HIV Cure and Remission
Questions and a Few Answers

Steven G. Deeks, MD
Professor of Medicine
University of California San Francisco
San Francisco, California

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HIV Cure: Lots of questions and a few answers
- How much is there?
- How stable is the reservoir?
- Where does it reside?
- Can it be measured?
- How will we cure HIV?
  - Gene therapy
  - Shock and kill
  - Early ART
  - Remission
What do we know about the size and stability of the “reservoir”? 

Although ART reduces viremia > 6 to 7 log₁₀ some virus persists indefinitely (0.1-3 copies RNA/mL)
Source of the viremia is not known but it is not from an actively replicating population

The vast majority of HIV resides in the lymphoid organs, most of it assumed to be in CD4+ T cells, but the macrophage-rich tissues are understudied.

<table>
<thead>
<tr>
<th>Source of HIV</th>
<th>Copies/mL</th>
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<tbody>
<tr>
<td>Kidney</td>
<td>10⁶-7</td>
</tr>
<tr>
<td>Large bowel</td>
<td>10⁵</td>
</tr>
<tr>
<td>Small bowel</td>
<td>10⁴-5</td>
</tr>
<tr>
<td>Spleen</td>
<td>10⁴</td>
</tr>
<tr>
<td>Macrophage</td>
<td>10⁴-5</td>
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(Courtesy of Tim Schacker)
The "active" reservoir in lymph nodes declines slowly over many years and appears to be correlated with the level of lymphoid inflammation (germinal centers).

What do we know about the types of CD4+ T cells that harbor HIV during ART?

Modest enrichment of HIV has been reported in certain CD4+ T cell subsets

- Activated/proliferating
  - HLA-DR, PD-1, LAG-3, CTLA-4, TIGIT
- T follicular helper cells (nodes)
- Migrating: CCR6, α4β7
- Effector cells
HIV enriched (100 to 1000 fold) in CD32a-expressing CD4+ T cells

Most (> 50%) of reservoir may be in these cells, even though they are rare (~1% of CD4+ T cell population)

How does HIV persist indefinitely?

Cell proliferation maintains the reservoir during ART

Up to 50% of infected cell population (blood) is clonal in nature

Integration sites enriched for genes associated with cell growth/cancer
B cell follicles: a relative sanctuary (low CTL, low ART) and may be a site for “cryptic” replication


Can the reservoir be measured?

HIV Reservoir
Vast majority of genomes are defective

- Reservoir: Population of replication-competent HIV that persists during ART and ignites new rounds of replication when ART is stopped
- Rare, tissue-based, may be impossible to directly measure
• Cancer: rare tissue based cells that are similar to healthy cells and hard to detect
• Sensitive tracers that detect cancer (or HIV) being developed

How will we cure HIV infection?

Viable pathways toward a durable remission/cure

• Gene and cell-based therapy
• Shock and kill
• Lock and block
• Early ART
• Remission
Viable pathways toward a durable remission/cure

**Gene and cell-based therapy**

- Proof of concept: Berlin Patient
- Allogeneic stem cell transplant: several “near-cures”
  - Studies illustrate that very low levels of HIV (< 1000 virions) are sufficient to ignite new systemic infection
- Multiple feasible pathways, including direct enzymatic excision of provirus
- Will this ever be scalable on a global level and safer than ART?

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Viable pathways toward a durable remission/cure

**Shock and kill**

- Latency reversal is possible, but has not yet been associated with reservoir reduction
- Approach requires that all or nearly all virus be eliminated, which will be challenging if not possible
- May be an important adjuvant to other approaches

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Viable pathways toward a durable remission/cure

**Block and lock**

Most provirus is difficult to reactivate ex vivo
Permanent latency may be inducible by inhibiting tat or several host pathways, including mTOR
Early ART

Can we cure HIV by starting ART before the reservoir is fully established?

At about the time HIV RNA becomes detectable, the reservoir size begins to increase dramatically, with an apparent 100-fold increase over the next two weeks. Reservoir largely established by week 4 of infection.

Very early ART reduces the reservoir but is not curative.

N=8; ART in Fiebig I for 96 weeks; VL<50 c/ml; CD4>400 cells/ul

Ananworanich J et al., CROI 2017, Seattle, WA
ART (PrEP) during “Fiebig 0” Stage

Lack of Detectable HIV DNA in a PrEP Study Participant: Treatment Interruption

- 20 adults (and one child) who started therapy early (but not in “hyperacute” stage), remained on therapy for years, and had no rebound after stopping therapy
- Low reservoir size, low T cell activation and strong immune responses
African child with durable remission post-ART

- **Pre-ART (Infant)**
  - High viral load (> 750,000)
  - Received ART for 40 weeks
  - Controlled interruption (CHER)
  - Lost to follow-up

- **Post-ART (Age 9)**
  - Sustained virus control (> 8.5 years)
  - Normal CD4+ T cell count,
  - Weak antibody test (negative ELISA),
  - Low HIV DNA (2.2 copies/million PBMCs)
  - No protective HLA alleles, low T cell activation

DNA prime/rVSV boost among those treated during early HIV infection (n=30): Many (~25%) in each arm maintained virus control (< 400) during ATI

HIV Remission

*Can an HIV remission be routinely achieved therapeutically?*
All models of durable SIV/HIV remission suggest that durable control of established infection will require (1) low disease burden, (2) low inflammation and (3) sustained T cell responses that are primed, reside in tissues, and target susceptible epitopes.

These same attributes apply to cancer immunotherapy.

Immunotherapy for HIV infection
Two decades of largely failed approaches

- Weak immunogenicity
  - Pre-existing immuno-dominant responses
  - CTL escape
- Inflammation and counter-regulatory immunosuppression
- High virus burden
- Immune-privileged tissue sanctuaries

Broadly neutralizing antibodies blocked SIV replication (as expected) and induced a sustained host response (likely CD8+ T cell mediated)

Durable virus control observed post ART in people given combination bNAbs (Nussenzweig, IAS 2017)
Vaccine (Ad26/MVA prime-boost) alone had minimal effect on reservoir
Vaccine + TLR7 agonist reduces reservoir during ART and controls SIV post-ART
Vesatolimod now being tested in phase I/II clinical trials

α4β7 integrin expression enables migration of T cells to gut mucosa
SIV infected monkeys on ART treated with anti-α4β7 integrin antibody controlled SIV post-ART
Effect mediated by NK cells

Cancer immunotherapy is reshaping a fatal and progressive disease much as ART reshaped HIV
Most therapies aim to enhance capacity of CD8+ T cells to recognize and clear rare tissue-based cells that reside in inflamed tissues

- Upregulation of checkpoint blockers (PD-1, CTLA-4)
- Immunosuppressive cytokines (TGF-β, IL-10, IDO)
- Immunosuppressive immune cells (Tregs, MDSCs)
State of the ART: 2017

- Location, size and stability of reservoir remain to be characterized
  - Measuring total body replication-competent reservoir not possible
  - Cellular reservoirs now being explored
- Mechanisms for persistence known: latency, poor CTL, cell proliferation
- The reservoir can be reduced with early ART and cell therapy but not with anything scalable
- It is possible to reverse latency (shock) but the impact on the reservoir is negligible and most approaches are toxic
- Therapeutic vaccines work in monkeys and perhaps humans
- Combination approaches will be needed and are now moving into the clinic (era of "experimental medicine")

Question and Answer Period

- Use the microphones or Q-cards for questions
- If you are participating via the live webcast, please email your questions to RWCCwebcast@iasusa.org