The role of the genital microbiome and injectable hormonal contraception in HIV acquisition in 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
FRESH Study

- >700 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

HIV Prevalence in sub-Saharan Africa

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.
Differences in *Lactobacillus* predominant communities in U.S. and black South African women

**U.S. White women**

- **IV:** 90% *Lactobacillus* dominant
- **I:** 45%
- **II:** 8%
- **III:** 27%
- **V:** 9%

Source: Ravel *et al.*, PNAS 2011

**FRESH women**

- **CT4:** 35% *Lactobacillus* dominant
- **CT3:** 28%
- **CT2:** 28%
- **CT1:** 9%

Source: Anahtar *et al.*, Immunity 2015
High bacterial diversity and low *Lactobacillus* abundance predicts genital inflammation.
Upregulation of APC pathways involved in bacterial sensing

Predicted upstream regulators:
• LPS (p=9.47e^{-26}),
• IFN-γ (p=6.31e^{-24}),
• IL-1β (p=1.51e^{-23}), and
• CSF2 (p=6.74e^{-22})

Gene Set Enrichment:
- LPS-treated monocytes
  q = 6.16 e^{-36}
- LPS-treated dendritic cells
  q = 1.11 e^{-33}

KEGG Pathway
<table>
<thead>
<tr>
<th>Pathway Description</th>
<th>Enriched in</th>
<th>LDA Score (Log 10)</th>
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<tbody>
<tr>
<td>ko00780</td>
<td>Biotin metabolism</td>
<td>HighInflamm</td>
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<tr>
<td>ko00540</td>
<td>Lipopolysaccharide biosynthesis</td>
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<tr>
<td>ko02040</td>
<td>Flagellar assembly</td>
<td>HighInflamm</td>
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</table>

Antigen presenting cells from the endocervix

Epithelial cells

Intra- and sub-epithelial APCs
IPC use is associated with increased HIV acquisition in FRESH

Byrne, Anahtar et al. Lancet ID 2016
Summary

Recruitment
Activation
Proliferation
Differentiation

LPS
Progestins

IL-1α
IL-1β
IL-8

CT 4 bacteria
Epithelial cells

APC
Prostaglandins

TNF-α
CXCL10

CD4+ T cell

Recruitment
Activation
Proliferation
Differentiation
Future questions and gaps

• What is the cause of increased vaginal bacterial community diversity in South African women?
• Can we more specifically define the mechanisms of host immune sensing of bacteria in the FGT that results in increased HIV target cells?
• Are other domains of life important in HIV acquisition risk?
• What are the cellular mechanisms by which progestins lead to increased HIV target cell frequency in the FGT?
• How will progestins and the cervicovaginal microbiome affect MPT efficacy
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