

Rectal Microbiome Alterations Associated with TDF/FTC for Pre-Exposure Prophylaxis

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Background

- Oral daily tenofovir (TFV) disoproxil fumarate/emtricitabine (TDF/FTC) for HIV pre-exposure prophylaxis (PrEP) is a highly effective HIV prevention strategy; however, long-term adverse effects are not fully defined.
- The rectal microbiome helps maintain gut immune homeostasis, and perturbations may influence HIV susceptibility.
- Numerous factors influence microbiome composition including behavioral factors, which are important considerations in study design and analysis.
- This study sought to examine the effects of oral TDF/FTC for PrEP on the rectal microbiome using a well-characterized cohort of men who have sex with men (MSM).

Results

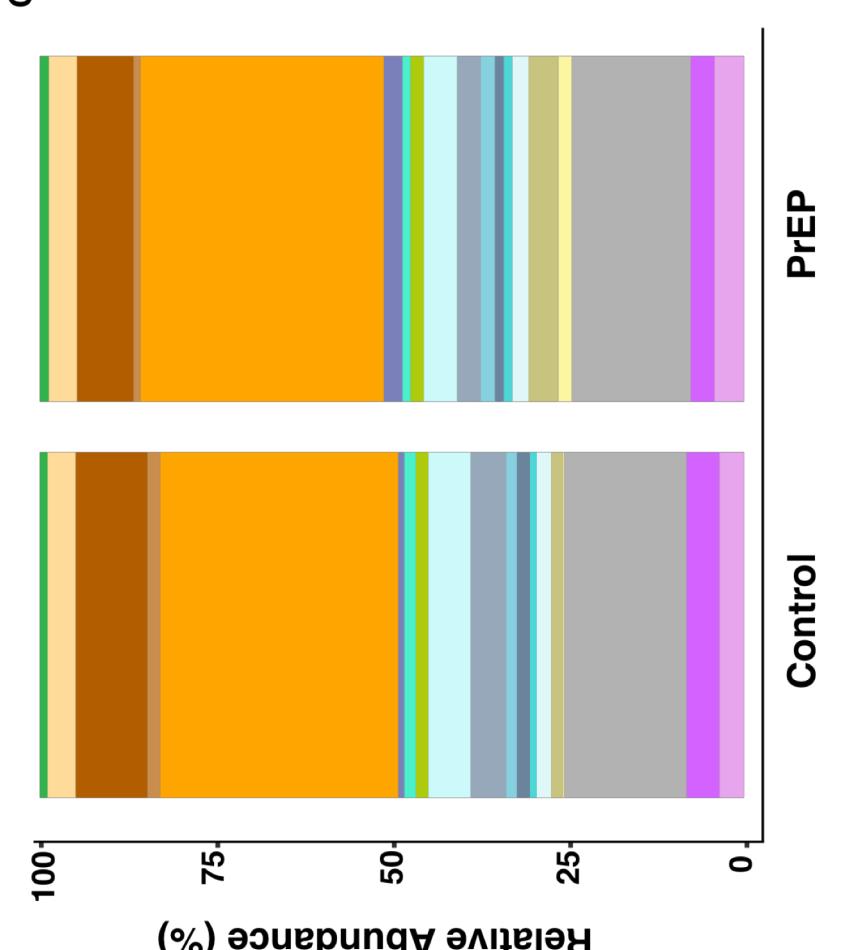


Figure 1. Taxonomic distribution between PrEP and control participants. Stacked columns show averaged relative abundance as a percentage of total bacterial sequences at the genus level. No differences in alpha diversity measures or overall composition (PCoA) were seen between PrEP and control (data not shown).

Methods

- Participants: HIV-negative participants currently on PrEP (n=37) were selected from an ongoing cohort (The mSTUDY). Control participants (n=37) not on PrEP were selected using 1:1 matching on a propensity score which included:
 - Smoking
 - Alcohol use
 - BMI
 - Recent receptive anal intercourse (RAI)
 - Frequency of RAI
 - Drug use
- Specimens: Rectal swabs and hair samples used in this study were collected August 2014 – July 2017.
- Microbiome: Microbiome profiling was performed using 16S rRNA gene sequencing and data processed using DADA2.
- Associations between PrEP use and bacterial abundance were examined using zero-inflated negative binomial regression (ZINB) and binomial least absolute shrinkage and selection operator (LASSO) regression.

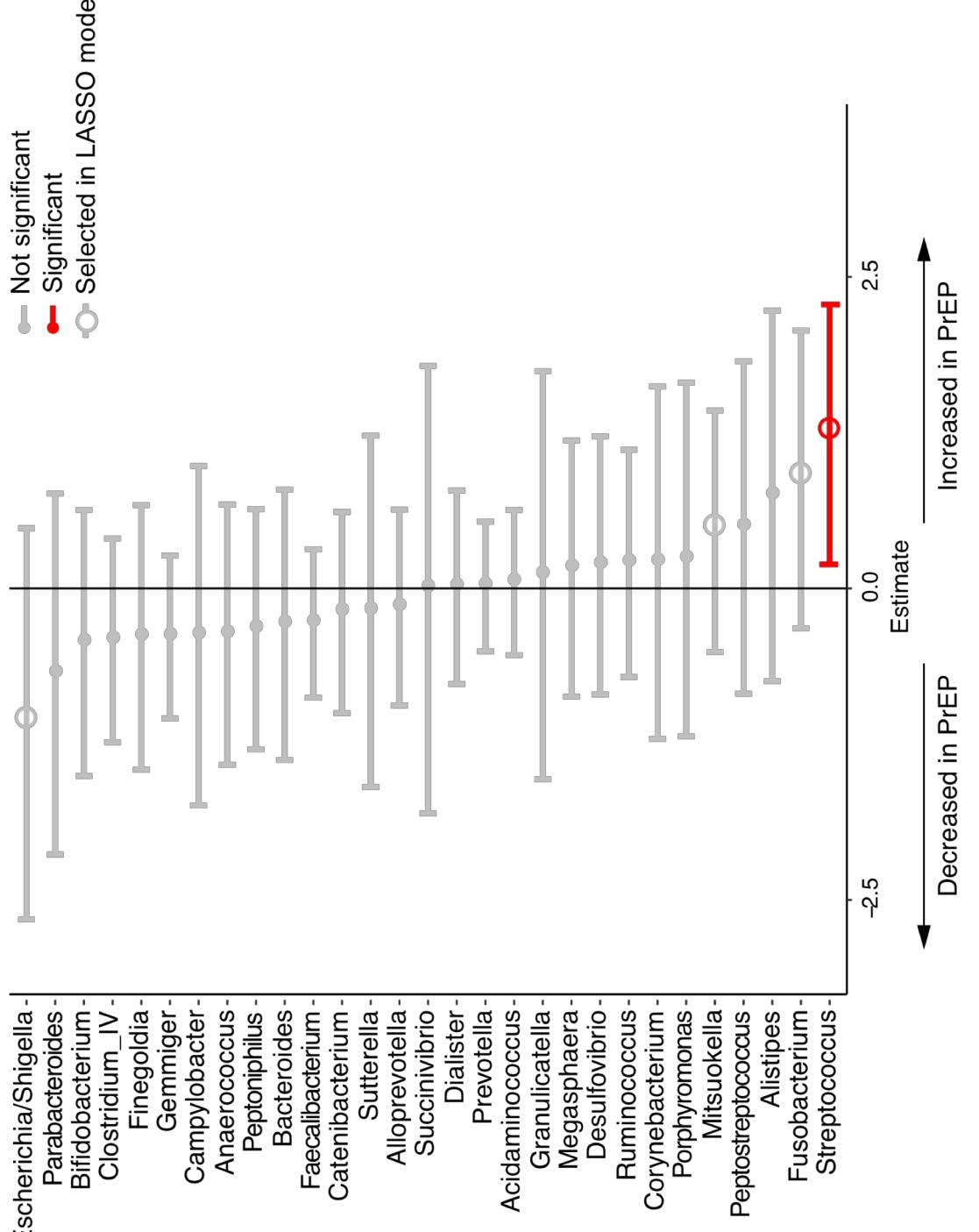


Table 2. TDF/FTC concentrations in hair samples^a

On average, a TFV value of 0.038 ng/mg hair is consistent with doing 4 days per week Liu et al. PLUS ONE, 2014). In our small subset, 75% (11/15) had TFV values indicating at least 4 days per week adherence to PrEP.

Conclusions

- Oral TDF/FTC for PrEP is associated with changes in the rectal microbiome compared to well-matched controls.
- Streptococcus* abundance was increased in PrEP use (adjusted p=0.015).
- Other important alterations include increased *Mitsuokella* and *Fusobacterium*, as well as decreased *Escherichia/Shigella*.
- Increased *Fusobacterium* was similarly associated with TFV levels by hair analysis in a small subset (n=15) of PrEP users.
- This study highlights the need for investigation of the role of microbiome changes in HIV susceptibility and effectiveness of PrEP.

We are grateful to all of the participants of The mSTUDY (U01 DA036267). Funding support provided by the UCLA CFAR (P30 AI028897), IMPAACT (UM1AI068632 IMPAACT LOC, UM1AI068616 IMPAACT SDMC and UM1AI106716 IMPAACT LC) and K08 AI124979 to J.A.F.

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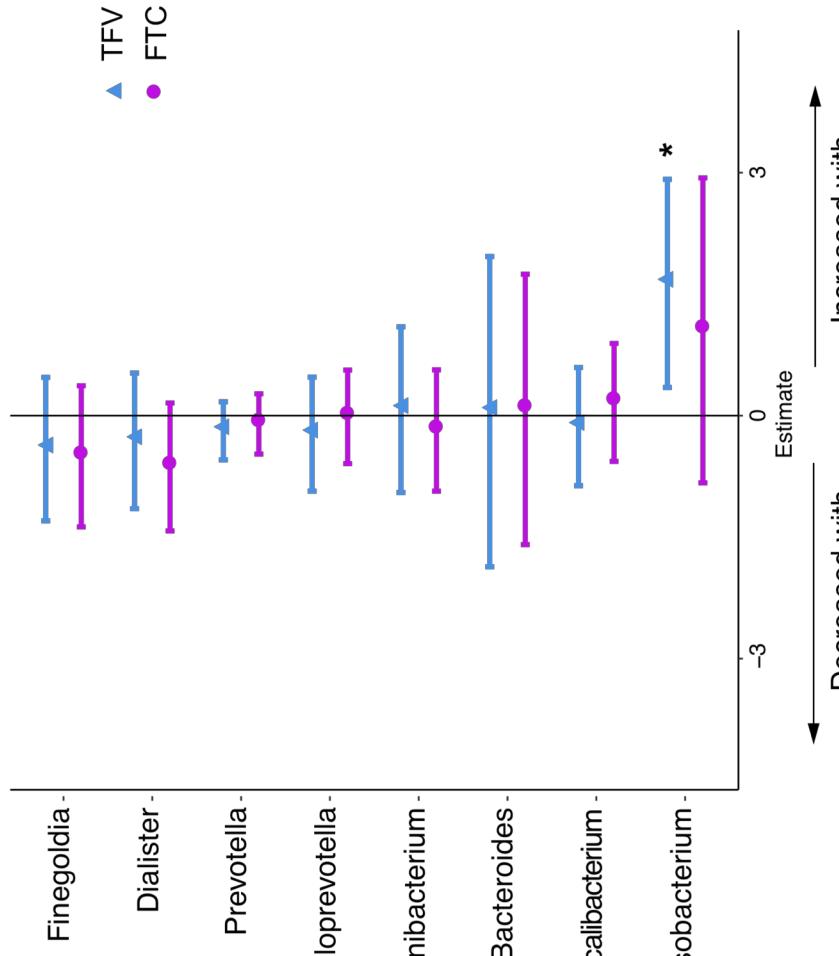


Figure 3. Associations between microbiome composition and PrEP use. Forest plot showing associations of specific bacterial genera with PrEP use using ZINB regression analysis of genera with 1% relative abundance in at least 10% of samples. Red indicates associations that remained statistically significant after FDR-adjustment. Open circles indicate bacterial genera that were also selected using LASSO regression.

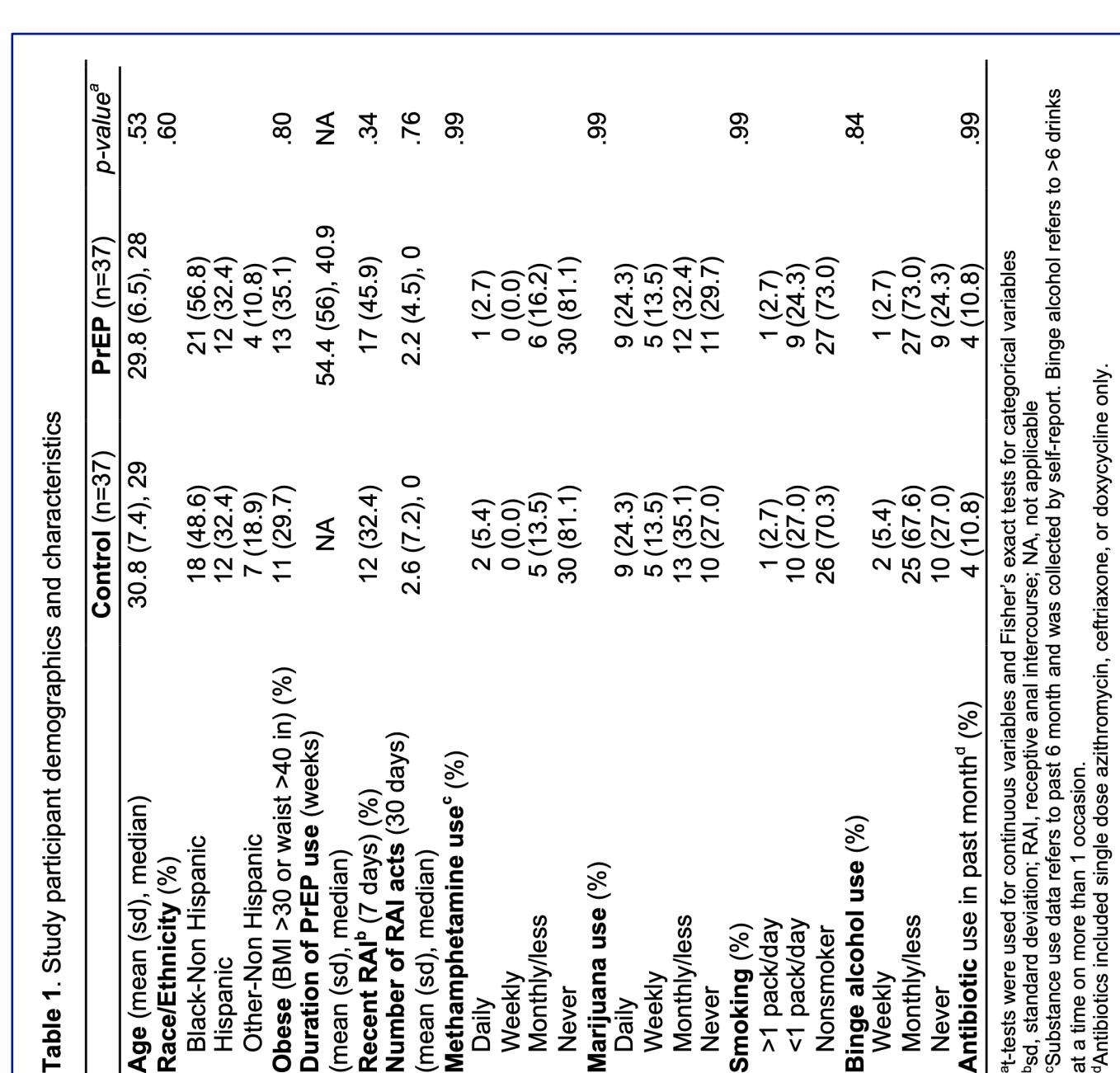


Figure 4. Associations between microbiome composition and TVF or FTC exposure levels. Forest plots showing associations of specific bacterial genera with TVF (blue) or FTC (purple) levels using ZINB regression analysis. * indicates associations that remained statistically significant after FDR-adjustment. Analysis based on limited subset of participants with available hair samples (n=15).

^aTests were used for continuous variables and Fisher's exact tests for categorical variables.
^{b,c}Standard deviation >30, receptive anal intercourse, NA if not applicable.
Substance use data refers to past 6 months and was collected by self-report. Binge alcohol refers to >6 drinks at time on more than 1 occasion.
^dAntibiotics included single dose aztreonam, ceftazidime, or doxycycline only.