Vaginal proteome alterations associated with HIV acquisition in the VOICE trial

CROI 2022
Poster 00211

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Background

- Mucosal barrier of the female genital tract is the first site for most sexual transmission of HIV
- Identification of mucosal factors predictive of HIV susceptibility could inform prevention strategies
- Here we used an unbiased mass spectrometry-based proteomics approach to characterize vaginal proteins associated with HIV acquisition in women enrolled in VOICE (MTN-003) trial
- VOICE was a Phase IIb randomized, placebo-controlled trial to assess daily oral or vaginal pre-exposure prophylaxis conducted in South Africa, Uganda, and Zimbabwe

Objective

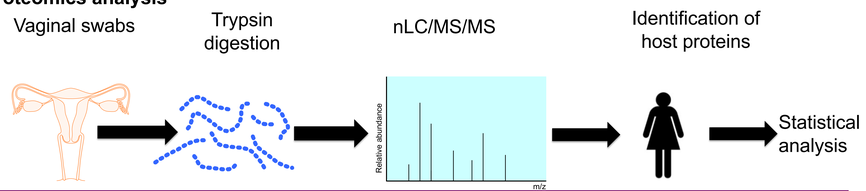
- To assess host proteome changes associated with HIV acquisition in women enrolled in MTN-003 using a mass spectrometry-based proteomics approach

Methods

Treatment:
Oral Placebo n=133
Oral Tenofovir (TDF) n=128
Oral Tenofovir + Emtricitabine (FTC/TDF) n=144
Vaginal Placebo n=158
Vaginal Tenofovir n=23

HIV Acquisition:
Case: Vaginal swabs analyzed from last timepoint (3 or 6 months) prior to HIV seroconversion; n=150
Control: Matched 3 to 1 to cases based on study arm and time in trial; n=436

Proteomics analysis



Participant Characteristics

Variable		Case (n=150)	Control (n=436)	P value
Treatment (No., %)	Oral placebo	34 (22.7)	99 (22.7)	0.911
	Oral TDF	34 (22.7)	94 (21.6)	
	Oral FTC/TDF	37 (24.7)	107 (24.5)	
	Vaginal placebo	40 (26.7)	118 (27.1)	
	Vaginal tenofovir	5 (3.3)	18 (4.1)	
Lactobacillus microbiome (No., %)		54 (36)	195 (44.7)	0.151
Age (Mean ± SD; range)		23 ± 4.1 (18-37)	25 ± 5 (18-39)	2.02E-04
No. Sex Acts last 7 days (Mean ± SD; range)		2 ± 2.2 (0-15)	2 ± 2.2 (0-20)	0.488
No. Sex Partners last 3 months (Mean ± SD; range)		1 ± 0.5 (0-3)	1 ± 0.9 (0-11)	0.893
Unprotected sex last 7 days (No, %)		32 (21.3)	82 (18.8)	0.303
Contraceptives (No., %)	Injectables	127 (84.7)	320 (73.4)	0.031
	Oral	15 (10)	84 (19.3)	
	Other	8 (5.3)	32 (7.3)	
Country (No., %)	South Africa	140 (93.3)	406 (93.1)	1.00*
	Uganda	4 (2.7)	11 (2.5)	
	Zimbabwe	6 (4.0)	19 (4.4)	

*Fisher's Exact Test South Africa vs Other

Results

Figure 1: Human proteins differentially abundant between placebo and treatment arms

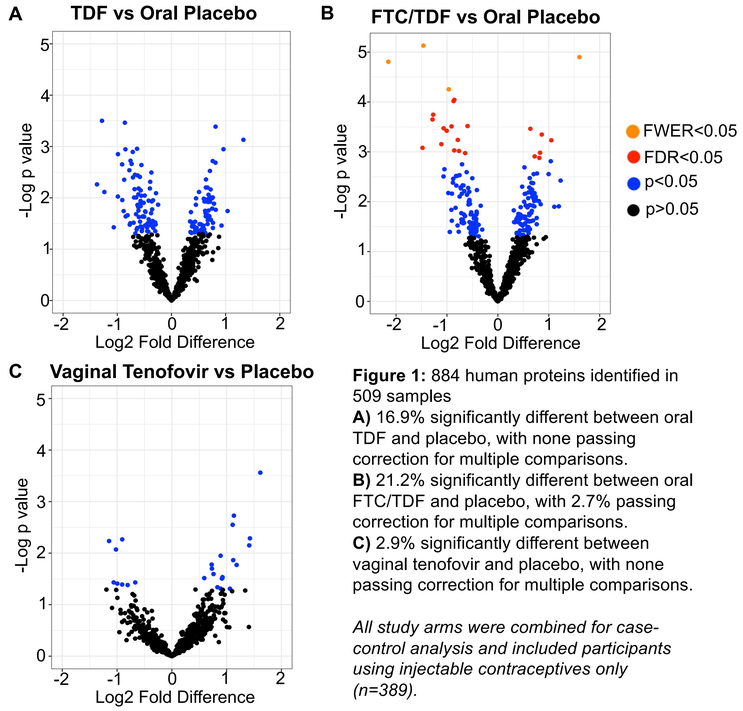


Figure 1: 884 human proteins identified in 509 samples
A) 16.9% significantly different between oral TDF and placebo, with none passing correction for multiple comparisons.
B) 21.2% significantly different between oral FTC/TDF and placebo, with 2.7% passing correction for multiple comparisons.
C) 2.9% significantly different between vaginal tenofovir and placebo, with none passing correction for multiple comparisons.

All study arms were combined for case-control analysis and included participants using injectable contraceptives only (n=389).

Figure 2: Human proteins differentially abundant between cases and controls in injectable contraceptive users

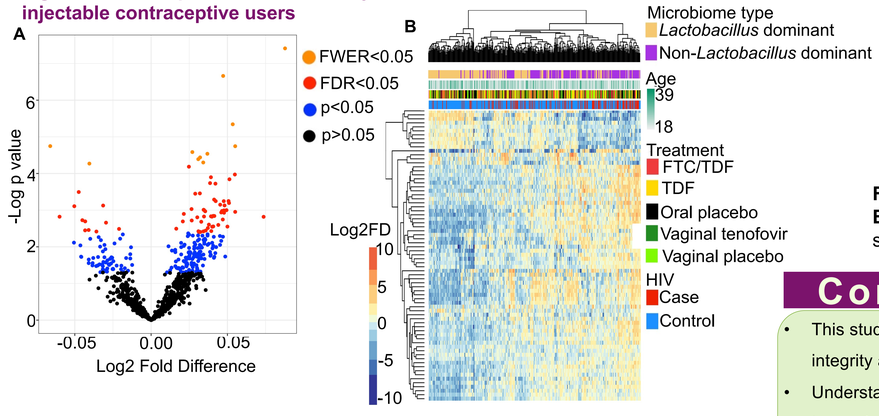


Figure 2: A) 29.0% human proteins significantly different between cases and controls, with 73 proteins (8.3%) passing correction for multiple comparisons in injectable contraceptive users
B) Unsupervised hierarchical clustering of proteins passing correction for multiple comparisons indicated participants clustered by HIV (OR 3.493, 1.70-7.92, p=1.72E-04)

Figure 3: Inflammatory pathways increasing in HIV cases

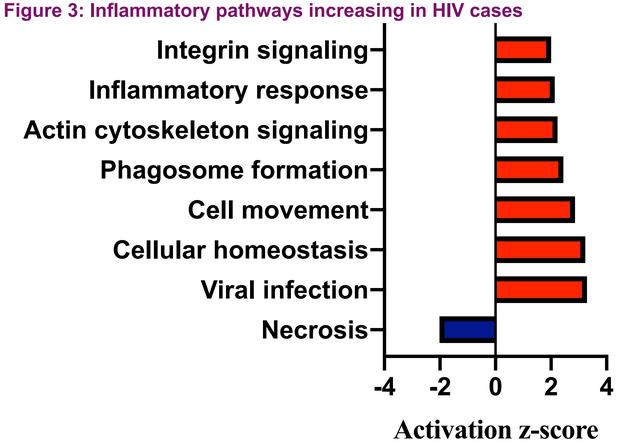


Figure 3: Ingenuity pathway analysis of proteins significantly different between cases and controls indicates pathways related to inflammation are significantly increased in HIV cases.

Figure 4: Six human proteins can predict HIV cases

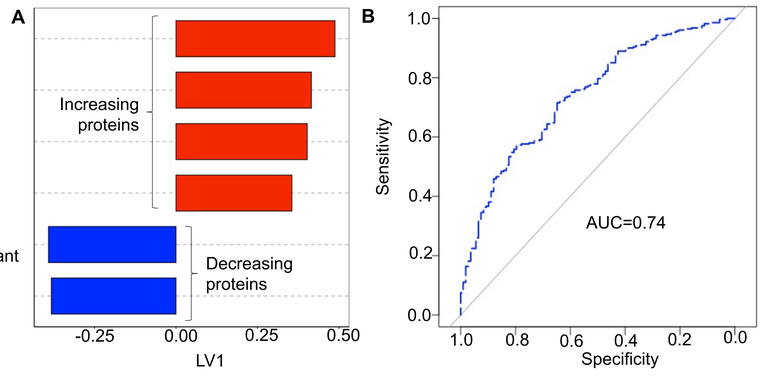


Figure 4: A) Six proteins selected by LASSO, 4 increased and 2 decreased in cases.
B) Logistic regression was used to predict case vs control outcome using the LASSO selected proteins and obtained an AUC of 0.74.

Conclusions

- This study identified a high-risk phenotype of reduced mucosal innate immunity and epithelial barrier integrity associated with increased risk of HIV acquisition
- Understanding the underlying impact of these biomarkers to mucosal immunity critical to understand HIV transmission and improve HIV prevention options
- Analysis and integration of vaginal microbiome data is ongoing

Acknowledgements

We thank the VOICE study participants and research team for their support for this study and we thank CONRAD and Gilead for providing the study drugs.

The Microbicide Trials Network was funded by the National Institute of Allergy and Infectious Diseases (UM1AI068633, UM1AI068615, UM1AI106707), with co-funding from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and the National Institute of Mental Health, all components of the U.S. National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH

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