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Descovy® (FTC/TAF)
Lipid Safety Profile of FTC/TAF-Containing Regimens in Participants With HIV-1

This document is in response to your request for data from Gilead studies regarding the lipid safety profile of Descovy® (emtricitabine/tenofovir alafenamide [FTC/TAF])-based regimens, including Biktarvy® (bictegravir/emtricitabine/tenofovir alafenamide [BIC/FTC/TAF]), Genvoya® (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide [E/C/F/TAF]), and Odefsey® (rilpivirine/emtricitabine/tenofovir alafenamide [RPV/FTC/TAF]) in people with HIV-1 (PWH).

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Summary

Lipid Safety Profile of TAF vs Other NRTI-Based Regimens[1-8]

Four randomized studies compared TAF-based regimens with other NRTI-based regimens (including ABC/3TC and FTC/TDF) in ARV-naive or VS participants.

- Although there were numerical differences in fasting lipid changes from baseline to end of study between treatment arms, most were not statistically or clinically significant. In studies that measured initiation of lipid-lowering medication, no significant differences were observed between treatment arms.

Lipid Safety Profile of TAF vs Other TFV-Based Regimens[9-30]

Nine randomized studies compared TAF-based regimens with other TFV-based regimens (including FTC/TDF or FTC/TAF) in treatment-naive or VS participants.

- In most studies, TAF-based regimens resulted in larger median increases from baseline in fasting lipid parameters than TDF-based regimens.
- Most studies that assessed initiation of lipid lowering medications found no significant difference between TAF and TDF-based regimens. In the studies that found significant differences, more participants receiving TAF-based regimens started lipid-lowering medication than in the TDF-based regimens.

Lipid Safety Profile of TAF in a Single-Arm Study[40-44]

A phase 3, single-arm, open-label trial evaluated the efficacy and safety of switching to E/C/F/TAF from a variety of different ARV regimens in VS adults (N=242) with mild to moderate renal impairment (eGFRCG 30 to 69 mL/min).

- Switching from a TDF-containing regimen to E/C/F/TAF led to increases from baseline to Week 144 in all fasting lipid parameters; no change was observed in HDL. Switching from an ABC-containing regimen to E/C/F/TAF led to decreases in some parameters (TC, LDL, and TC: HDL), and an increase in TG.

Lipid Safety Profile of TAF vs Other NRTI-Based Regimens

Study GS-US-380-1489[1,2,3]

A phase 3, prospective, randomized, double-blind, active-controlled clinical trial compared BIC/FTC/TAF (n=314) to DTG/ABC/3TC (n=315) in ARV-naive adults with HIV-1. Key inclusion criteria were HIV-1 RNA ≥500 c/mL at screening, $eGFR_{CG}$ ≥50 mL/min, and genotypic sensitivity to the NRTI components of study drugs. The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 c/mL at Week 48 by the FDA Snapshot analysis, with a pre-specified non-inferiority margin of 12%. Secondary endpoints were efficacy and safety through Week 96 and Week 144. Baseline demographics and disease characteristics were similar in both treatment groups. The median age across groups was 31 to 32 years old, most participants were male, white and HIV-1 RNA <100,000 c/mL at baseline.[1]

Lipid safety results through Week 144

Statistically significant differences between treatment arms were observed in change from baseline for total cholesterol, LDL, and TC:HDL ratio at Week 144 (Table 1).[31] Five percent of participants in each arm initiated lipid-modifying medications during the study (*P*=1).[32] LDL elevations were reported as a Grade 3 or 4 laboratory abnormality in 5% of participants in each arm.[31]

Table 1. Change from Baseline in Fasting Lipid Parameters at Week 144[31]

Lipid Parameters	BIC/FTC/TAF (n=314)		DTG/ABC/3TC (n=315)		*P*-Value[a]
	Baseline Values	Median Change From Baseline	Baseline Values	Median Change From Baseline	
TC, mg/dL	159	+14	162	+10	0.034
LDL, mg/dL	101	+21	101	+14	0.004
HDL, mg/dL	42	+5	42	+6	0.096
TG, mg/dL	93	+6	96	+5	0.23
TC:HDL ratio	3.7	-0.1	3.7	-0.3	0.007

[a]*P*-values were from the 2-sided Wilcoxon rank sum test to compare median changes from baseline between the two treatment groups

Lipid safety results through Week 240[8,33]

At the Week 144 secondary endpoint all participants were offered enrollment in the OLE phase with BIC/FTC/TAF. In Study 1489, 254 participants who were initially randomized to DTG/ABC/3TC switched to BIC/FTC/TAF and 252 participants continued BIC/FTC/TAF in the OLE phase.

In participants who were initially randomly assigned to receive BIC/FTC/TAF, changes in fasting lipids from baseline through Week 240 were reported (Table 2). There were numerical increases in most fasting lipid parameters, and the TC:HDL ratio remained stable from baseline to Week 240. At BIC/FTC/TAF initiation 4% of study participants were taking lipid-lowering medications and 7% initiated lipid-lowering medications during the study. Additionally, 1% of participants initiated lipid-lowering medications between Weeks 192 and 240.

Table 2. Changes From Baseline in Fasting Lipid Parameters at Week 240[8a]

Lipid Parameters	BIC/FTC/TAF	
	Median Baseline Values (n=314)	Median Change From Baseline at Week 240
TC, mg/dL	159	+20
LDL, mg/dL	101	+20
HDL, mg/dL	42	+5
TG, mg/dL	93	+9
TC:HDL ratio	3.7	-0.1

[a]Only included participants who were initially randomized to receive BIC/FTC/TAF.

Study GS-US-380-1878[7]

A phase 3, prospective, randomized, open-label clinical trial that compared switching to BIC/FTC/TAF 50/200/25 mg (n=290) vs staying on a baseline regimen of boosted DRV or ATV + 2 NRTIs (n=287) VS adults with HIV-1. Key inclusion criteria were HIV-1 RNA <50 c/mL at screening for ≥6 months, $eGFR_{CG}$ ≥50 mL/min, and no documented or suspected resistance to NRTI components of study drugs. The primary endpoint was the proportion of participants with plasma HIV-1 RNA ≥50 c/mL at Week 48 by FDA Snapshot analysis with a pre-specified non-inferiority margin of 4%. Secondary endpoint was the proportion of participants with plasma HIV-1 RNA <50 c/mL at Week 48. Baseline demographics and disease characteristics are presented below (Table 3).

Table 3. Baseline Demographics and Disease Characteristics[7]

		BIC/FTC/TAF (n=290)	Boosted DRV or ATV + 2 NRTIs (n=287)
Age, median years (range)		48 (20–74)	47 (21–79)
Male, %		84	82
Race or ethnicity, %	White	65	66
	Black or African descent	27	25
	Latinx	21	16
Median CD4 cell count, cells/mcL		617	626
HBV co-infection/HCV co-infection, n		8/5	6/5
Median $eGFR_{CG}$, mL/min		107	105
Screening ARVs by NRTIs and PIs, %	FTC/TDF / ABC/3TC	84/15	84/15
	DRV / ATV	56/43	53/46

Lipid safety results through Week 48

Switching to BIC/FTC/TAF was associated with small, significant decreases in TG and TC:HDL ratio (Table 4). At baseline, 16.2% of BIC/FTC/TAF participants and 15.7% of boosted DRV or ATV + 2 NRTIs participants were taking lipid-lowering agents (*P*=0.91). During the study, 3% of BIC/FTC/TAF and 3% of ATV + 2 NRTIs participants initiated lipid-lowering medications (*P*=0.64).[7] LDL elevations were reported as a Grade 3 or 4 laboratory abnormality in 4% of participants in both arms through Week 48.[34]

Table 4. Change From Baseline in Fasting Lipid Parameters at Week 48[34]

	BIC/FTC/TAF		Boosted DRV or ATV + 2 NRTIs		*P*-Value[a]
	Baseline Values (n=283)	Median Change From Baseline[b]	Baseline Values (n=277)	Median Change From Baseline[b]	
TC, mg/dL	188	+1	183	+5	0.32
LDL, mg/dL	121	0	118	+3	0.47
HDL, mg/dL	47	+3	46	+1	0.13
TG, mg/dL	122	-6	121	+4	0.002
TC:HDL ratio	4.0	-0.2	3.8	0	0.033

[a]*P*-values from the 2-sided Wilcoxon rank sum test to compare the changes at Week 48 between the two treatment groups.
[b]Week 48 values were not available for all participants.

Extension phase – lipid safety results[35]

A total of 533 participants completed the 48-week randomized phase and entered the OLE to evaluate the long-term efficacy and safety of BIC/FTC/TAF. The all BIC/FTC/TAF group consisted of participants who received ≥1 dose of BIC/FTC/TAF; this was measured at the first dose of BIC/FTC/TAF in the OLE for participants who switched from boosted DRV or ATV + 2 NRTIs at Week 48 and participants who continued to receive BIC/FTC/TAF from baseline.

In the all BIC/FTC/TAF group, changes from baseline through Week 96 in fasting lipids were reported (Table 5). There were small numerical changes across all fasting lipid parameters except HDL; TC:HDL ratio remained stable.

Table 5. Change From Baseline in Fasting Lipid Parameters Through Week 96[35]

Lipid Parameters	All BIC/FTC/TAF			
	Median at BIC/FTC/TAF Start	Median Change After BIC/FTC/TAF Start		
		Week 48	Week 72	Week 96
TC, mg/dL	188	-1	-2	-1
LDL, mg/dL	123	-3	-4	-7
HDL, mg/dL	47	+1	+1	+1
TG, mg/dL	123	-12	-9	-11
TC:HDL ratio	3.9	-0.1	-0.2	-0.2

Study GS-US-380-1844[4]

A phase 3, randomized, double-blind study evaluated the safety and efficacy of switching to BIC/FTC/TAF (n=282) vs remaining on a baseline regimen of DTG + ABC/3TC or DTG/ABC/3TC STR (n=281) in VS adults with HIV-1. Key inclusion criteria were HIV-1 RNA <50 c/mL at screening for ≥3 months with no history of treatment failure, $eGFR_{CG}$

≥50 mL/min, and no documented or suspected resistance to study drugs. The primary endpoint was the proportion of participants with plasma HIV-1 RNA ≥50 c/mL at Week 48 by the FDA Snapshot analysis with a pre-specified non-inferiority margin of 4%.[5] Baseline demographics and disease characteristics were similar in both treatment groups. The median age across groups was 45 to 47 years old, most participants were male and 73% were white in both groups.[4]

Lipid safety results through Week 48[4,5]

Switching to BIC/FTC/TAF was associated with similar changes in fasting lipid parameters compared to remaining on DTG/ABC/3TC, though there was a small, significant decrease in TG (Table 6). LDL elevations (fasting >190 mg/dL) were reported as Grade 3 or 4 laboratory abnormalities in 5% of participants in each arm through Week 48.

Table 6. Change From Baseline in Fasting Lipid Parameters at Week 48[4]

Lipid Parameters	BIC/FTC/TAF (n=282)		DTG/ABC/3TC (n=281)		*P*-Value[a]
	Baseline Values	Median Change From Baseline	Baseline Values	Median Change From Baseline	
TC, mg/dL	182	0	186	+2	0.77
LDL, mg/dL	113	+1	118	+2	0.42
HDL, mg/dL	49	-1	48	0	0.13
TG, mg/dL	111	-5	111	+3	0.028
TC:HDL ratio	3.7	0	3.8	0	0.56

[a]*P*-values from 2-sided Wilcoxon rank-sum test.

Extension phase – lipid safety results[36]

The long-term efficacy and safety of BIC/FTC/TAF were evaluated in an OLE. A total of 526 participants completed the 48-week randomized phase and 524 participants entered the OLE phase. The all-BIC/FTC/TAF group consisted of participants who received ≥1 dose of BIC/FTC/TAF; this was measured at the first dose of BIC/FTC/TAF in the OLE for participants who switched from DTG/ABC/3TC at Week 48 and participants who continued to receive BIC/FTC/TAF from baseline.

In the all-BIC/FTC/TAF group, changes from baseline through Week 96 in fasting lipids were reported (Table 7). An increase in LDL was reported at Week 96; all other fasting lipids were stable. During the study 17 participants (3%) initiated lipid-modifying agents.

Table 7. Change From Baseline in Fasting Lipid Parameters Through Week 96[36]

Lipid Parameters	All BIC/FTC/TAF		
	Median at BIC/FTC/TAF Start	Median Change After BIC/FTC/TAF Start	
		Week 48 (n=468)	Week 96 (n=269)
TC, mg/dL	184	-3	+2
LDL, mg/dL	117	+2	+12
HDL, mg/dL	49	-1	-1
TG, mg/dL	111	-3	+1
TC:HDL ratio	3.7	0	0.1

Study GS-US-311-1717[6]

Study 1717 is a phase 3b, randomized, double-blind, multicenter, active-controlled clinical trial in VS adult participants with HIV-1 evaluating the efficacy and safety of switching to FTC/TAF (n=280) or continuing 3TC/ABC (n=276) while remaining on the same third agent. Participants were virologically stable (HIV-1 RNA <50 c/mL) on 3TC/ABC plus a third agent for ≥6 months and with $eGFR_{CG}$ ≥50 mL/min prior to switch. The primary endpoint was the percentage of participants maintaining virologic suppression (HIV-1 RNA <50 c/mL) by FDA Snapshot analysis at Week 48, with a pre-specified non-inferiority margin of 10%. Participants in the FTC/TAF arm on boosted PIs (ATV or DRV boosted by RTV or COBI, LPV + RTV) vs an unboosted third agent (nevirapine, EFV, RPV, RAL, DTG, MVC), received FTC/TAF 200/10 mg vs 200/25 mg, respectively. Baseline demographics and disease characteristics were similar between treatment arms, with similar demographics for age, gender, race and duration on 3TC/ABC before enrollment in each treatment group.[6]

Lipid safety results through Week 48

Switching to FTC/TAF was associated with decreases or smaller increases in lipids vs remaining in the 3TC/ABC arm (Table 8). There were no changes in the TC:HDL ratios in either arm (*P*=0.14). The proportion of participants who initiated lipid-lowering medications during the study was 9% in the FTC/TAF arm vs 7% in the 3TC/ABC arm (*P*=0.43).

Table 8. Median Change From Baseline in Fasting Lipid Parameters at Week 48[6]

Lipid Parameters	FTC/TAF + Third Agent (n=280)		3TC/ABC + Third Agent (n=276)		*P*-Value
	Baseline Values	Median Change From Baseline	Baseline Values	Median Change From Baseline	
TC, mg/dL	198	-1	201	+3	0.18
LDL, mg/dL	122	+2	125	+4	0.54
HDL, mg/dL	55	-2	52	+2	<0.001
TG, mg/dL	125	0	131	0	0.48

Lipid Safety Profile of TAF vs Other TFV-Based Regimens

Integrated Data through Week 144: GS-US-292-0104 and GS-US-292-0111[9-13]

An integrated analysis of two phase 3, prospective, randomized, double-blind, active-controlled clinical trials was conducted to compare E/C/F/TAF (n=866) to E/C/F/TDF (n=867) in ARV-naive adults with HIV-1. Key inclusion criteria were HIV-1 RNA ≥1000 c/mL, $eGFR_{CG}$ ≥50 mL/min, and genotypic sensitivity to study drugs. The primary endpoint was the percentage of participants with HIV-1 RNA <50 c/mL at Week 48 by the FDA Snapshot analysis. The secondary endpoints were efficacy and safety through Week 96 and Week 144. The predefined criterion for non-inferiority was a pre-specified non-inferiority margin of 12%. Baseline demographics and disease characteristics were similar between treatment arms, with similar demographics for age, gender, and race in each treatment group.[9]

Lipid safety results through Week 144[10,12,13]

There were no differences in serious cardiovascular or cerebrovascular events between the two arms: E/C/F/TAF, n=24 (2.8%) vs E/C/F/TDF, n=33 (3.8% [*P*=0.28]). Lipid parameters at Week 144 were similar to Week 48 and Week 96 in both treatment arms. There were small, but significant, differences in the median change from baseline to Week 144 for fasting lipid parameters in participants on E/C/F/TAF vs E/C/F/TDF, respectively: TC (+31 vs +13 mg/dL; *P*<0.001), LDL (+19 vs +6 mg/dL; *P*<0.001), HDL (+6 vs +2 mg/dL; *P*<0.001), and TG (+20 vs +12 mg/dL; *P*=0.02). The median TC:HDL ratio was 3.7 at Week 144 in both arms. There was no difference in rate of initiation of lipid-modifying agents between the two arms (E/C/F/TAF, 5.5% [n=48]; E/C/F/TDF, 5.8% [n=50]; *P*=0.92).

Sub-analysis of age ≥50 years through Week 96[37]

No significant differences in median fasting lipid values or in the TC:HDL ratio were observed, and similar proportions of participants (12.4% for E/C/F/TAF vs 12.3% for E/C/F/TDF; *P*>0.05) initiated a lipid-lowering agent.

Study GS-US-380-1490[14,15,16]

A phase 3, prospective, randomized, double-blind, active-controlled clinical trial compared BIC/FTC/TAF (n=320) to DTG + FTC/TAF (n=325) in ARV-naive adults with HIV-1. Key inclusion criteria were HIV-1 RNA ≥500 c/mL at screening, $eGFR_{CG}$ ≥30 mL/min, and genotypic sensitivity to the NRTI components of study drugs. The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 c/mL at Week 48 by the FDA Snapshot analysis, with a pre-specified non-inferiority margin of 12%. Secondary endpoints were efficacy and safety through Week 96 and Week 144. Baseline demographics and disease characteristics were similar in both treatment groups. The median age across groups was 33 to 34 years old, most participants were male, white and HIV-1 RNA <100,000 c/mL at baseline.[16]

Lipid safety results through Week 144[31]

Table 9. Changes From Baseline in Fasting Lipid Parameters at Week 144[31]

Lipid Parameters	BIC/FTC/TAF (n=320)		DTG + FTC/TAF (n=325)		*P*-Value[a]
	Baseline Values	Median Change From Baseline	Baseline Values	Median Change From Baseline	
TC, mg/dL	156	+12	161	+12	0.88
LDL, mg/dL	98	+19	99	+19	0.68
HDL, mg/dL	43	+3	43	+5	0.17
TG, mg/dL	97	+2	95	+2	0.97
TC:HDL ratio	3.7	0	3.7	-0.1	0.24

[a]*P*-values were from the 2-sided Wilcoxon rank sum test to compare the median change from baseline between the 2 treatment groups.

Lipid safety results through Week 240[8,33]

At the Week 144 secondary endpoint all participants were offered enrollment in the OLE phase with BIC/FTC/TAF. In Study 1490, 265 participants who were initially randomized to DTG + FTC/TAF switched to BIC/FTC/TAF and 254 participants continued BIC/FTC/TAF in the OLE.

In participants who were initially randomly assigned to receive BIC/FTC/TAF, changes from baseline through Week 240 in fasting lipids were reported (Table 10). There were numerical increases in most fasting lipid parameters and TC:HDL ratio remained stable from baseline. At BIC/FTC/TAF initiation 7% of study participants were taking lipid-lowering medications and 6% initiated lipid-lowering medications during the study. Additionally, 1% of participants initiated lipid-lowering medications between Weeks 192 and 240.

Table 10. Change From Baseline in Fasting Lipid Parameters at Week 240[8a]

Lipid Parameters	BIC/FTC/TAF	
	Median Baseline Values (n=320)	Median Change at Week 240
TC, mg/dL	156	+22
LDL, mg/dL	98	+21
HDL, mg/dL	43	+3
TG, mg/dL	97	+16
TC:HDL ratio	3.7	-

[a]Only included participants who were initially randomized to receive BIC/FTC/TAF.

Study GS-US-311-1089[18,38]

Study 1089 was a phase 3, randomized, double-blind, multicenter, active-controlled clinical trial in VS adult participants with HIV-1 (N=663) that evaluated the efficacy and safety of switching to FTC/TAF (n=333) or continuing FTC/TDF (n=330) while remaining on the same third drug. Participants were virologically stable (HIV-1 RNA <50 c/mL) on FTC/TDF plus a third agent for ≥6 months and with $eGFR_{CG}$ ≥50 mL/min prior to the switch. The primary endpoint was the percentage of participants maintaining virologic suppression (HIV-1 RNA <50 c/mL) by FDA Snapshot analysis at Week 48, with a pre-specified non-inferiority margin of 10%. Participants randomized to the FTC/TAF treatment arm and on boosted PIs (ATV + RTV, DRV + RTV, LPV + RTV) vs an unboosted third agent, received FTC/TAF 200/10 mg vs 200/25 mg, respectively. Baseline demographics and disease characteristics were similar between treatment arms, with similar demographics for age, gender, race, and duration on 3TC/ABC before enrollment in each treatment group.

Lipid safety results[18]

Median changes in lipid parameters (mg/dL) from baseline to Week 96 in the FTC/TAF and FTC/TDF arms were: TC, +14 vs +1 (P<0.001); LDL, +14 vs +4 (P<0.001); HDL, +1 vs -1 (P=0.023), respectively. There were no differences in change in TC:HDL ratio in either arm through Week 96 (+0.1 for both FTC/TAF and FTC/TDF; P=0.26). Similar proportions of participants initiated lipid-lowering agents: 7.2% of participants receiving FTC/TAF and 6.4% of participants receiving FTC/TDF (P=0.76).

Sub-analysis of participants age ≥50 years old through Week 96[39]

In a subgroup analysis in participants ≥50 years old, there were no significant differences (P>0.05) in median fasting lipid values or in the TC:HDL ratio when switching to FTC/TAF vs remaining on FTC/TDF. Additionally, initiation of lipid-lowering agents was similar regardless of FTC/TAF or FTC/TDF treatment arm (8% FTC/TAF vs 6% FTC/TDF; P=0.65).

Sub-analysis of Black vs non-Black participants through Week 96[40]

In a subgroup-analysis by race, Black participants on FTC/TAF vs Black participants on FTC/TDF had higher TC (212 vs 183 mg/dL; P=0.04) and HDL (60 vs 54 mg/dL; P=0.01).

There were no significant differences in LDL, TG, and TC:HDL ratios between the subgroups of Black participants treated with FTC/TAF or FTC/TDF (all *P*>0.05).

Study GS-US-366-1216 and Study GS-US-366-1160

Two phase 3, randomized, double-blind, active-controlled, non-inferiority studies evaluated the efficacy, safety, and tolerability of switching to RPV/FTC/TAF vs continuing on RPV/FTC/TDF (N=630) or EFV/FTC/TDF (N=875) for 96 weeks in VS (HIV-1 RNA <50 c/mL) adults with HIV-1.[19,20]

The primary endpoint for both studies was to evaluate the efficacy of switching from RPV/FTC/TDF or EFV/FTC/TDF to RPV/FTC/TAF, measured by the proportion of participants who maintained virologic suppression at Week 48 by FDA Snapshot Analysis.[19,20] Fasting lipids (TC, LDL, HDL, and TG) were measured at baseline and every 24 weeks up to Week 96.[20] Baseline demographics and disease characteristics are presented below (Table 11).

Table 11. Baseline Demographics and Disease Characteristics[19,20]

Key Demographics		Study 1216		Study 1160	
		RPV/FTC/TAF (n=316)	RPV/FTC/TDF (n=314)	RPV/FTC/TAF (n=438)	EFV/FTC/TDF (n=437)
Age, median, years		46	44	49	48
Male, n (%)		275 (87)	289 (92)	373 (85)	390 (89)
Race or ethnicity, n (%)	White	238 (75)	235 (75)	291 (66)	292 (67)
	Black or African descent	65 (21)	54 (17)	118 (27)	120 (27)
Duration of current regimen, median, years		2.3	2.5	6.5	6.6
Diabetes mellitus, n (%)		5 (2)	10 (3)	26 (6)	24 (5)
Hypertension, n (%)		66 (21)	55 (18)	118 (27)	122 (28)

Lipid safety results through Week 96

Fasting lipid changes from baseline are presented in Table 12.[19,20]

Study 1216: At baseline, 44 participants (14%) in the RPV/FTC/TAF group and 45 (14%) in the RPV/FTC/TDF group were taking lipid-lowering medications (*P*=0.91). Twenty-six participants (8%) on RPV/FTC/TAF and 8 (3%) on RPV/FTC/TDF initiated therapy during the study (*P*=0.002).[41]

Study 1160: At baseline, 89 participants (20%) in the RPV/FTC/TAF group and 80 (18%) in the EFV/FTC/TDF group were taking lipid-lowering medications (*P*=0.49). Twenty-two participants (5%) on RPV/FTC/TAF and 26 (6%) on the EFV/FTC/TDF initiated therapy during the study (*P*=0.56).[41]

Table 12. Fasting Lipid Changes at Week 96 From Baseline[19,20]

Lipid Parameters	Study 1216					Study 1160				
	RPV/FTC/TAF		RPV/FTC/TDF		*P*-Value[a]	RPV/FTC/TAF		EFV/FTC/TDF		*P*-Value[a]
	Baseline Values	Median Change From Baseline	Baseline Values	Median Change From Baseline		Baseline Values	Median Change From Baseline	Baseline Values	Median Change From Baseline	
TC, mg/dL	173	+19	167	+3	<0.001	191	-13	192	-3	<0.001
LDL, mg/dL	109	+15	105	+3	<0.001	115	-2	117	0	0.22
HDL, mg/dL	47	+2	46	0	0.006	52	-4	53	0	<0.001
TG, mg/dL	101	+16	100	+3	<0.001	116	+1	116	+4	0.14
TC:HDL	3.6	+0.2	3.5	0	0.03	3.6	+0.1	3.5	0	0.06

[a]Two-sided Wilcoxon rank-sum test was used to compare treatment groups within each study.

Study GS-US-380-1961[21,22]

A phase 3, prospective, randomized, multi-center, open-label clinical trial compared switching to BIC/FTC/TAF 50/200/25 mg STR (n=234) vs staying on a baseline regimen of E/C/F/(TAF or TDF) or ATV + RTV + FTC/TDF (n=236) in VS adult women with HIV-1. Key inclusion criteria were completion of the Week 48 OLE, Week 96, or Week 144 visits from Gilead-sponsored studies GS-US-236-0128, GS-US-292-0109, and GS-US-292-0104/GS-US-292-0111, respectively. Participants had received a stable ARV regimen with documented HIV-1 RNA plasma levels <50 c/mL for ≥6 months and had $eGFR_{CG}$ ≥50 mL/min. The primary endpoint was the proportion of participants with plasma HIV-1 RNA ≥50 c/mL at Week 48 by the FDA Snapshot analysis with a pre-specified non-inferiority margin of 4%. Baseline demographics and disease characteristics are presented below (Table 13).

Table 13. Baseline Demographics and Disease Characteristics[21,42]

Key Demographics		BIC/FTC/TAF (n=234)	E/C/F/(TAF or TDF) or ATV + RTV + FTC/TDF (n=236)
Age, median (range), years		39 (21–63)	40 (20–63)
Race or ethnicity, %	Black or African descent	39	35
	White	28	28
	Asian	21	23
	Latinx	15	16
Baseline regimen at randomization, n (%)	E/C/F/TAF	124 (53)	125 (53)
	E/C/F/TDF	99 (42)	98 (42)
	ATV + RTV + FTC/TDF	11 (5)	13 (6)

Lipid safety results through Week 48[21]

Switching to BIC/FTC/TAF was associated with similar changes in fasting lipid parameters compared to remaining on the baseline regimen, though there was a small, statistically significant decrease in TG (Table 14). A higher proportion of participants were taking lipid lowering agents at baseline in the BIC/FTC/TAF arm (BIC/FTC/TAF 3% vs remaining on baseline regimen 6%) and initiated treatment during the study (BIC/FTC/TAF 2% vs remaining on baseline regimen 4%) compared to staying on a baseline regimen. LDL elevations (fasting >190 mg/dL) were reported as Grade 3 or 4 laboratory abnormalities in

3% of participants on BIC/FTC/TAF and 6% of participants remaining on baseline regimen through Week 48.

Table 14. Change From Baseline in Fasting Lipid Parameters at Week 48[21]

Lipid Parameters	BIC/FTC/TAF (n=234)		Remained on Baseline Regimen (n=236)		*P*-Value
	Baseline Values	Median Change From Baseline	Baseline Values	Median Change From Baseline	
TC, mg/dL	196	-4	193	-1	0.22
LDL, mg/dL	120	-3	122	-1	0.37
HDL, mg/dL	56	-1	56	-1	0.56
TG, mg/dL	105	-10	99	+4	<0.001
TC:HDL	N/A	0	N/A	0	0.55

GS-US-292-0109[23-29]

GS-US-292-0109 was a phase 3, randomized, open-label, active-controlled clinical trial that evaluated the efficacy and safety of switching to E/C/F/TAF (n=959) compared to continuing a TDF-containing regimen (n=477) in VS participants with HIV-1. Key inclusion criteria were HIV-1 RNA <50 c/mL for ≥6 months on a stable TDF-containing regimen and eGFR ≥50 mL/min. The primary endpoint was to evaluate if E/C/F/TAF was non-inferior to continuing a TDF-containing regimen by determining the proportion of participants who maintained virologic suppression (HIV-1 RNA <50 c/mL) at Week 48 by FDA Snapshot analysis. The pre-specified non-inferiority margin was 12%. The secondary endpoints were efficacy of E/C/F/TAF through Week 96, and safety and tolerability of E/C/F/TAF through Week 48 and Week 96. Baseline demographics and disease characteristics were similar between treatment arms (Table 15).

Table 15. Baseline Demographics and Disease Characteristics[23]

Key Demographics and Characteristics		E/C/F/TAF (n=959)	FTC/TDF + Third Agent (n=477)
Age, median, years		41	40
Female, %		11	11
Race or ethnicity, %	White	68	66
	Black or African descent	18	21
	Latinx	26	17
Baseline regimen, n	EFV/FTC/TDF	251	125
	ATV + (RTV or COBI) + FTC/TDF	402	199
	E/C/F/TDF	306	153

Lipid safety results through Week 96[23,27,29]

Lipid parameters at Week 96 were similar to Week 48 in both treatment arms. Fasting lipids at Week 96 showed small, but statistically significant increases in participants switched to E/C/F/TAF vs participants who continued their TDF-containing regimen (TC, 200 mg/dL vs 186 mg/dL; LDL, 128 mg/dL vs 117 mg/dL; HDL, 52 mg/dL vs 50 mg/dL; TG, 125 mg/dL vs 114 mg/dL, respectively). TC:HDL ratios were 3.9 in participants who received E/C/F/TAF vs 3.7 in participants who continued their TDF-containing regimen (*P*=0.01). Lipid-lowering

medications were initiated in 8% of participants on E/C/F/TAF and 5% of participants on a TDF-containing regimen (*P*=0.04).

GS-US-236-0128[30]

A phase 3, randomized, double blind, active-controlled trial evaluated the efficacy and safety of E/C/F/TDF vs RTV-boosted ATV + FTC/TDF in treatment-naive adult women with HIV-1. After the double-blinded phase, VS women in the RTV-boosted ATV + FTC/TDF treatment group were re-randomized in a 3:1 fashion to switch to E/C/F/TAF (n=159) or continue RTV-boosted ATV + FTC/TDF (n=53) in an OLE phase. Endpoints were virologic suppression (HIV-1 RNA <50 c/mL), renal and bone density parameters, safety, and tolerability at Week 48.

Lipid safety results through Week 48

Changes in fasting lipid values showed small, but statistically significant increases in participants switched to E/C/F/TAF vs continuation of RTV-boosted ATV + FTC/TDF (TC, +33 mg/dL vs 0 mg/dL; *P*<0.001; LDL, +23 mg/dL vs -2 mg/dL; *P*<0.01; HDL, +8 mg/dL vs -2 mg/dL; *P*=0.01). There were no significant differences in TC:HDL ratios (3.5 vs 3.3, *P*=0.08) or changes in TG (+2 mg/dL vs +5 mg/dL; *P*=0.3). Lipid-lowering medications were initiated in 1% of participants on E/C/F/TAF and 0% of participants on boosted ATV + FTC/TAF.

Lipid Safety Profile of TAF in a Single-Arm Study

GS-US-292-0112[42-46]

A phase 3, single-arm, open label trial evaluated the efficacy and safety of switching to E/C/F/TAF in VS adults with HIV-1 (N=242) with renal impairment. Key inclusion criteria were HIV-1 RNA <50 c/mL for ≥6 months on a stable ARV regimen and stable $eGFR_{CG}$ between 30 to 69 mL/min. The primary endpoint was the change from baseline in eGFR and actual GFR at Week 24. Secondary endpoints included efficacy, safety, and tolerability of E/C/F/TAF through Week 144. Baseline demographics and disease characteristics by baseline $eGFR_{CG}$ strata are shown (Table 16). Pre-switch NRTIs were TDF (65%), ABC (22%), other NRTIs (7%), or none (5%); third agents included PI (44%), non-nucleoside reverse transcriptase inhibitors (42%), integrase strand transfer inhibitors (24%) and MVC (3%).

Table 16. Baseline Demographics and Disease Characteristics[43,44]

Key Demographics and Characteristics	Baseline eGFR 30 to <50 mL/min (n=80)	Baseline eGFR 50–69 mL/min (n=162)	Total (N=242)
Age, median (Q1, Q3), years	59 (52, 66)	58 (51, 64)	58 (52, 65)
Age ≥65 years, n (%)	25 (31)	38 (23)	63 (26)
Female, n (%)	21 (26)	29 (18)	50 (21)
Black or African descent, %	18	19	18
Hypertension, %	50	34	39
Diabetes, %	15	13	14

Lipid safety results through Week 144[46]

Switching from a TDF-containing regimen to E/C/F/TAF led to increases from baseline to Week 144 in TC (194 to 210 mg/dL), LDL (122 to 132 mg/dL), TG (122 to 139 mg/dL), and TC:HDL ratio (3.6 to 3.7), but no change in HDL (54 mg/dL). Switching from an ABC-containing regimen led to decreases in most fasting lipid parameters (TC, 198 to 181 mg/dL; LDL, 114 to 110 mg/dL; TC:HDL, 3.7 to 3.5), an increase in TG (160 to 179 mg/dL) and no change in HDL (54 mg/dL).

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Abbreviations

3TC=lamivudine
ABC=abacavir
ARV=antiretroviral
ATV=atazanavir
BIC=bictegravir
CG=Cockcroft-Gault
c/mL=copies/mL
COBI=cobicistat
DRV=darunavir
DTG=dolutegravir
E/C/F/TAF=elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
E/C/F/TDF=elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate
EFV=efavirenz
FTC=emtricitabine
LPV=lopinavir
MVC=maraviroc
NRTI=nucleos(t)ide reverse transcriptase inhibitor
OLE=open label extension
PI=protease inhibitor
PWH=people with HIV-1
RPV=rilpivirine
RTV=ritonavir
STR=single tablet regimen
TAF=tenofovir alafenamide
TC=total cholesterol
TDF=tenofovir disoproxil fumarate
TFV=tenofovir
TG=triglycerides
VS=virologically suppressed

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