O10 Healthy HIV-1-seropositive individuals have impaired alveolar immunity despite highly active antiretroviral therapy

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HIV+ individuals risk pneumococcal infection and chronic lung disease in the HAART era

Clinical Infectious Diseases
Hospitalization for Pneumonia among Individuals With and Without HIV Infection, 1995–2007: A Danish Population-Based, Nationwide Cohort Study

AIDS
Invasive pneumococcal disease among HIV-positive individuals, 2000–2009

BMC Pulmonary Medicine
Pulmonary symptoms and diagnoses are associated with HIV in the MACS and WIHS cohorts

Driven by host factors, systemic and lung effects of chronic HIV

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- HIV, Smoking, Substance use

- Additional cofactors
  - Occupational and environmental exposures
  - Malnutrition
  - Genetic susceptibility
  - Impact of antiretroviral treatment unknown

- Aging

- Host factors

- Systemic and lung effects

- Chronic inflammation
- HIV persistence and immune dysfunction
- Respiratory infections/colonization
- Oxidative stress

- Potential pathogenetic mechanisms
  - Inflammation
  - Immune dysfunction
  - Apoptosis
  - Protease/anti-protease imbalance

- Lung function decline

- COPD, other chronic lung disease
Alveolar macrophages (AM) play a pivotal role in the control of bacteria in the lung. HIV-1 promotes resistance to apoptosis in macrophages which contributes to these cells acting as a viral reservoir for HIV-1.

We hypothesised that there is a persistently altered virologic and immunologic environment in the HIV lung during HAART that impairs apoptosis-associated pneumococcal killing by AM.
<table>
<thead>
<tr>
<th></th>
<th>HIV ARV (n = 14)</th>
<th>HIV NAÏVE (n = 3)</th>
<th>CONTROL (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>42.4 ± 2.4</td>
<td>41.7 ± 5.3</td>
<td>40.8 ± 2.7</td>
</tr>
<tr>
<td><strong>Male Sex</strong></td>
<td>8, 57%</td>
<td>3, 100%</td>
<td>8, 67%</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>9</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Black African</td>
<td>4</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Other ethnicity</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Nadir CD4 (cells/mm3)</strong></td>
<td>213 ± 26</td>
<td>587 ± 105</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>CD4 (cells/mm3)</strong></td>
<td>643 ± 51</td>
<td>672 ± 176</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>CD4:CD8</strong></td>
<td>0.83 ± 0.07</td>
<td>0.66 ± 0.003</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>HIV RNA (log10 copies/mL)</strong></td>
<td>all undetectable</td>
<td>4.43 ± 3.84</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>ART</strong></td>
<td></td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Protease Inhibitor</td>
<td>6</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>NNRTI</td>
<td>7</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Mixed or other</td>
<td>1</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Duration (months)</strong></td>
<td>87.2 ± 14.5*</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Data expressed as mean ± SEM.
**HIV+ AM demonstrated impaired intracellular killing of pneumococci**

**Associated with reduced apoptosis**

**20 hours**

- **4 hours**:
  - Control vs. HIV: ns

- **20 hours**:
  - Control vs. HIV: *

- **Cells per HPF**:
  - MI vs. D39: ns

- **% Nuclear Fragmentation**:
  - MI vs. D39: *

- **Caspase 3/7 Activity**:
  - Fold change from MI: *

**16 hours**

- **Caspase 3/7 Activity**:
  - Fold change from MI: *
HIV+ on ART have a BAL lymphocytosis

**CD3**

**CD8**

**CD4+**

**CD8+**

**HIV** control

**HIV**

**on ART**

have a BAL lymphocytosis

**...with a CD8+ predominance of T cells**

**HIV+ on ART**

**have a BAL lymphocytosis**

**...with a CD8+ predominance of T cells**

**BAL**

**leukocytes**

**CD4+**

**CD8+**

**cell ratio**

**control**

**HIV+ on ART**

**have a BAL lymphocytosis**
<<10% AM infected with HIV in vivo - indirect mechanism?

HIV-Infected Individuals with Low CD4/CD8 Ratio despite Effective Antiretroviral Therapy Exhibit Altered T Cell Subsets, Heightened CD8+ T Cell Activation, and Increased Risk of Non-AIDS Morbidity and Mortality

Sergio Serrano-Villar1*, Talia Sainz2, Sulggi A. Lee3, Peter W. Hunt3, Elizabeth Sinclair3, Barbara L. Shacklett4, April L. Ferre5, Timothy L. Hayes6, Ma Somsouk5, Priscilla Y. Hsue5, Mark L. Van Natta5, Curtis L. Meinert5, Michael M. Lederman6, Hiroyu Hatano5, Vivek Jain5, Yong Huang7, Frederick M. Hecht7, Jeffrey N. Martin6, Joseph M. McCune5, Santiago Moreno5, Steven G. Deeks5

Human monocyte derived macrophage

Is gp120 present in the alveolar space?
Is gp120 mediating the pneumococcus associated anti-apoptotic effect on AM?
gp120 detectable in BAL fluid despite HAART

BAL fluid gp120

n = 11

not detected detected

sandwich ELISA with anti-gp120 monoclonal Ab: 14E,17B, EH21

gp120 treatment of MDM impairs apoptosis associated killing of pneumococci

4 hours

20 hours

0 1 2 3 4 5

Log_{10} cfu/mL

control gp120

ns

* 1.0 1.5 2.0

Log_{10} cfu/mL

control gp120

ns

* 0 0.5 1.0

Log_{10} cfu/mL

control gp120

ns

* 4 hours

20 hours

% Nuclear Fragmentation

0 10 20 30 40 50

control gp120

ns

* 0 10 20 30 40 50

% Nuclear Fragmentation

0 10 20 30 40 50

control gp120

ns

* 0 10 20 30 40 50

% Nuclear Fragmentation

0 10 20 30 40 50

control gp120

ns

* 0 10 20 30 40 50

% Nuclear Fragmentation

0 10 20 30 40 50

control gp120

ns

*
gp120 impairs apoptosis associated Mitochondrial ROS generation which may impair killing
Conclusions

In HIV seropositive individuals

• A CD8 lymphocytosis persists and gp120 remains detectable in the lung despite HAART.

• Alveolar macrophages have an impaired apoptotic response to pneumococci which limits their killing capacity

• gp120 causes macrophage oxidative stress and impairs apoptosis-associated killing of pneumococci.

Thus, the immune environment of the lung fails to correct with HAART and may play a role in HIV associated lung disease.
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