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Feminizing Hormone Therapy and the Rectal Mucosal Immune Environment

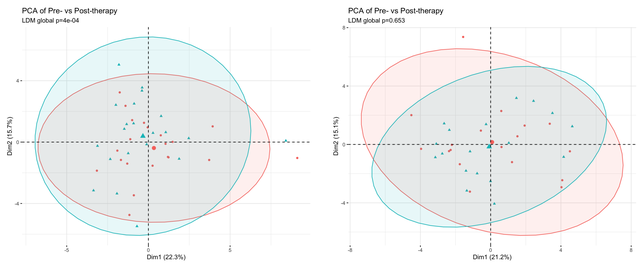
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BACKGROUND

- Transgender women (TGW) have historically been grouped with cisgender men who have sex with men (CGMSM) in HIV prevention research.
- The effects of feminizing hormone therapy (FHT) on the rectal mucosal immune environment, a primary site of HIV exposure, remain insufficiently understood.

METHODS

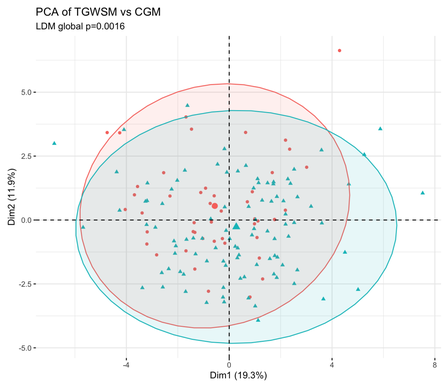
- Participants were enrolled in **Bangkok, Thailand.**
- Cross-sectional Cohort: **100** TGW, **50** CGMSM
- Longitudinal Cohort: **21** TGW **before** and 3-12 months **after FHT initiation**
- **Flow cytometry** was performed on **PBMC** (30 immune cell subsets) and **rectal musical** cells (31 immune cell subsets).
- Rectal biopsies were challenged with **HIV-1 BaL *ex vivo***, with p24 quantified over time in explant supernatants (Day 3-14 post-infection).
- **Bulk transcriptomics** (Illumina HiSeq3000) was performed on **rectal biopsies** and analyzed for differential gene expression and with gene set enrichment analysis (**GSEA**).

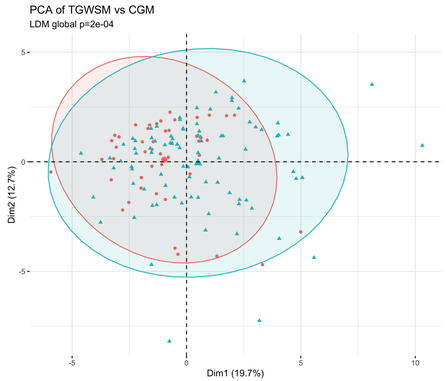


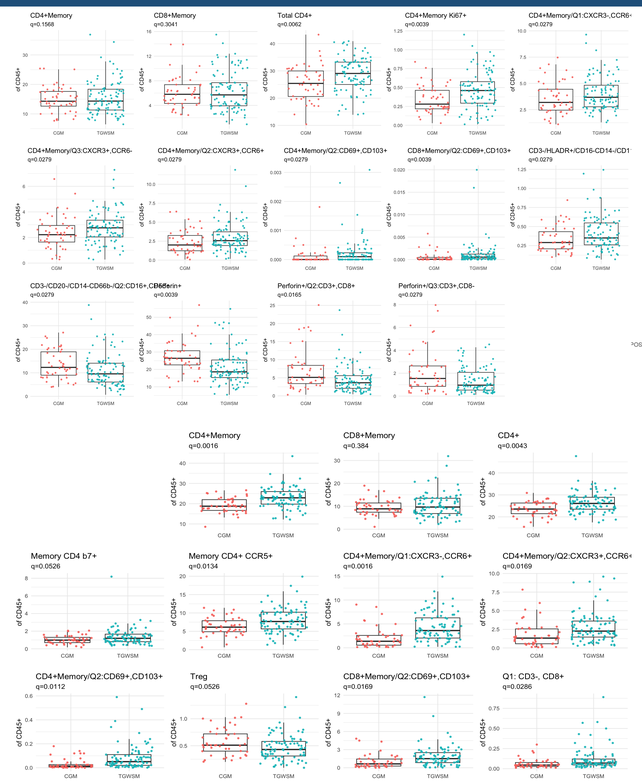
RESULTS: Longitudinal cohort

- Among TGW before and after FHT initiation, analyses of **PBMC** (**left**) revealed a significant global difference between **Pre-** (**blue**) and **Post-** (**red**) FHT (p=0.0004).
- Differences include elevated CD4+ T cells post-hormone therapy (q=0.0045), including CD4+ Memory (q=0.0096), and activated CD38+ CD4+ Memory cells and Th17 subsets (q=0.015, 0.0045). There was also a significant decrease in Perforin+ cells (q=0.0045),
- In contrast to the longitudinal cohort, analyses of **rectal tissues** (**right**) did not identify a significant global difference in tissue-residing immune cell subsets before and after FHT.

Differences between the systemic and rectal mucosal immune environment in transgender women, as compared to cisgender men, could influence risk of HIV acquisition.

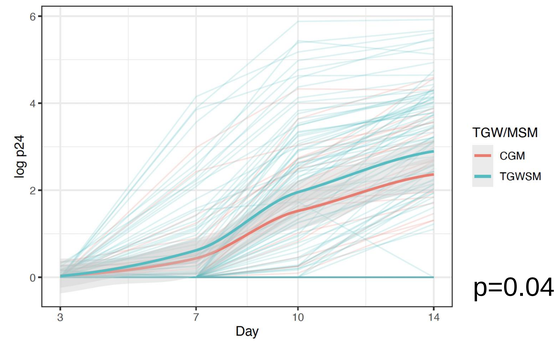






RESULTS: Cross-sectional cohort

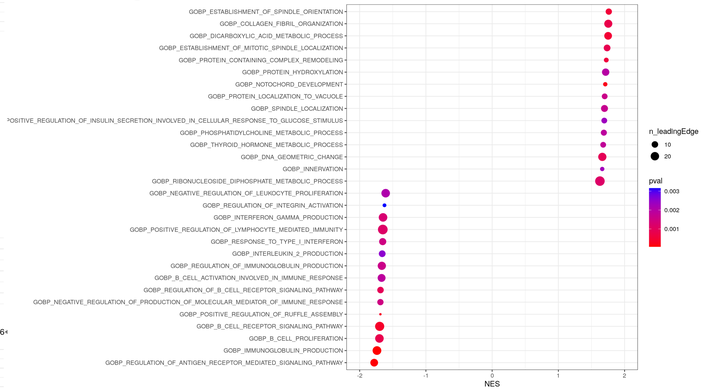
- Analyses of **PBMC** (**top**) revealed a significant differences between **CGMSM** (**red**) and **TGW** (**blue**) (p=0.0016), including an increase in activated memory CD4+ T cells (q=0.004), decreases in CD56+CD16+ NK cells (q=0.028) and perforin+ cells (q=0.004) among TGW.
- Analyses of **rectal tissues** (**bottom**) identified a significant differences between TGW and CGMSM (p=2e-04), including an increase in CCR5+ (q=0.01), Th17 (q=0.002), and Th1Th17 (q=0.02) memory CD4+ T cells among TGW.



p=0.04

RESULTS: *Ex vivo* rectal explant challenge

- With the cross-sectional cohort, here was a significantly higher slope of p24 production among TGW compared to cisgender men (p=0.04).
- There no significant difference between 24 production between CGMSM (red) and TGW (blue) at individual time-point or comparing area under the curve (AUC).
- No significant differences were observed in the longitudinal cohort before and after FHT initiation.



RESULTS: Rectal mucosal transcriptomics

- GSEA identified a number of highly relevant immune pathways that were downregulated in rectal mucosa among TGW compared to CGMSM

CONCLUSIONS

- The rectal mucosal immune environment among TGW using FHT is distinct from CGMSM.
- Rectal tissue in TGW may support higher HIV replication.
- Cellular changes in blood, but not rectal tissues, are apparent after short-term FHT use.
- Understanding the effects of FHT on HIV acquisition risk in the context of rectal exposure merits urgent investigation.