Spontaneous HIV expression during ART is associated with HIV-specific CD4 and CD8 T responses

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Anti-HIV immunity is expected to play an important role in future cure strategies (Moysi et al. 2018, Trautmann et al. 2016):
- purging reservoirs
- exerting immunosurveillance
- supporting development of broadly neutralizing HIV-specific antibodies
The quantitative and qualitative features of leaky latent reservoirs are not yet established.

Still unclear how HIV-specific immunity can persist during ART.

Is there a connection between the leaky latent reservoir and the HIV-specific immunity?
Single-cell RNA detection by HIV RNAflow-FISH

A. Probeset design
Single-cell RNA detection by HIV RNAflow-FISH

A. Probeset design

B. vRNA+ cells gating

Type of reservoir      Stimulation
Inducible              PMA+iono.

Uninfected          ART

5’exon AF647

gagRNA AF488

Probe sets:
- 5’exorRNA
- gagRNA
- p24 RNA

ART
PMA+iono. Inducible

Inducible

6.31E-6
6.011
Single-cell RNA detection by HIV RNAflow-FISH

A. Probeset design

B. vRNA+ cells gating

Type of reservoir  Stimulation

Inducible           PMA+iono.

Leaky              Unstim.  

Uninfected  ART

5‘exon RNA

5‘exon RNA

gag RNA

po RNA

probe sets

p24

pol

tat

rev

vpu

vif

env

gag

pol

RNA

RNA

RNA

probe sets

Uninfected

ART

Uninfected

ART

5‘exon AF647

5‘exon AF647

gagRNA AF488

5‘exon AF647

5‘exon AF647
Spontaneous vRNA expression is detectable

A. vRNA+ cells quantification

Spontaneous vRNA expression is detectable
Spontaneous vRNA expression is detectable

A. vRNA+ cells quantification

B. Metrics comparisons

Spontaneous vRNA expression is detectable
Spontaneous vRNA expression is detectable

A. vRNA+ cells quantification

B. Metrics comparisons

C. Association inducible vs leaky
Leaky reservoirs are dominated by abortive \textit{gag}RNA$^+$ cells

A. p24$^+$

- Inducible (PMA/iono)

- Leaky (unstim.)

B. Detection of leaky p24$^+$

Frequency per $10^6$ CD4 T cells

Leaky latent
Leaky reservoirs are dominated by abortive gagRNA⁺ cells

A. p24+

![CD4⁺ vRNA⁺ FSCA p24 - PE Inducible (PMAiono) Leaky (unstim.)](image)

B. Detection of leaky p24⁺

![Frequency per 10⁶ CD4 T cells vRNA⁺ p24⁺ Leaky latent](image)

C. gagRNA vs polRNA

![Inducible (PMAiono) Leaky (unstim.)](image)

D. Profile

![Inducible (PMAiono) Leaky (unstim.)](image)
Leaky reservoirs are phenotypically diverse

A. UMAP representation

CD4+ T cells

Leaky vRNA+ cells

B. Cluster heat map

Clusters

1 2 3 4 5 6 7 8

CXCR5
CD103
Integrin β1
CD45RA
CD38
CD27
CCR7
CCR6
CCR4
Ki67
PD1
HLA-DR
ICOS
CXCR3

C. Phenotyping

total CD4

vRNA+

51K

1418
Leaky reservoirs are phenotypically diverse

A. UMAP representation

CD4+ T cells

Leaky vRNA+ cells

B. Cluster heat map

Clusters

1 2 3 4 5 6 7 8

CXCR5
CD103
Integrin β1
CD45RA
CD38
CD27
CCR7
CCR6
CCR4
Ki67
PD1
HLA-DR
ICOS
CXCR3

C. Phenotyping

- total CD4
- vRNA+

D. Cluster enrichment

Down
Up

p values

0.002
<0.001
0.002
0.940
0.375
<0.001
<0.001
<0.001

Naive-like clusters

CXCR5+CXCR3+
CXCR5+
CXCR5+ITGB+
CCR6+CCR4+
CCR6+CCR4+activated
Leaky reservoirs correlate with HIV-specific CD4 and CD8 T cells

A. Signal from various AIM pairs

B. Signal from various AIM pairs

- Pair 1
- Pair 2
- Pair 3
- Pair 4
- Pair 5
- Pair 6

Uns. Gag

B. Signal from various AIM pairs

- Pair 1
- Pair 2
- Pair 3
- Pair 4
- Pair 5
- Pair 6

Uns. Gag
Leaky reservoirs correlate with HIV-specific CD4 and CD8 T cells

C. Net AIM responses
Leaky reservoirs correlate with HIV-specific CD4 and CD8 T cells

C. Net AIM responses

D. Correlations

Integrated DNA

Inducible (total vRNA⁺)

Leaky (total vRNA⁺)
Leaky reservoirs correlate with HIV-specific CD4 and CD8 T cells

C. Net AIM responses

D. Correlations

Integrated DNA

Inducible (total vRNA\(^+\))

Leaky (total vRNA\(^+\))
Asymetric network of correlations between Leaky reservoirs and CD4 T cell responses
Asymmetric network of correlations between Leaky reservoirs and CD4 T cell responses

<table>
<thead>
<tr>
<th>AIM+ CD4 responses</th>
<th>Total AIM</th>
<th>CCR6</th>
<th>CXCR3+ + CCR6</th>
<th>CXCR3+</th>
<th>CXCR5</th>
<th>CXCR3+ + CXCR5+</th>
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- Naive-like
- Activated
- CCR6+CCR4+CCR5+
Asymmetric network of correlations between Leaky reservoirs and CD4 T cell responses

- AIM+ CD4 responses

<table>
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<tr>
<th></th>
<th>Total AIM</th>
<th>CCR6</th>
<th>CXCR3+ + CCR6</th>
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- vRNA+

- p24+ inducible
- p24+ leaky

Leaky reservoirs and CD4 T cell responses
Asymmetric network of correlations between Leaky reservoirs and CD4 T cell responses

**AIM+ CD4 responses**

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<td>0.06</td>
<td>0.01</td>
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</table>

**Legend**

- Naive-like
- Activated
- CCR6+CCR4+CCR5+
- CCR6+CCR4+
- CCR5+CCR6+CCR3+
- CCR5+CCR3+

**Colors**

- Blue: Naive-like
- Green: Activated
- Red: CCR6+CCR4+CCR5+
- Orange: CCR6+CCR4+
- Pink: CCR5+CCR6+CCR3+
- Purple: CCR5+CCR3+
Key questions:
- What are leaky reservoirs? Do they have a biological relevance?

Key findings:
- Leaky reservoir cells are rare in blood (25 cell/10^6 CD4), but appear detectable in most participants.
- Leaky reservoirs preferentially reside in memory CD4 T cells, and enriched in CCR6+ cells.
- vRNA+ and p24+ leaky reservoirs correlate with HIV-specific CD4 and CD8 T cell responses. They may maintain cellular immunity against HIV during ART.

What next?
- Would this mechanism be good (improved immunosurveillance) or bad (exhaustion/dysfunction)?
Acknowledgement

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Daniel Kaufmann
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Chomont’s lab
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Rémi Fromentin
Amélie Pagliuizza

Prat’s lab
Olivier Tastet
Flow cytometry platform
NC3 platform

Study participants
Clinical teams

Jean-Pierre Routy
Josée Girouard

McGill
A. vRNA+ cells quantification

B. Association between total DNA and leaky vRNA

C. Association with clinical parameters

<table>
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<th>Parameter</th>
<th>Leaky</th>
<th>Inducible</th>
<th>Int. DNA</th>
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<td>CD8</td>
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<td>CD4/CD8</td>
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Asymmetric network of correlations between reservoirs and immune responses

AIM+ CD4 responses

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vRNA+

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p24+

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Leaky reservoirs is dominated by abortive $gag$RNA+$pol$RNA- cells
Leaky reservoirs are phenotypically diverse

A

B

C

Relative distribution

Leaky vRNA+

Clusters

0.0 0.2 0.4 0.6

Leaky vRNA+

C1 C2 C3 C4 C5 C6 C7 C8 total

PMAiono - 0.03 0.47 0.69 0.61 0.54 0.79 0.59 0.78 0.65
combi - 0.13 0.54 0.71 0.49 0.49 0.80 0.78 0.57 0.65

0 0.25 0.50 0.75 1.00
Leaky reservoirs are phenotypically diverse
Leaky reservoirs are phenotypically diverse
Leaky reservoirs correlate with HIV-specific CD4 and CD8 T cells

A. Raw AIM responses

B. Correlations

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<td>Nef</td>
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<td>0.145</td>
</tr>
<tr>
<td>int.DNA</td>
<td>0.554</td>
<td>0.234</td>
</tr>
<tr>
<td>Inducible (vRNA+)</td>
<td>0.660</td>
<td>0.288</td>
</tr>
<tr>
<td>Leaky</td>
<td>0.486</td>
<td>0.510</td>
</tr>
</tbody>
</table>
Leaky reservoirs correlate with HIV-specific CD4 and CD8 T cells

A. ICS gating

B. Raw ICS

C. Net ICS

D. Correlations

---

**5c**
Asymmetric network of correlations between reservoirs and immune responses
Leaky latency

**TILDA**

Procopio et al. EBioMedicine 2015

**ddRT-PCR**

Yukl et al, STM 2018
Single-cell RNA detection by RNAflow-FISH

A. Probeset design

B. vRNA+ cells gating

Type of reservoir  Stimulation
Leaky Unstim.
Inducible PMA+iono.
Spontaneous vRNA expression is detectable in most participants

A. vRNA+ cells quantification

B. Metrics comparisons

C. Association between metrics

Leaky RV vs int.DNA

Leaky vs inducible RV

Leaky vRNA+ / 10^6 CD4^+ T cells

Inducible vRNA+ / 10^6 CD4^+ T cells
Correlations with magnitude of CD8 subsets

<table>
<thead>
<tr>
<th></th>
<th>AIM CD8</th>
<th>HLA-DR+</th>
<th>CD38+</th>
<th>PD-1+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>0.07</td>
<td>0.24</td>
<td>0.14</td>
<td>0.07</td>
</tr>
<tr>
<td>C1</td>
<td>0.74</td>
<td>0.42</td>
<td>0.42</td>
<td>0.34</td>
</tr>
<tr>
<td>C2</td>
<td>0.33</td>
<td>0.26</td>
<td>0.30</td>
<td>0.11</td>
</tr>
<tr>
<td>C3</td>
<td>0.25</td>
<td>0.63</td>
<td>0.64</td>
<td>0.27</td>
</tr>
<tr>
<td>C4</td>
<td>0.02</td>
<td>0.20</td>
<td>0.15</td>
<td>0.10</td>
</tr>
<tr>
<td>C5</td>
<td>0.07</td>
<td>0.07</td>
<td>0.02</td>
<td>0.04</td>
</tr>
<tr>
<td>C6</td>
<td>0.06</td>
<td>0.29</td>
<td>0.29</td>
<td>0.08</td>
</tr>
<tr>
<td>C7</td>
<td>0.08</td>
<td>0.55</td>
<td>0.26</td>
<td>0.20</td>
</tr>
<tr>
<td>C8</td>
<td>0.01</td>
<td>0.21</td>
<td>0.12</td>
<td>0.06</td>
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</tbody>
</table>

**Inducible (p24+)**

<table>
<thead>
<tr>
<th>AIM CD8</th>
<th>HLA-DR+</th>
<th>CD38+</th>
<th>PD-1+</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.49</td>
<td>0.90</td>
<td>0.53</td>
<td>0.72</td>
</tr>
</tbody>
</table>

**Leaky (p24+)**

<table>
<thead>
<tr>
<th>AIM CD8</th>
<th>HLA-DR+</th>
<th>CD38+</th>
<th>PD-1+</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01</td>
<td>0.03</td>
<td>0.03</td>
<td>0.01</td>
</tr>
</tbody>
</table>