Advances Toward a Cure for HIV Infection

Daniel C. Douek, MD, PhD
Bethesda, Maryland

Learning Objectives

After attending this presentation, learners will be able to:

- Describe the primary objectives of different cure approaches
- Contrast the benefits and drawbacks of different cure approaches
- Describe how different approaches may achieve a cure goal

The HIV Reservoir
Quiescent infection
CD4 T cell
Productive infection
Slide courtesy of Jonno Jacobsen
Time post ART cessation
Plasma HIV RNA (Copies/ml)

10^6
10^5
10^4
10^3
10^2
10^1

Untreated infection
Effective ART

Long half-life (forever)
Clonal expansion

HIV Remission
Quiescent infected T cells

"Latency": HIV-Infected T Cell Persistence

Quiescent HIV-infected cells persist indefinitely on ART
**HIV Cure: Some Definitions**

- **HIV Reservoir**: cells harboring replication-competent virus that could rekindle HIV replication and transmission in absence of cART
- **Cure**: elimination of all replication-competent HIV
- **Remission**: a sustained period of aviremia in absence of cART

**How To Cure HIV-Infected People**

- 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)
  - Reduce immune activation
  - Gene therapy targeting the virus and the host
  - Allogeneic stem cell transplantation

  **Combination therapy may be necessary**

**Hematopoietic transplantation with cells resistant to infection**

- Doing well off ARV therapy > 10 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

Even though this procedure works, it is highly unlikely that it will ever translate into an accessible approach.
Despite 1000–10,000 fold reductions in reservoir size, virus rebounded.

Modeling: latent reservoir will have to be depleted > 10^5 fold (Hill, PNAS '14)

A single virus accounts for recrudescence

---

Early HIV Reservoir Dynamics

At about the time HIV RNA becomes detectable, the reservoir size begins to increase dramatically, with an apparent 100x increase over next 2 weeks.

Reservoir largely established by week 4 of infection.

Early cART can significantly reduce the size of the reservoir.
Early cART in HIV Infection

Very early ART reduces the reservoir size
But no clinically significant delay in time to virus rebound
We are up against the limit here
**Latency Reversing Agents (LRAs)**

- Epigenetic modifiers
  - HDAC inhibitors
  - Methyltransferase inhibitors
  - Bromodomain inhibitors
- TLR agonists
  - TLR2 agonist (X)G4
  - TLR3 agonist (X)G4
- New Pathways
  - STAT5 signaling
  - Bromodomain inhibitors
- Activators of NF-κB
  - Bryostatin
  - Ingenol B / PEP 005
- Other
  - Disulfiram
  - Quinolines
  - Immune checkpoint blockers

**Current Status of LRA Clinical Trials**

- Numerous LRAs identified in studies with cell lines and primary T cells
- Relative to T cell activation, few LRAs work well *ex vivo* with cells from HIV+ people
- In clinical trials, evidence for increase in cell-associated and plasma HIV RNA
- In clinical trials, no reduction in the reservoir yet demonstrated

**Do LRAs Reduce HIV Reservoir Size?**

<table>
<thead>
<tr>
<th>LRA</th>
<th>Site of action</th>
<th>HIV latency</th>
<th>CA-RNA</th>
<th>pl-RNA</th>
<th>CA-DNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disulfiram</td>
<td>AKT activation</td>
<td>High dose</td>
<td>↑</td>
<td>↑</td>
<td>e+</td>
</tr>
<tr>
<td>Vorinostat</td>
<td>HDAC</td>
<td>Single dose</td>
<td>↑</td>
<td>e+</td>
<td>e+</td>
</tr>
<tr>
<td>Romidepsin</td>
<td>HDAC</td>
<td>Intermediate dose</td>
<td>↑</td>
<td>e+</td>
<td>e+</td>
</tr>
</tbody>
</table>


*Many clinical trials but none eliminate latently infected cells*
**The Kill?**

Reactivate the virus with LRA and then clear the infected cells

**Will the virus kill the infected cells?**

- “After reversal of latency in an in vitro model, infected resting CD4 T cells survived despite viral cytopathic effects” (Shan, Immunity 2012)

**Can the immune system help?**

- Most of the virus has mutated to escape the immune response and escape variants dominate in the latent reservoir of chronic subjects (Deng, Nature 2015)

**Therapeutic vaccination?**

- Transient expansion of T cells that do not recognize escaped HIV epitopes (Koup, JID 2014)

---

**Therapeutic Vaccines**

- > 40 clinical trials completed to date
  - DNA-based vaccines
  - RNA-based vaccines
  - Viral vectors: MVA, VSV
  - Peptide-based vaccines,
  - Lentiviral vector-based vaccines
  - Dendritic cell-based vaccines

**Two decades of largely failed approaches**

Despite this, therapeutic vaccine field remains active

---

**Combination Shock and Kill Studies**

<table>
<thead>
<tr>
<th>HDACi</th>
<th>Combination</th>
<th>Patient population</th>
<th>Study name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vorinostat</td>
<td>Prime:ChAdV63.HIVconsv Boost: MVA.HIVconsv</td>
<td>Acute n=52</td>
<td>RIVER UK (Final)</td>
</tr>
<tr>
<td>Vorinostat</td>
<td>A26-004 (DC vaccine)</td>
<td>Chronic</td>
<td>US (Margolis)</td>
</tr>
<tr>
<td>Romidepsin</td>
<td>MVA.HIVconsv</td>
<td>Acute n=24</td>
<td>Spain, UK, Germany (Moethe)</td>
</tr>
<tr>
<td>Panobinostat</td>
<td>IFN-2a</td>
<td>Chronic n=8</td>
<td>US (Lichterfeld)</td>
</tr>
<tr>
<td>Romidepsin</td>
<td>3BNC117 (bnAb)</td>
<td>Chronic n=40</td>
<td>US, Germany, Denmark (Stiegler)</td>
</tr>
</tbody>
</table>
TLR7 + SIV Vaccination

TLR7 agonist and Adenovirus 26 prime + Modified Vaccine Ankara boost

TLR7 + vaccine lowers pVL after cART interruption

HIV Peptide Vaccine + Romidepsin

Non-randomised observational study
n=20
HIV+ on cART
VL<50 c/ml for >3 years

Leth, Lancet HIV 2016

No change in integrated DNA or infectious virus
Decline in total HIV DNA is statistically significant
But clinically meaningless because time to virus rebound unaffected

ChAd.V63/MVA HIVcons Vaccine + Romidepsin

8 individuals recrudesced within 4 weeks
5 individuals had sustained HIV “control”
Immunotherapy

Reversing T Cell Exhaustion

mAbs to CTLA-4, PD-1 and PDL-1 for melanoma, lung and bladder Ca
Ex vivo blockade of PD-1, PDL-1, CTLA-4 and TIGIT enhances HIV-specific T cell responses

Immune Checkpoint Blockade as an LRA

• HIV is enriched in cells that express immune checkpoint markers
• Immune checkpoint expression may maintain HIV in latent state
• Immune checkpoint blockade could also release HIV from latency

Ex vivo and in vivo evidence for LRA of anti-PD1 and anti-CTLA4
**Immune Checkpoint Blockade: Clinical trials**

<table>
<thead>
<tr>
<th>Target</th>
<th>Study design</th>
<th>Patient population</th>
<th>Sites</th>
<th>N (n to date)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-PD1 (Merck)</td>
<td>Phase 1B</td>
<td>Malignancy: AIDS-defining or non-AIDS</td>
<td>CITN / CITN-12 (US)</td>
<td>N=37 (n=12)</td>
</tr>
<tr>
<td>Anti-PD1 + Anti-CTLA4 (BMS)</td>
<td>Phase 3</td>
<td>Malignancy: HIV-associated tumors: lung, anal and Kaposi’s sarcoma</td>
<td>AMC / AMC-095 (US, Australia)</td>
<td>N=42 (n=7)</td>
</tr>
<tr>
<td>All immune checkpoint blockers</td>
<td>Observational study</td>
<td>Malignancy: melanoma, lung small cell, bladder</td>
<td>U Melb / iCHIP; (Australia, US, Denmark)</td>
<td>N=20 (just opened)</td>
</tr>
</tbody>
</table>

CITN = Cancer Immunotherapy Network; AMC = AIDS Malignancy Consortium; Pembro = pembrolizumab; nivo = nivolumab; ipi = ipilimumab; atezo = atezolizumab

**Trials underway in HIV+ people with malignancies**

---

**Gene Therapy**

Deliver a therapeutic agent to a cell using a gene

Provide something to inhibit or kill HIV
  - Anti-HIV antisense RNA, targeted DNA nucleases, transdominant Rev

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

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

**Nuclease Based Gene Therapy Targeting CCR5**

Minimally invasive immunotherapy with no severe adverse events
Much more accessible than HSCT
No need for compatible donors and no risk of GVHD

**Trials in Aviremic HIV+ People on cART**

- Single infusion of CCR5-modified CD4 T cells persist long-term in vivo
- Durable increases seen in T<sub>SCM</sub> CD4 T cells enriched for modified CCR5
- All participants had reduction in size of the HIV reservoir over 3 years, the kinetics of which suggests replacement of infected cells over time
- ATI 6 weeks after infusion showed reduction in pVL set-point that correlates with level of CCR5-modified CD4 T cells (4/16 remain off cART past 22 weeks)

**Therapy with Broadly Neutralizing Antibodies Against HIV Envelope**
Clinical Use of HIV-Specific Antibodies

Prevention and treatment with antibodies are different

**Prevention**
- Prevent acquisition of infection
  - Breastfeeding infants
  - High risk young adults
  - Discordant couples
  - High risk MSM

**Treatment**
- Have to deal with greater virus diversity
- Reduce viremia in acute infection
- Treatment interruption
- Maintenance therapy (+/- LA-ARVs)
- Potential to reduce HIV reservoir (Cure)

Block transmission

Block virus entry

Cell killing

CD4 T-cell NK cell killing of infected cells

Antibody Potency and Breadth

Panel of 208 HIV Env pseudoviruses from all major clades

Newly discovered Env-specific bnAbs are broad and potent

Phase I Trial of VRC01: Single Infusion

3 Patterns:
- Profound and maintained suppression
- Transient suppression
- No suppression

Suppression of pVL determined by sensitivity of virus to VRC01


Days post VRC01 infusion

Δ log virus load (copies/ml)
Phase I Trials of VRC01 During ATI

- Majority rebounded by wk 5 even with high plasma VRC01 levels
- Modestly delayed virus rebound compared to historical controls
- Similar findings with 3BNC117 (Scheid, Nature 2016)

Profile of a 2nd Generation mAb Product

- 10-fold more potent than current mAbs
- Cover 98-99% of virus diversity (prevents escape)
- Given by s.c. injection once every 4-6 months (vs i.v. infusion every 2 months)
- Cost comparable to ARV drugs

Engineering Greater Potency and Breadth

- More potent
- Less broad but 500x more potent
- Very broad, very potent
- Panel of 208 HIV Env pseudoviruses from all major clades
**Engineering Greater Potency and Breadth**

**Cross-mAb technology**

Crossing of heavy and light chain domains between species or strains

**Greater breadth of coverage (%)**

More potent (median IC$_{50}$ titer $\mu$g/ml)

**Engineering Greater Potency and Breadth**

Huang, Cell 2016

**Fc Mutations to Increase Half-Life**

2 aa mutation (LS) increases affinity for FcRn; protects mAb from endosomal degradation

Single 20 mg/kg infusion of VRC01-LS maintains >50 µg/mL for 6 months

At least 4x increase in half-life in healthy adults

Decreases dose 5-10x, may extend interval to every 6 months

**Conclusions for an HIV Cure**

- Greater understanding of size, shape, location and maintenance of the reservoir
- We can reduce reservoir size with early cART — but is it clinically significant?
- LRAs show poor reactivation and no reduction in reservoir size
- Therapeutic vaccines show some effects in monkeys but in humans it is debatable
- HSC transplantation works (once) but it is not scalable
- Gene therapy may be used to target HIV and/or CCR5 and clinical studies show some reservoir reduction but how scalable is it?
- Env-specific mAbs are in promising proof of concept studies with more potent mAbs, combinations of mAbs and bi-specific mAbs being developed
- Combinations of approaches may have to be used:
  - LA-ARVs + mAbs, LRAs + BITEs, gene therapy + mAbs + LRAs and so on...
**SUGGESTED READINGS**

   Ref ID: 14944

   Ref ID: 15071

   Ref ID: 14167

   Ref ID: 14168

   Ref ID: 14169

   Ref ID: 14170

   Ref ID: 14172