Virologic and immunologic features of viral control after ART interruption in SIV-infected rhesus macaques

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HIV reservoir prevents eradication of HIV infection and supports viral rebound

- ART is unable to eliminate virally infected cells
  

- Viral reservoir is established early during infection
  

- Resting memory CD4+ T cells are the best characterized viral reservoir
  

- ART interruption consistently results in viral rebound to pre-treatment levels, even after prolonged suppression and low viral burden
  
Example of human post-treatment controllers (PTC)

ANRS VISCONTI: 14 subjects
Months on cART: 36.5 (12-92)
Months post-cART: 89 (48-115)

Therapy started within 10 weeks following primary infection (median 39 days p.i.)

6 new PTC: All treated early after infection. Time off therapy: 6.5 years [2.8-14.0]

Estimated frequency: 5–15% of HIV-infected subjects interrupting at >12 months of treatment initiated during primary infection

Understanding the mechanisms behind durably containing HIV replication may guide new strategies towards HIV remission

14 RMs, all females, B08- & B17-; Infected with SIVmac239 (i.v.; 300 TCID$_{50}$)

Treated with ART for seven months; Followed for eight months after ART interruption

**Study Objective**: to determine virologic and immunologic parameters associated with control of viremia after ART interruption
CAVEATS

1. The study was not designed to address the specific question of post-treatment control

2. Results are preliminary, and many analyses are still in progress (today’s talk is largely limited to blood)

3. Some PTC received immune-based interventions in addition to ART

4. Small number of animals, particularly PTC, limits the use of more complex statistical analyses (multivariate analyses)
**Post Treatment Control in SIV-infected RMs**

- **PTC (n=5):** animals maintaining plasma VL < 10^4 copies/ml for the entire post-treatment follow up and < 200 copies at the latest experimental point (8 months off-ART)

- Control is partial (detectable VL in 4/5), but VL is > 3 log lower than NC
Is this a TRUE post-treatment control?

MamuA*01+ infected with SIVmac (239 or 251)

MamuA*01+ infected with same SIV$_{mac239}$ stock

Low set point VL

3 out of 49 with <400

0 out of 13 with <400

1 out of 28 with <400

RM$\text{s}$ MamuA*01+ and/or RM$\text{s}$ with comparable set-point viremia RARELY spontaneously control viral replication
Virologic features: PTC had reduced SIV “exposure”

Reduced pre-ART viral load

Faster and more effective control of residual VL on ART

LOD: 3 copies SIV-vRNA/mL
Virologic features: cell associated SIV-DNA

SIV-DNA levels (blood CD4 T cells) in PTC are:
- Lower than NC at pre-ART
- Lower than NC at ART interruption (though similar kinetics of decline during ART)
- Stable or even decreasing after ART interruption
Immunologic features: blood CD4 T cells

![Graphs showing changes in CD4 T cells over time.](image-url)
- PTC do not have higher CD8 T cell cytotoxicity or function as compared to NC
- Same results found in blood, LN and RB
Summary of pre-ART measures associated with increased probability of becoming PTC

- Intestinal %Th22 (per 2 unit) $P=0.03$
- Intestinal %Th17 (per 2 unit) $P=0.06$
- PB #CD4 count (per 100 cell) $P=0.06$
- PB %CD4 Mem. DR+38+ (per 5 unit) $P=0.04$
- PB %CD8 Perforin+ (per 5 unit) $P=0.08$
- PB %CD4 TCM (per 5 unit) $P=0.08$
- Plasma Viral Load (per 1 log10) $P=0.03$
- PB CD4+ SIV-DNA (per 1 log10) $P=0.03$

Odds ratio of predictors associated with controller status
Partial control of SIV replication after ART interruption is highly beneficial to the host.
Conclusions

• Some RMs treated early after infection can partially control (<200 copies/ml) viral rebound after discontinuation of ART

• Key features of RMs PTC include:
  – A less progressive SIV infection, with reduced viremia, higher CD4 T cell counts, and low levels of blood T cell activation
  – Low SIV DNA levels in blood CD4 T cells, before both initiation and interruption of ART
  – Faster control of residual plasma viremia during ART

• PTC appear to maintain control with cytotoxic potential of CD8 T cells not superior to NC

• Ability to partial control viral rebound results in a clear virologic (CD4 T cells SIV DNA content declining after ART interruption) and immunologic benefit for the host
IMPLICATIONS:

- These data support the rationale for early treatment initiation in HIV-infected individuals

- It is critical that control and treated animals are matched as much as possible (VL, CD4 count, immune activation, etc.) before ART initiation in studies aimed at testing the curative potential of therapeutic interventions.
### Main differences and similarities between rPTC and hPTC

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<thead>
<tr>
<th>Rhesus PTC (&lt;200 copies)</th>
<th>Human PTC (&lt;50 copies)</th>
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<tr>
<td><strong>Primary infection</strong></td>
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<tr>
<td>Lower viral loads and higher CD4 T-cell counts than NC</td>
<td>Viral loads and CD4 T-cell counts comparable to NC</td>
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<td>Early; 58 days p.i.</td>
<td>Early; estimated median 39 days p.i.</td>
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<td>Total and SIV-specific CD8 T cells expressing cytotoxic molecules not superior to NC</td>
<td>Generally very weak HIV-specific T-cell responses with poor capacity to eliminate infected cells</td>
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<td>Low levels of T-cell activation</td>
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<td>Reduced CM/EM ratio than NC</td>
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<td>Lower at ART interruption; stable or decreasing off ART</td>
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**T-cell responses**

**T-cell activation**

**CD4 CM cells**

**Cell-associated viral DNA content**
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