Advances Toward a Cure for HIV Infection

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Learning Objectives
After attending this presentation, participants will be able to:
- Describe the importance of HIV latency and its relationship to HIV cure research
- Differentiate between eradication cure, functional cure, and hybrid cure
- List current approaches to achieving HIV cure

Overview
- HIV remission and eradication
- Reducing HIV reservoirs
- Combined strategies towards a cure
Classification of HIV Cure

HIV Reservoir Persists during ART

Antiretroviral Therapy: How Early is Early Enough?
Mechanisms of HIV persistence

- Ongoing replication
- "Latent reservoir"
  - T cell survival
- "Active reservoir"
  - T cell proliferation

From N Chomont, CROI 2017, HIV reservoirs: Obstacles to an HIV cure

Approach to Curing HIV

- Multiple mechanisms account for HIV persistence
- Unifying theme: find and diminish size of the HIV reservoir
  - Reduce seeding of latent pool with early/more ART
  - Reverse latency (shock and kill)
  - Increase HIV-specific immune function (vaccines or anti PD-L1)
  - Reduce immune activation
  - Gene therapy targeting the virus and the host
  - Allogeneic stem cell transplantation
- Combination therapy may be necessary

From DC Douek at Atlanta, GA, 2016, IAS-USA

Only HIV Cure to date

Hematopoietic transplantation with cells resistant to infection

- Doing well off ARV therapy > 7 years
- No replication competent HIV
- No PBMC DNA, intermittent very low plasma HIV RNA and rectal DNA
- Waning HIV antibodies and no HIV-specific T cells
- Not very practical or easily accessible
Despite 1000 – 10,000 fold reductions in reservoir size, virus rebounded. Modeling: latent reservoir will have to be depleted > 10⁵ fold (Hill, PNAS ’14) 
A single virus accounts for recrudescence

Hematopoietic transplantation with cells susceptible to infection

Strategies for HIV Remission

To limit the establishment of the reservoir
- Early ART
- Functions for latency reversal
- Deplete infected cells

To reduce the size of the reservoir
- Treatment interruption
- Immune activation
- Cell turnover

To control the reservoir
- Vaccine
- Immunotherapy

Half life of the latent reservoir

Time on ART to eliminate 10⁶ cells: 73.4 years
**Diversity of CD4 T cells**

- Naive
- Memory
  - Stem cell memory
  - Central memory
  - Transitional memory
  - Effector memory
  - Terminally differentiated

**IL-2**
- Survival
- Apoptosis
- Self renewal

Reference:

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**T follicular helper cells**

- T follicular helper cells in B cell follicles may constitute 'sanctuaries' for persistent HIV replication in the presence of potent anti-viral CD8+ T cell responses

Reference:

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**Measuring the reservoir**

<table>
<thead>
<tr>
<th>Assay target</th>
<th>Assay type</th>
<th>Assay</th>
<th>Estimated frequency per million CD4+ T cells</th>
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</thead>
<tbody>
<tr>
<td>Gag DNA</td>
<td>PCR assay</td>
<td>HIV DNA</td>
<td>&gt;10,000</td>
</tr>
<tr>
<td>LTR env</td>
<td>Afl-PDR</td>
<td>HIV DNA</td>
<td>&gt;200</td>
</tr>
<tr>
<td>Integrase</td>
<td>Full genome sequencing and cloning</td>
<td>HIV DNA</td>
<td>&gt;50</td>
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<tr>
<td>Reverse transcriptase</td>
<td>&gt;1000</td>
<td>HIV DNA</td>
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</tr>
<tr>
<td>Genomes producing viral transcripts</td>
<td>RT-PCR for viral transcripts</td>
<td>HIV DNA</td>
<td>&gt;1000</td>
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<tr>
<td>Genomes producing viral proteins</td>
<td>RT-PCR for viral proteins</td>
<td>HIV DNA</td>
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<tr>
<td>Genomes producing virions</td>
<td>RT-PCR for viral particles</td>
<td>HIV DNA</td>
<td>&gt;1000</td>
</tr>
</tbody>
</table>

Reference:
Flush out the latent reservoir (Shock and kill)

"Latency reversing agent"  →  Cytotoxic effect  →  Immune response  →  ART stops new infection

From N Chomont, CROI 2017, HIV reservoirs: Obstacles to an HIV cure

Reversing Latency in the Shock and Kill Model

Latency reversing agent (LRA)  →  HDAC inhibitors
- Minimally latency-reversed
- Minimally depleted of intact inducible proviruses

Future strategies
- Multiple latency reversing agents
- New classes
- Use in combination with immune therapies
- Safety monitoring for CNS toxicity


CROI 2017: Brehm (2105); Ho (1133); Cillo (1795); Huang (506); Winckelmann (738); Murry (1219); Lim (338LB)

Molecular mechanisms of HIV latency

HIV latency results from multiple mechanisms

D. Richman et al. Science 2009

PKC agonists: Prostratin, Bryostatin
Gamma-C cytokines: IL-7, IL-15
Jak/STAT inhibitors (ruxolitinib)
Bromodomain inhibitors: JQ1, I-BET
HDAC inhibitors (Saha (vorinostat), Panobinostat, Romidepsin)
Disrupting latency in vitro

Combinations of latency reversing agents induce robust levels of HIV production in latently infected cells

Disrupting latency in vivo

Anti-latency drugs induce HIV transcription in latently infected cells

... but do not significantly reduce the size of the latent reservoir
**Immune checkpoints**

- **PD-1, LAG-3, TIM3**
- **Anti-CTLA-4 in vivo** (ipilimumab)

Immune checkpoints identify latently infected cells and their blockade may reverse latency.


**TLR7 Agonist+Ad26MVA Vaccine Reduced Viral Load in Monkeys after ART Discontinuation**

Combination TLR7 agonist+Ad26/MVA delayed time to viral load rebound and decreased viral load set point and viral DNA.

**Combination Latency Reversing Agent (Romidepsin) and Therapeutic Vaccine (HIVconv)**

- BCN or ChAd + MVA
- BCN or MVA + RGD+ + MVA
- Treatment interruption

Los Angeles, California: April 28, 2017
VRC01 bNAb in Chronic HIV Infection did not Prevent Viral Load Rebound After ART Interruption

![Graph showing plasma viral load over weeks of ART interruption with labels for rebound at weeks 2-4, 5-8, and 9-12.]

A544: VRC01 in virally suppressed individuals did not clear low level viremia or infected cells.

Barr, NEJM 2016
Riddler, CROI 2017 (330LB)

Total n=23

Future Strategies: Multiple bNAb therapies with Higher Potency

![Graph showing IC80 cut-off for VRC01, VRC07-523LS, and 2bNAb combination (with CAP256).]

IC80 cut-off (μg/ml)
Richard Koup (NIAID VRC); Kong, J Virol 2015

Use in combination with other agents:
- TLR7 agonist improved antibody-mediated killing of infected cells by PGT121 bNAb
Murry, CROI 2017 abst 1219

Approach in Chronic HIV Infection

- Maintain viral suppression
- Reduce HIV reservoirs
- Reduce immune activation
- Reverse immune exhaustion
- Improve HIV-specific immune responses

![Diagram showing approaches for better ART and combination therapies.]

Los Angeles, California: April 28, 2017
Gene therapy

**Rationale for Gene Therapy**

Deliver a therapeutic agent to a cell using a gene

Remove something that HIV needs: CCR5
- Using antisense RNA, intrabodies, targeted DNA nucleases

Provide something to inhibit or kill HIV
- Anti-HIV: antisense RNA, fusion inhibitor C46, transdominant Rev

Lesson we learned from the Berlin and Boston patients:
- You need to remove the virus and the target cells

**Summary of ZnF CCR5 Gene Therapy Trials**

- Infusion of CCR5-specific zinc-finger nuclease-treated ex vivo expanded autologous T cells is generally safe and well tolerated
- Durable increases seen in both CD4 and total T cell counts
- CCR5 modified T cells persist long-term in vivo and persist longer than unmodified cells during treatment interruption

*All subjects in a cohort of chronically infected immune-non-responders saw long-term CD4 T cell reconstitution and HIV reservoir decay.*

(Tebas P et al. NEJM 2014, 320(10):901-10)
(Blick G et al. CROI 2015, abst 141.)
The First “CAR” Trial: CD4 ZETA Chimeric Antigen Receptor


June C. CROI 2017, abst 13

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• Results of 3 clinical trials with the CD4ζ CAR
• Half-life of CAR-modified T-cells was >17 yrs (!)
• CAR gene expression up to 10 years post infusion
• No integration-related toxicity

Clinical results:
• No adverse effects, but no long-term, CAR-dependent decreases in viral load or viral reservoir
• Saw transient decreases in HIV burden as defined by rectal biopsy HIV DNA/RNA and virus outgrowth assays


Decade-long safety and function of CAR T cells in HIV

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Dual affinity re-targeting protein (DART)

Potential to mediate cell killing of infected CD4 T cell
Bi-functional antibodies exist and are in clinical trials for cancer
Products being developed for HIV

From DC Douek at Atlanta, GA, 2016, IAS-USA

Los Angeles, California: April 28, 2017
HIV remission is not the same as eradication, but both imply control of HIV without ART.

LRAs show some reactivation but little reduction in reservoir size.

Combination studies are ongoing and may show reservoir reduction, especially with LRA and immunotherapy (vaccines, bNAb, ICI).

More potent bNAb and combinations are on the horizon.

New approaches to cell-mediated killing of infected T cells (CAR-Ts).

Combinations of approaches will likely be required:
- LA-ARVs + bNAb
- LRAs + DARTs
- LRAs + immunotherapy + gene therapy
SUGGESTED READINGS

Ref ID: 14943

Ref ID: 14944

Ref ID: 14945

Ref ID: 14946

Ref ID: 14947

Ref ID: 14948

Ref ID: 14949

Ref ID: 14950