HIV, Asymptomatic STI, and the Rectal Mucosal Immune Environment Among Young Men Who Have Sex with Men

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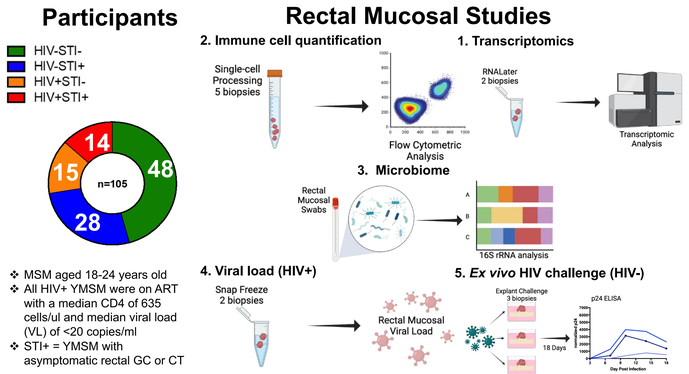
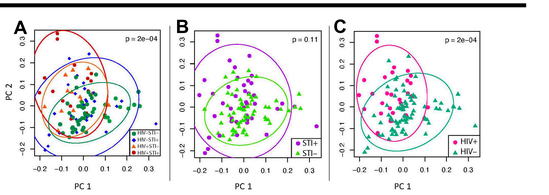
BACKGROUND

- Among young men who have sex with men (YMSM), asymptomatic rectal sexually transmitted infections (STI) such as *Neisseria gonorrhoeae* (GC) and *Chlamydia trachomatis* (CT) are common
- The inflammatory effects of asymptomatic rectal STI on the rectal mucosa (RM) are poorly understood and could have implications for HIV transmission and cure interventions

METHODS



- MSM aged 18-24 years old
- All HIV+ YMSM were on ART with a median CD4 of 635 cells/ul and median viral load (VL) of <20 copies/ml
- STI+ = YMSM with asymptomatic rectal GC or CT



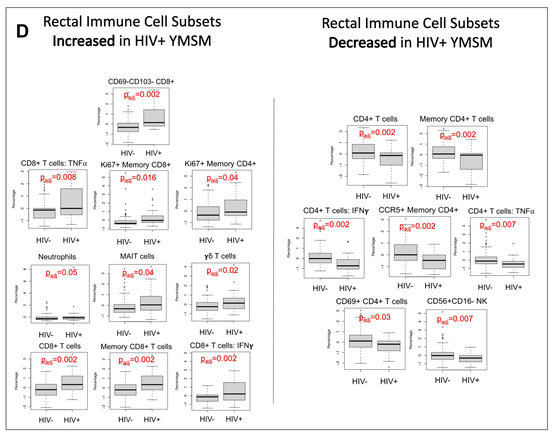


Figure 1: 26 innate and adaptive cell subsets from rectal mucosal tissues were analyzed by flow cytometry. A two-dimensional PCA plot (A) evaluating the rectal immune cell subsets demonstrated a significant difference between the four groups. However, there was no significant effect of asymptomatic STI on rectal mucosal cell subsets (B). Significant separation of the populations was seen when stratifying by HIV status (C). Linear decomposition modeling (LDM) enabled analyses of the independent effects of HIV and STI on cell subsets. After adjusting for HIV, there were no significant differences in cell subsets between STI+ and STI– YMSM. After adjusting for STI, 17 cell subsets were significantly different between HIV+ and HIV– YMSM (D).

Asymptomatic STI is associated with differential inflammatory effects on the rectal mucosa of YMSM based on HIV status

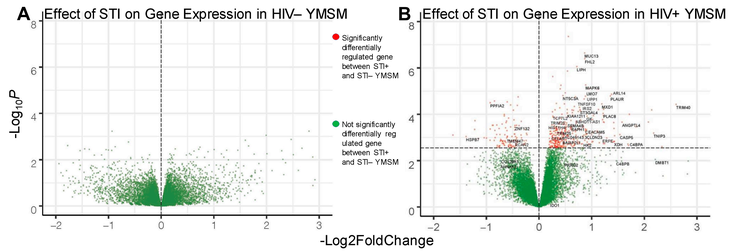


Figure 2: Among HIV– YMSM, stratified analyses of RNASeq data with DESeq2 identified no differentially expressed genes (DEGs) between STI+ and STI– YMSM (A); however, rectal STI was associated with significant (p_{adj}<0.1) differences in the expression of genes involved in inflammation, cell signaling, and mucosal integrity among HIV+ YMSM (B). Among HIV+ YMSM, rectal STI was associated with significant upregulation of 323 and downregulation of 109 DEGs (B). Consistent with the stratified analyses, LDM showed a significant interaction between STI and HIV (p=0.0084) attributed to 47 significant genes labeled in plot B. These interaction genes include those affecting mucosal barrier integrity such as MUC13 and CLDN23 as well as inflammatory cascades (TNFSF10, PLAUR, CASP5, MAPK6, C4BPA, C4BPB, TRIM25, and TRIM40 among others).

Figure 3: To further characterize the differential effect of asymptomatic STI on the rectal mucosal transcriptome among HIV+ YMSM vs HIV– YMSM, Gene Set Enrichment Analyses (GSEA) were undertaken with the Molecular Signatures Database and Reactome Pathway Database. These demonstrated differential regulation by STI status in many pathways within HIV+ YMSM. However, we did not see similar differences among HIV– YMSM, supporting a differential effect of asymptomatic STI based on HIV status. Here we highlight a selection of differentially expressed pathways from the Hallmark geneset (A) and the Reactome geneset (B) involved in inflammation and cell signaling.



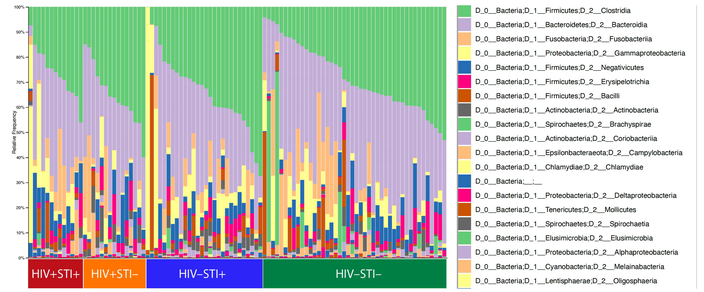


Figure 4: Microbiome composition, represented here at the class level but analyzed down to the genus level, differed minimally between the four groups. LDM showed no overall global difference between HIV+ vs HIV–, or STI+ vs STI–, YMSM. When we looked at the effect of STI when controlling for HIV status, the only taxa detected as having a higher probability of presence in the STI+ YMSM group were unsurprisingly *Neisseria* (p=0.001) and *Chlamydia* (p=0.003), and *Neisseria* was the only genus with significantly higher relative abundance (p=0.002). When we looked at the effect of HIV when controlling for STI status, we found no significant differences between taxa. The legend lists the top 20 (of 46 total) most abundant classes of bacteria.

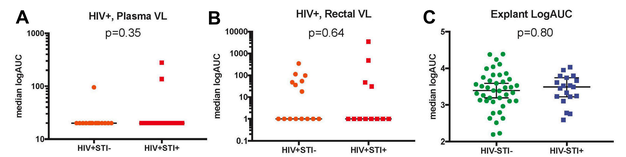


Figure 5: STI had no significant effect on plasma (A) or rectal (B) viral load in HIV+ YMSM or on explant p24 concentration in HIV– YMSM (C).

RESULTS

1. HIV infection alone was associated with an expected profound effect on RM immune cell composition among YMSM on ART (**Figure 1**)
2. STI had a significant effect on the rectal mucosal transcriptome within the HIV+, but not the HIV–, YMSM group (**Figures 2 & 3)**
3. There was little effect of STI or HIV on the rectal microbiome among YMSM (**Figure 4**)
4. There was no effect of STI on HIV viral load among HIV+ YMSM or p24 production in explant challenge experiments among HIV– YMSM (**Figure 5**)

CONCLUSIONS

- Asymptomatic rectal STI is not associated with significant RM inflammation among HIV– YMSM
- However, among HIV+ YMSM, rectal STI is associated with significant RM inflammation
- Given the contribution of chronic gut inflammation to HIV morbidity and as a barrier to HIV cure, the role of asymptomatic rectal STI, particularly recurrent STI, in mediating inflammation should be further examined among HIV+ MSM

SUPPORT
This work was funded by NIH R01 AI108335 and HD092033 (CFK) and supported by the Center for AIDS Research at Emory University, P30AI050409, and the Stimulating Access to Research in Residency Program of the National Institutes of Health under Award Number R38AII40299.