Altered TDF/FTC pharmacology in a transgender female cohort: implications for PrEP

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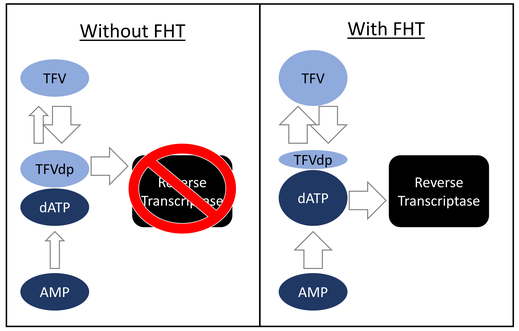
Background

- HIV disproportionately impacts transgender women (TGW) who frequently take feminizing hormone therapy (FHT).
- Estradiol concentrations in TGW are 2-9 fold higher than typical peak concentrations in premenopausal, cisgender women (CGW)[1].
- Estradiol may impact TDF/FTC pharmacology by increasing nucleotidases.[2]
  - Increased cell surface nucleotidase expression may increase dATP.[3]
  - Increased intracellular nucleotidase expression may decrease TFVdp.[3]
- Thus we hypothesized that TGW would exhibit an altered balance of TFVdp:dATP in rectal tissue.



Methods

Population: HIV infected patients ≥18years, on TDF/FTC containing HAART with HIV RNA <50copies/mL, and normal renal function were enrolled into 3 cohorts: CGW, TGW, and cisgender men; CGM. Only postmenopausal CGW were enrolled for low and stable estrogen among this female control group.

Sample collection at single study visit:

- Whole blood was collected into the following BD vacutainers: 3mL EDTA for plasma, 6mL SST for serum, and 8mL CPT for peripheral blood mononuclear cells (PBMCs), processed according to standard methods, and stored at -80°C until bioanalysis.
- Rectal tissue biopsies obtained via anoscopy with RJ4 radial jaws were placed into #3 1.8mL cryovials, immediately snap frozen in liquid nitrogen, and stored at -80°C until bioanalysis.

Bioanalytical methods: TFV and FTC were quantified in plasma and TFVdp, FTCtp, dATP and dCTP in PBMCs and tissue homogenates by HPLC-MS/MS. Serum steroid hormones were quantified by enzyme immunoassay (EIA) and HIV RNA/DNA in tissue homogenates by digital droplet PCR.

Data Analysis

- Values below limits of quantification were imputed (0.5 * mass-based lower limit of quantification) and data are presented as median (min, max).
- One-way ANOVA and Spearman correlation were performed in SASv9.4.

Demographics; Median (Min, Max)	CGW (N=4)	TGW (N=4)	CGM (N=2)	
Age, years	57 (55, 59)	42 (34, 46)	58, 59	p<0.05
BMI, kg/m^2	36 (27, 38)	30 (24, 42)	23, 23	
Creatinine clearance, mL/min	108 (61, 138)	114 (99, 191)	79, 75	
Estradiol, pg/mL	13 (8, 17)	193 (30, 619)	22, 22	p<0.05
Progesterone, ng/mL	0.21 (0.17, 0.30)	0.50 (0.27, 0.72)	0.34, 0.14	
Testosterone, ng/dL	33 (25, 53)	33 (12, 125)	257, 303	p<0.05

Figure 1. No significant difference in rectal tissue intracellular nucleotide concentrations of TGW compared to CGW or CGM

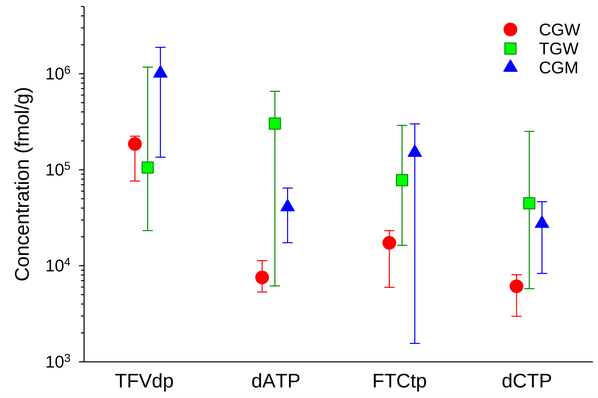


Figure 2. Median rectal TFVdp:dATP ↓ by ~10-fold among TGW compared to CGW or CGM

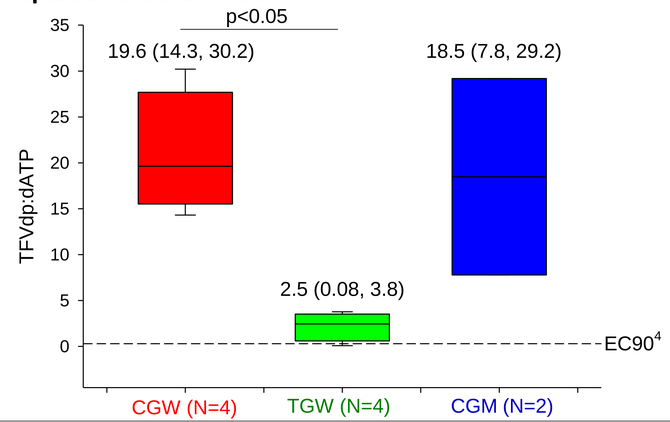


Figure 3. Serum estradiol and progesterone inversely correlated with rectal TFVdp:dATP

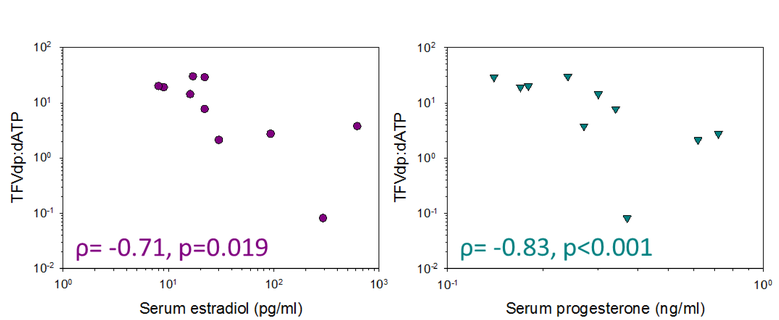
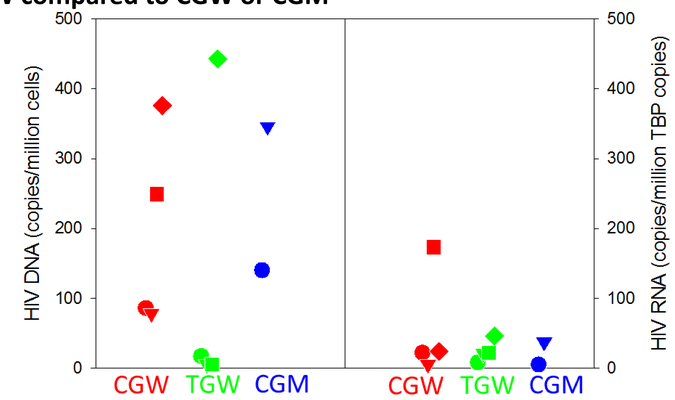


Figure 4. HIV DNA and RNA in rectal tissue were not different in TGW compared to CGW or CGM



Conclusions

- This is the first description of TFVdp/FTCtp rectal concentrations in TGW on feminizing hormone therapy.
- TFVdp relative to dATP was significantly lower in TGW and decreased with increasing concentrations of estradiol and progesterone.
- Despite altered pharmacology, HIV RNA and DNA were not different in the rectal tissues of patients on HAART.
- These data confirm *in vitro* findings and suggest that feminizing estradiol impacts TDF/FTC pharmacology, warranting further study to determine if efficacy is impaired for PrEP users.

Acknowledgements

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