Poster #478

Depot medroxyprogesterone acetate effects on tenofovir-dp and lamivudine-tp in cervical tissue

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BACKGROUND

- Effective concentrations of antiretrovirals in the female genital tract (FGT) are critical for suppression of viral shedding, or, in the case of pre-exposure prophylaxis, HIV prevention.
- The disposition of tenofovir diphosphate (TFVdp) and emtricitabine triphosphate (FTCtp) in the FGT have been previously described.[1] Despite widespread lamivudine use, lamivudine triphosphate (3TCtp) exposure in FGT is unknown.
- Depot-medroxyprogesterone acetate has been implicated in increased risk of HIV acquisition.[2] *In vitro* studies have implicated sex hormones in modulating nucleotide metabolism[3] and DMPA increases TFVdp in vaginal tissue following topical TFV gel use.[4] Whether DMPA alters TFVdp or 3TCtp exposure following oral dosing could inform on potential PrEP efficacy.
- To facilitate development of multipurpose prevention for contraception and HIV, a better understanding of exogenous hormone effect on FGT antiretroviral exposure is needed.

METHODS

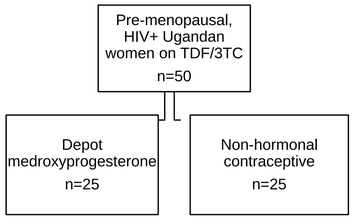

Table 1: Sampling Schema	
Blood draw	TFV and 3TC plasma Estradiol and progesterone plasma TFVdp and 3TCtp in PBMC
2 Cervical Biopsies	TFVdp and 3TCtp in tissue *Genomics and proteomics*
2 Cervicovaginal Swabs	*Cytokine Analysis* *Microbiome*

Italics indicate future analyses not included in this presentation

- Women living with HIV, receiving daily 300 mg tenofovir disoproxil fumarate plus 300 mg lamivudine (TDF/3TC) as part of antiretroviral therapy, were co-enrolled with ongoing NIH R01 funded BONE:CARE study in Kampala, Uganda.
- Inclusion: Stable on TDF/3TC regimen for at least 2 weeks and virally suppressed (<50 copies HIV/mL plasma) for at least 6 months.
- Exclusion: Currently pregnant or pregnant within 3 months, currently breastfeeding, symptomatic vaginal infection within 2 weeks, unexplained or abnormal vaginal bleeding within 90 days, history of genital dysplasia or HPV in past year, or use of oral/vaginal antibiotics or antifungals within 30 days (exception made for sulfamethoxazole/trimethoprim).
- Women receiving depot-medroxyprogesterone (DMPA group) or using non-hormonal contraception (non-HC group) participated in a single visit study.
- Cervical biopsies and PBMC were obtained for quantification of TFVdp, 3TCtp, and endogenous dATP and dCTP using liquid chromatography with tandem mass spectrometry (tissue LLOQ 0.02 ng/mL).
- TFV and 3TC were measured in blood plasma (LLOQ 1 ng/mL) to assess medication adherence. Those non-adherent were excluded from further drug concentration comparisons between groups.
- Estradiol and progesterone were quantified in blood plasma using enzyme immunoassay.
- Multivariable linear regression was performed on log-transformed data and adjusted for age, BMI, and plasma drug concentrations. Multivariate analyses (MANOVA) were also performed to test effect of DMPA on overall drug exposure. Statistics were performed in SAS 9.4.

RESULTS

Study Subjects

Table 2: Subject Characteristics	Non-hormonal[1] (n=25)	DMPA (n=25)
Age Median (25^{th}, 75^{th})	26.0 (23.9 – 30.7)	26.4 (24.6 – 29.9)
BMI Median (25^{th}, 75^{th})	22.9 (21.3-25.0)	24.8 (22.1-27.5)
Years on ART median (25^{th}, 75^{th})	1.0 (0.9-1.2)	1.0 (0.8-1.2)
Sexually active n (%)	23 (92)	24 (96)
Days since last menstrual period[2] median (25^{th}, 75^{th})	22 (13-29)	19 (16-25)
Months on contraceptive method Median (25^{th},75^{th})	20 (12-36)	15(12-48)
Days since last DMPA injection median (25^{th}, 75^{th})	N/A	34 (12-51)
Estradiol pg/mL Median (25^{th},75^{th})	87.2 (63.8-125.9)	27.3 (16.1-39.3)
Progesterone ng/mL Median (25^{th},75^{th})	5.5 (0.2-11.1)	0.4 (0.2-0.5)
Gonorrhea n (%)	2 (8)	2 (8)
Chlamydia n (%)	0 (0)	0 (0)
Syphilis n (%)	3 (12)	0 (0)

[1]Within non-hormonal group, 12/25 (48%) women were using copper IUD
[2]As expected in DMPA users, 15/25 (60%) of women in DMPA group had amenorrhea while 0/25 (0%) in non-hormonal group reported amenorrhea

- Efavirenz was the third agent in regimen with exception of one participant in DMPA group on boosted atazanavir
- Three individuals (one in DMPA group) had plasma TFV and 3TC <1ng/mL suggesting non-adherence. Their data were not included in drug analyte analyses but were included in endogenous analyses.

PBMC Analytes

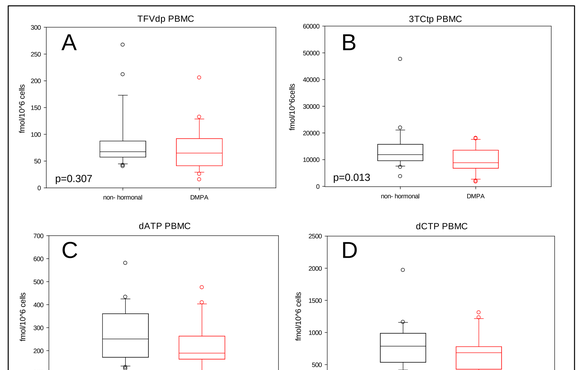

Figure 1: Analytes in PBMCs by contraceptive group. P-values represent significance after multivariable regression adjusting for age, BMI, and plasma concentration. In multivariate analysis, DMPA use was significantly associated with drug concentrations in PBMC (p=0.029) but not endogenous nucleotide concentrations (p=0.236)

- DMPA did not have significant effect on TFV or 3TC plasma concentrations (p=0.8)
- 3TCtp in PBMCs was lower in DMPA-users **(Figure 1B).**
- In multivariable regression models:
  - BMI was associated with 3TCtp in PBMC (p=0.01) but not TFVdp (p=0.9).
  - Age was not associated with 3TCtp (p=0.19) or TFVdp (p=0.2) in PBMC.
- DMPA had no effect on TFVdp:dATP or 3TCtp:dCTP ratios in PBMCs (**Table 3**).

Table 3: Nucleotide Ratios in PBMC Median (25^{th}, 75^{th} percentile)	Non-hormonal	DMPA	Adjusted p-value
TFVdp:dATP	0.30 (0.21-0.44)	0.33 (0.24-0.43)	0.822
3TCtp:dCTP	16.6 (13.3-20.9)	14.1 (12.5-18.8)	0.249

Tissue Analytes

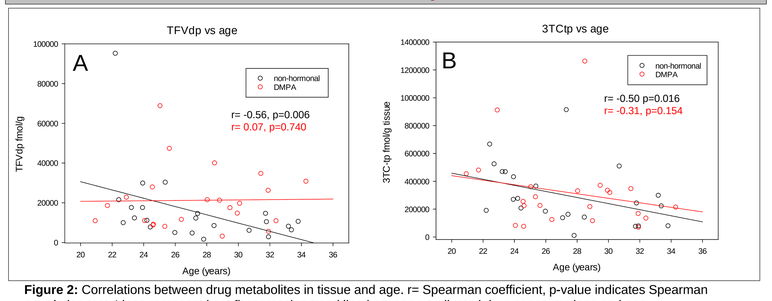

Figure 2: Correlations between drug metabolites in tissue and age. r= Spearman coefficient, p-value indicates Spearman correlation test. Lines represent best fit regression trend line between unadjusted drug concentrations and age.

- Age was negatively correlated with TFVdp and 3TCtp in tissues (**Figure 2**) and was significant in multivariate regression models (p=0.021).
- DMPA use seemed to negate this effect on TFVdp (**Figure 2A**).
- BMI was not associated with TFVdp or 3TCtp in tissues in multivariable or multivariate models (p>0.4)

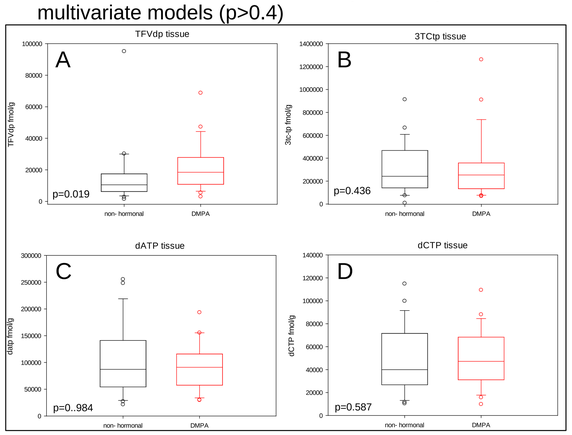

Figure 3: Analytes in tissue by contraceptive group. p-values represent adjusted after multivariable regression. In multivariate analysis, DMPA was not significantly associated with overall drug exposure (p=0.064) or endogenous nucleotides (p=0.630).

- Tissue TFVdp was 76% higher in the DMPA group (**Figure 3A**)
- No differences in 3TCtp or endogenous nucleotides based on DMPA use (**Figure 3B-D)**
- TFVdp:dATP ratio was higher in DMPA group **(Table 4).**
- 3TCtp:dCTP ratio was similar between groups (**Table 4**).

Table 4: Nucleotide Ratios in Tissue Median (25^{th}, 75^{th} percentile)	Non-hormonal	DMPA	Adjusted p-value
TFVdp:dATP	0.11 (0.07-0.17)	0.19 (0.11-0.34)	0.015
3TCtp:dCTP	6.3 (3.1-8.8)	5.6 (4.8-7.5)	0.932

CONCLUSIONS

- TFVdp was significantly higher in DMPA users compared to women using non-hormonal contraception, suggesting prevention efficacy is unlikely to be compromised by DMPA use.
- These data provide the first information on drug exposure of 3TCtp in the FGT following oral dosing.
- Similar to reports of FTCtp, 3TCtp was significantly higher than TFV-DP in cervical tissue, suggesting it may be an option for prophylaxis.

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