DISCOVER: No Effect of Hormones on F/TAF or F/TDF PK, Efficacy, and Safety in Transwomen

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Introduction

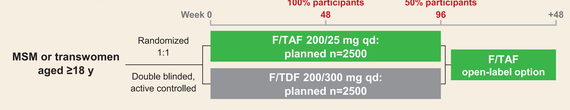
- Transwomen are at high risk of HIV infection, with an estimated HIV infection prevalence of nearly 20%[1]
- The DISCOVER study (NCT02842086) is an ongoing Phase 3, randomized, controlled trial evaluating the efficacy and safety of emtricitabine/tenofovir alafenamide (F/TAF) for pre-exposure prophylaxis (PrEP) among cismen who have sex with men (MSM) and transwomen at high risk of HIV infection
- At the primary endpoint (when 100% of participants completed Week 48 and 50% completed Week 96)[2]:
  - F/TAF was noninferior to emtricitabine/tenofovir disoproxil fumarate (F/TDF) in preventing HIV infection
  - F/TAF had significantly better bone and renal safety measures than F/TDF
- Drug-interaction studies have shown that F/TAF and hormonal contraceptives can be coadministered with no effect on ethinyl estradiol exposures, or follicle-stimulating hormone, luteinizing hormone, or progesterone levels in women taking F/TAF with hormonal contraceptives (data on file, Gilead)[3]

Objectives

- To assess the pharmacokinetics (PK), efficacy, and safety of F/TAF in transwomen, including those taking gender-affirming hormones, in DISCOVER

Methods

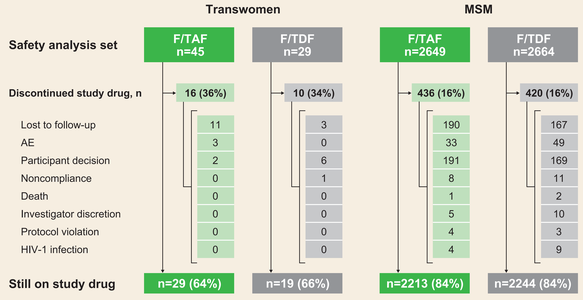
Study Design



- Eligibility: high sexual risk of HIV
  - 2+ unique condomless anal sex partners in past 12 wk, or rectal gonorrhea/chlamydia or syphilis in past 24 wk
  - HIV and hepatitis B virus negative, and estimated glomerular filtration rate by Cockcroft-Gault ($eGFR_{CG}$) ≥60 mL/min
- Study conducted in Europe and North America in cities/sites with high HIV incidence
- Assessments:
  - Safety: adverse events (AEs), bone mineral density, and renal biomarkers
  - HIV lab testing: rapid HIV testing on site and central laboratory
  - Sexually transmitted infection assessment at every visit
  - PK assessment: in a subset of participants at Week 4, tenofovir-diphosphate (TFV-DP) and FTC–triphosphate (TP) concentrations were quantified by liquid chromatography–tandem mass spectrometry methodology in peripheral blood mononuclear cell (PBMC) samples drawn 20–28 h postdose (C_{tau})
    - For participants receiving F/TAF, C_{tau} levels for TFV-DP and FTC-TP were statistically compared between transwomen taking gender-affirming hormones (n=17) and MSM (n=161) in the study using a lack of PK alteration boundary of 50–200% (based on historical safety and efficacy data)
    - For participants receiving F/TDF, C_{tau} levels for TFV-DP and FTC-TP in transwomen taking gender-affirming hormones (n=10) were descriptively compared with levels in MSM (n=155) due to the smaller sample size

Results

Reasons for Discontinuations: Transwomen vs MSM



Baseline Characteristics

	Transwomen		MSM	
	F/TAF n=45	F/TDF n=29	F/TAF n=2649	F/TDF n=2664
Demographics				
Median age, y (range)	33 (20–54)	28 (20–50)	34 (18–76)	34 (18–72)
Race, n (%)				
White	24 (53)	16 (55)	2240 (85)	2231 (84)
Black*	12 (27)	6 (21)	228 (9)	228 (9)
Asian	2 (4)	1 (3)	111 (4)	119 (4)
Hispanic or Latinx ethnicity, n (%)	17 (38)	16 (55)	618 (23)	667 (25)
Other baseline characteristics				
Taking F/TDF for PrEP at baseline, n (%)	4 (9)	2 (7)	461 (17)	438 (16)
Syphilis in past 24 wk, n (%)	5 (11)	4 (14)	225 (8)	259 (10)
Rectal gonorrhea in past 24 wk, n (%)	3 (7)	2 (7)	271 (10)	260 (10)
Rectal chlamydia in past 24 wk, n (%)	2 (4)	2 (7)	340 (13)	331 (12)
Condomless receptive anal sex, mean no. of partners in 90 d prior to screening (SD)	3.2 (3.3)	7.1 (11.6)	3.6 (6.0)	3.4 (6.1)
Recreational drug use in 3 mo prior to screening, n (%)	19 (43)	13 (46)	1766 (67)	1773 (67)
Binge drinking, n (%)†	13 (29)	10 (34)	1463 (56)	1496 (56)

*Includes black/mixed race; †≥6 drinks on 1 occasion. SD, standard deviation.

Concomitant Hormone Use by Transwomen

Participants, n (%)	F/TAF n=45	F/TDF n=29
Receiving ≥1 concomitant hormone	32 (71)	21 (72)
Receiving any concomitant hormone by preferred drug name		
Estradiol	25 (56)	15 (52)
Estradiol valerate	9 (20)	5 (17)
Progesterone	9 (20)	5 (17)
Estrogens conjugated	4 (9)	4 (14)
Estradiol cipionate	2 (4)	1 (3)
Medroxyprogesterone	0	2 (7)
Medroxyprogesterone acetate	1 (2)	0

Primary Endpoint Analysis: HIV Incidence

	Transwomen		MSM	
	F/TAF n=45	F/TDF n=28	F/TAF n=2625	F/TDF n=2637
HIV incidence rate/100 PY (95% CI)	0 (0, 6.00)	0 (0, 9.59)	0.16 (0.07, 0.34)	0.35 (0.19, 0.57)
Infections	0	0	7	15
Total PY of follow-up	62	39	4308	4348

CI, confidence interval; PY, person-years.

Treatment-Emergent AEs

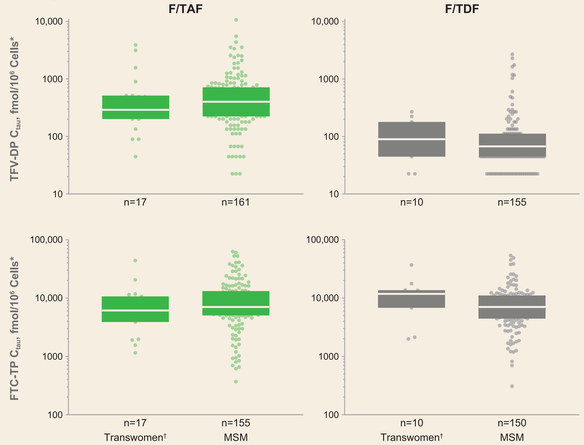
≥10% of Participants in Any Subgroup, n (%)	Transwomen		MSM	
	F/TAF n=45	F/TDF n=29	F/TAF n=2649	F/TDF n=2664
Any AE	39 (87)	23 (79)	2459 (93)	2471 (93)
Anal chlamydia infection	9 (20)	8 (28)	761 (29)	784 (29)
Oropharyngeal gonococcal infection	8 (18)	3 (10)	732 (28)	719 (27)
Proctitis gonococcal	8 (18)	3 (10)	685 (26)	668 (25)
Exposure to communicable disease	3 (7)	5 (17)	462 (17)	436 (16)
Diarrhea	11 (24)	3 (10)	419 (16)	419 (16)
Nasopharyngitis	5 (11)	1 (3)	345 (13)	354 (13)
Upper respiratory tract infection	11 (24)	4 (14)	345 (13)	306 (11)
Syphilis	3 (7)	3 (10)	339 (13)	318 (12)
Urethritis chlamydial	0	0	280 (11)	259 (10)
Nausea	8 (18)	3 (10)	188 (7)	184 (7)
Headache	5 (11)	5 (17)	181 (7)	175 (7)
Pharyngeal chlamydia infection	5 (11)	4 (14)	170 (6)	145 (5)
Oropharyngeal pain	5 (11)	4 (14)	148 (6)	136 (5)
Depression	3 (7)	3 (10)	93 (4)	89 (3)
Flatulence	0	3 (10)	39 (1)	51 (2)

Safety Assessments at Week 48

Change From Baseline at Week 48	Transwomen			MSM		
	F/TAF n=45	F/TDF n=29	p-Value	F/TAF n=2649	F/TDF n=2664	p-Value
Median urine β2M:Cr, % (Q1, Q3)	2.2 (-43.8, 46.2)	13.3 (-35.9, 51.7)	0.93	-10.9 (-41.9, 25.8)	15.4 (-22.6, 98.1)	<0.001
Median urine RBP:Cr, % (Q1, Q3)	-8.7 (-24.7, 37.8)	-4.1 (-36.1, 25.2)	0.69	0.3 (-24.9, 35.2)	20.1 (-12.6, 68.4)	<0.001
Median $eGFR_{CG}$, mL/min (Q1, Q3)	-4.0 (-12.8, 16.6)	-1.3 (-26.1, 19.6)	0.71	1.8 (-7.2, 11.1)	-2.3 (-10.8, 7.2)	<0.001
Dipstick proteinuria, n (%)	13 (29)	9 (33)	0.82	555 (21)	638 (24)	0.008
Median body weight, % (Q1, Q3)	1.6 (-2.8, 3.7)	1.9 (-4.2, 4.5)	0.81	1.3 (-1.5, 4.1)	0.0 (-2.8, 2.6)	<0.001
Median body weight, kg (Q1, Q3)	1.0 (-2.3, 2.5)	1.4 (-3.6, 3.1)	0.75	1.0 (-1.2, 3.3)	0.0 (-2.3, 2.1)	<0.001

β2M:Cr, β2-microglobulin:creatinine; Q, quartile; RBP:Cr, retinol-binding protein:creatinine.

Trough PBMC Concentrations



C_{tau}, fmol/10⁶ cells		F/TAF		F/TDF	
		Transwomen† n=17	MSM n=161	Transwomen† n=10	MSM n=155
TFV-DP	Geometric mean (%CV)	366 (144)	407 (157)	82.4 (76)	74.0 (235)
	GLSM ratio % (90% CI)	89.9 (54.0, 150)		N/A	
FTC-TP	Geometric mean (%CV)	5856 (114)	7268 (102)‡	9164 (80)	6710 (92)§
	GLSM ratio % (90% CI)	80.6 (53.8, 121)		N/A	

*Boxes depict median (Q1, Q3); *circles* depict individual data outside interquartile range; †Transwomen taking gender-affirming hormones; ‡n=155; §n=150. CV, coefficient of variation; GLSM, geometric least-squares mean; N/A, not applicable.

Conclusions

- The majority of transwomen in DISCOVER were taking gender-affirming hormones
- No transwomen in DISCOVER acquired HIV infection
- Safety outcomes in transwomen taking F/TDF and F/TAF were similar to those observed in MSM
- Intracellular PBMC concentrations of TFV-DP were higher in transwomen receiving F/TAF vs those receiving F/TDF
- Intracellular PBMC concentrations of TFV-DP and FTC-TP were similar between transwomen taking gender-affirming hormones and MSM

References: **1.** Becasen JS, et al. Am J Public Health. 2018 Nov 29:e1-8; **2.** Hare CB, et al. CROI 2019; abstr 104; **3.** Descovy [package insert]. Foster City, CA: Gilead Sciences, Inc.

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