**Background:** Men who have sex with men (MSM) are disproportionately affected by HIV and STIs as compared to men who have sex with women (MSWo). We compared the penile microbiome of MSM to that of MSWo, to identify differences in penile microbiome composition, and whether these differences were associated with mucosal inflammation.

**Methods:** In this cross-sectional study, we enrolled 43 HIV negative MSM in Kisumu, Kenya. From a contemporaneously ongoing cohort study of the penile microbiome of MSWo, we randomly selected 43 MSWo who were matched to MSM on age and circumcision status, from their baseline visit. The penile microbiome was assessed via a shallow meatal swab, with 16s rRNA amplicon sequencing of the V3-V4 regions. Urinary cytokine concentrations were measured using the Luminex LabMAP multiplex system. After filtering and normalization, Random Forest (RF) with 5-fold cross validation was used to identify genus level taxa differing between MSM and MSWo. Taxa were regressed on cytokine outcomes, with multiple testing correction.

**Results:** Men were median age 24 and 77% circumcised. There were substantial differences in educational attainment, employment status, alcohol consumption, drug use, condom use, and number of sexual partners, with MSM in general having lower SES and greater behavioral risks. Microbiome composition differed substantially between MSM and MSWo: RF importance coefficients were greatest for *Lactobacillus* (greater relative abundance (RA) for MSWo), while *Veillonella*, *Staphylococcus*, and *Streptococcus* had lower RA for MSWo. Cytokines TNF-α, IL-1β, IL-10, and IP-10 were statistically significantly elevated among MSWo as compared to MSM, while IL-8 did not differ. In regression analyses, controlling for taxa differences in penile microbiome did they still differ? What was most important in determining cytokines?

Based on regression, *Corynebacterium,* *Peptoniphilus* and *Gardnarella* showed statistically significant association with the MSWo cytokines, while there was no significant association between MSM taxa and cytokines. Expected value of cytokines increased mostly in response to *Lactobacillus*, *Corynebacterium* and *Peptoniphilus*. There is a statistically significant difference between MSM and MSWo for cytokines(IL-1β,Il-8) based on microbial composition.

**Conclusions:** To our knowledge, this is the first direct comparison between MSM and MSWo of penile microbiome and urinary cytokines. Inflammatory markers were elevated for MSWo as compared to MSM, even when controlling for differences in penile microbiome composition?.

Note : Based on the correlation plots we see a trend, il10 is positively correlated with staph and anaerococcus, which is in higher abundance in MSWo, thus resulting in higher inflammation.

Surprising results:

Il8 is highly correlated(positive) with MSM Corynebacterium and negatively correlated with MSW Corynebacterium.

IL8 is highly correlated with MSW Gardnarella

Tnfa positively correlated with finegoldia(MSM), and negatively correlated with finegoldia(MSW)