Bidirectional Relationship between Exogenous Hormones and TDF/FTC Pharmacology in Transgender Women

Poster 482

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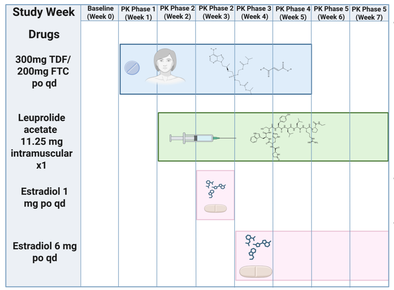
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BACKGROUND

Effective HIV prevention strategies are needed for all populations, including transgender women (TGW). TGW may access exogenous hormone therapies, including estrogens and gonadotropin releasing hormone agonists to promote feminization and reduce dysphoria. Yet, reports of exogenous hormone effects on the pharmacokinetics (PK) and antiviral rectal tissue pharmacodynamics (PD) of oral pre-exposure prophylaxis (PrEP) drugs are conflicting and incomplete. We conducted a phase I open-label 6-period study to evaluate the interactions between estrogen-based exogenous hormones and oral TDF/FTC PrEP.

Meaningful PK/PD interactions between testosterone suppression and low-dose or high-dose estradiol use and TDF/FTC were not observed. TDF/FTC can be used without dose adjustment in the background of exogenous estrogens and leuprolide.

METHODS AND DESIGN



- At baseline and the end of each PK dosing phase:
  - Safety assessments
  - TDF/FTC PK (plasma, PBMC, colon tissue)
  - *ex vivo* cumulative weight-adjusted p24
  - Hormone measurements
  - Iohexol-derived measured glomerular filtration rate (mGFR)
- All doses performed under in-person or virtual directly observed therapy (DOT).
- PK and PD statistical analyses performed in R v. 4.5.1; non-compartmental analysis (NCA) done using Phoenix® v.8.6 (Certara, Radnor, PA).

RESULTS

- Fifty-five adverse events were observed (93% grade 1, 7% grade 2) and were evenly distributed across dosing phases; no grade 3 adverse events occurred (**Table 1**).
- Changes in hormone levels were as expected with hormone therapy, and high-dose estradiol concentrations were unaffected by PrEP discontinuation (**Table 2**).
- Compared to PrEP alone, PBMC TFV-DP concentrations at 24 hours were significantly higher post-leuprolide injection (p=0.019) and with low- (p=0.002) and high-dose estradiol (p=0.004), based on Friedman testing with post-hoc pairwise Wilcoxon comparisons between drug-containing study stages (**Table 3**).
- No significant changes were observed in iohexol-determined mGFR, plasma TFV/FTC PK (C_{max}, $AUC_{0\text{-}tau}$), PBMC FTC-TP, or rectal tissue TFV-DP/FTC-TP across study periods (all p>0.05) (**Tables 2 and 3**).
- Colon biopsy ex vivo HIV challenges demonstrated complete suppression of p24 antigen in all participants throughout all TDF/FTC dosing phases (**Figure 1**).

Table 1. Participant Demographics and Safety Assessments

Number of Enrolled Participants	13
Median Age, years (IQR)	26 (24, 31)
Median Weight, kg (IQR)	79 (69, 98)
Median Body Mass Index, kg/m^2 (IQR)	27 (22, 33)
Race, n (%)	
African American	2/13 (15%)
White, non-Hispanic	11/13 (85%)
Adverse events	55
Grade 1 adverse events, n (%)	51/55 (93%)
Laboratory-related	13/55 (24%)
Gastrointestinal-related	9/55 (16%)
Hormone-related*	11/55 (20%)
Other (fever, headache, congestion)	18/55 (33%)
Grade 2 adverse events, n (%)	4/55 (7%)
Laboratory-related	2/55 (4%)
Gastrointestinal-related	1/55 (2%)
Other (fever, headache, congestion)	1/55 (2%)

*Includes mood changes, hot flashes, and breast tenderness

Table 2. Hormone and renal measurements at baseline and through each PK dosing phase. Median measurements are presented with interquartile ranges.

PK Dosing Phase	Estradiol, pg/mL (IQR)	Total Testosterone (ng/dL)	Free Testosterone, % (IQR)	FSH, mIU/mL (IQR)	LH, mIU/mL (IQR)	Cystatin C, mg/L (IQR)	mGFR, mL/min/1.73m^2 (IQR)
Baseline	22 (16, 27)	478 (360, 581)	3.44 (1.18, 4.16)	2.18 (1.80, 5.30)	3.79 (3.01, 5.48)	0.83 (0.79, 0.89)	85.4 (73.4, 92.8)
TDF/FTC	21 (14, 28)	490 (396, 554)	3.19 (2.69, 3.19)	2.07 (1.79, 5.55)	4.19 (3.07, 4.92)	0.87 (0.84, 0.99)	94.3 (91.0, 104)
TDF/FTC + Leuprolide (Leu)	9 (6, 10)*	151 (121, 274)*	3.22 (1.96, 3.59)	1.02 (0.68, 1.23)*	2.73 (2.28, 3.76)*	0.90 (0.83, 0.93)	94.6 (79.8, 104)
TDF/FTC + Leu + Low Estradiol	17 (9, 20)	60.5 (41, 72)*	3.51 (2.48, 4.93)	1.04 (0.83, 1.16)*	1.23 (1.20, 1.74)*	0.88 (0.78, 0.90)	91.3 (89.1, 96.3)
TDF/FTC + Leu + High Estradiol±	92 (71, 119)*	43 (27, 56)*	3.54 (3.08, 4.63)	0.56 (0.41, 0.86)*	1.60 (1.15, 3.16)*	0.85 (0.80, 0.94)	92.6 (85.0, 100)
Leu + High Estradiol	107 (76, 124)*	41 (25, 103)*	3.36 (2.49, 5.18)	0.34 (0.25, 0.50)*	1.66 (0.76, 2.46)*	0.84 (0.79, 0.89)	94.7 (91.4, 99.6)

*Results differ from baseline (p <0.05). Observed hormone changes are expected based on leuprolide and estradiol administration.
± Hormone and renal measurements not statistically different when compared to leuprolide and high-dose estradiol dosing alone.

Table 3. Non-compartmental analysis (NCA) of TFV/TFV-DP and FTC/FTC-TP PK parameters.

PK Dosing Phase	Plasma C_{max}, ng/mL (IQR)	Plasma C_{24}, ng/mL (IQR)	Plasma $AUC_{0\text{-}24}$, ng*hr/mL (IQR)	Plasma $T_{1/2}$, hr (IQR)	PBMC C_{24}, fmol/10^6 (IQR)	Colon Tissue C_{24}, fmol/mg (IQR)
	TFV				**TFV-DP**	
TDF/FTC	286 (244, 372)	53 (48, 69)	2640 (2363, 3633)	13 (12, 16)	59 (54, 75)	951 (483, 1423)
TDF/FTC + Leuprolide (Leu)	276 (233, 362)	49 (45, 60)	2504 (2134, 3377)	15 (11, 17)	81 (63, 100)*	1973 (432, 5568)
TDF/FTC + Leu + Low Estradiol	274 (223, 334)	49 (41, 57)	2726 (1849, 3090)	14 (12, 16)	94 (72, 122)*	1374 (696, 6491)
TDF/FTC + Leu + High Estradiol	277 (191, 322)	47 (39, 62)	2464 (2047, 2897)	15 (12. 17)	101 (82, 142)*	1569 (391, 4306)
	FTC				**FTC-TP**	
TDF/FTC	1681 (1392, 2195)	77 (72, 87)	13184 (10749, 16243)	6 (5, 6)	6506 (5968, 8979)	48 (33, 86)
TDF/FTC + Leuprolide (Leu)	1903 (1432, 2281)	81 (71, 102)	13828 (10333, 18656)	6 (5, 6)	7462 (6594, 8954)	61 (49, 132)
TDF/FTC + Leu + Low Estradiol	1662 (1250, 1953)	82 (74, 107)	12022 (9025, 16043)	6 (6, 7)	8291 (6282, 12403)*	157 (42, 345)
TDF/FTC + Leu + High Estradiol	1601 (1274, 1882)	79 (66, 106)	12469 (10076, 15805)	6 (5, 6)	9314 (7407, 10254)	69 (33, 128)

*Results differ from TDF/FTC dosing alone (p <0.05).

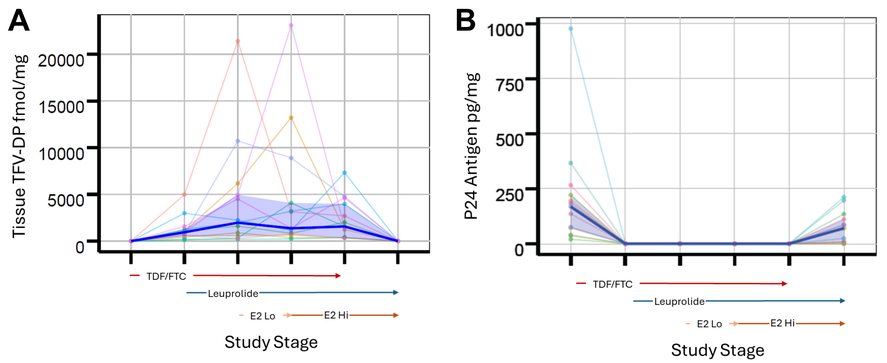


Figure 1. (A) Individual colon tissue TFV-DP concentrations (fmol/mg) under each PK dosing phase and (B) Individual cumulative (Days 0-14) weight-adjusted p24 antigen concentrations (pg/mg) post-*ex vivo* HIV-1 exposure. The solid blue line depicts median measurements; shaded blue region depicts the interquartile range

CONCLUSIONS

- Testosterone suppression and exogenous estradiol do not alter TDF/FTC PK/PD.
- TDF/FTC does not reduce estradiol concentrations.
- Renal function is not altered by addition of leuprolide and estradiol.
- TDF/FTC in combination with exogenous hormonal therapies involving testosterone suppression and exogenous estrogens is effective in suppressing HIV and can be used jointly without the need for dose adjustments.

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