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Genital Inflammation Is Not Associated with Decreased Vaginal Tenofovir Levels in Women Taking Oral PrEP

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Background

- African studies demonstrate that genital inflammation decreases tenofovir (TFV) gel's efficacy
- We evaluated the impact of inflammation and dysbiosis on cervicovaginal fluid (CVF) TFV concentrations in US women taking oral TDF/FTC for PrEP

Methods

- Adherence Enhancement Guided by Individualized Texting and Drug Levels (AEGiS) is a 48-week PrEP clinical trial of 136 HIV-negative cisgender women ≥18 years old at risk for HIV in Southern California
- Women at CCTG sites (UCSD, Harbor-UCLA and USC) were offered enrollment into CVF substudy
- CVF collected at week 24 to evaluate:

(i) sexually transmitted bacterial (gonorrhea, chlamydia, and trichomonas), viral (HPV, CMV and HSV-1/2) and vaginitis (Candida and Gardnerella) organisms
(ii) microbiome composition by 16S sequencing (V3-V4 region)
(iii) cytokine profiles by ELISA (IL-8, MIP1a, MIP-1b, and IP-10)

- Microbiome Community State Types (CSTs) were assigned based on described characteristics (i.e. CST I, II, III, V dominated by *lactobacilli* and CST IV containing mostly non-*lactobacilli* species)
- TFV in CVF and tenofovir diphosphate (TFV-DP) in dried blood spots (DBS) measured at week 24
  - DBS TVF-DP ≥700fmol/punch suggested long-term adherence
  - CVF TFV of 100-1000ng/mL benchmarked typical genital concentrations
- Univariate statistical analysis was used to determine factors associated with low and high CVF TFV with cut-off of 1000 ng/ml used as median value

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Results

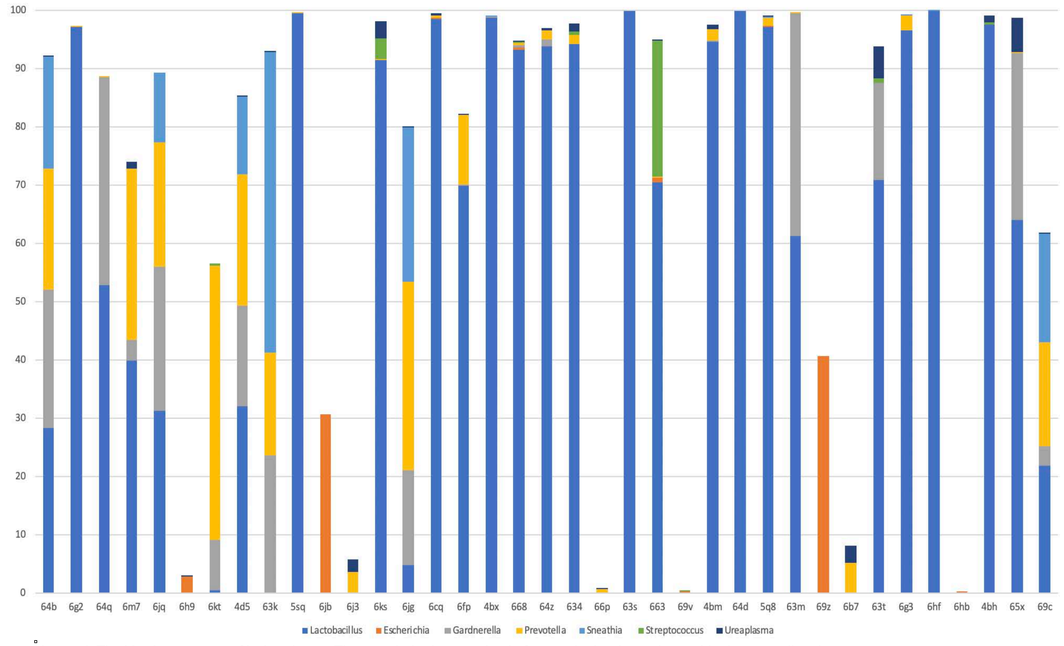
- 34 women had CVF specimens collected at week 24
- Median age 43 (IQR 35-47) years
  - 49% Non-Hispanic White, 11% NH Black, 31% Latina
  - Median vaginal sex acts last 3 months 1 (IQR 1-3)
- 15% (5/34) had discordant tenofovir concentrations (i.e. DBS TFV-DP≥700 and CVF TFV<100)
- **No inflammatory process was associated with lower CVF TFV concentrations or tenofovir discordance**
- Among n=26 assessed for vaginitis, women with possible vaginitis (n=13) more likely to have high CVF TFV concentrations compared to those without (77% vs 31%, p<0.05)
  - Remains significant when controlling for DBS TFV concentrations as continuous variable (AOR 9.99, 95% CI 1.48-67.32)
- No difference in CVF TFV concentrations by microbiome type
- 3 of the 5 women with discordance had non-lactobacillus dominant microbiomes→ dominated by non-vaginitis organisms (2 *E. cloacae*, 1 *E. coli*)

TABLE 1: INFLAMMATORY FACTORS EVALUATED AT WEEK 24*

Factor		TFV CVF level>1000 n (%)	P-value
CMV	Detected	1 (50.0)	0.51
	Not Detected	15 (46.9)	
HSV	Detected	1 (33.3)	0.41
	Not Detected	15 (48.4)	
HPV	Detected	3 (50)	1.00
	Not Detected	11 (52.4)	
Vaginitis (yeast or BV) N=26	Any	10 (76.9)	**<0.05**
	None	4 (30.8)	
Candida N=26	Detected	1 (50)	1.00
	Not Detected	13 (54.2)	
Gardnerella N=26	Detected	9 (81.8)	**0.02**
	Not Detected	5 (33.3)	
MIP1 alpha	Detected	4 (57.1)	0.68
	Absent	12 (44.4)	
MIP 1 beta	Detected	2 (28.6)	0.41
	Absent	14 (51.9)	
IP 10	Detected	4 (50.0)	1.00
	Absent	12 (46.2)	
IL8	Detected	8 (40.0)	0.49
	Absent	8 (57.1)	
Vaginal Microbiome Type	I, II, III, V	8 (38.1)	0.30
	IV	7 (58.3)	

*No person positive for gonorrhea, chlamydia or trichomonas at week 24.

FIGURE 1: Vaginal Microbiome Composition ordered by CVF Concentration



Legend: The Y-axis represents % abundance. The remainder is comprised of several other bacteria outside the group listed

Conclusions

- **Presence of genital viruses, cytokines or *Gardnerella* spp. were not associated with low CVF TFV levels in women taking oral TDF/FTC for PrEP**
- Women with *Gardnerella* present may actually have higher CVF TFV levels, perhaps due to inflammatory processes augmenting blood flow and TFV penetration into the vaginal compartment