The Role of the Intestinal Microbiome in Modulating HIV Transmission risk

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Disclosures

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• Chair of the Scientific Advisory Board at ABIVAX, Paris, France

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Overview

• The risk of HIV infection associated with anal sex
• The intestinal microbiome in health and disease
• MSM and the intestinal microbiome
• Factors that modulate the microbiome
• Potential interventions to restore a healthy intestinal microbiome
The Risk of HIV Infection Associated with Anal Sex
Anatomical Considerations
GALT Vulnerability to HIV

CD4+/CCR5+ T cell in blood & gut

Anton PA et al AIDS 2000
## Risk of Condomless Anal Sex

<table>
<thead>
<tr>
<th>Author</th>
<th>Estimate (95% CI)</th>
<th>Study participants</th>
<th>Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anal sex, receptive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DeGruuttola (1989)</td>
<td>0.50-3.00%</td>
<td>MSM</td>
<td>Retrospective-partner</td>
</tr>
<tr>
<td>Leynaert (1998)</td>
<td>3.38% (1.85-4.91)</td>
<td>Heterosexuals</td>
<td>Retrospective-partner</td>
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<tr>
<td>Jin (2010)</td>
<td>0.91% (0.41-2.07)</td>
<td>MSM</td>
<td>Prospective cohort of individuals</td>
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<tr>
<td>Scott (2014), pre-ART</td>
<td>0.60% (0.34-1.09)</td>
<td>MSM</td>
<td>Prospective cohort of individuals</td>
</tr>
<tr>
<td>Scott (2014), early ART</td>
<td>0.73% (0.45-0.98)</td>
<td>MSM</td>
<td>Prospective cohort of individuals</td>
</tr>
<tr>
<td>Updated pooled</td>
<td>1.25% (0.55-2.23)</td>
<td>MSM</td>
<td>Prospective cohort of individuals</td>
</tr>
<tr>
<td><strong>Test for heterogeneity:</strong> $\hat{i}^2 = 87%$ ($P = 0.0002$)</td>
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</tbody>
</table>

| Anal sex, insertive |                          |                     |                               |
| Jin (2010) | 0.16% (0.05-0.31) | MSM       | Prospective cohort of individuals |
| Scott (2014), pre-ART | 0.14% (0.04-0.29) | MSM       | Prospective cohort of individuals |
| Scott (2014), early ART | 0.22% (0.05-0.39) | MSM       | Prospective cohort of individuals |
| Updated pooled   | 0.17% (0.09-0.26) | MSM       | Prospective cohort of individuals |
| **Test for heterogeneity:** $\hat{i}^2 = 0\%$ ($P = 0.7716$) | | |                               |

- **HIV-1 transmission probability per anal sex act (%)**

### Table: Summary of pooled estimates

<table>
<thead>
<tr>
<th>Estimate type</th>
<th>Pooled estimate, % (95% CI)</th>
<th>$P^a$</th>
<th>$I^2,b$, (%)</th>
<th>N</th>
<th>References</th>
<th>$P$-value$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>URAI</td>
<td></td>
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<tr>
<td>Gender</td>
<td></td>
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<tr>
<td>Women</td>
<td>3.38 (1.85-4.91)</td>
<td>1.000</td>
<td>0.0</td>
<td>1</td>
<td>$^{20}$</td>
<td></td>
</tr>
<tr>
<td>MSM</td>
<td>0.75 (0.56-0.98)</td>
<td>0.278</td>
<td>&lt;0.1</td>
<td>4</td>
<td>$^{7,8,19_c}$</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Baggaley RF et al. AJRI 2018
The Intestinal Microbiome in Health and Disease
The Normal Microbiome

Jandhyala SM et al. World J Gastro 2015
Intestinal Enterotypes

Arumugam M et al. Nature 2011
The Intestinal Microbiome in HIV

MSM and the Intestinal Microbiome
Microbiome in Spanish MSM

Prevotella Dominance in MSM

Hts: Heterosexual
MSM: men who have sex with men
PWID: IV drug use
Microbiome in US MSM

Kelley CF et al. Mucosal Immunology 2016
Sampling is Important!

Pescatore N et al. AIDS Res Human Retroviruses 2018
The Neovaginal Microbiome
The Neovagina and HIV Risk

• According to current estimates, around a quarter (22-28%) of transgender women are living with HIV

• Approximately 11-16% of transgender women undergo vaginoplasty

• The neovagina may have unique vulnerability to HIV infection as a consequence of neovaginal dysbiosis
Factors That Can Modulate the Microbiome
Factors That Can Modulate the Intestinal Microbiome

- Age, sex, diet, and geography
- Antibiotic therapy
- Sexual / parasexual behaviour
- Anorectal STIs
- Recreational drug use
- Antiretroviral therapy
- Microbicides
Parasexual Behaviour (1)

Sensitivity Analysis - Incident vs. Prevalent Cases of Rectal Infections

- **Rectal Infection**
  - Less than weekly: 1.8 (Incidental cases), 1.7 (All cases)
  - Weekly or more: 3.9 (Incidental cases), 3.6 (All cases)

- **Rectal Gonorrhoea**
  - Less than weekly: 2.6 (Incidental cases), 2.1 (All cases)
  - Weekly or more: 4.7 (Incidental cases), 3.6 (All cases)

- **Rectal Chlamydia**
  - Less than weekly: 1.7 (Incidental cases), 1.7 (All cases)
  - Weekly or more: 2.8 (Incidental cases), 3 (All cases)

**Odds Ratio**

**NOTE:** 'Incident' cases are new infections after week 0. 'Prevalent' cases are infections from week 0-48.

Hassan A et al. Sex Trans Dis 2018
Parasexual Behaviour (2)

Predicted Probability of Rectal Infections - Interaction between Douching and Median No. of Partners

- **No Douching**

- **Douching**

**NOTE:** * Median number of male sexual partners in past 3 months. Shaded area is 95% CI.

Hassan A et al. Sex Trans Dis 2018
Anorectal STIs

Nguyen VK et al AIDS 2018

IRR: Incidence Rate Ratios
Recreational Drug Use (1)

- Study based on samples from 37 MSM living in Los Angeles
- All participants HIV positive
- 92% Black or Hispanic
- Age 36 (28-39) years

Fulcher JA et al. JID 2018
Recreational Drug Use (2)

Fulcher JA et al. JID 2018
Recreational Drug Use (3)

Fulcher JA et al. JID 2018
Antiretroviral Therapy (PrEP)

Dube MP et al. Nature Scientific Reports 2018
Microbicides

DREAM Program

Tenofovir prodrug enemas
PI: Craig Hendrix, JHU

PREVENT Program

Griffithsin rectal enema
PI: Kenneth Palmer, University of Louisville
Rectal Microbiome Changes in NHP

- Effect of GRFT or placebo gel exposure in NHP
- Volcano plots display the log10-fold change
- Significant effects were observed
  - 24 h post HEC placebo gel application relative to baseline samples
  - 24 h post-GRFT-HEC gel relative to 24 h post-HEC placebo gel applications

Girard L et al. Nature Scientific Reports 2018
Perturbation of the Intestinal microbiome and Impact on HIV Risk
Prevotella and Mucosal Inflammation

- SHIV vaccine study
- Intrarectal challenge with SHIVSF162P4
- Macaques from different sources had variable risk of infection
- Increased risk associated with
  - Activated CD4+CCR5+Ki67+ T cells in the rectal mucosa
  - Lower ratios of Bacteroides to Prevotella
  - Lower levels of Firmicutes

Sui Y et al. Mucosal Immunology 2018
Potential Interventions to Restore a Healthy Intestinal Microbiome
Potential Interventions to Reduce the Risk of HIV Infection

• Reduce ‘damage’
  ➢ Sexual behaviour
  ➢ Douching
  ➢ Lubricant choice
  ➢ Rectal STIs
  ➢ Antibiotic exposure

• Restore the Microbiome
  ➢ Diet
  ➢ Probiotics
  ➢ Prebiotics
  ➢ Synbiotics
  ➢ Fecal transplant
Further Research

• Better characterisation of the rectal microbiome in populations at risk of HIV infection
• Define key variables associated with changes in the intestinal microbiome
• Evaluate the linkage between perturbations of the rectal microbiome and GALT immunology
• Intervention / pathogenesis studies in the NHP model
• Longitudinal studies in high-risk populations
• Intervention studies in high-risk populations
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Thank You