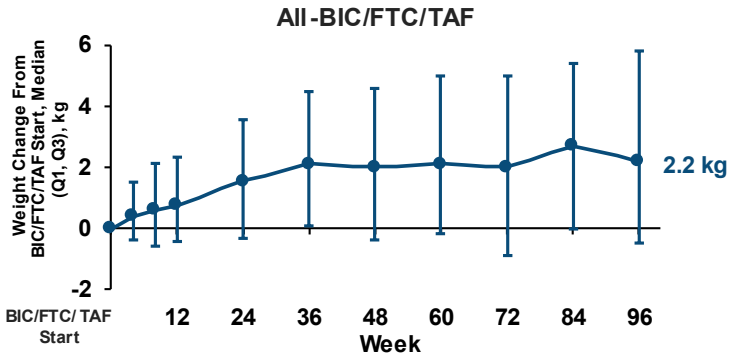
[a]Shown for reference.
[b]There were 12 participants with data through Week 168, and their median change in weight was +2.1 kg.

Study 1878

A phase 3, prospective, randomized, open-label clinical study compared switching to BIC/FTC/TAF 50/200/25 mg (n=290) vs staying on a BL regimen of boosted DRV or ATV + 2 NRTIs (n=287) in virologically suppressed PWH.[32] The long-term efficacy and safety of BIC/FTC/TAF were evaluated in an OLE phase. Of the 533 participants who completed the 48-week randomized phase, 516 entered the OLE phase. The all-BIC/FTC/TAF arm (N=534) consisted of participants who received ≥1 dose of BIC/FTC/TAF, including those who received BIC/FTC/TAF in the OLE phase.[33] Most participants were White, male, and on a BL regimen containing FTC/TDF, and the median age was 48 years.[33,34]

The median weight change from BL to Week 96 was +2.2 kg among the all-BIC/FTC/TAF participants and was generally stable from Weeks 48 to 96 (Figure 9).[33]

Figure 9. Study 1878: Median Weight Change From BL to Week 96[33]

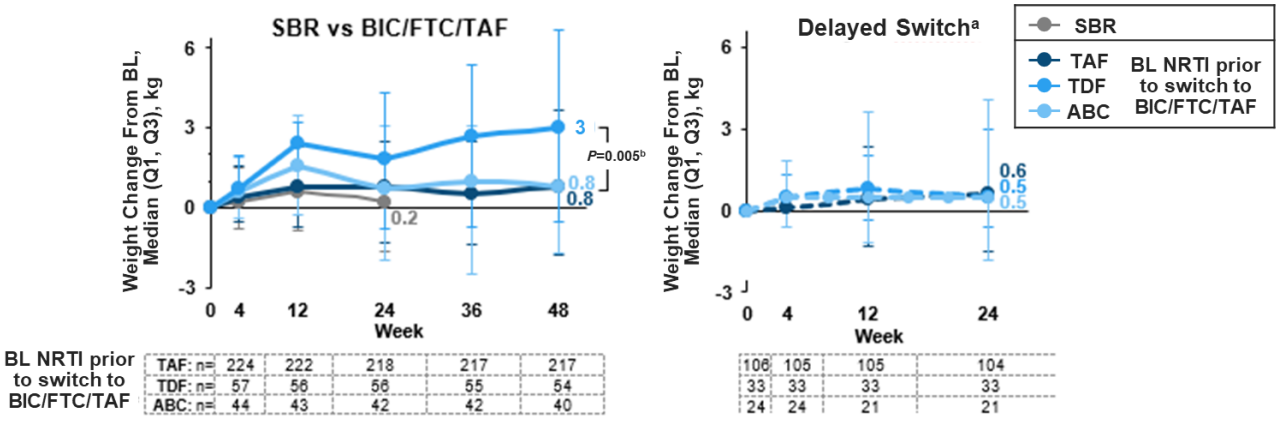


BRAAVE 2020

A phase 3, randomized, open-label, active-controlled study that enrolled participants from 82 sites evaluated the efficacy and safety of switching to BIC/FTC/TAF or staying on a BL regimen of 2 NRTIs plus a third agent with a delayed switch to BIC/FTC/TAF at Week 24 in virologically suppressed PWH who self-identified as African American; Black; or mixed race, including Black. At BL, similar proportions of participants in both arms were on an NRTI backbone of FTC/TAF (BIC/FTC/TAF, 68%; SBR, 65%) and on a BL third agent of EVG/c (BIC/FTC/TAF, 38%; SBR, 35%) or DTG (BIC/FTC/TAF, 20%; SBR, 24%).[35] Most participants were male, and the median age was 49 years. The median body weight was 88 kg for participants in the BIC/FTC/TAF arm and 89 kg for participants in the SBR arm.[35]

The median weight change from BL to Week 24 was similar between participants who switched to BIC/FTC/TAF (+0.9 kg) and those who continued their BL regimen (+0.2 kg; *P*=0.09).[31] In participants who switched to BIC/FTC/TAF, the median weight change from BL to Week 48 was +1.3 kg in participants assigned female at birth and +0.8 kg for participants assigned male at birth. Through Week 48, greater increases in body weight were observed in participants who were initially randomly assigned to switch to BIC/FTC/TAF from a BL regimen containing TDF than in those with BL regimens containing TAF or ABC (Figure 10).[35,36]

Figure 10. BRAAVE 2020: Weight Changes From BL to Week 48 by BL NRTIs[36]



[a]BL for delayed switch: time of first BIC/FTC/TAF dose.
[b]From two-sided Wilcoxon rank-sum test comparing BL regimens containing TAF vs TDF.

Pooled Analyses of Studies on BIC/FTC/TAF Use and Weight Changes in Both ARV-Naive and TE Participants

Pooled Analysis of Data on PWH Aged ≥50 Years[9]

A pooled analysis was conducted using data from six phase 3 trials of ARV-naive and TE participants to assess the long-term efficacy and safety of BIC/FTC/TAF in PWH aged ≥50 years. In the included studies, changes in body weight were assessed from BL to Week 240 among ARV-naive participants and from BL to Week 48 in TE participants.

Table 8. BL Demographics and Disease Characteristics in Participants Aged <50 and ≥50 Years (Kityo et al)[9]

Key Demographics and Characteristics		ARV-Naive		Virologically Suppressed	
		<50 Years (n=538)	≥50 Years (n=96)	<50 Years (n=640)	≥50 Years (n=450)
Age, median (IQR), years		30 (25–37)	55 (52–60)	39 (33–45)	56 (52–60)
Male sex at birth, n (%)		484 (90)	81 (84.4)	393 (61.4)	342 (76)
Race, n (%)	White	304 (56.5)	59 (61.5)	369 (57.7)	291 (64.7)
	Black	181 (33.7)	30 (31.3)	166 (25.9)	131 (29.1)
	Other[a]	36 (6.7)[b]	4 (4.2)[b]	38 (5.9)[b]	17 (3.8)[b]
Hispanic or Latinx ethnicity, n (%)		144 (26.9)[b]	11 (11.5)	131 (20.5)[c]	72 (16)[b]
HIV-1 VL, median (IQR), log_{10} c/mL		4.4 (4–4.9)	4.5 (4–4.9)	N/A	N/A
CD4 count, median (IQR), cells/mcL		442 (299–590)	436 (235–601)	691 (523–887)	640 (486–852)

[a]Included American Indian or Alaska Native, Asian, Native Hawaiian or Pacific Islander, and other.
[b]Datum was missing for 1 participant.
[c]Data were missing for 2 participants.

There was no significant difference in weight change between age groups in either cohort from BL to Week 48 or Week 240 (Table 9).

Table 9. Median Weight Changes From BL to End of Study in Participants Aged <50 and ≥50 Years (Kityo et al)[9]

Weight, Median (IQR), kg	ARV-Naive		*P*-Value	Virologically Suppressed		*P*-Value
	<50 Years	≥50 Years		<50 Years	≥50 Years	
BL	75.9 (67.3–87.1); n=538	79.3 (70.7–89.9); n=96	0.0285	76 (66–87.1) n=640	81.1 (71.9–92.5); n=450	<0.0001
Change at end of study[a]	+6.4 (2.4–12) n=363	+4.8 (0.7–10.2) n=68	0.087	+1.8 (-0.4 to 4) n=609	+1.5 (-0.8 to 3.8) n=429	0.2857

[a]End of study was Week 240 in studies of ARV-naive participants and Week 48 in studies of virologically suppressed, TE participants.

Pooled Analysis of Participants Assigned Female at Birth[10]

The efficacy and safety of BIC/FTC/TAF in participants assigned female at birth (N=679) were assessed in a pooled analysis of five phase 2 or 3 clinical studies through 48 weeks. Studies 1489 and 1490 were conducted in ARV-naive populations, while Studies 1961, 1474, and 4449 were conducted in virologically suppressed TE populations. In Studies 1489 and 1490, participants received either BIC/FTC/TAF or an active comparator regimen (DTG/ABC/3TC or DTG + FTC/TAF). Participants from Study 1961 either continued treatment with their BL regimen (E/C/F/TAF, E/C/F/TDF, or ATV/r + FTC/TDF) or switched to BIC/FTC/TAF. In the single-arm Studies 1474 and 4449, participants switched to BIC/FTC/TAF from other ARVs. Efficacy and safety assessments included virologic suppression (HIV-1 VL <50 c/mL), treatment-emergent resistance, AEs, and laboratory parameters.

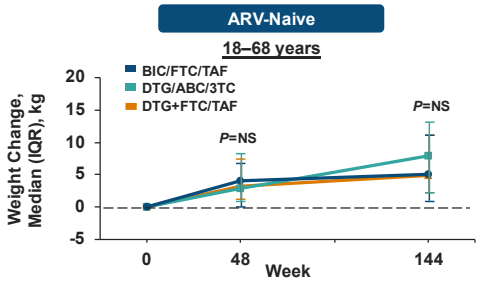
Table 10. BL Demographics and Disease Characteristics of Female Participants Who Received BIC/FTC/TAF by Age (Orkin et al)[10]

Key Demographics and Characteristics		ARV-Naive		Virologically Suppressed			
		18–49 Years (n=54)	50–68 Years (n=15)	6–17 Years (n=59)	18–49 Years (n=191)	50–64 Years (n=43)	65–75 Years (n=11)
Race, %	Black	48.1	46.7	76.3	37.7	44.2	9.1
	White	35.2	40	3.4	29.3	23.3	90.9
	Asian	0	0	16.9	22.5	11.6	0
Hispanic/Latina ethnicity, %		25.9	20	3.4	12	30.2	27.3
HIV-1 VL, median, log_{10} c/mL		4.3 (3.9–4.6)	4.3 (3.9–4.6)	All <50			
CD4, median, cells/mcL		411 (276–535)	522 (285–713)	848 (665–1038)	666 (531–867)	682 (554–836)	726 (511–829)
eGFR, median, mL/min[a]		129 (104.8–163.1)	85.5 (75.4–109)	147 (135–173)	101.4 (85.2–117.7)	86.6 (75.6–111.6)	69.6 (61.2–82.2)
Weight, median (IQR), kg		73.3 (59.4–89.2)	73.6 (66.9–79.4)	40.5 (29.8–49.2)	65.5 (55.2–76.5)	76.2 (63–92.1)	61.8 (59–71)

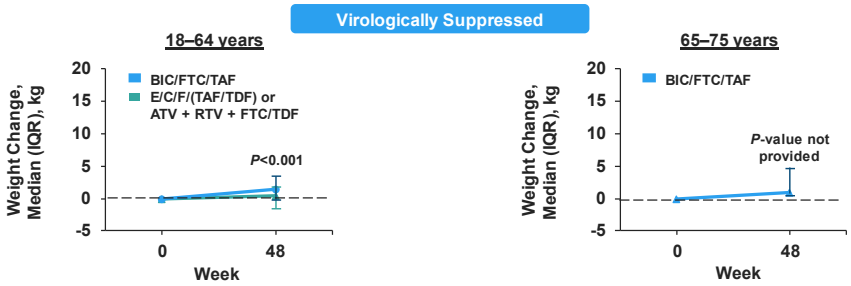
[a]eGFR was calculated with the Cockcroft-Gault formula for adults and the Schwartz formula for pediatric participants (mL/min/1.72 m^2).

In virologically suppressed participants aged 18 to 64 years, significantly greater gains in weight were observed from BL to Week 48 in participants who switched to BIC/FTC/TAF than in comparator regimen-treated participants (P<0.001; Figure 11). In virologically suppressed participants aged 65 to 75 years, median weight gains of 1 kg from BL to Week 48 were observed in participants who switched to BIC/FTC/TAF. As shown in Figure 11, among ARV-naive participants aged 18 to 68 years, weight gains were observed from BL to Week 48 and from Weeks 48 to 144 in all treatment groups. No significant differences in weight change from BL to Weeks 48 and 144 were observed between the BIC/FTC/TAF and comparator arms. In adult participants, weight gain/loss was an uncommon AE and occurred in 1.2% of BIC/FTC/TAF-treated participants (4/314) and <1% of comparator regimen-treated participants (2/306).

Figure 11. Weight Changes From BL Through Weeks 48 and 144 According to ARV and Virologic Status and Participant Age (Orkin et al)[10]



ARV-Naive Participants Aged 18–68 Years		BIC/FTC/TAF	DTG/ABC/3TC	DTG + FTC/TAF
BL	n	63	30	32
	Weight, median (IQR), kg	67 (56–79)	84 (71–97)	70 (62–90)
Week 48	Weight change, median (IQR), kg	4 (0–6.8)	2.9 (0.9–8.5)	3.2 (1.1–7.3)
Week 144	Weight change, median (IQR), kg	5 (1–11.1)	7.9 (1.3–12.7)	4.9 (1.6–11)



TE Participants Aged 18–68 Years		BIC/FTC/TAF	Comparators
BL	n	229	230
	Weight, median (IQR), kg	67 (56–79)	68 (58–79)
Week 48	Weight change, median (IQR), kg	1.5 (-0.5 to 3.4)	0.4 (-1.5 to 2)

TE Participants Aged 65–75 Years		BIC/FTC/TAF
BL	n	11
	Weight, median (IQR), kg	62 (59–71)
Week 48	Weight change, median (IQR), kg	1 (0–3)

Real-World Data on BIC/FTC/TAF Use and Weight Changes

BICSTaR Study

BICSTaR is a 2-year, multicountry (pan-Europe, Canada, and Israel), prospective, observational cohort study in PWH to evaluate the effectiveness, safety, and tolerability of BIC/FTC/TAF in clinical practice.[37,38]

12-month pooled analysis

Month 12 data were pooled from 1135 participants who started BIC/FTC/TAF between June 2018 and September 2020 across France, Germany, Ireland, Italy, the Netherlands, Spain, the UK, Canada, and Israel (Table 11). The analysis included ARV-naive (n=180) and TE (n=955) participants who had BL and Month 12 data available and participants who had discontinued the study at the time of data cutoff (February 22, 2021).[38] The most frequent reason for initiating BIC/FTC/TAF in ARV-naive participants was early treatment according to guidelines (77%), and a majority (59%) of TE participants switched to BIC/FTC/TAF to simplify their treatment regimen.[37,38]

Table 11. BICSTaR: BL Demographics and Disease Characteristics of Participants Treated With BIC/FTC/TAF for 12 Months[37,38]

Key Demographics and Characteristics		ARV-Naive (n=180)	TE (n=955)
Male, n (%)		159 (88)	791 (83)
Age	Median (Q1, Q3), years	38 (30, 48)	49 (39, 56)
	≥50 years, n (%)	42 (23)	454 (48)
Weight, median (Q1, Q3), kg		70 (63, 81)	76 (67, 87)
White, n (%)		139 (77)	741 (78)
HIV-1 VL	>100,000 c/mL, n (%)	62 (35)	6 (1)
	<50 c/mL, %	1	92
CD4 count, median (Q1, Q3), cells/mcL		400 (184, 553)	652 (424, 850)
Prior ART regimens, median (Q1, Q3), n		–	2 (1, 4)[c]
Prior ART regimen, %	INSTI/NNRTI/PI	–	65/20/16
	TAF/TDF/ABC-based	–	46/36/13
Any comorbidity, n (%)		85 (47)[d]	691 (72)

[a]n=177. [b]n=849. [c]n=945. [d]n=178.

The most common (3%) DRAE was weight increased, which led to BIC/FTC/TAF discontinuation in 2% of participants. There were statistically significant median increases in weight and BMI from BL to Month 12 in participants with available data at both time points; more ARV-naive participants than TE participants experienced categorical weight changes (>5%, >10%, and >5 kg) from BL to Month 12 (Table 12).[37,38]

Table 12. BICSTaR: Categorical Weight Changes and Median Change in Weight and BMI at Month 12[37,38]

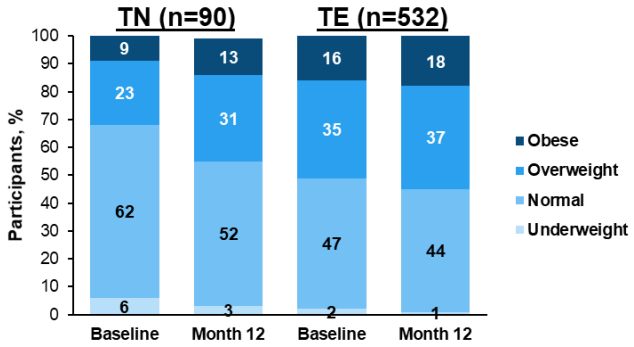
Parameter		ARV-Naive (n=90)			TE (n=532)		
Change in weight from BL, n (%)	>5%	44 (49)			117 (22)		
	>10%	25 (28)			31 (6)		
	>5 kg	33 (37)			71 (13)		
Parameter		**BL**	**Month 12**	**Median Change[a,b]**	**BL**	**Month 12**	**Median Change[a,b]**
Weight, median (Q1, Q3), kg		70 (62.5, 80.4)	75.9 (68, 84)	+3.4; *P*<0.001	75.9 (67, 87)	77 (68, 87.8)	+1; *P*<0.001
BMI, median (Q1, Q3), kg/m^2		22.4 (20.4, 25.7)	24.5 (21.9, 28)	+1.1; *P*<0.001	25.1 (22.5, 28.1)	25.5 (22.9, 28.5)	+0.3; *P*<0.001

[a]Individual participant changes from BL to Month 12 were calculated.
[b]The sign test was used for the absolute change from BL to Month 12 within ARV-naive or TE groups to calculate the *P*-values.
Note: Table included participants with data at BL and Month 12.

A multivariate analysis assessed the association of weight gain with the following variables: sex, age, race, ongoing metabolic disorders at BL, and HIV-1 VL (≤100,000 vs >100,000 c/mL) in 86 ARV-naive participants and found that Black race was the only variable associated with a relative weight increase of >5% from BL to Month 12 (OR, 6.58; 95% CI: 1.31–33.09; *P*=0.022); however, only 13 participants identified as Black, so caution should be used when interpreting these data. In a multivariate analysis that assessed the association of the same variables in addition to ongoing cardiovascular disorder at BL, BL BMI, third agent ARTs, and HIV-1 VL (≤50 c/mL vs >50 c/mL) in 506 TE participants, the following factors were significantly associated with a >5% weight gain at Month 12: female sex (OR, 2.13; 95% CI: 1.2–3.8; *P*=0.01); NNRTIs (vs INSTIs) taken as a third agent prior to

BIC/FTC/TAF initiation (OR, 2.16; 95% CI: 1.26–3.71; *P*=0.005). Increasing age was associated with lower odds of >5% weight gain (OR, 0.97; 95% CI: 0.96–0.99; *P*=0.009). There were small numerical increases from BL to Month 12 in the percentages of participants categorized as obese and overweight (Figure 12).[37,38]

Figure 12. BICSTaR: BMI Categories at BL and Month 12[38]



Note: Only participants with BMI data at BL and Month 12 were included.

Pooled analysis of 24-month data

The effectiveness and safety of BIC/FTC/TAF in 135 ARV-naive and 703 TE PWH were evaluated in a 24-month pooled analysis of data from clinical sites in France, Germany, Ireland, Italy, Spain, the Netherlands, the UK, Canada, and Israel (data cutoff of August 4, 2021). Data were included from participants who had completed study visits at BL and at Month 24 or had discontinued the study at the time of the data cutoff. BL demographics were similar to those of the 12-month cohort.[39] Significant increases in body weight occurred in both ARV-naive (n=75; 4.3 kg; *P*<0.05) and TE (n=376; 1.2 kg; *P*<0.05) participants. In the ARV-naive cohort, a greater increase in body weight from BL to Month 24 was observed in participants with a CD4 count <350 cells/mcL (n=33; 6.6 kg; *P*<0.05) than in those with a CD4 count ≥350 cells/mcL (n=39; 4 kg; *P*<0.05).[39]

Table 13. BICSTaR: Weight Changes in Subgroups of TE Participants at 24 Months[39a]

Subgroups	TE Cohort			
	BL	24 Months	BL	24 Months
Sex	**Female (n=49)**		**Male (n=327)**	
Body weight, median (Q1-Q3), kg	65 (59–74)	65 (58–78)	78 (69–88)	79 (70–90)
Change from BL, median (Q1-Q3), kg	+0.5 (-1.6 to +3)		+1.3 (-1 to +4.8)	
P-value for 24 months vs BL	Not significant		<0.05	
Age	**<50 years (n=185)**		**≥50 years (n=191)**	
Body weight, median (Q1-Q3), kg	76 (66–86)	77 (68–88)	77 (68–87)	78 (70–89)
Change from BL, median (Q1-Q3), kg	+1.5 (-0.9 to 4.7)		+1 (-1 to 4.3)	
P-value for 24 months vs BL	<0.05		<0.05	
Race	**Black (n=36)**		**Other (n=340)[b]**	
Body weight, median (Q1-Q3), kg	72 (65–85)	74 (66–86)	77 (67–87)	78 (69–89)
Change from BL, median (Q1-Q3), kg	+0.9 (-1 to 4.3)		+1.2 (-1 to 4.5)	
P-value for 24 months vs BL	Not significant		<0.05	
Prior TDF use	**Without TDF (n=237)**		**Prior TDF (n=137)**	
Body weight, median (Q1-Q3), kg	77 (67–87)	78 (69–90)	74 (67–86)	77 (68–88)
Change from BL, median (Q1-Q3), kg	+1 (-1 to 4.5)		+2 (0–4.3)	
P-value for 24 months vs BL	<0.05		<0.05	

[a]Participants with available weight and BMI data at BL and Month 24 were included in the analysis.
[b]People of other races, of whom the majority were White.

Weight increased was the most common (5%) DRAE and was reported in 10 participants (7%) in the ARV-naive cohort and in 29 participants (4%) in the TE cohort.[40] Weight increased was the most common (3%) DRAE that led to BIC/FTC/TAF discontinuation.[39]

36-month pooled analysis[41]

A total of 67 ARV-naive and 382 TE PWH in Germany, France, and Canada who completed 24 months of BIC/FTC/TAF participated in the extension phase, with a 36-month data cutoff date of August 12, 2022.

Among participants with available weight at BL and Month 36, the median (Q1, Q3) weight changes from BL were 4.3 (-0.5, 7.3) kg (*P*=0.003) in the ARV-naive group and 1.7 (1, 4.3) kg (*P*<0.001) in the TE group. Among participants with available BMI data at BL and Month 36, the median (Q1, Q3) change was 1.5 (-0.1, 2.5) kg/m^2 (*P*=0.003) in the ARV-naive group and 0.5 (-0.3, 1.5) kg/m^2 (*P*<0.001) in the TE group. At 36 months, 48% of ARV-naive participants had a normal BMI.

4-year pooled analysis[42]

An analysis was conducted among 125 ARV-naive and 675 TE participants from Canada, France, and Germany who had ≥4 years of follow-up data (2 years in the main BICSTaR study plus ≥2 years in the extension phase), with a data cutoff of September 1, 2023.

At 4 years, the median weights in the ARV-naive and TE groups were 74.2 and 78 kg, respectively. The median change in weight from BL to 4 years in participants with available data at both time points was +4.4 kg (*P*=0.019) among 29 ARV-naive participants and +1.6 kg (*P*<0.001) among 269 TE participants. The median BMIs in the ARV-naive and TE groups at 4 years were 25.3 and 25.4 kg, respectively. The median change in BMI from BL to 4 years was +1.6 kg/m^2 in the 29 ARV-naive participants (*P*=0.022) and +0.5 kg/m^2 in the 269 TE participants (*P*<0.001).

The most common DRAE was weight increased (ARV-naive, n=9 [7%]; TE, n=25 4%]) and led to discontinuation of BIC/FTC/TAF in 21 participants overall.

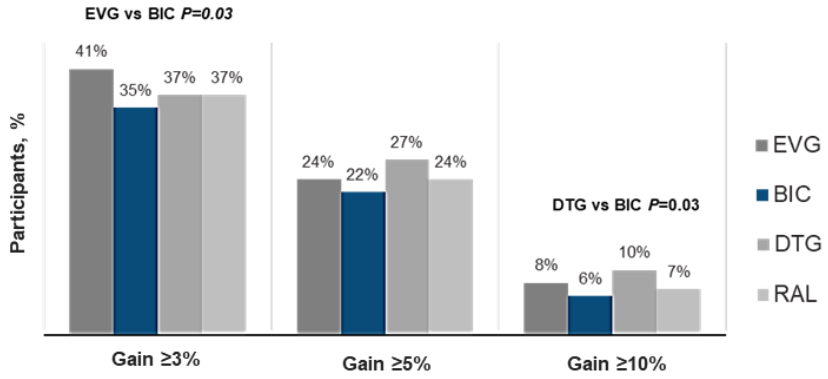
Trio Cohort[43]

The Trio Health HIV Research Network electronic medical records database was used in a retrospective observational cohort study that evaluated the impact of INSTIs on weight gain in virologically suppressed adults (N=2272) who switched to a new INSTI-based treatment regimen in clinical practice. This design allowed both prior switches from TDF to TAF and prior exposures to TDF to be accounted for.

One year after therapy switch, the mean increases in weight were 1.9 kg for RAL, 1.5 kg for EVG, 1.2 kg for DTG, and 0.9 kg for BIC.

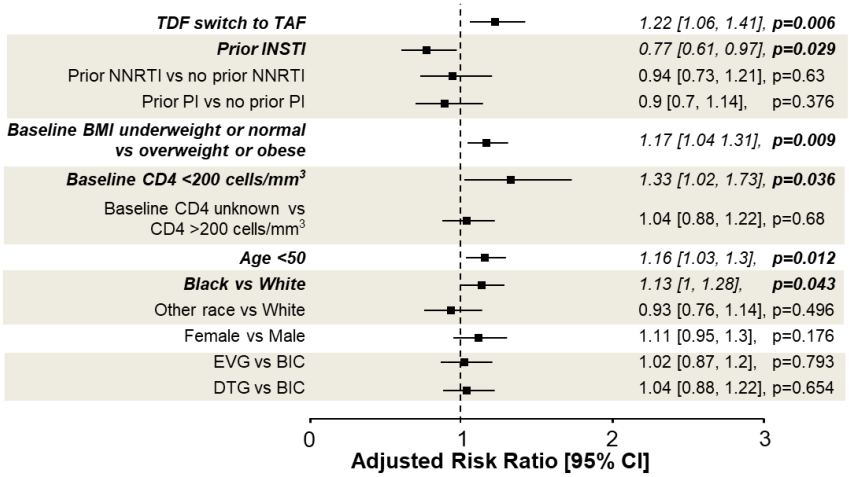
There was no difference in weight gain (≥3%, 5%, or 10% at 12 months) between the different INSTIs after accounting for BL characteristics, pre- and post-switch drug class, and TDF to TAF switch or pre-switch TDF (Figure 13).

Figure 13. Trio Cohort: Observed Proportion of PWH With Weight Gain 1 Year After INSTI Switch[43]



Note: There were no differences in weight gain by INSTI at all weight thresholds in the adjusted analysis.

Figure 14. Trio Cohort: Variables Associated With Risk of Weight Gain ≥3% 12 Months After INSTI Switch[43]



Additional Weight Change Data

Several studies regarding weight change have included BIC/FTC/TAF, with varying patient populations. This summary document includes data from Gilead phase 3 studies and large real-world studies. Studies not included can be found by conducting a literature search via PubMed or other databases.

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Abbreviations

3TC=lamivudine
ABC=abacavir
AE=adverse event
ART=antiretroviral therapy
ARV=antiretroviral
ATV=atazanavir
ATV/r=atazanavir/ritonavir
AZT=zidovudine
BIC=bictegravir
BL=baseline
CARDIA=Coronary Artery Risk Development in Young Adults
CD4=cluster of differentiation 4
DRAE=drug-related adverse event
DTG=dolutegravir
EFV=efavirenz
EVG=elvitegravir
EVG/c=elvitegravir/ cobicistat
E/C/F/TAF=elvitegravir/ cobicistat/emtricitabine/ tenofovir alafenamide
E/C/F/TDF=elvitegravir/ cobicistat/emtricitabine/ tenofovir disoproxil fumarate
FTC=emtricitabine
INSTI=integrase strand transfer inhibitor
LSM=least squares mean
NHANES=National Health and Nutrition Examination Survey
NNRTI=non-nucleos(t)ide reverse transcriptase inhibitor
NRTI=nucleos(t)ide reverse transcriptase inhibitor
OLE=open-label extension
OR=odds ratio
PI=protease inhibitor
PWH=people with HIV
PrEP=pre-exposure prophylaxis
Q=quartile
RAL=raltegravir
RPV=rilpivirine
SBR=stay(ed) on baseline regimen
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate
TE=treatment experienced
VL=viral load

Product Label

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FDA MedWatch Program by ☎ 1-800-FDA-1088 or ✉MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or 🖱 www.accessdata.fda.gov/scripts/medwatch

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