Overview

- Recent data on host predictors of HIV acquisition
  - Mucosal cytokines & chemokines
  - Mucosal proteomics
  - Systemic CD4+ T cell correlates
- Potential impact of age & sex work
  - Particularly at the start of sex work

A spectrum of HIV susceptibility

KwaZulu Natal, SA: Peak incidence in women aged 20-24 years
CAPRISA 004: 2/3 of infections in first 2/5 of follow up
VOICE: incidence of >7% in the first year compared to 5% overall

Mucosal immunology of HIV transmission

Mucosal Inflammation is a strong predictor of HIV risk

<table>
<thead>
<tr>
<th>Acquired HIV</th>
<th>Remained uninfected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammation + *</td>
<td>19</td>
</tr>
<tr>
<td>Inflammation -</td>
<td>39</td>
</tr>
<tr>
<td>Total</td>
<td>58</td>
</tr>
<tr>
<td>Pair-matched OR (95% CI)</td>
<td>3.2 (1.3, 7.9)</td>
</tr>
<tr>
<td>P value</td>
<td>0.014</td>
</tr>
</tbody>
</table>

* Upper quartile for 5 of 9 inflammatory cytokines (IL-1α, IL-1β, TNF-α, IL-8, IFN-γ, MCP-1, MIP-1α, MIP-1β)
Elevated mucosal cytokines associated with a >2-fold increase in endocervical CD4+ T cells

11/14 cytokines correlated positively with the # of mucosal T cells

CD4+ T cells are immunologically heterogeneous

HIV target cells & viral dissemination

Blockade of α4β7 protected non-human primates from low dose repeat vaginal SIVmac251 challenge

Summary of Part 1

• Several host immune factors, measured pre-infection, are associated with higher rates of HIV acquisition during prospective follow-up
• Is inflammation a surrogate for some other biological process? What is the mechanism by which inflammation increases HIV transmission? Are there any ‘host targets’?
• Can these markers be validated in different cohorts? Younger populations? Sex workers? Can these be used for risk stratification?
Per-coital rates of HIV acquisition: Age as a co-factor

  - Those under 30 years of age were 15x more likely to acquire HIV per contact
- Gray et al. (2001) Prospective cohort of HIV serodiscordant couples.
  - Highest per-coital rates were in women 15-24 years of age
  - 18% decrease in risk (95% CI 6-29) for uninfected partner by 5 years of age

Age effects for transmission co-factors?

- DMPA: Highest HIV risk in 18-20 year old women (HR 9.3, 2.7-31.7) compared to the 21-24 year old group (HR 2.0, 1.1-3.6)
- HPV: Peak prevalence in CAPRISA004 was in the 18-19 years group (81%), 2.8x increased risk of HIV acquisition, greater risk with HPV clearance. Mucosal impact poorly defined.
- HSV2: (next slide)
- Bacterial STIs: (slide after that)

Rapid acquisition of HSV2 and increased rates of HSV2 shedding in the first year post-infection

<table>
<thead>
<tr>
<th>Age group</th>
<th>HSV2 % prevalence (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤15</td>
<td>4.1 (24/590)</td>
</tr>
<tr>
<td>16-17</td>
<td>8.6 (46/537)</td>
</tr>
<tr>
<td>18-19</td>
<td>22.6 (48/212)</td>
</tr>
<tr>
<td>20-22</td>
<td>36.1 (30/83)</td>
</tr>
</tbody>
</table>

* Based on data from 14 schools, grades 9-10

Are STIs more inflammatory in younger populations?

Effect estimate for NG and IL6 by age

Effect due to differences in immunity? Tolerance?

Further analysis of Masson et al., Sex Trans Infect 2014

Intersection of age, sex work, and mucosal immunology in the Transitions project

Peak in HIV risk

Transition into sex work
Intersection of age, sex work, and mucosal immunology in the Transitions project

• Does the age at the time of sex work transition matter? Or the duration/nature of the transition? How heterogeneous are these variables?
• What is the impact of frequency of sex & whether it is with one or more partners?
• What is the impact of condom exposure in a transactional setting vs. low condom use observed with regular partners and boyfriends?
• How do HIV risk proteins/cells change over time/SW transition?
• What are the interactions between overlapping co-factors?
• How do mucosal host interactions with STIs / the microbiome change over time?
• What is the impact of vaginal practices (common in FSW, but in the general population)?

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