The Roles of Immune activation and Inflammation on CD4 Depletion and HIV shedding at the Female Genital Tract

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Immune cells primarily detect antigens and initiate *immune responses* to prevent further antigen spread.

- **T cells become activated**
  - *increased transcription, translation*
  - *cell cycle entry, proliferation*
  - *increased ‘help’ for B cells + CTL*
  - *increased cell-mediated effector function*

- **Recruitment to sites of infection**

**BUT:** HIV preferentially infects activated T cells
- **Non-pathogenic SIV infection**
  - limited or early resolved immune activation \(\text{(Estes et al., 2008; Silvestri et al., 2003)}\)

- **HIV-resistant cohorts:**
  - limited immune activation \(\text{(Begaud et al., 2006; Koning et al., 2005; Jennes et al., 2006)}\)
  - enhanced frequencies of regulatory T cells \(\text{(Card et al., 2009)}\)
  - decreased effector function \(\text{(Jennes et al., 2006)}\)
The micro-environment within the female genital tract has a strong influence on both the acquisition and transmission of HIV-1 during penetrative vaginal sex.

Genital tract inflammation is associated with HIV disease progression and susceptibility to infection (Roberts et al., 2010; Roberts et al., manuscript in press).

Attempts at local protective immunity to invading pathogens may ironically also provide the virus with a steady supply of activated susceptible target cells at the predominant site of heterosexual transmission of HIV in women.
Objective

This study investigated the role of inflammation and immune activation in the features associated with HIV pathogenesis: CD4 depletion and HIV shedding in the female genital tract.
35 HIV+ and 38 healthy HIV- women

Blood and Cervical Cytobrush Specimens at a single visit

- Viral Load Testing

  - Luminex: Concentration of Inflammatory Cytokines

  - Flow Cytometry: Characterisation of T cell Activation
Flow Cytometry Analysis Gating Strategy

Singlets

Live cells

Lymphocytes

CD3 T cells

CD4 & CD8 T cells

Individual Activation Markers

Dual Marker Expression
Comparison between blood and genital tract T cell activation
T cell Activation between compartments

T cell activation was enhanced at the genital tract, irrespective of HIV status

Mann-Whitney U test; p<0.05 significant after adjusting for multiple comparisons
T cell Activation between compartments

Mann-Whitney U test; p<0.05 significant after adjusting for multiple comparisons
T cell Activation between compartments

Strong positive associations between T cell activation at the blood and at the female genital tract

Univariate quantile regression β-coefficients; p-values ≤0.05 considered significant after adjustment for multiple comparisons
What is the impact of HIV infection on T cell activation at the genital tract?
The effect of HIV status on T cell activation

T cell activation was elevated during HIV infection, in both blood and the genital tract.
The effect of HIV status on T cell activation

T cell activation was elevated during HIV infection, in both blood and the genital tract.
Does cervical T cell activation impact on CD4 depletion and HIV shedding into the genital tract?
CD4+ T cell depletion at the female genital tract

T cell activation is associated with the depletion of CD4+ T cells at the genital tract
T cell activation and genital HIV shedding

T cell activation is associated with the magnitude of HIV RNA at the genital tract
T cell activation, CD4 depletion and genital HIV shedding

- Activation
- HIV Shedding
- CD4+ T cell depletion
What role does inflammation play?
Inflammation at the genital tract

**Chemokines**

- Eotaxin
- IP-10
- MCP-1
- MIP-1alpha
- MIP-1beta
- RANTES

**Pro-inflammatory**

- IL-1alpha
- IL-6
- IL-8
- IL-10

*Log Cytokine Concentration (pg/ml)*

- **HIV negative**
- **HIV positive**

\[ p < 0.05 \]
Inflammation and T cell activation

T cell activation is associated with inflammation at the genital tract
Inflammation, HIV shedding and CD4 depletion at the genital tract

Genital tract inflammation was associated with CD4 depletion and the magnitude of HIV RNA at the genital tract
In Summary:

• Cervical T cell activation was elevated in both HIV+ and HIV- women

• T cell activation was greater in HIV+ women than HIV- women

• Increased frequencies of activated T cells was associated with increased levels of HIV RNA at the genital tract and reduced CD4+ T cell frequencies

• Elevated T cell activation was associated with increased inflammation, RANTES

• RANTES concentrations were associated with elevated HIV RNA levels and CD4 depletion
The role of T cell activation and inflammation on CD4 depletion and genital HIV shedding
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The role of T cell activation and inflammation on CD4 depletion and genital HIV shedding

• Predictors of HIV shedding into the genital tract

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<th>Predictors of magnitude of HIV RNA at the cervix</th>
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<td><strong>Linear model</strong></td>
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<td>RANTES concentration</td>
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<td>Cervical CD4%</td>
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<td>Cervical CD8+ CD38/HLA-DR%</td>
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<td>Plasma HIV RNA copies/ml</td>
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<th>Predictors of the odds of HIV shedding into the genital tract</th>
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<td><strong>Inflated model</strong></td>
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<td>Cervical CD8+ CD38/HLA-DR%</td>
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RANTES at the genital tracts of HIV- women exposed to HIV

RANTES levels higher in women exposed but sero-negative

Associated with elevated immune activation at the genital Tract

Is RANTES protective? Is there a threshold concentration for conferring protection/fuelling HIV replication?

What other factors are contributing to the prevention of infection? Is RANTES production a biomarker for the production of some other protective factor or is it in synergy with some other protective factor?

How can we improve on this knowledge and harness it into biomedical moulding of genital tract environments that do not support HIV replication?