GILEAD | Medical Information

Antiretroviral Therapy and Weight Changes

This document is a summary of key Gilead data regarding the use of Atripla® (efavirenz/emtricitabine/tenofovir disoproxil fumarate [EFV/FTC/TDF]), Biktarvy® (bictegravir/emtricitabine/tenofovir alafenamide [BIC/FTC/TAF]), Complera® (rilpivirine/emtricitabine/tenofovir disoproxil fumarate [RPV/FTC/TDF]), Descovy® (emtricitabine/tenofovir alafenamide [FTC/TAF]), Emtriva® (emtricitabine [FTC]), Genvoya® (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide [E/C/F/TAF]), Odefsey® (rilpivirine/emtricitabine/tenofovir alafenamide [RPV/FTC/TAF]), Stribild® (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate [E/C/F/TDF]), Truvada® (emtricitabine/tenofovir disoproxil fumarate [FTC/TDF]), and Viread® (tenofovir disoproxil fumarate [TDF]) and weight changes. This response was developed according to principles of evidence-based medicine and is limited to pooled analyses of Gilead Phase 3 studies and a longitudinal analysis of four large real-world cohort studies.

Some data may be outside of the US FDA-approved Prescribing Information. In providing this data, Gilead Sciences, Inc. is not making any representation as to its clinical relevance or to the use of any Gilead product(s). For information about the approved conditions of use of any Gilead drug product, please consult the FDA approved prescribing information.

The full indication, important safety information, and boxed warnings for Atripla, Biktarvy, Complera, Descovy, Emtriva, Genvoya, Odefsey, Stribild, Truvada,and Viread are available at:
www.gilead.com/-/media/files/pdfs/medicines/hiv/atripla/atripla_pi;
www.gilead.com/-/media/files/pdfs/medicines/hiv/biktarvy/biktarvy_pi;
www.gilead.com/-/media/files/pdfs/medicines/hiv/complera/complera_pi;
www.gilead.com/-/media/files/pdfs/medicines/hiv/descovy/descovy_pi;
www.gilead.com/-/media/files/pdfs/medicines/hiv/emtriva/emtriva_pi;
www.gilead.com/-/media/files/pdfs/medicines/hiv/genvoya/genvoya_pi;
www.gilead.com/-/media/files/pdfs/medicines/hiv/odefsey/odefsey_pi;
www.gilead.com/-/media/files/pdfs/medicines/hiv/stribild/stribild_pi;
www.gilead.com/-/media/files/pdfs/medicines/hiv/truvada/truvada_pi;
www.gilead.com/-/media/files/pdfs/medicines/hiv/viread/viread_pi.

Summary

Background Information

The global obesity epidemic has grown steadily in both PLWH and the general population.[1-3]

TDF and Weight Loss

Weight decrease was an AE reported in >2% of FTC/TDF subjects and more frequently than by placebo subjects in HIV-1 uninfected adults in PrEP trials.[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]

Assessments of Weight Change in Gilead Studies

In a pooled analysis of TN participants (N=5680) who initiated ART[5]:

- Median weight increases were observed in all study arms.
- 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.
- 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.
- Weight changes that occurred 96 weeks after ART initiation were not associated with impacts on metabolic parameters

In a pooled analysis of virologically suppressed participants (N=7316) who switched their ART or remained on SBR[8]:

- Weight increases were observed in both switch and SBR participants but were greater in participants who switched their ART than in SBR participants, with most weight gain occurring within the first 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.
- Younger age and lower BL BMI were associated with ≥10% weight gain.
- BL ARV regimens were predictors of weight gain after switch.

A longitudinal analysis (N=2666) using data from four prospective, observational cohort studies was performed to assess the impact of initiating or switching to an INSTI- or NNRTI-based ART and the effect of the NRTI backbone on weight change in TE and TN PLWH.[9,10]

- Through Month 12, the mean weight of patients increased from BL by 2.7 kg in the TN group and by 1.4 kg in the TE group.[9]
- TN PLWH who received FTC/TAF with an INSTI had greater weight gain at Month 12 than those who received an NNRTI (3.4 vs 1.6 kg, respectively); weight increases were similar when comparing third agents in TE PLWH (INSTI: +1.6 kg, NNRTI: +1.4 kg).[9]
- TE PLWH who received an INSTI or NNRTI and switched from FTC/TDF to FTC/TAF had more weight gain at Month 12 than those who switched from ABC/3TC to FTC/TAF or did not switch backbone agents.[9]
- In a multivariate logistic regression analysis that examined potential risk factors associated with weight gain or loss of ≥10% of body weight from BL at 12 months in the pooled longitudinal analysis population: 67% of TN patients experienced any weight gain and 66% of TE patients experienced any weight gain.[11]

Background on BIC/FTC/TAF Use and Weight Changes

Weight Changes in the General Population

The global obesity epidemic has grown steadily in both PLWH and the general population.[1-3] According to an analysis of NHANES data, US adults aged 36-79 years had a mean 10-year weight gain of 4.2±0.2 kg from 2011-2018.[12] 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]

TDF and Weight Loss

Weight decrease was an AE reported in >2% of FTC/TDF subjects and more frequently than by placebo subjects in HIV-1 uninfected adults in PrEP trials.[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] 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 with FTC/TDF compared with placebo was -0.8% (95% CI: -1.5% to -0.1%; *P*=0.02).[6]

Weight changes in individuals who were not HIV-infected 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]

Assessments of Weight Change in Gilead Studies

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 effects of BL demographics, HIV disease characteristics, and treatment-related contributors (Table 1) on weight gain in TN participants who initiated ART from 2003 to 2015. 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. Baseline 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)

Key Demographics and Characteristics		Pooled Population (N=5680)
	Obese (BMI ≥30 kg/m^2)	924 (16.3)
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, RPV/FTC/TDF vs EFV/FTC/TDF, E/C/F/TAF vs E/C/F/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 more weight gain than the comparator arms. The greatest increase in weight gain occurred during the first 48 weeks of treatment and then started to plateau from Weeks 72 to 144. At Week 96, the median weight gain was 2 kg (IQR: -0.9, 5.9), and from BL to Week 96, 17.3% of participants experienced weight increases ≥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 at Week 48 (Sax et al)[5]

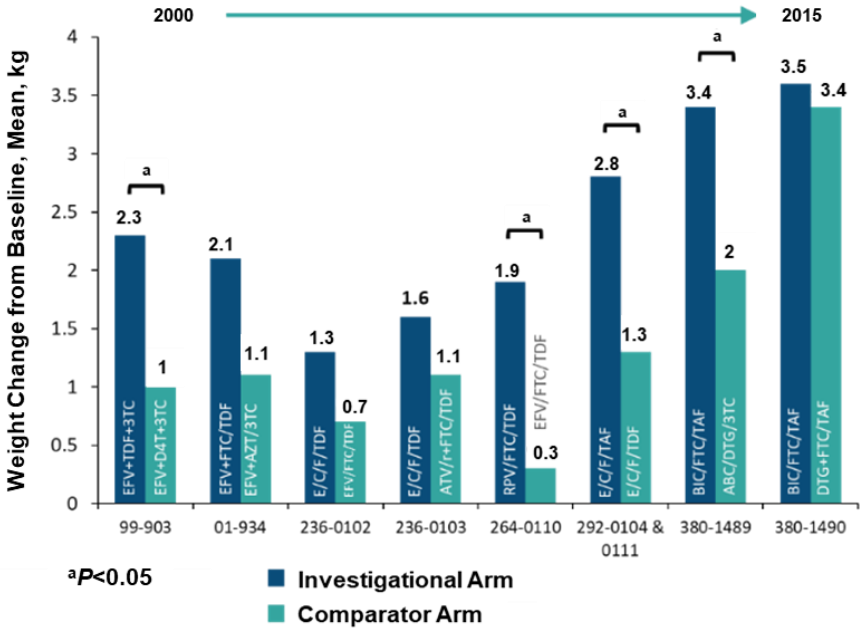
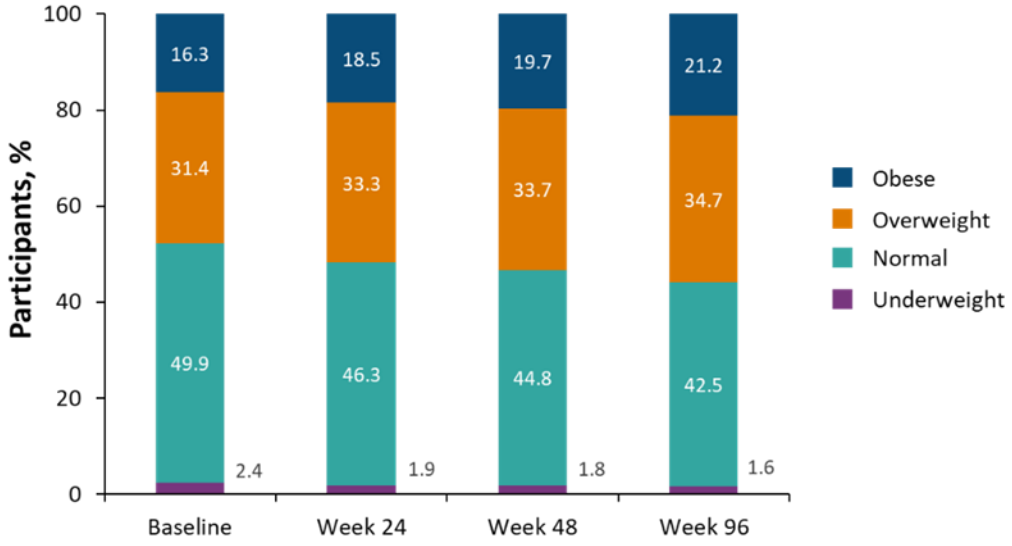


Figure 2. BMI Categories Through Week 96 (Sax et al)[5]



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/µL, HIV-1 RNA >100,000 c/mL, and symptomatic HIV or AIDS) gained more weight than each of their counterparts without these characteristics. Other BL risk factors associated with weight gain included no IV drug use, Black race, female sex, age <50 years, and BMI ≥25 kg/m2 (P<0.006 for all). The BL risk factors associated with ≥10% weight gain in participants who initiated ART are presented in Table 2.

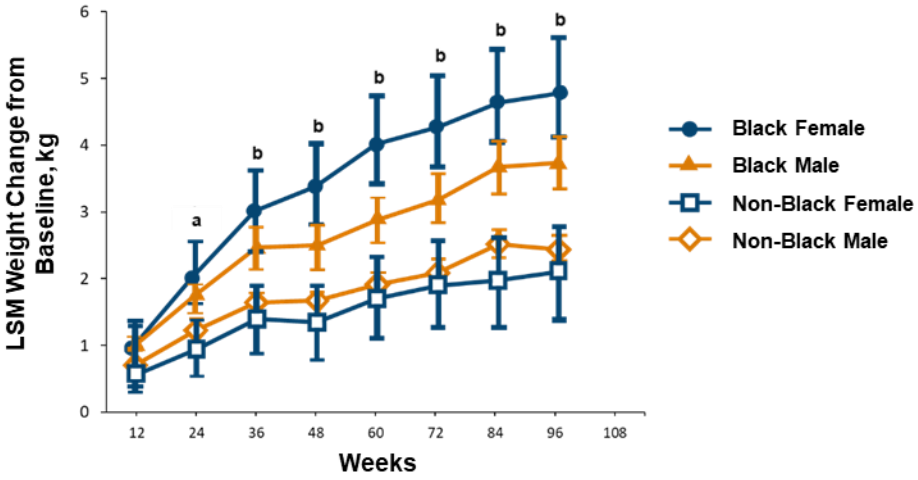
Table 2. Risk Factors Associated with ≥10% Weight Gain (Sax et al)[5]

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 differences were noted at Weeks 60, 72, and 96 (*P*<0.05 for all three time points). An 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 did Black male participants (95% CI: 0.25–1.99; *P*=0.011; Figure 3).

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



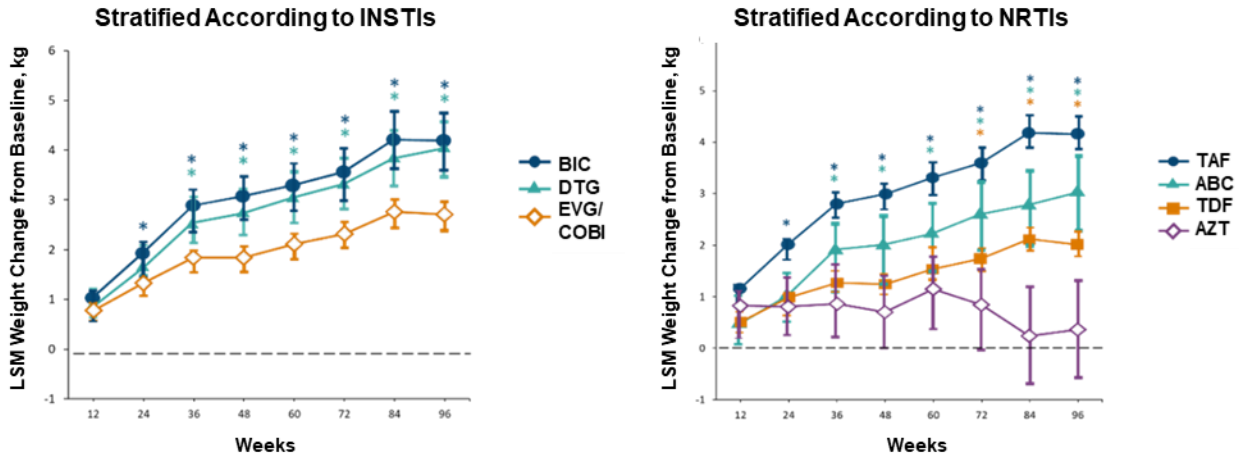
[a]*P*<0.05 for Black vs non-Black females only.
[b]*P*<0.05 for Black vs non-Black females and Black females vs Black males.
Note: Published peer-reviewed data were only available at Week 48

Weight changes 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, greater weight gain was observed at Week 96 in participants treated with BIC or DTG than in those treated with boosted EVG (least squares mean 4.24 kg, 4.07 kg, and 2.72 kg, respectively; Figure 4). For participants treated with NNRTIs, more weight gain was reported with RPV (3.01 kg) than with EFV (1.7 kg). 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]

The weight changes seen with EFV in this pooled analysis were similar to those observed in the ADVANCE CYP2B6 weight gain substudy. The authors concluded that PLWH with extensive EFV metabolizer genotypes, which presumably lead to lower EFV concentrations, gained a similar amount of weight to PLWH taking DTG,[16] while intermediate and slow metabolizers gained less weight and lost weight, respectively.[16,17]

Figure 4. Weight Changes in TN Participants According to ART (Sax et al)[5]



*$P \leq 0.05$ (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 difference in changes in fasting glucose at Week 96 from BL was observed in participants with ≥10% weight gain compared with those with <10% weight gain. A small 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.[18] 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]

The incidence rate of diabetes- or hyperglycemia-related AEs was higher in those with ≥10% weight gain compared to those without; however, this difference was not statistically significant. No clinically significant changes were observed in the 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.

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

Study design and demographics

Pooled analyses to identify the factors associated with weight change following ARV switch were conducted with data from 12 randomized, active-controlled studies in virologically suppressed participants (HIV-1 RNA <50 c/mL for ≥3 months) who were randomized to switch their ART (n=4166) or remain on an SBR (n=3150). Body weight measurements were performed at least every 12 weeks, and participants had follow-up for ≥48 weeks following ART switch. Of the participants included in the pooled analyses, 1949 switched both their NRTIs and third agents, 1326 switched their NRTIs only, and 891 switched their third agent only (Table 3).

Table 3. Participants According to NRTI or Third Agent Switch or SBR (Erlandson et al)[8]

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

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

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 had a larger proportion of Black participants, and one study (GS-US-292-1826) enrolled participants with a median age of 65 years, and <3% of participants were of Black race.

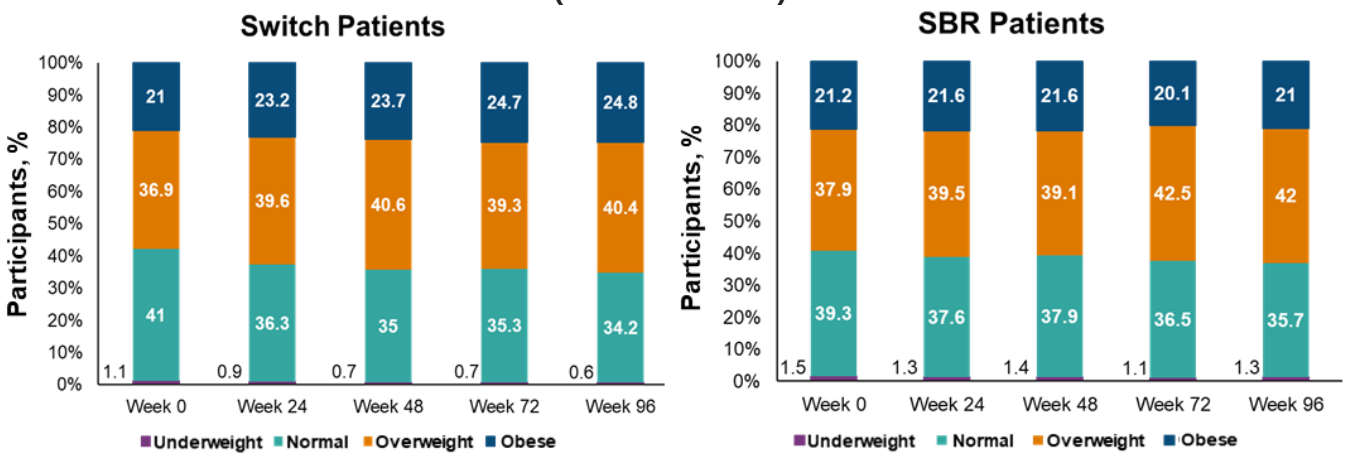
Results

Weight change

Weight increases were observed in both groups; however, the median increases from BL were 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 5).

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 5. BMI Categories Through Week 96 for Switch and SBR Participants (Erlandson et al)[8]



Participants who experienced ≥10% weight gain were younger in age and had a lower BMI at BL (Table 4). Race, ethnicity, sex, and CD4 count were not predictors of ≥10% weight gain in this pooled analysis.

Table 4. Risk Factors Associated with ≥10% Weight Gain Up to Week 48 (Erlandson et al)[8]

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

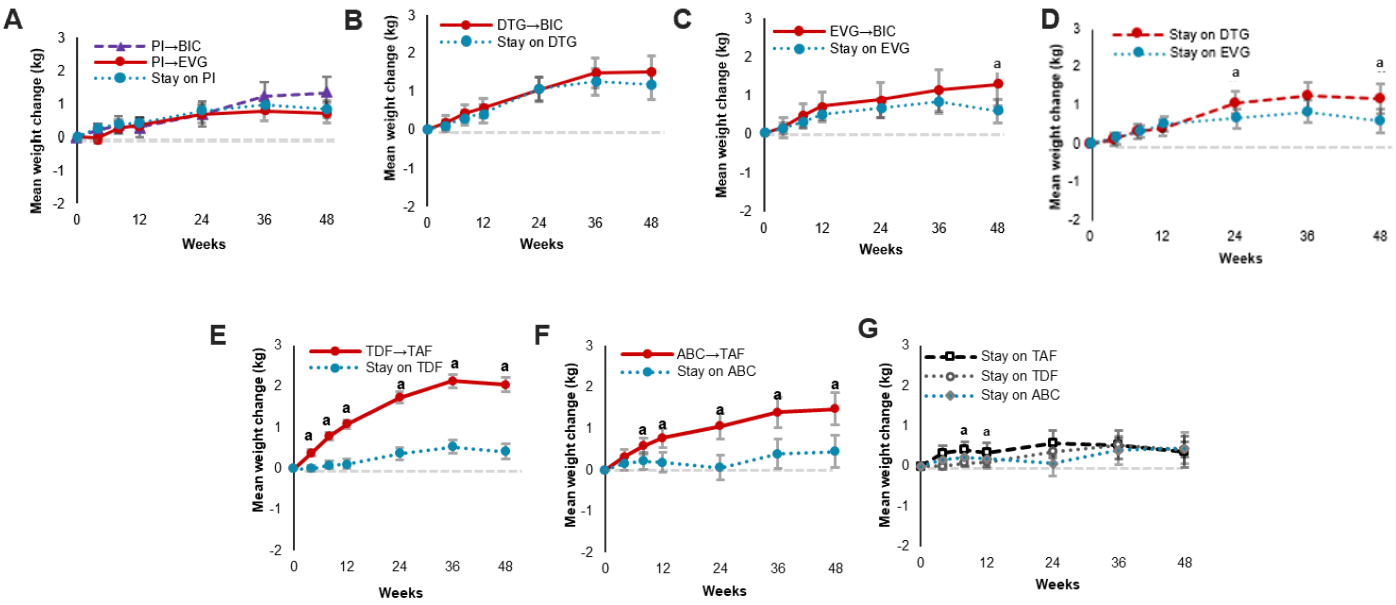
Note: *P*-values are derived from a logistic regression model that included BL BMI and age as risk factors.

Evaluation of the data showed some impact of gender and race on weight changes. There was greater weight gain at Week 48 for females vs males (0.3 kg; *P*=0.0046), Black males vs non-Black males (0.3 kg; *P*=0.041), and non-Black females vs non-Black males (0.5 kg; *P*=0.013). Similar weight gain was observed between Black vs non-Black participants, Black males vs Black females, and females 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,[5,7,19] 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 6. Weight Changes From BL to Week 48 by ART Switch (Erlandson)[8]



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

- Similar weight change was reported between groups that switched from a boosted PI to EVG/c or BIC (Figure 6A).
- The change in weight reported when switching from DTG to BIC was similar to remaining on DTG (Figure 6B).
- 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 6C).
- Remaining on DTG was associated with greater weight gain (0.6 kg) at Week 48 than staying on EVG/c (P=0.02; Figure 6D).
- Among participants who switched NRTIs, switching from TDF (+1.6 kg) or ABC to TAF resulted in greater weight gain (*P*<0.001; Figure 6E–F).
- Participants who stayed on TDF or ABC experienced similar weight changes compared to those who stayed on TAF (Figure 6G).

Effect of weight changes on metabolic outcomes[8]

Among participants who experienced ≥10% weight gain, changes in cholesterol components 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.

Longitudinal Assessment of Weight Change in Patients Initiating or Switching to an INSTI- or NNRTI-Based ART

Study design and demographics[9]

A longitudinal analysis was performed to assess the impact of initiating or switching to an INST- or NNRTI-based ART and the effect of the NRTI backbone on weight change in PLWH. The study utilized datasets from four prospective, observational cohort studies (2010–2020) that included patients who initiated or switched to an INSTI- or NNRTI-based ART (with FTC/TAF and FTC/TDF backbones; Figure 7).

Figure 7. Longitudinal Study Design and Third ARV and Backbone Agents According to TN and TE Status (Robineau et al)[9,10]

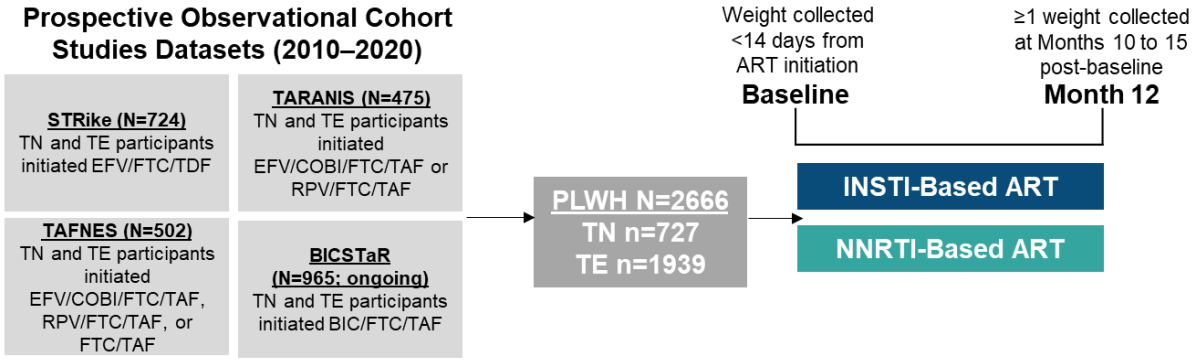


Table 5. Baseline Demographics and Disease Characteristics (Robineau et al)[9]

Key Demographics and Characteristics	TN (n=727)		TE (n=1939)	
	INSTI n=507	NNRTI n=220	INSTI n=1253	NNRTI n=731
Age, median (Q1, Q3), years	37 (30, 47)	39 (31, 44)	48 (39, 55)	45 (35, 53)
Male, %	91	89	84	87
Weight, median (Q1, Q3), kg	72 (65, 81)	75 (68, 85)	76 (67, 85)	75 (67, 83)
BMI, median (Q1, Q3), kg/m^2	23.1 (21.3, 25.4)	23.5 (21.8, 25.6)	24.6 (22.2, 27.5)	23.8 (21.6, 26)
Concurrent medications associated with weight change				
Medications associated with weight increase,[a] %	12	10	18	14
Medications associated with weight decrease,[a] %	5	1	6	3
CD4, median (Q1, Q3), cells/μL	397 (237, 563)	370 (272, 493)	635 (420, 859)	571 (398, 771)
HIV-1 RNA, median (Q1, Q3), $\log_{10}$ c/mL	4.6 (4.6, 5.15)	4.44 (3.96, 4.81)	1.55 (1.28, 1.69)	1.69 (1.28, 1.69)
Late presenter,[b] %	42	46	–	–
Backbone				
FTC/TAF, %	84	14	91	52
FTC/TDF, %	16	86	9	48
Previous to current ART backbone agents				
FTC/TDF→FTC/TAF, %	–	–	46	49

Key Demographics and Characteristics	TN (n=727)		TE (n=1939)	
	INSTI n=507	NNRTI n=220	INSTI n=1253	NNRTI n=731
ABC/3TC→FTC/TAF, %	–	–	12	3
Pre-switch EFV,[c] %	–	–	9	6

[a]According to the Summary of Product Characteristics.
[b]Defined as CD4 <350 cells/μL and/or CDC Stage A3, B3, or any C stage.
[c]All patients switched to FTC/TAF.

Results

Weight change[9]

Through Month 12, the mean weight of patients increased from BL by 2.7 kg in the TN group and by 1.4 kg in the TE group (Figure 8). The proportion of TE PLWH within each BMI category remained similar at BL and at Month 12, whereas there were small changes in the proportions of TN PLWH within each BMI category during the same time period (Figure 9).

Figure 8. Weight Changes from Baseline Through Month 12 in TN and TE PLWH (Robineau et al)[9]

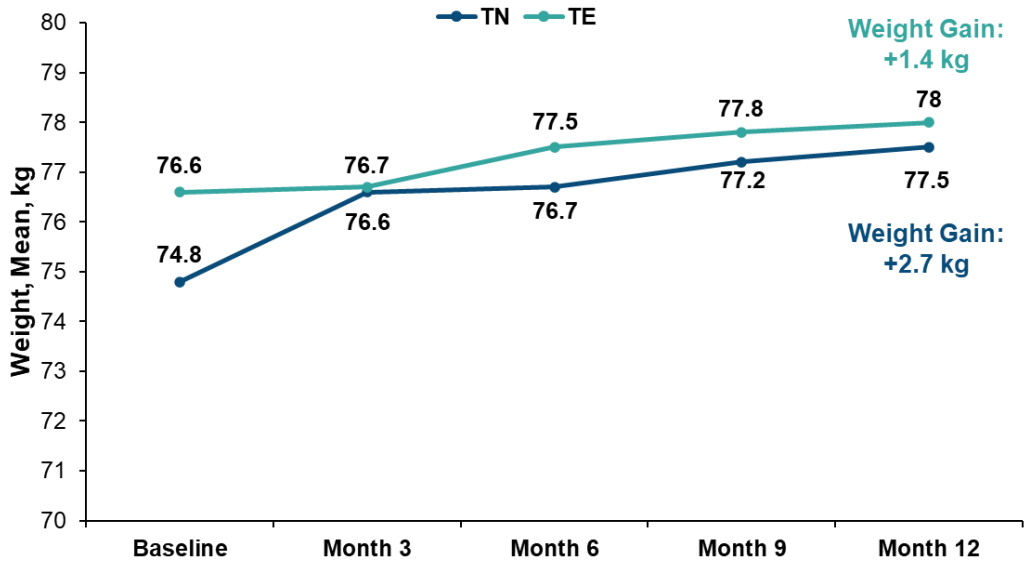
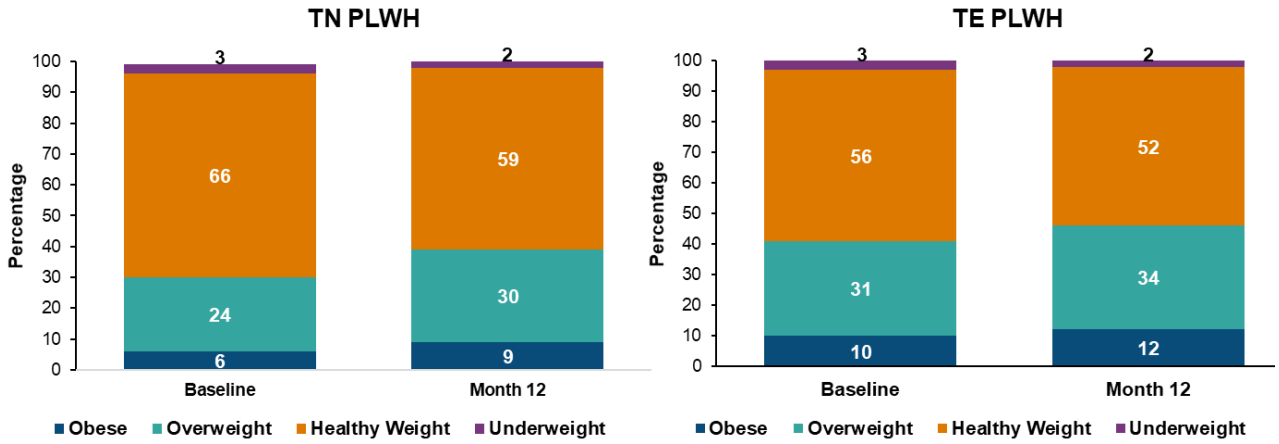


Figure 9. BMI Categories at Baseline and Month 12 in TN and TE PLWH (Robineau et al)[9]



Note: BMI was categorized as follows: obese, 30 to 39.9 kg/m^2; overweight, 25 to 29.9 kg/m^2; healthy weight, 18.5 to 24.9 kg/m^2; underweight, <18.5 kg/m^2.

Weight change and type of ART

A linear mixed model was used to predict mean weight changes after 12 months and to evaluate the impact of backbone therapy (FTC/TAF or FTC/TDF) in TE and TN PLWH who received an INSTI or NNRTI. TE PLWH who received FTC/TAF or FTC/TDF had similar trajectories of mean weight increases from BL to Month 12, irrespective of whether they received treatment with an INSTI or an NNRTI. As shown in Table 6, TN PLWH who received FTC/TAF or FTC/TDF and an INSTI had a greater increase in weight gain from BL to Month 12 than those who received an NNRTI.[9]

Table 6. Predicted Population Mean Changes in Weight from Baseline to Month 12 in TN and TE PLWH According to Backbone and Third ARV Agent (Robineau et al)[9]

Backbone ARV	TN				TE			
	INSTI		NNRTI		INSTI		NNRTI	
	Weight at BL, kg	Change in Weight at Mo 12, kg	Weight at BL, kg	Change in Weight at Mo 12, kg	Weight at BL, kg	Change in Weight at Mo 12, kg	Weight at BL, kg	Change in Weight at Mo 12, kg
FTC/TAF	74	+3.4	76.3	+1.6	77.1	+1.6	75.5	+1.4
FTC/TDF	77.2	+2.3	74.4	+1.6	75.2	+1.9	74.5	+1.7

Among TE PLWH, regardless of the third ARV agent (INSTI and NNRTI), those who underwent a switch in their backbone agent from FTC/TDF to FTC/TAF had more weight gain than those who did not switch the backbone agent or those who switched from ABC/3TC to FTC/TAF (Table 7).[9]

Table 7. Predicted Population Mean Changes in Weight from Baseline to Month 12 in TE PLWH According to Backbone ARV and Third ARV Agent Switching (Robineau et al)[9]

Backbone ARV Switch	TE			
	INSTI		NNRTI	
	Weight at Baseline, kg	Change in Weight at Month 12, kg	Weight at Baseline, kg	Change in Weight at Month 12, kg
FTC/TDF→FTC/TAF	76.7	+1.9	75	+1.9
ABC/3TC→FTC/TAF	80.1	+0.7	78.4	+0.7
No switch	76.8	+1.4	75.1	+1.4

Patients who did and did not receive EFV before the ART switch were predicted to have similar increases in weight from BL to Month 12, regardless of whether they were switched to an INSTI or NNRTI as the third agent.[10]

Risk factors associated with ≥10% change in weight[11]

A multivariate logistic regression analysis examined potential risk factors associated with weight gain or loss of ≥10% of body weight from BL at 12 months in the pooled longitudinal analysis population.

Among TN patients (N=727), 21% experienced any weight loss, 1% experienced ≥10% weight loss, 67% experienced any weight gain, and 31% experienced ≥10% weight gain at 12 months.

Among TE patients (N=1939), 22% experienced any weight loss, 2% experienced ≥10% weight loss, 66% experienced any weight gain, and 23% experienced ≥10% weight gain at 12 months.

Table 8. Selected Baseline Demographics and Clinical Characteristics Among Participants with ≥10% Weight Gain or Loss (Robineau et al)[11]

Key Baseline Demographics and Characteristics	TN (N=727)		TE (N=1939)	
	≥10% Loss (n=8)	≥10% Gain (n=229)	≥10% Loss (n=40)	≥10% Gain (n=451)
Age, median (Q1, Q3) years	40 (31, 50)	38 (30, 46)	49 (36, 55)	47 (37, 55)
Male, %	88	90	83	79*
Third agent in ART regimen, %				
NNRTI	38	15	33	28
INSTI	63	85[a]	68	72[a]
Backbone during study, %				
FTC/TAF	63	82[a]	75	87[a]
FTC/TDF	38	18	25	13
NRTI prior to switching to FTC/TAF, %				
FTC/TDF	-	-	45	55
ABC/3TC	-	-	5	9[b]
No switch from FTC/TDF to FTC/TAF	-	-	50	37
EFV prior to switching, %	-	-	10	10

Key Baseline Demographics and Characteristics	TN (N=727)		TE (N=1939)	
	≥10% Loss (n=8)	≥10% Gain (n=229)	≥10% Loss (n=40)	≥10% Gain (n=451)
CD4 count, median (Q1, Q3), cells/mm^3	502 (248, 578)	377 (158, 544)	654 (458, 784)	606 (410, 834)
HIV-1 RNA <50 c/mL, %	0	1	80	85[†]
Late presenter, %[c]	25	48	-	-
Weight, median (Q1, Q3), kg	80 (75, 94)	71 (65, 79)[d]	89 (75, 105)[a]	74 (65, 84)
BMI, median (Q1, Q3), kg/m^2	25.4 (23.9, 30.5)[d]	22.9 (21.1, 25.3)	27.6 (24.8, 31.6)[d]	24.2 (21.7, 27.2)
Comorbidity associated with obesity, %[e]	25	11	23	28
Comedications, %[f]				
Associated with weight gain	-	12	-	18
Associated with weight loss	0	-	13[d]	-

Note: *P*-values compared ≥10% weight gain/loss vs without ≥10% weight gain/loss.
[a]*P*<0.001. [b]*P*<0.01. [c]Participants with CD4 count <350 cells/mm3 and/or CDC Stage A3, B3, or any C stage. [d]*P*<0.05. [e]Hypertension, hyperlipidemia, diabetes mellitus, and/or cardiovascular disease. [f]Insulin, antidiabetics, antidepressants/psychoanaleptics, antipsychotics, antiepileptics, contraceptives, corticosteroids, antihistamines, beta-adrenergic blockers, and antigout medications.

Multivariate logistic regression analyses found that in TN participants, treatment with FTC/TAF (aOR vs FTC/TDF, 3.86; *P*<0.001), a BMI in the underweight range (aOR vs normal BMI, 2.72; *P*=0.024), and low CD4 count at BL (vs high count; *P*=0.01) were associated with ≥10% weight gain; no factor had an association with ≥10% weight loss. In TE participants, female gender (vs male, *P*=0.002), treatment with INSTI (aOR vs NNRTI, 1.33; *P*=0.029) or FTC/TAF (aOR vs FTC/TDF, 2.13; *P*<0.001) during the study, switching from FTC/TDF to FTC/TAF (aOR vs no switch, 1.47; *P*=0.001), having a BMI in the underweight range (aOR vs normal BMI, 2.85; *P*<0.001), and not having a comorbidity (vs having a comorbidity; *P*=0.046) were associated with ≥10% weight gain, while taking comedications associated with weight change (aOR vs no comedications associated with weight change, 2.73; *P*=0.046) was associated with ≥10% weight loss.

Additional Weight Change Data

Several non-Gilead studies regarding weight change have included Gilead ARVs, with varying patient populations and results. Non-Gilead clinical studies are not included in this summary document and can be found by conducting a literature search via PubMed or other databases.

References

1. Crum-Cianflone N, Roediger MP, Eberly L, et al. Increasing Rates of Obesity among HIV-Infected Persons during the HIV Epidemic. *Plos ONE.* 2010;5(4).
2. Finucane MM, Stevens GA, Cowan MJ, et al. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. *Lancet.* 2011;377(9765):557-567.
3. Centers for Disease Control and Prevention (CDC), National Center for Health Statistics, Division of Analysis and Epidemiology. Health, United States, 2018 Table 21 Selected health conditions and risk factors, by age: United States, selected years 1988-1994 through 2015-2016. Available at: https://www.cdc.gov/nchs/hus/contents2018.htm#Table_021. Accessed: 05 August 2020. Last Updated: 30 October. 2019.
4. Enclosed. Gilead Sciences Inc, TRUVADA® (emtricitabine/tenofovir disoproxil fumarate) tablets, for oral use. U.S. Prescribing Information. Foster City, CA.
5. Sax PE, Erlandson KM, Lake JE, et al. Weight Gain Following Initiation of Antiretroviral Therapy: Risk Factors in Randomized Comparative Clinical Trials. *Clin Infect Dis.* 2020;71(6):1379-1389. https://www.ncbi.nlm.nih.gov/pubmed/31606734
6. Glidden D, Mulligan K, McMahan V, et al. Metabolic Effects of Preexposure Prophylaxis With Coformulated Tenofovir Disoproxil Fumarate and Emtricitabine. *Clinical Infectious Diseases (CID).* 2018.
7. Spinner CD, Brunetta J, Shalit P, et al. DISCOVER STUDY for HIV Pre-Exposure Prophylaxis: F/TAF has a more Rapid Onset and Longer Sustained Duration of HIV Protection Compared with F/TDF [Presentation]. Paper presented at: IAS 2019; 21-24 July, 2019; Mexico City, Mexico.
8. Erlandson KM, Carter CC, Melbourne K, et al. Weight Change Following Antiretroviral Therapy Switch in People with Viral Suppression: Pooled Data from Randomized Clinical Trials. *Clin Infect Dis.* 2021.
9. Robineau O, Marongiu A, Stellbrink H, et al. Longitudinal Analysis of Weight Change in HIV-1 Treatment-Naïve and -Experienced People Living With HIV (PLWH Initiating/Switching to an NNRTI-or INSTI-Based AntiretroviralTherapy in Four Large Cohort Studies [Poster EPB118]. Paper presented at: AIDS 2022; 29 July-2 August, 2022; Montreal, Quebec, Canada.
10. Robineau O, Marongiu A, Stellbrink H, et al. Longitudinal Analysis of Weight Change in HIV-1 Treatment-Naïve and -Experienced People Living With HIV (PLWH) Initiating/Switching to an NNRTI-or INSTI-Based Antiretroviral Therapy in Four Large Cohort Studies [Poster EPB118 Presentation]. Paper presented at: AIDS 2022; 29 July-2 August, 2022; Montreal, Quebec, Canada.
11. Robineau O, Marongiu A, Stellbrink H, et al. Risk Factors Associated With ≥ ±10% Weight Change in Treatment-Naïve and Treatment-Experienced People Living With HIV Initiating or Switching to an NNRTI- or INSTI-Based Antiretroviral Therapy in Four Large Cohort Studies [Poster P156]. Paper presented at: HIV Glasgow 23-26 October, 2022; Glasgow, UK.
12. Tucker LA, Parker K. 10-Year Weight Gain in 13,802 US Adults: The Role of Age, Sex, and Race. *J Obes.* 2022;2022:7652408.
13. Mayer KH, Molina JM, Thompson MA, et al. Emtricitabine and tenofovir alafenamide vs emtricitabine and tenofovir disoproxil fumarate for HIV pre-exposure prophylaxis (DISCOVER): primary results from a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial. *Lancet.* 2020;396(10246):239-254.
14. Landovitz RJ, Donnell D, Clement M, et al. HPTN 083 Final Results: Pre-exposure Prophylaxis containing long-acting injectable cabotegravir is safe and highly effective for cisgender men and transgender women who have sex with men [Presentation]. Paper presented at: 23rd International AIDS Conference Virtual; 06-10 July, 2020.
15. Ruane P, Clarke A, Post FA, et al. Phase 3 Randomized, Controlled DISCOVER Study of Daily F/TAF or F/TDF for HIV Pre-exposure Prophylaxis: Week 96 Results [Poster PE3/16]. Paper presented at: 17th European AIDS Conference; 06-09 November, 2019; Basel, Switzerland.
16. Griesel R, Maartens G, Sokhela S, et al. CYP2B6 Genotype and Weight-Gain Differences Between Dolutegravir and Efavirenz. Paper presented at: 27th Annual Conference On Retroviruses And Opportunistic Infections (CROI) - CROI Foundation2020; Boston, MA; USA

17. Leonard MA, Cindi Z, Bradford Y, et al. Efavirenz Pharmacogenetics and Weight Gain following Switch to Integrase Inhibitor-containing Regimens. *Clin Infect Dis.* 2020.
18. Sax PE, Erlandson KM, Lake JE, et al. Weight Gain Following Initiation of Antiretroviral Therapy: Risk Factors in Randomized Comparative Clinical Trials [Supplemental Material]. *Clin Infect Dis.* 2019. https://www.ncbi.nlm.nih.gov/pubmed/31606734
19. Glidden D, Mulligan K, McMahan V, et al. Metabolic Effects of Preexposure Prophylaxis With Coformulated Tenofovir Disoproxil Fumarate and Emtricitabine. *Clinical Infectious Diseases (CID).* 2018;67(3):411-419.

Abbreviations

3TC=lamivudine
ABC=abacavir
AE=adverse event
aOR=adjusted odds ratio
ART=antiretroviral therapy
ARV=antiretroviral
ATV/r=atazanavir/ritonavir
AZT=zidovudine
BL=baseline
BIC=bictegravir
c/mL=copies/mL
CARDIA=Coronary Artery Risk Development in Young Adults
CDC=Centers for Disease Control
DTG=dolutegravir
EFV=efavirenz
EVG=elvitegravir
EVG/COBI=EVG/cobicistat
E/C/F/TAF=elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
E/C/F/TDF=elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate
EFV=efavirenz
EVG=elvitegravir
EVG/COBI=EVG/cobicistat
FTC=emtricitabine
INSTI=integrase strand transfer inhibitor
LSM=least squares mean
NHANES=National Health and Nutrition Examination Survey
NNRTI=non-nucleoside reverse transcriptase inhibitor
NRTI=nucleoside reverse transcriptase inhibitor
NVP=nevirapine
PI=protease inhibitor
PLWH=people living with HIV
PrEP=pre-exposure prophylaxis
Q=quartile
RAL=raltegravir
RPV=rilpivirine
SBR=stable baseline regimen
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate
TE=treatment-experienced
TN=treatment-naïve

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Atripla, Biktarvy, Complera, Descovy, Emtriva, Genvoya, Odefsey, Stribild, Truvada, and Viread US Prescribing Information available at:
www.gilead.com/-/media/files/pdfs/medicines/hiv/atripla/atripla_pi;
www.gilead.com/-/media/files/pdfs/medicines/hiv/biktarvy/biktarvy_pi;
www.gilead.com/-/media/files/pdfs/medicines/hiv/complera/complera_pi;
www.gilead.com/-/media/files/pdfs/medicines/hiv/descovy/descovy_pi;
www.gilead.com/-/media/files/pdfs/medicines/hiv/emtriva/emtriva_pi;
www.gilead.com/-/media/files/pdfs/medicines/hiv/genvoya/genvoya_pi;
www.gilead.com/-/media/files/pdfs/medicines/hiv/odefsey/odefsey_pi;
www.gilead.com/-/media/files/pdfs/medicines/hiv/stribild/stribild_pi;
www.gilead.com/-/media/files/pdfs/medicines/hiv/truvada/truvada_pi;
www.gilead.com/-/media/files/pdfs/medicines/hiv/viread/viread_pi.

Follow Up

For any additional questions, please contact Gilead Medical Information at:

☎1-866-MEDI-GSI (1-866-633-4474) or 🖱 www.askgileadmedical.com

Adverse Event Reporting

Please report all adverse events to:

Gilead Global Patient Safety ☎ 1-800-445-3235, option 3 or
🖱 https://www.gilead.com/utility/contact/report-an-adverse-event

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

Data Privacy

The Medical Information service at Gilead Sciences may collect, store and use your personal information to provide a response to your medical request. We may share your information with other Gilead Sciences colleagues to ensure that your request is addressed appropriately. If you report an adverse event or concern about the quality of a Gilead or Kite product, we will need to use the information you have given us in order to meet our regulatory requirements in relation to the safety of our medicines.

It may be necessary for us to share your information with Gilead's affiliates, business partners, service providers and regulatory authorities located in countries besides your own. Gilead Sciences has implemented measures to protect the personal information you provide. Please see the Gilead Privacy Statement (www.gilead.com/privacy-statements) for more information about how Gilead handles your personal information and your rights. If you have any further questions about the use of your personal information, please contact gilead.privacy@gilead.com.

ATRIPLA, BIKTARVY, COMPLERA, DESCOVY, DESCOVY for PrEP, EMTRIVA, GENVOYA, ODEFSEY, STRIBILD, TRUVADA, TRUVADA for PrEP, VIREAD, GILEAD, and