The cervicovaginal microbiome, genital inflammation and HIV acquisition in sub-Saharan African women

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The unequal burden of HIV in sub-Saharan Africa

HIV prevalence in young women is up to 8 times greater than young men


UNAIDS, courtesy of Slim Karim
Insights into the role of genital inflammation and HIV acquisition from the CAPRISA 004 trial

Women with high levels of genital inflammatory cytokines had a **3.2 fold increased risk of becoming infected with HIV**

Masson *et al.*, CID, 2015
>900 HIV seronegative women between ages 18-23 in Umlazi, South Africa
Classes twice a week – focus on poverty alleviation
HIV viral load testing twice weekly
Pelvic exams and blood draws every 3 months
High frequency mucosal and blood sampling in early HIV infection
Burden of HIV in sexually active young women in KwaZulu Natal, South Africa

HIV Prevalence in sub-Saharan Africa

UNAIDS 2014


HIV Prevalence (%) vs Age

66%
Asymptomatic women display a broad range of baseline genital inflammation.

Cytokine levels were also not associated with hormonal contraceptive usage or sexual behavior.

Anahtar et al., Immunity 2015
Bacterial genital microbial community structures in healthy women in FRESH have high diversity
No differences in the FGT virome across cervicotypes
No significant differences in baseline HIV risk behavior or demographic factors between CTs

Bacterial community structures did not vary with:

- STIs
- Hormonal contraceptive use
- Condom use
- Use of intravaginal drying agents
- Frequency of sex
- Anal sex
- Demographic factors
High bacterial diversity and low *Lactobacillus* abundance predicts genital inflammation
Longitudinal intra-individual correlation between vaginal bacteria and pro-inflammatory cytokines

Participant 13

Participant 14

No CT change

CT change

Aerococcus
Clostridiales
Gardnerella
Shuttleworthia
Lactobacillus
Fusobacterium
Gardnerella
Prevotella
Mobiluncus
Lactobacillus
Alophobium vaginale
Peptostreptococcus
Anaerobius
Sneathia
Porphyromonas
Megasphaera
Other (unassigned)
Prevotella intermedia
Taux with <2% abundance.

IL-1α (pg/ml)

IL-1β (pg/ml)

TNF-α (pg/ml)

Time 1

Time 2

Lower CT

Higher CT

p=0.033

p=0.042

p=0.030
Genital inflammation is associated with cervical HIV target cell frequency
Cervicovaginal bacterial communities are associated with HIV acquisition in young women in sub-Saharan Africa.
No specific clustering of HIV acquisition within cervicovaginal community types
Specific bacterial taxa are significantly associated with increased genital inflammation and HIV acquisition.
In vivo proinflammatory bacterial species induce inflammatory cytokine production by human vaginal epithelial cells in vitro
Upregulation of APC LPS-sensing pathways involved in bacterial sensing

<table>
<thead>
<tr>
<th>KEGG Pathway</th>
<th>Enriched in:</th>
<th>LDA Score (Log 10)</th>
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</thead>
<tbody>
<tr>
<td>ko00740 Lipopolysaccharide biosynthesis</td>
<td>HighInflamm</td>
<td>3.290</td>
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<tr>
<td>ko06540 Lipopolysaccharide biosynthesis</td>
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<tr>
<td>ko02040 Flagellar assembly</td>
<td>HighInflamm</td>
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</tbody>
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Gene Set Enrichment:
- LPS-treated monocytes: $q = 6.16 \times 10^{-26}$
- LPS-treated dendritic cells: $q = 1.11 \times 10^{-33}$

Predicted upstream regulators:
- LPS ($p = 9.47 \times 10^{-26}$)
- IFN-g ($p = 6.31 \times 10^{-24}$)
- IL-1b ($p = 1.51 \times 10^{-23}$)
- CSF2 ($p = 6.74 \times 10^{-22}$)

Epithelial cells

Intra- and sub-epithelial APCs

CD14
Inflammatory bacteria from women induce increased HIV target cells in the genital tract of germ free mice.
**Summary**

**Cervicotype 1:** *Lactobacillus crispatus*

**Cervicotype 4:** Diverse anaerobes: *Prevotella, Gardnerella, Shuttleworthia, Sneathia, Megasphaera*
Next questions

• Can the cervicovaginal microbiome be leveraged to reduce HIV acquisition risk in women?
• What is the cause of increased baseline vaginal bacterial community diversity in South African women?
• Can we more specifically define the mechanisms of host immune sensing of bacteria in the FGT?
• What other genital mucosal factors modulate risk of HIV acquisition in women?
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Postdoc positions available! (see kwonlab.org)