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Descovy® (FTC/TAF) Coadministration With Feminizing Hormone Therapy

This document is in response to your request for information regarding Descovy® (emtricitabine/tenofovir alafenamide [FTC/TAF]) and coadministration with feminizing hormone therapy (FHT).

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Summary

PK DDI Evaluation

Based on the known PK profile (ie, absorption, distribution, metabolism, and excretion) of each active ingredient within FTC/TAF, estrogen, and progestin FHT, a clinically significant PK interaction would not be predicted.[1]

Clinical Studies: FTC/TAF Coadministered With FHT

In a subanalysis of DISCOVER, a phase 3 study, PBMC samples of TGW who were receiving GAHT concomitantly with FTC/TAF (n=17) had 10.1% lower trough levels of TFV-DP and 19.4% lower levels of FTC-TP (20–28 hours post dose at steady state) than those of a representative group of 161 MSM. These decreases are not expected to be clinically significant based on historical safety and efficacy data.[2]

In an observational cohort study performed in a subset of participants in TAF4TRANS, transgender participants AMAB did not have significant changes in hormone or TFV-DP concentrations while receiving FTC/TDF or FTC/TAF, regardless of GAHT use.[3] In another subset study of transgender participants AMAB who were receiving GAHT, there were no significant changes in hormone concentrations upon a switch from FTC/TDF to FTC/TAF.[4]

In two other subsets of data from TAF4TRANS, irrespective of concomitant GAHT use, levels of TFV in urine and TFV-DP in DBS were correlated during the use of FTC/TAF,[5] and TFV-DP levels were similar between users and non-users of GAHT during FTC/TAF use after stratification by sex assigned at birth.[6]

In the iFACT3 PK analysis of DDIs between FHT and FTC/TAF in TGW, there was no clinically significant effect of FHT on FTC/TAF.[7]

- In a subanalysis, levels of TFV and FTC in urine were similar when administered with and without FHT. TFV-DP and FTC-TP levels in PBMCs were comparable during FTC/TAF for PrEP use but did not correlate during FTC/TDF for PrEP use.[8]

PK DDI Evaluation[1]

Based on the known PK profile (ie, absorption, distribution, metabolism, and excretion) of each active ingredient within FTC/TAF, estrogen, and progestin FHT, a clinically significant PK interaction would not be predicted.

FTC/TAF PK

Table 1. FTC/TAF DDI Potential

DDI Mechanism		FTC	TAF
Drug Transporters	P-gp/BCRP	N/A	Substrate
	OATP1B1	N/A	Substrate
	OATP1B3	N/A	Substrate
Drug Metabolizing Enzymes	CYP3A	N/A	Minor substrate

Abbreviations: BCRP=breast cancer resistance protein; CYP=cytochrome; OATP=organic anion transporting polypeptide; P-gp=p-glycoprotein.

Relevant FTC/TAF Label Information

Based on drug interaction studies conducted with FTC and TAF, no clinically significant drug interactions have either been observed or are expected when FTC/TAF is combined with norgestimate/ethinyl estradiol.

Clinical Studies: FTC/TAF Coadministered With FHT

DISCOVER: Daily FTC/TAF vs FTC/TDF in MSM and TGW[2]

Study design and efficacy results

DISCOVER was a phase 3, randomized, double-blind, active-controlled, multinational study in 5387 HIV-negative adult MSM and TGW that compared the safety and efficacy of FTC/TAF (n=2694) vs FTC/TDF (n=2693). GAHT was common among TGW in the FTC/TAF (n=45) and FTC/TDF (n=29) arms (71% and 72% of TGW reported receiving ≥1 hormone, respectively; Table 2). No TGW in either arm of the study acquired HIV through Week 96.[2]

Subanalysis: PK results

In a subanalysis, PBMC samples of TGW who were receiving GAHT concomitantly with FTC/TAF had 10.1% lower trough levels of TFV-DP and 19.4% lower levels of FTC-TP (20–28 hours post dose at steady state) than those of a representative group of MSM (Table 2). These decreases were not expected to be clinically significant, based on historical safety and efficacy data.

Table 2. DISCOVER: Trough Concentrations of TFV-DP and FTC-TP in PBMC Samples[2]

	FTC/TAF		FTC/TDF	
	TGW on FHT (n=17)	MSM (n=161)	TGW on FHT (n=10)	MSM (n=155)
TFV-DP C_T, GM (%CV), fmol/10^6 cells	366 (144)	407 (157)	82.4 (76)	74 (235)
GLSM ratio, % (90% CI)	89.9 (54–150)		N/A	

	FTC/TAF		FTC/TDF	
	TGW on FHT (n=17)	MSM (n=161)	TGW on FHT (n=10)	MSM (n=155)
FTC-TP C_T, GM (%CV), fmol/10^6 cells	5856 (114)	7268[a] (102)	9160 (80)	6710[b] (92)
GLSM ratio, % (90% CI)	80.6 (53.8–121)		N/A	

Abbreviations: C_T= drug concentration at trough (20–28 hours post dose); GLSM=geometric least squares mean.
[a]n=155. [b]n=150.

TAF4TRANS: FTC/TAF for PrEP Switch Study for Transgender Individuals

Subanalysis: bidirectional effects of TFV-DP and hormone concentrations in GAHT users and non-users[3]

An observational cohort study was conducted among a subset of participants (N=39) enrolled in the TAF4TRANS clinical trial (NCT04616963) to evaluate the bidirectional effects of hormone and intraerythrocytic TFV-DP concentrations in transgender and gender-diverse participants who did and did not use GAHT. Eligible participants were ≥18 years old; were transgender or nonbinary (identifying as a gender different than their sex assigned at birth); were negative for HIV antigen/antibody; used FTC/TDF for ≥12 weeks, followed by FTC/TAF for ≥12 weeks; and had stored dried blood spot cards for assessment of hormone and TFV-DP levels.

Overall, the mean (SD) age was 34.7 (9.2) years, 27 participants (69%) were AMAB, 22 (56%) identified as TGW, and 9 (23%) were nonbinary or gender nonconforming. Eighteen participants AMAB were using GAHT, and most (89%) received a combination of estrogen, progesterone, and an antiandrogen, while the remaining participants received estrogen only.

Regardless of sex assigned at birth and use or non-use of GAHT, there were no significant differences in hormone or TFV-DP concentrations between when participants were receiving FTC/TDF and when they were receiving FTC/TAF. (Table 3).

Table 3. TAF4TRANS Observational Cohort: Hormone Levels in Participants AMAB During FTC/TDF and FTC/TAF Use by GAHT Use[3]

Hormone Measures, Median (IQR)	Users of GAHT (n=18)			Non-Users of GAHT (n=9)		
	During FTC/TDF	During FTC/TAF	*P*-Value	During FTC/TDF	During FTC/TAF	*P*-Value
Estradiol, pg/mL	108 (43–147)	114 (76–168)	0.35	27 (21–32)	26 (25–38)	0.1
Total testosterone, ng/dL	50 (9–379)	24 (8–281)	0.72	523 (372–626)	501 (356–634)	0.68
Free testosterone, pg/mL	6 (1–98)	6 (1–60)	0.88	150 (116–200)	168 (116–198)	0.59
SHBG, nmol/L	35 (21–55)	35 (25–59)	0.85	16 (13–21)	19 (12–22)	0.86

Subanalysis: hormone concentrations before and after switch from FTC/TDF to FTC/TAF for PrEP[4]

An observational cohort study was conducted among a subset of participants (N=30) enrolled in the TAF4TRANS clinical trial to evaluate and compare hormone concentrations among transgender individuals AMAB who switched from FTC/TDF to FTC/TAF for PrEP. Eligibility criteria were as follows: age ≥18 years, identified as a transgender person AMAB, had a negative HIV test before study enrollment, used FTC/TDF and FTC/TAF for ≥12 weeks, and had stored blood samples collected while on each PrEP agent. The primary

outcome was an assessment and comparison of hormone concentrations (estradiol, SHBG, and free/total testosterone) while participants were receiving FTC/TDF and FTC/TAF.

Table 4. TAF4TRANS Observational Cohort: Baseline Demographics by GAHT Use[4]

Key Demographics		Users of GAHT (n=20)	Non-Users of GAHT (n=10)
Age, mean ± SD, years		35.9±9.8	36.1±9.9
Gender identity, n (%)	TGW	19 (95)	5 (50)[a]
	Gender non-conforming	1 (5)	5 (50)
Type of GAHT, n (%)	Estrogen, progesterone, anti-androgen	17 (85)	N/A
	Estrogen alone	3 (15)	–
Duration of FTC/TDF use, median (IQR)		48 (13–59)	60 (39–102)
Duration of FTC/TAF use, median (IQR)		48 (36–48)	48 (35–48)

[a]*P*=0.004 for users vs non-users of GAHT.

There were no significant differences in hormone concentrations in participants using GAHT while they were taking FTC/TDF or after they switched to FTC/TAF (Table 5), and study investigators were unable to determine whether the different types of GAHT had similar effects on hormone concentrations.

Table 5. TAF4TRANS Observational Cohort: Hormone Levels in Participants AMAB During FTC/TDF and FTC/TAF Use by GAHT Use[4]

Hormone Measures, Median (IQR)	Users of GAHT (n=20)			Non-Users of GAHT (n=10)		
	During FTC/TDF	During FTC/TAF	*P*-Value	During FTC/TDF	During FTC/TAF	*P*-Value
Estradiol, pg/mL	92 (43–144)	104 (49–163)	0.68	28 (22–34)	27 (26–39)	0.36
Total testosterone, ng/dL	75 (11–394)	27 (10–396)	0.5	544 (378–686)	545 (378–621)	0.45
Free testosterone, pg/mL	14 (2–115)	7 (1–115)	0.56	160 (121–221)	169 (117–197)	0.39
SHBG, nmol/L	34 (20–52)	34 (20–54)	0.91	17 (14–20)	18 (13–21)	0.96

Subanalysis: GAHT and TFV-DP concentrations during FTC/TDF and FTC/TAF use[5]

An observational cohort study in a subset of TAF4TRANS participants assessed the correlation between TFV concentrations in urine and DBS during FTC/TDF and FTC/TAF use. The study further aimed to determine whether GAHT impacted the identified correlation. Participants in the TAF4TRANS study who had received ≥12 weeks of FTC/TDF and FTC/TAF for PrEP and had both urine and DBS samples available were included. Thirty-seven individuals met the inclusion criteria: 48.6% were White; the median (IQR) age was 33 (28.5–39) years. Seventeen of the 25 individuals who were AMAB and 10 of the 12 individuals assigned female at birth were receiving GAHT.

Regardless of the use of concomitant GAHT, a significant correlation was seen in levels of TFV in urine and TFV-DP in DBS with FTC/TAF but not with FTC/TDF use (Table 6).

Table 6. GAHT and TFV-DP Substudy of TAF4TRANS: Correlation Between ARV PKs in DBS and Urine by GAHT Use[5]

Use or Non-Use of GAHT		TFV PKs, Median (IQR)		Correlation Between Urine TFV and DBS TFV-DP Levels	
		DBS, fmol/punch	Urine, ng/mL	r^2 (95% CI)[a]	*P*-Value
FTC/TDF	Users	1623 (1313–22,245)	21,389 (13,291–44,963)	0.22 (-0.17 to 0.56)	0.27
	Non-Users	1669 (1136–2106)[b]	15,335 (5046–21,585)[c]	-0.08 (-0.67 to 0.58)	0.83

Use or Non-Use of GAHT		TFV PKs, Median (IQR)		Correlation Between Urine TFV and DBS TFV-DP Levels	
		DBS, fmol/punch	Urine, ng/mL	r^2 (95% CI)[a]	*P*-Value
FTC/TAF	Users	2655 (2099–3480)	3969 (749–7863)	0.47 (0.13–0.72)	0.01
	Non-Users	2614 (1729–3344)[d]	3500 (1403–5669)[e]	0.94 (0.77–0.98)	<0.001

[a]Pearson correlation coefficient. [b]*P*=0.78 for users vs non-users of FTC/TDF. [c]*P*=0.19 for users vs non-users of FTC/TDF. [d]*P*=0.63 for users vs non-users of FTC/TAF. [e]*P*=1 for users vs non-users of FTC/TAF.

Subanalysis: GAHT and TFV-DP levels stratified by sex assigned at birth[6]

TFV-DP levels in DBS were assessed in individuals (N=40) who had received ≥12 weeks of FTC/TDF and FTC/TAF for PrEP to determine the relationship between TFV-DP levels and use of GAHT, and whether this relationship was modified by sex assigned at birth.
After stratification by sex assigned at birth, TFV-DP levels were similar between users and non-users of GAHT during FTC/TDF and FTC/TAF use (Table 7).

Table 7. TFV-DP and Gender Assigned at Birth Substudy of TAF4TRANS: Relationship Between TFV-DP Levels in DBS by GAHT Use[6]

TFV-DP, Median (IQR), fmol/punch	AMAB			Assigned Female at Birth		
	GAHT Users (n=19)	GAHT Non-Users (n=9)	*P*-Value	GAHT Users (n=10)	GAHT Non-Users (n=2)	*P*-Value
FTC/TDF	1653 (1320–2245)	1839 (1131–2014)	0.66	1607 (796–2174)	1643 (1188–2098[a])	1
FTC/TAF	3323 (2349–4190)	2842 (2375–3474)	0.56	2528 (1202–2836)	1246 (266–2226[a])	0.27

[a]Values represent the range due to the low number of individuals in the group.
Note: The Mann-Whitney U test was used to compare levels by use and non-use of GAHT.

iFACT3: DDI Study of FHT and FTC/TAF in TGW[7]

Study design and demographics

The PK of FTC, TAF, TFV, and estradiol were assessed in TGW in Thailand who were receiving FHT to evaluate the potential for DDIs between FTC/TAF and FHT. TGW who had not been treated with injectable FHT ≤3 months before enrollment and had not undergone orchiectomy were eligible to participate. Participants received FHT (2 mg of estradiol valerate and 25 mg of cyproterone acetate) from Week 0 to Week 9 and PrEP (FTC/TAF 200 mg/25 mg) from Week 3 to Week 12. PK sampling was performed at Week 3 for FHT, Week 9 for FHT + FTC/TAF, and Week 12 for FTC/TAF to assess study drug concentrations; FSH, LH, and bioavailable testosterone levels were also measured at Weeks 3 to 9. Eighteen out of 20 participants who enrolled in the study were included in the analysis and had a median (IQR) age of 28 (23–32) years and BMI of 20.8 (19.9–21.9) kg/m^2.

Results

Although plasma estradiol, FTC, and TFV exposure parameters trended downward when FTC/TAF was taken concomitantly with FHT, the AUC and C_{max} GMRs of FTC and TFV stayed within the bioequivalence range. These results indicated that there was no clinically significant effect of FHT on FTC/TAF (Table 8 and Table 9). Between Week 3 and Week 9, no significant changes in FSH, LH, or bioavailable testosterone levels were observed.

Table 8. iFACT3: Estradiol PK Data at Weeks 3 and 9[7]

PK Parameter, GM (%CV)	Week 3: FHT	Week 9: FHT + FTC/TAF	GMR (90% CI)	*P*-Value
$AUC_{0\text{-}24}$, pg × h/mL	799.41 (35.63)	642.65 (50.29)	0.8 (0.72–0.9)	0.002
C_{max}, pg/mL	60.13 (36.46)	66.59 (39.78)	1.11 (0.96–1.27)	0.23

Table 9. iFACT3: ARV PK Data at Weeks 9 and 12[7]

ARV	PK Parameter, GM (%CV)	Week 9: FHT + FTC/TAF	Week 12: FTC/TAF	GMR (90% CI)	*P*-Value
TAF	$AUC_{0\text{-}24}$, ng × h/mL	208.09 (65.5)	197.88 (50.04)	1.05 (0.83–1.33)	0.73
	C_{max}, ng/mL	166.78 (90.76)	146.65 (56.84)	1.14 (0.85–1.52)	0.46
TFV	$AUC_{0\text{-}24}$, ng × h/mL	295.01 (18.43)	319.75 (16.25)	0.92 (0.88–0.97)	0.01
	C_{max}, ng/mL	19.47 (24.37)	20.17 (16.79)	0.97 (0.89–1.05)	0.5
FTC	$AUC_{0\text{-}24}$, ng × h/mL	9944.74 (15.66)	10,791.14 (13.56)	0.92 (0.88–0.97)	0.009
	C_{max}, ng/mL	2197.23 (33)	2366.24 (23.17)	0.93 (0.84–1.03)	0.24

Subanalysis: ARV PKs in PBMCs and urine[8]

A subanalysis evaluated the impact of FHT on TFV-DP and FTC-TP concentrations in PBMCs (collected 2 and 24 hours after FTC/TAF administration) and TFV and FTC concentrations in urine (24-hour collection). TFV-DP and FTC-TP levels in PBMCs are shown in Table 10. Levels of TFV and FTC in urine per GMR (95% CI) were similar when FTC/TAF was administered with and without FHT: TFV, 1.05 (0.84–1.32; *P*=0.67); FTC, 0.92 (0.75–1.13; *P*=0.42). The study authors concluded there were no clinically significant DDIs between FHT and FTC/TAF for PrEP.

Table 10. iFACT3 Subanalysis: ARV PK Data in PBMCs at Weeks 9 and 12[8]

PK Parameter		GM (%CV), fmol/10^6 cells		GMR (95% CI)	*P*-Value
		Week 9: FHT + FTC/TAF	Week 12: FTC/TAF Only		
TFV-DP	C_2	528.47 (28.2)]	509.2 (30.02)	1.04 (0.91–1.19)	0.59
	C_{24}	427.07 (27.2)	443.77 (32.4)	0.96 (0.82–1.13)	0.65
FTC-TP	C_2	6044.03 (37.9)	6244.14 (33.7)	0.97 (0.85–1.1)	0.61
	C_{24}	3492.81 (39.1)	3850.55 (45.4)]	0.91 (0.75–1.1)	0.33

Abbreviations: C_2=concentration 2 hours after dose; C_{24}=concentration 24 hours after dose.

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Abbreviations

AMAB=assigned male at birth
ARV=antiretroviral
AUC=area under the concentration-time curve
AUC_{0-24}=area under the concentration-time curve from time 0 to 24 hours
C_{max}=maximum concentration
CV=coefficient of variation
DBS=dried blood spots
DDI=drug-drug interaction
FHT=feminizing hormone therapy
FSH=follicle-stimulating hormone
FTC=emtricitabine
FTC-TP=emtricitabine triphosphate
GAHT=gender-affirming hormone therapy
GM=geometric mean
GMR=geometric mean ratio
LH=luteinizing hormone
MSM=men who have sex with men
PBMC=peripheral blood mononuclear cell
PK=pharmacokinetic(s)
PrEP=pre-exposure prophylaxis
SHBG=sex hormone-binding globulin
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate
TFV=tenofovir
TFV-DP=tenofovir diphosphate
TGW=transgender women

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Descovy US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/hiv/descovy/descovy_pi.

Follow-Up

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