HIV in the lung: virological and immunological findings in long-term ART

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HIV+ individuals still at risk of pneumococcal infection and chronic lung disease in the HAART era.
Driven by host factors and systemic and lung effects of chronic HIV

14 HIV+ patients
With UDE VL and Normal CD4 on HAART
Vs
3 HIV+ not on HAART
Vs
12 HIV-ve controls

ALL
Non smokers
No HBV/HCV
No Acute lung pathology

HIV+ AM demonstrated impaired intracellular killing of pneumococci

* p<0.05 Mann-Whitney

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HIV+ on ART have a BAL lymphocytosis

....with a CD8+ predominance of T cells
Effect of Highly Active Antiretroviral Therapy on Viral Burden in the Lungs of HIV-Infected Subjects

HIV-1 in the lung?

<table>
<thead>
<tr>
<th>Sample ID</th>
<th>HIV status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
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<td></td>
<td>Positive</td>
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<td>Positive</td>
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<td>Positive</td>
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<td></td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>Positive (ART naïve)</td>
</tr>
<tr>
<td></td>
<td>Seronegative</td>
</tr>
<tr>
<td></td>
<td>Seronegative</td>
</tr>
<tr>
<td></td>
<td>Seronegative</td>
</tr>
</tbody>
</table>

BAL analysed for HIV-1 RNA
- 14 HIV-positive
  - 13/14 on ART; 1/13 ART naïve
- 3 HIV-negative

All volunteers were
- non-smoking adults
- no active or chronic lung disease
- No active viral hepatitis.

p24 in AM cultures from 2/2 ART-naïve and 3/10 ART-treated HIV-1-seropositive donors
HIV-1 in the lung?

6 -12 ml of acellular BAL

Ultracentrifuged 240,000g x 20 min at 4°C

Abbott m2000rt platform

Tested for inhibition and sensitivity
Plasma & BAL obtained from HIV-negative volunteers spiked with WHO 3rd International HIV-1 RNA Standard & BAL from HIV-positive ART naive

<table>
<thead>
<tr>
<th>Standard Input (log_{10} cps/ml)</th>
<th>Plasma detection (log_{10} cps/ml)</th>
<th>BAL detection (log_{10} cps/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean of 2</td>
<td>Mean of 2</td>
<td></td>
</tr>
<tr>
<td>2.0</td>
<td>1.8</td>
<td>1.8</td>
</tr>
<tr>
<td>2.7</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>3.0</td>
<td>2.7</td>
<td>2.8</td>
</tr>
<tr>
<td>3.7</td>
<td>3.5</td>
<td>3.5</td>
</tr>
<tr>
<td>4.0</td>
<td>3.8</td>
<td>3.9</td>
</tr>
<tr>
<td>RP2003 (ART Naive)</td>
<td>1.9 log_{10}cps/ml</td>
<td></td>
</tr>
</tbody>
</table>

Input Vol.   LLD
------------------------------
12 mL        ND < 1 cp/mL
6 mL         ND < 2cps/mL

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<table>
<thead>
<tr>
<th>Sample</th>
<th>Volume (ml)</th>
<th>Replicate 1</th>
<th>Replicate 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZP2303</td>
<td>12</td>
<td>&lt; 1 cp/ml</td>
<td>&lt; 1 cp/ml</td>
</tr>
<tr>
<td>WP2102</td>
<td>12</td>
<td>&lt; 1 cp/ml</td>
<td>&lt; 1 cp/ml</td>
</tr>
<tr>
<td>UP2307</td>
<td>12</td>
<td>4 cps/ml</td>
<td>2 cps/ml</td>
</tr>
<tr>
<td>AP1109</td>
<td>12</td>
<td>&lt; 1 cp/ml</td>
<td>&lt; 1 cp/ml</td>
</tr>
<tr>
<td>VP0910</td>
<td>12</td>
<td>&lt; 1 cp/ml</td>
<td>1 cp/ml</td>
</tr>
<tr>
<td>TP2401</td>
<td>12</td>
<td>&lt; 1 cp/ml</td>
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<tr>
<td>SP1501</td>
<td>11</td>
<td>&lt; 1-2cps/ml</td>
<td>&lt; 1-2cps/ml</td>
</tr>
<tr>
<td>MP2802</td>
<td>6</td>
<td>&lt; 2cps/mL</td>
<td></td>
</tr>
<tr>
<td>HP1402</td>
<td>11</td>
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<tr>
<td>EP1101</td>
<td>9.5</td>
<td>&lt; 1-2cps/ml</td>
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<tr>
<td>OP1604</td>
<td>9.5</td>
<td>&lt; 1-2cps/ml</td>
<td></td>
</tr>
<tr>
<td>QP2310</td>
<td>12</td>
<td>&lt; 1 cp/ml</td>
<td></td>
</tr>
<tr>
<td>XP3007</td>
<td>12</td>
<td>&lt; 1 cp/ml</td>
<td></td>
</tr>
</tbody>
</table>

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HIV-1 in the lung?
HIV gp120 Induces Mucus Formation in Human Bronchial Epithelial Cells through CXCR4/α7-Nicotinic Acetylcholine Receptors

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¹Respiratory Immunology Division, Lovelace Respiratory Research Institute, Albuquerque, New Mexico, United States of America, ²Pulmonary and Critical Care Medicine, University of
does gp120 mediate lung pathology?

gp120 detectable in BAL fluid despite HAART

sandwich ELISA monoclonal anti-gp120 1.4E, 1.7B, EH21

gp120 treatment of MDM impairs apoptosis associated killing of pneumococci

gp120 induces oxidative stress in bronchial-epithelial cells

BEAS-2Bs + CellROX stain 30mins

gp120 detectable in BAL fluid gp120

n = 11
detected
not detected

n=15, *p<0.05, paired t-test

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Conclusions

• There remains elevated risk of pneumococcal infection and chronic lung disease risk despite suppressive ART
• Evidence of persistent lower respiratory tract T cell population imbalance and macrophage dysfunction
• Detectable HIV-1 RNA and gp120
• gp120 may macrophage dysfunction and damage bronchial epithelium
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