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Lipid Parameters and Lipid-Modifying Agent Use in Participants Initiating F/TAF or F/TDF for PrEP in the DISCOVER Trial

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Introduction

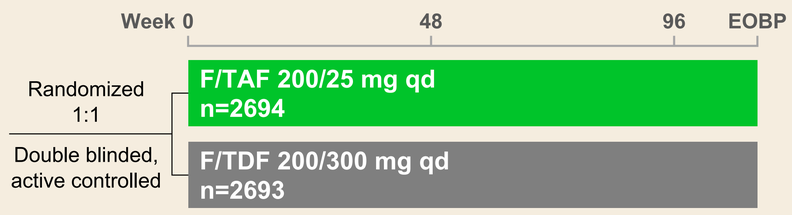
- The DISCOVER study (ClinicalTrials.gov NCT02842086) is a Phase 3, randomized, double-blind, controlled trial that demonstrated the noninferiority of emtricitabine/tenofovir alafenamide (F/TAF) to emtricitabine/tenofovir disoproxil fumarate (F/TDF) for pre-exposure prophylaxis (PrEP) in men who have sex with men (MSM) and transgender women (TGW)[1]
- The tenofovir prodrugs TAF and TDF have differing effects on lipid levels
  - TDF causes reductions in low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol by unknown mechanisms[2,3]
  - In HIV treatment studies, switching from TDF to TAF has been associated with increases in lipids, likely attributable to removal of the lipid-reducing effect of TDF[4]
  - The DISCOVER study offers a unique opportunity to examine the effects of TAF and TDF on lipid parameters, avoiding the potentially confounding effects of viremic suppression and antiretroviral regimen switching present in people with HIV
- The present analysis examines the effects of F/TAF and F/TDF on lipid parameters in people without HIV initiating PrEP

Objectives

- To assess the effects of initiating F/TAF or F/TDF for PrEP on lipid parameters in participants in the DISCOVER study
- To identify factors associated with lipid-modifying agent (LMA) initiation

Methods

Study Design



EOBP, end of blinded phase.

- Eligibility:
  - 2+ episodes of condomless anal sex in the past 12 wk, or rectal gonorrhea/chlamydia or syphilis in the past 24 wk
  - HIV and hepatitis B virus negative, and estimated glomerular filtration rate by Cockcroft-Gault method ($eGFR_{CG}$) ≥60 mL/min
- Study conducted in Europe and North America in cities/sites with high HIV incidence
- At EOBP, participants had the option to receive F/TAF in the open-label phase
- Fasting lipids (total cholesterol [TC], direct LDL and HDL, and triglycerides [TG]) were measured every 24 wk
- The present analysis compares fasting lipids between treatment groups from baseline through Week 96 in participants who were not on PrEP at randomization; nonfasting measurements were excluded
- LMA initiations were identified in the blinded phase from concomitant medication records
  - LMAs defined as medication with Anatomical Therapeutic Chemical classification of "lipid modifying agents" and CMDECOD (Standardized Medication Name) containing "statin" per World Health Organization Drug Dictionary version BMAR2020
- Multivariable logistic regression was used in a predictive analysis, including study arm, age, body mass index (BMI), race, and baseline history of diabetes, hypertension, cardiovascular disease, or hyperlipidemia as potential predictors of LMA initiation

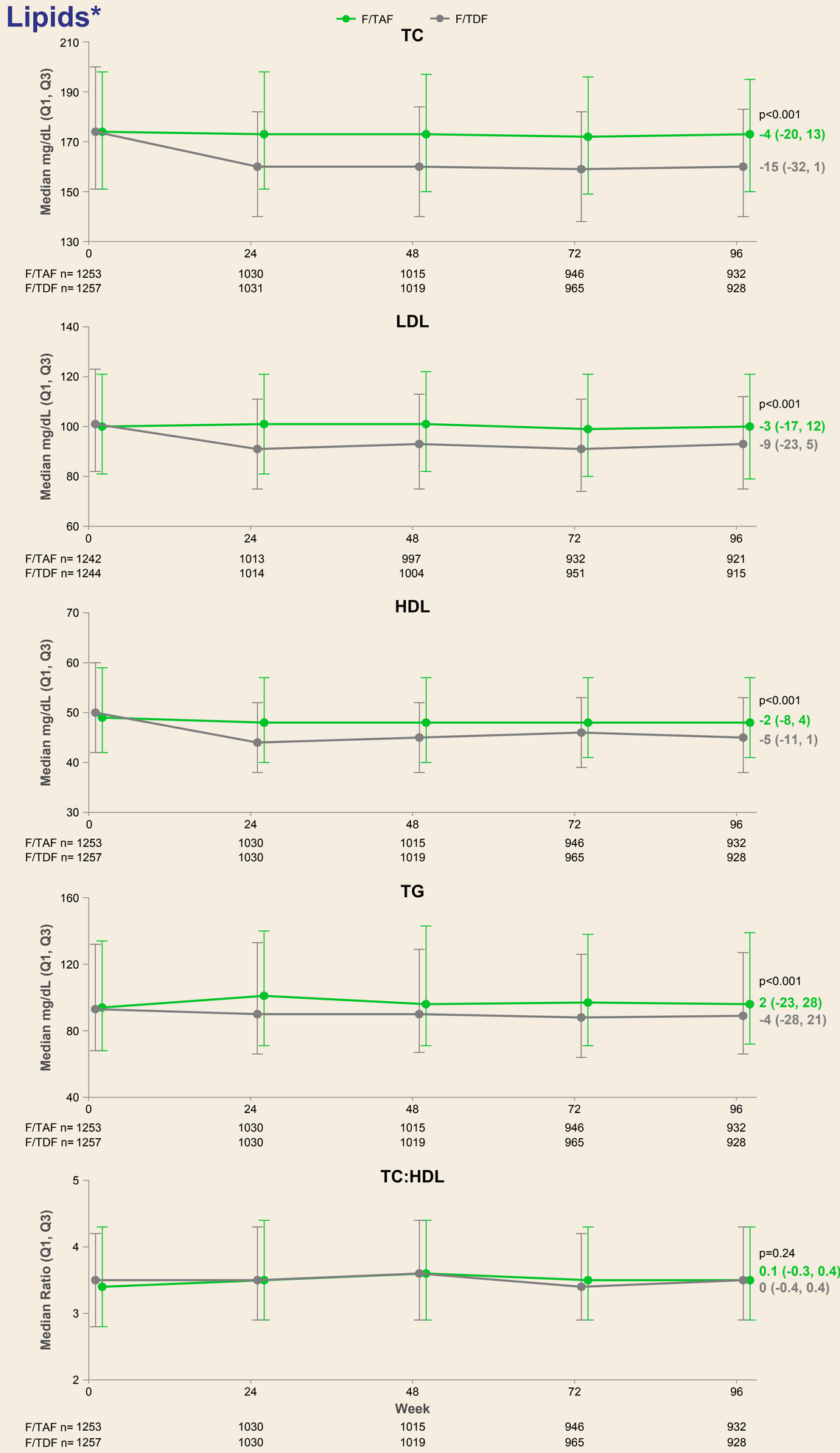
Results

Baseline Demographics and Clinical Characteristics

		F/TAF: n=2229	F/TDF: n=2253
Demographics	Median age, y (Q1, Q3)	34 (27, 43)	34 (28, 43)
	Race, n (%)		
	White	1873 (84)	1868 (83)
	Black/mixed Black	199 (9)	206 (9)
	Asian	92 (4)	102 (5)
	Hispanic or Latinx, n (%)	554 (25)	610 (27)
	TGW, n (%)	41 (2)	27 (1)
	Median BMI, kg/m^2 (Q1, Q3)	25.3 (23.1, 28.5)	25.3 (22.9, 28.3)
	LMA use, n (%)	102 (5)	90 (4)
Comorbidities, n (%)	History of diabetes mellitus	69 (3)	67 (3)
	History of hypertension	226 (10)	230 (10)
	History of cardiovascular disease	28 (1)	15 (1)
	History of hyperlipidemia	260 (12)	248 (11)

Q, quartile.

Lipids*

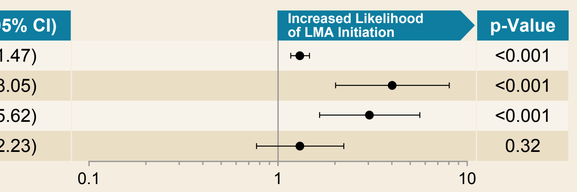


*p-values from 2-sided Wilcoxon rank-sum test comparing change at Week 96 between study arms; data labels show median (Q1, Q3) changes from baseline at Week 96.

- Median TC, LDL, and HDL decreased in both arms through Week 96, but by a greater degree in the F/TDF arm; TC:HDL ratios were similar and not significantly changed from baseline
- Median TG levels increased slightly with F/TAF and decreased slightly with F/TDF

Multivariate Model for Initiation of Lipid-Modifying Agents

Variable	Comparison	Odds Ratio (95% CI)	p-Value
Age	Every 5-y increase	1.31 (1.17, 1.47)	<0.001
History of diabetes mellitus	Yes vs No	4.03 (2.02, 8.05)	<0.001
History of hyperlipidemia	Yes vs No	3.05 (1.66, 5.62)	<0.001
Study arm	F/TAF vs F/TDF	1.31 (0.77, 2.23)	0.32



CI, confidence interval.

- In the F/TAF vs F/TDF arms, 102 (5%) vs 90 (4%) participants were taking an LMA at the time of randomization, and 33 (1%) vs 26 (1%), respectively, initiated an LMA during the study (p=0.36)
- Stepwise multivariable logistic regression revealed that traditional cardiovascular risk factors (older age, diabetes, and hyperlipidemia) were associated with LMA initiation, whereas study arm assignment was not

Conclusions

- Among DISCOVER participants who initiated PrEP, F/TAF was associated with generally stable lipids through 96 wk of follow-up, whereas F/TDF was associated with expected reductions, especially in TC, LDL, and HDL
  - The clinical significance of lipid changes in the F/TDF arm is uncertain given the proportional declines in LDL and HDL
- TC:HDL ratios were similar between arms and clinically significant TG changes were not observed in either arm
- Neither F/TAF nor F/TDF for PrEP was associated with initiation of a lipid-modifying agent, whereas traditional cardiovascular risk factors including age, diabetes, and hyperlipidemia were
- These results suggest that daily oral PrEP has minimal overall effect on lipids in this participant population over 96 wk

References: **1.** Mayer K, et al. Lancet 2020;396:239-54; **2.** Tungsiripat M, et al. AIDS 2010;24:1781-4; **3.** Santos JR, et al. Clin Infect Dis 2015;61:403-8; **4.** Lacey A, et al. AIDS 2020;34:1161-70.

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