Cervicovaginal microbial dynamics and its impact on HIV acquisition risk

Doug Kwon, M.D. Ph.D.
Ragon Institute of MGH, MIT and Harvard

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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
Opportunities to prevent HIV transmission by targeting events in the FGT

Modified from Haase, Nature, 2010
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
FRESH Study

Females Rising through Education, Support and Health

- >1100 HIV seronegative women ages 18-23 in Umlazi, South Africa
- HIV viral load testing twice weekly
- Pelvic exams & blood draws every 3 months
- Twice weekly classes – focus on poverty alleviation
- 87% go on to jobs, internships, schooling
- However... **8.4 HIV infections per 100 person-years**
Burden of HIV in sexually active young women in KwaZulu Natal, South Africa

HIV Prevalence in sub-Saharan Africa

HIV Prevalence in pregnant women in rural Vulindlela, South Africa (2005-2008)

<table>
<thead>
<tr>
<th>Age Group (Years)</th>
<th>HIV Prevalence (N=1237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤16</td>
<td>10.6%</td>
</tr>
<tr>
<td>17-18</td>
<td>21.3%</td>
</tr>
<tr>
<td>19-20</td>
<td>33.0%</td>
</tr>
<tr>
<td>21-22</td>
<td>44.3%</td>
</tr>
<tr>
<td>23-24</td>
<td>51.1%</td>
</tr>
</tbody>
</table>

Kharsany et al., JAIDS 2015

UNAIDS 2014

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
Behavioral factors impacting HIV acquisition risk in FRESH

- Condom use, 30 days
- Partner HIV tested
- Days since last sex
- Number of casual sex partners, 30 days
- Number of sex acts, 30 days
- Age current partner
- Number of pregnancies
- Self reported STI
- STI symptoms
- IPC use
- Number of sex partners, 30 days
- IPV use, 30 days

ODR (HIV acquisition)
No differences in bacteriophages or other viruses in the FGT across cervicotypes.
High bacterial diversity and low *Lactobacillus* abundance predicts genital inflammation.
Bacterial community structure better predictor of genital inflammation than STIs
Genital inflammation is associated with cervical HIV target cell frequency

\[ p = 0.0237 \]
Cervicovaginal bacterial communities are associated with HIV acquisition in young women in sub-Saharan Africa

Gosmann et al., Immunity 2017
Specific bacterial taxa are significantly associated with increased HIV acquisition

<table>
<thead>
<tr>
<th>Taxon</th>
<th>PC1 Correlation Coefficient</th>
<th>Q Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Megasphaera</td>
<td>0.60 ± 0.10</td>
<td>3.1e-07</td>
</tr>
<tr>
<td>Clostridium</td>
<td>0.45 ± 0.07</td>
<td>4.2e-07</td>
</tr>
<tr>
<td>Prevotella</td>
<td>0.43 ± 0.08</td>
<td>1.8e-06</td>
</tr>
<tr>
<td>Atoportium vaginai</td>
<td>0.42 ± 0.08</td>
<td>3.0e-05</td>
</tr>
<tr>
<td>Sneathia</td>
<td>0.37 ± 0.08</td>
<td>3.3e-04</td>
</tr>
<tr>
<td>Dialister</td>
<td>0.37 ± 0.07</td>
<td>2.0e-05</td>
</tr>
<tr>
<td>Veillonellaceae</td>
<td>0.34 ± 0.05</td>
<td>1.2e-07</td>
</tr>
<tr>
<td>Coriobacteriacea</td>
<td>0.32 ± 0.07</td>
<td>3.0e-05</td>
</tr>
<tr>
<td>Parvimonas</td>
<td>0.31 ± 0.07</td>
<td>2.9e-04</td>
</tr>
<tr>
<td>Gardnerella vaginalis</td>
<td>0.31 ± 0.07</td>
<td>2.9e-04</td>
</tr>
<tr>
<td>Gemella</td>
<td>0.28 ± 0.08</td>
<td>6.0e-03</td>
</tr>
<tr>
<td>Leptotrichiaceae</td>
<td>0.26 ± 0.07</td>
<td>2.1e-03</td>
</tr>
<tr>
<td>Mobiluncus</td>
<td>0.25 ± 0.08</td>
<td>1.4e-02</td>
</tr>
<tr>
<td>Lactobacillus iners</td>
<td>-0.41 ± 0.09</td>
<td>3.4e-04</td>
</tr>
<tr>
<td>Lactobacillus crispatus</td>
<td>-0.46 ± 0.09</td>
<td>6.8e-06</td>
</tr>
</tbody>
</table>

Taxa differentially associated (p<0.01) with:
- Protection
- Acquisition
- Prevotella melaninogenica
- Veillonella montpellierensis
- Mycoplasma
- Prevotella bivia
- Sneathia sanguinegens
- L. crispatus
No specific clustering of HIV acquisition within cervicovaginal community types
Differences in *Lactobacillus* predominant communities in U.S. and South African women

- **U.S. White women**
  - 90% *Lactobacillus* dominant
  - Ravel *et al*., PNAS 2011

- **FRESH women**
  - 37% *Lactobacillus* dominant
  - Anahtar *et al*., Immunity 2015
Vaginal bacterial community dynamics lead to equilibrium states that favor greater microbial diversity.
Net movement from *Lactobacillus* dominance to higher diversity communities
Vaginal bacterial community dynamics lead to equilibrium states that favor microbial diversity
Predicted equilibrium closely matches distribution of communities observed in FRESH
Impacting equilibrium by targeting the $L.\ crispatus - L.\ iners$ transition probability
Proinflammatory bacteria induce inflammation in FGT epithelial cells and APCs

**A.** Diagram showing bacterial species such as *Lactobacillus crispatus* and *Prevotella amnii* interacting with vaginal epithelial cells.

**B.** Timeline showing inoculation events over six days, leading to changes in FGT and blood samples.

**C.** Heatmap displaying gene expression levels from antigen-presenting cells (APCs) from the endocervix, with gene set enrichment analysis showing significant upregulation in LPS-treated monocytes and dendritic cells.

**Gene Set Enrichment:**
- LPS-treated monocytes: $q = 6.16 \times 10^{-36}$
- LPS-treated dendritic cells: $q = 1.11 \times 10^{-33}$
SeqWell transcriptional profiling of FGT host responses to bacteria

Gierahn et al., Nat Meth 2017
SeqWell transcriptional profiling of FGT host responses to bacteria

CT1: *L. crispatus*

CT4: Diverse anaerobes
Role of cervicovaginal bacteria in HIV risk

**Cervicotype 1:** *Lactobacillus crispatus*

**Cervicotype 4:** Diverse anaerobes: *Prevotella, Gardnerella, Shuttleworthia, Sneathia, Megasphaera*
Multiple effects of cervicovaginal bacteria on the mucosal environment of the FGT
Next questions

• Can the cervicovaginal microbiome be leveraged to reduce HIV acquisition and reproductive health in women?
• What are the causes of increased baseline vaginal bacterial community diversity in South African women?
• What interventions will result in durable alterations in the equilibrium states of FGT bacterial communities?
• Can we more specifically define the mechanisms of host immune sensing of bacteria in the FGT?
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Postdoc positions available! (see kwonlab.org)