Drug-drug interactions between the use of feminizing hormone therapy and pre-exposure prophylaxis among transgender women: the iFACT study

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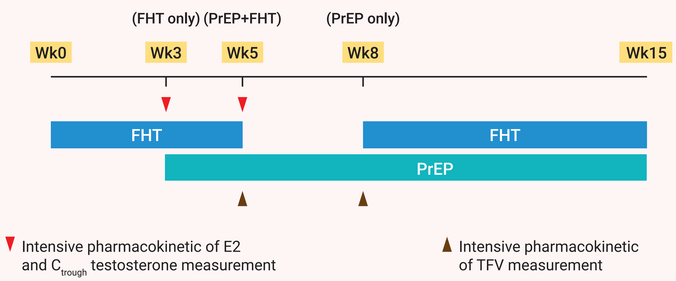
Background

- Concerns about potential drug-drug interactions (DDI) between feminizing hormone therapy (FHT) and pre-exposure prophylaxis (PrEP) have hampered uptake and adherence of PrEP among transgender women (TGW).
- To determine DDI between FHT and PrEP, we measured pharmacokinetic parameters of blood plasma tenofovir (TFV), estradiol (E2), and testosterone.

Methods

Figure 1 iFACT Study Scheme



At pharmacokinetic day, plasma was collected at t=0 (pre-dose), 1, 2, 4, 6, 8, 10, 12, and 24 hours after directly observed medication ingestion with a standardized meal (a total of 9 samples)

- Twenty TGW who never underwent orchiectomy and had not received injectable FHT within 6 months were enrolled between January and March 2018.
- FHT (estradiol valerate 2 mg and cyproterone acetate 25 mg) were prescribed to participants at baseline until week 5, and week 8 until the end of study. PrEP (tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg) was initiated at week 3 and continued without interruption (Figure 1).
- Intensive E2 pharmacokinetic parameters and trough serum testosterone con centration (Ctrough) were measured at weeks 3 and 5 (assessing DDI between PrEP and FHT), and intensive TFV pharmacokinetic parameters were measured at weeks 5 and 8 (assessing DDI between FHT and PrEP) (Figure 1).

Results

- Median (IQR) age, BMI, and CrCl were 21.5 (21-26) years, 20.6 (19.0-22.4) kg/m2, and 116 (101-126.5) mL/min, respectively.
- The geometric mean (%CV) of area under curve from time zero to 24 hr (AUC0-24), maximum concentration (Cmax), and concentration at 24 hr (C24) of E2 at weeks 3 and 5 were 775.13 (26.2) pg*h/mL, 51.47 (26.9) pg/mL, and 15.15 (42.0) pg/mL; and 782.84 (39.6), 55.76 (32.9), and 14.32 (67.4), respectively (Figure 2 and Table 1).
- The geometric mean (%CV) of TFV AUC0-24, Cmax, and C24 at weeks 5 and 8 were 2.28 (26.2) mg*h/L, 0.36 (34.8) mg/L, and 0.04 (28.8) mg/L; and 2.63 (26.9), 0.32 (25.3), and 0.05 (28.0), respectively (Figure 3 and Table 2).
- There were no significant changes in E2 pharmacokinetic parameters and median (IQR) Ctrough of bioavailable testosterone between week 3 and 5.

Figure 2 Median E2 concentration-time curves

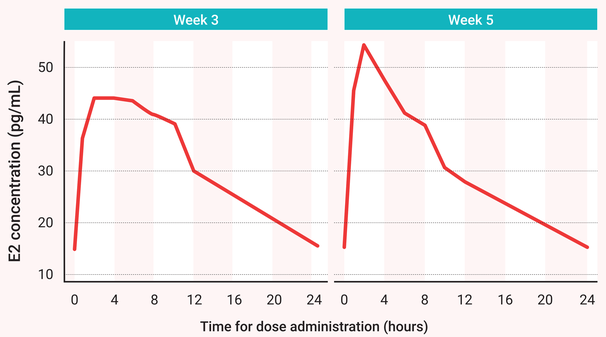


Table 1 Summary of E2 pharmacokinetic parameters; data are presented in geometric mean (%CV)

E2 PK parameter	Week 3 (FHT)	Week 5 (PrEP+FHT)	GMR (95%CI)	p-value
AUC0-24 (pg*h/mL)	775.13 (26.2)	782.84 (39.6)	1.01 (0.89 - 1.15)	0.88
Cmax (pg/mL)	51.47 (26.9)	55.76 (32.9)	1.08 (0.94 - 1.24)	0.25
C24 (pg/mL)	15.15 (42.0)	14.32 (67.4)	0.95 (0.75 - 1.19)	0.63
Half-life (h)	11.25 (32.6)	11.83 (50.9)	1.05 (0.87 - 1.27)	0.60

Figure 3 Median TFV concentration-time curves

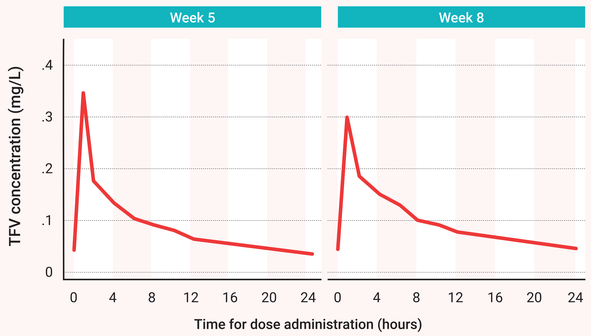


Table 2 Summary of TFV pharmacokinetic parameters; data are presented in geometric mean (%CV)

TFV PK parameter	Week 5 (PrEP+FHT)	Week 8 (PrEP only)	GMR (95%CI)	p-value
AUC0-24 (mg*h/L)	2.28 (26.2)	2.63 (26.9)	0.87 (0.78 - 0.96)	0.009
Cmax (mg/L)	0.36 (34.8)	0.32 (25.3)	1.10 (0.95 - 1.28)	0.2
C24 (mg/L)	0.04 (28.8)	0.05 (28.0)	0.83 (0.76 - 0.90)	<0.001
Half-life (h)	11.25 (32.6)	11.83 (50.9)	1.05 (0.87 - 1.27)	0.60

Conclusions

- Our study demonstrated lower plasma TFV exposure in the presence of FHT, suggesting that FHT may potentially affect PrEP efficacy among TGW; but E2 exposure was not affected by PrEP.
- Further studies are warranted to determine whether these reductions in TFV are clinically significant and whether these effects apply to the active metabolite tenofovir diphosphate (TFV-DP), and emtricitabine tri phosphate (TFC-TP), in the target tissue.