HIV Cure: Fact or Fiction?

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Learning Objectives

After attending this presentation, learners will be able to:

• Describe how the HIV-1 reservoir is the barrier to cure
• Describe how an HIV-1 cure can be defined
• Describe the state of current HIV-1 cure strategies

Slides for this lecture have been adapted in part from Dr. Steve Deeks, UCSF, with permission
The HIV Cure Agenda

• Why do we need a cure?
• How should we define a cure or remission?
• How will we achieve our goal?
  – Gene/cell therapy
  – Shock and kill
  – Block and lock
  – Early ART
  – Immunotherapy
  – Sanctuary disruption
  – Combination therapy

With effective treatment and prevention options, do we even need a cure?

Defining why a cure is needed has a huge impact on the preferred product profile

FACT SHEET – WORLD AIDS DAY 2017

GLOBAL HIV STATISTICS

20.3 million people were accessing antiretroviral therapy in June 2017.
38.7 million [30.8 million–42.8 million] people globally were living with HIV in 2016.
1 million [830 000–1.2 million] people died from AIDS-related illnesses in 2016.
78.1 million [68.2 million–88.0 million] people have become infected with HIV since the start of the epidemic.
35.0 million [28.9 million–41.5 million] people have died from AIDS-related illnesses since the start of the epidemic.
HIV Cure: Target Product Profile

**Efficacy:** aviremia in absence of therapy > 2 years; early failure is tolerable, late failures must be rare

**Product:** administered for limited period of time (e.g., 6 months); specialized (tertiary) care not required

**Target Population:** effective ART initiated at any stage and in all populations

**Long-term safety:** comparable to ART, transmission risk negligible

**Cost:** < $1400 (RLS)

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HIV Cure: The problem

*HIV persists as fully integrated (and often silent) genome in a hard-to-study tissue-based cell population designed to persist indefinitely*

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Microbiologic Cure vs Long-Term Remission

**Microbiologic Cure:**
- Complete removal of all replication-competent HIV
- May have been achieved with Berlin Patient and the London Patient, but proving a negative is hard
- People may never really know if they are cured
In absence of a complete cure (which is unprovable) some sustained (life-long) immune response targeting HIV will be needed.

There are now dozens of cases of very low reservoir states in which virus rebounded during an interruption, presumably due to lack of effective immunity.

Microbiologic Cure vs Long-Term Remission

Long-Term Remission ("Functional Cure"):

- Likely more achievable than a microbiologic cure
- Durable control of a persistent residual reservoir
- Undetectable viral loads in the absence of ART
- No transmission risk (U = U)
- Examples may include "elite controllers"
Some (10-20%) of people who start therapy early will exhibit at least partial control after ART is interrupted.

- Mechanism unknown
  - Low reservoir size, low T cell activation
  - Classic CTL responses low
  - Enriched for certain HLA/KIR
  - Non-cytolytic NK cell responses

What are the viable strategies by which a cure or remission might be achieved?

Viable pathways toward a durable remission/cure

- Gene and cell-based therapy
- Shock and kill
- Block and lock
- Early ART
- Immunotherapy
Viable pathways toward a durable remission/cure: Gene and cell-based therapy

- Proof of concept: Berlin Patient, London Patient
- Allogeneic stem cell transplant
- Multiple safer strategies being pursued, including direct excision of provirus
- Will this ever be scalable on a global level and safer than ART?

Viable pathways towards a durable remission/cure: Shock and kill

- Multiple latency reversing agents (LRAs) tested: effect is modest at best and inconsistent
- Basic discovery aimed at identifying novel pathways or combinations

Multiple latency reversal agents active in vitro

Kim, Anderson and Lewin. Cell Host Microbe 2018
Viable pathways toward a durable remission/cure: *Block and lock*

Most proviruses are difficult to reactivate *ex vivo*. Permanent latency may be inducible by inhibiting *tat* or several host pathways, including mTOR.

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Viable pathways towards a durable remission/cure: *Early ART*

- Prevention of latency?
- Preservation of immune function?
  - Post-treatment control

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Very early ART reduces the reservoir but is not curative

*Ananworanich J et al., CROI2017, Seattle, WA*
Viable pathways towards a durable remission/cure: Immunotherapy

- CAR-T cells (and related biologics)
  - Proof-of-concept: cancer
- Broadly neutralizing antibodies
  - Proof-of-concept: NHPs, humans
- Therapeutic vaccination
  - Proof-of-concept: herpes zoster vaccination, clearance of pre-cancerous lesions (HPV)
**CAR-T cells: Next generation approaches**

- Toxicity management
  - Cytokine release, neurotoxicity, off-target
- Improved CARs:
  - More specific, bi-specific, antiviral components
- HIV cure: ART is used to prevent antigen exposure as needed (prevent or reverse AEs)
  - NCT03240328: Guangzhou People's Hospital (China): HIV (N6),
  - NCT03617198: University of Pennsylvania, CD4 receptor (safe in 1990s), ART interruption

**Broadly neutralizing antibodies**

Combination therapy with anti-HIV-1 antibodies maintains viral suppression

Two of 9 individuals treated early maintained virus control after bNAb levels waned
• SHIV-SF162P3 infected monkeys
• Day 7 ART
• ART maintained for two years
• Reservoir reduced or eliminated with PGT121 antibody and TLR7 agonist
• Delayed or prevented viral rebound following ART discontinuation

Broadly neutralizing antibodies

• Recognition and elimination of virus-infected cells
• Activity may be enhanced by co-administration of an innate immune stimulator (such as a TLR agonist) that activates cells

Therapeutic vaccines
HIV Immunotherapy: Minimal success to date with therapeutic vaccines

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimen</th>
<th>Comment</th>
<th>Author/Paper</th>
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<tbody>
<tr>
<td>ACTG 5068</td>
<td>ALVAC (vCP1452) + enveloping interruptions but interrupting vaccinations associated with reduced IL-12</td>
<td>Jacobson, JID 2006</td>
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<tr>
<td>ACTG 5069</td>
<td>ALVAC (vCP1452) + IL-12</td>
<td>0.5 log VL reduction during ATI</td>
<td>Kilby, JID 2006</td>
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<tr>
<td>ACTG 5077</td>
<td>ALVAC</td>
<td>IL-12, no apparent effect on primary endpoint</td>
<td>Jacobson, JID 2016</td>
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<tr>
<td>MANON-02</td>
<td>ALVAC HIV</td>
<td>No apparent effect on primary endpoint; activated CD4 cells may have induced early failure</td>
<td>Papagno, AIDS 2011</td>
</tr>
<tr>
<td>Bionor Vacc-4</td>
<td>ALVAC-HIV</td>
<td>No apparent effect on primary endpoint</td>
<td>Pollard, Lancet HIV 2014</td>
</tr>
<tr>
<td>ERAMUNE 02</td>
<td>DNA prime/MVA boost</td>
<td>No effect (HIV DNA)</td>
<td>Achenbach, Lancet HIV 2015</td>
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<tr>
<td>GeoVax</td>
<td>DNA prime/MVA boost</td>
<td>No apparent effect during A3 (uncontrolled)</td>
<td>Thompson, PLoS ONE 2016</td>
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<tr>
<td>ACTG 5281</td>
<td>Gag/polypeptide mixture (weeks 0, 4, 12)</td>
<td>0.24 log10 reduction at primary endpoint; low dose IL-12 better than high dose IL-12</td>
<td>Jacobson, JAIDS 2016</td>
</tr>
<tr>
<td>BCN 02</td>
<td>ChAdV63.HIVconsv + MVA.HIVconsv</td>
<td>5/13 controlled (ATI)</td>
<td>Mothe, CROI 17</td>
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A randomized controlled safety/efficacy trial of therapeutic vaccination in HIV-infected individuals who initiated antiretroviral therapy early in infection

HIV-multiantigen and IL-12 DNA plasmids (weeks 0, 4, 12 and 36) and rVSVN4CT1 gag attenuated live viral vector (weeks 24 and 48) had no effect on post-ART viral dynamics in a cohort of early treated individuals.

Ad26/MVA therapeutic vaccination with TLR7 stimulation in SIV-infected rhesus monkeys

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
Therapeutic vaccines

- Enhance capacity of immune system to clear reservoir during ART
- Enhance capacity of immune system to control HIV in absence of ART
- Activity may be enhanced by co-administration of an innate immune stimulator

TLR-7 agonists contribute to a cure/remission in monkeys
TLR-9 agonists stimulate NK and T cell responses in people, and may cause latency reversal

Treatment interruptions are necessary to determine if any of these approaches work
Treatment interruptions are increasingly accepted as required to evaluate concepts in HIV cure studies

- Scientific and community engagement and support
- Legitimate informed consent
- Avoid coercion
- Mitigate against risk
  - Exclude those with low nadir, history of cancer/CAD
  - High baseline CD4+ T cell count
  - Age limits
  - Partner engagement (PrEP)
  - Strict ART restart criteria
    - Symptoms, CD4+ T cell decline, sustained viremia

ART Restart Criteria

- Confirmed decline to below 350 cells/mm³
- Acute retroviral syndrome
- Sustained or high–level viremia
  - (1) viremia > 50,000 copies RNA/mL for 4 weeks,
  - (2) viremia > 10,000 copies RNA/mL for 6 weeks,
  - (3) viremia > 2000 copies RNA/mL for 12 weeks or
  - (4) viremia > 400 copies/RNA for 24 weeks.
- Operationally, this will allow for an acute viremic state that will need to resolve within 4–12 weeks, with high-level viremia only being allowed for a brief period, or ART will be re-initiated

Report of a Consensus ATI Workshop

Recommendations for analytical antiretroviral treatment interruptions in HIV research trials—report of a consensus meeting


HIV Cure 2019: Summary

Two likely HIV cures have been reported with bone marrow transplantation, but this strategy is not scalable.

Proof-of-concept data exist for most steps in the “shock and kill” strategy, and early data are promising in animal models.

The “block and lock” strategy remains promising but has yet to be fully tested in animals or humans.

HIV cure research will require treatment interruption studies to determine the effectiveness of various approaches.

Question-and-Answer