State of the ART: HIV Cure – where are we now and where are we going?

Jintanat Ananworanich, MD, PhD

Associate Director for Therapeutics Research
US Military HIV Research Program (MHRP)
Maryland, USA

Deputy Director of SEARCH
The Thai Red Cross AIDS Research Center
Bangkok, Thailand

The views expressed are those of the authors and should not be construed to represent the positions of the U.S. Army or the Department of Defense.
Outline

- Is HIV cure possible?
  - HIV persistence
- Cure Strategies
- Ethical and social considerations
# A Case of Cure

## The Berlin Patient

<table>
<thead>
<tr>
<th>Off ART</th>
<th>6 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>CCR5-/- bone marrow transplant</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Make cells Resistant to HIV</td>
</tr>
<tr>
<td>Lesson</td>
<td>Eliminate CCR5+/+ cells</td>
</tr>
</tbody>
</table>

## Transient but Encouraging HIV Remission

<table>
<thead>
<tr>
<th></th>
<th>Two Boston Patients(^1,^2)</th>
<th>The Mississippi Child(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment</strong></td>
<td>CCR5+/+ bone marrow transplant</td>
<td>Early ART</td>
</tr>
<tr>
<td>Off ART</td>
<td>3 months and 7 months</td>
<td>2.5 years</td>
</tr>
<tr>
<td><strong>Lesson</strong></td>
<td><strong>Delayed viral rebound is achievable</strong></td>
<td><strong>But unknown biomarkers for HIV remission</strong></td>
</tr>
</tbody>
</table>

\(^1\)Henrich T, JID 2013; \(^2\)Annals Internal Medicine 2014; \(^3\)Persaud D, NEJM 2014
Challenges to Eradication

- HIV persistence
  - HIV can exist in a resting state where it persists, even in patients on suppressive antiretroviral therapy

- Accurately measuring the reservoir
  - Inability to detect all of the HIV that can replicate (called replication competent virus)
  - No definitive way to measure if HIV is eradicated
Reservoir and Immunity

latent virus

Boston patients

Mississippi child

immunity
Strategies to Eliminate HIV Persistence

Possible interventions:
- Latency reversing agents
- Broadly neutralizing antibody
- Gene-editing therapy
Novel vaccine given before exposure may aid in viral control: SIV/macaque model

Non-controllers (n=7)

Follow up discontinued

Controllers (n=9)

Plasma viral load (Log copy eq. per mL)

No protection but
Virus eradicated in 50%

Hansen SG and Picker LJ, Nature 2013
VISCONTI Cohort of Post-Treatment Controllers

14 people
ART in first 3 months

Control VL after stopping ART

Why are these patients able to control HIV without ART?

HIV reservoir amount and location?
- ✔ Low HIV DNA
- ✔ In shorter-lived CD4 cells

Saez-Cirion A, Plos Pathogens 2013
Early ART limits persistence of HIV reservoir

(RV254/SEARCH010)

Long-lived central memory CD4+ T cells

Integrated HIV DNA (copies/10^6 cells)

Duration of HIV at ART initiation

- ≤ 2 weeks
- 2-4 weeks
- ≥ 24 weeks

Nicolas Chomont (VGTI-Florida)
Updated from Ananworanich J, 2013 CROI
Shocked but not Killed
HDACi Panobinostat

n=16

Goal: Force the hidden HIV "out into the open" and expose them to the immune system to eradicate them

Result: Replication competent virus did not decline

ANOVA p<0.0001

Fold increase in CA-US RNA

Start Panobinostat
End Panobinostat

Rasmussen et al, 2014 CROI
Broadly Neutralizing Antibody

(bNABs) neutralize multiple HIV-1 viral strains

- > 30 antibodies identified
- Human studies
  - VRC01: RV397/398 in acute HIV
  - 3BNC117, 10-1074, PGT121

Barouch DH, Nature 2013
Gene therapy to eliminate CCR5

Leukapharesis
CD4+ T-cell isolation

ZFN cut CCR5 gene

Re-infuse

CCR5-
CCR5+
Examples of strategies currently in human studies

**MINIMIZE RESERVOIR**
Limit reservoir with early treatment
- Antiretroviral therapy
- Broadly neutralizing antibodies

**SHOCK**
Reactivating latently-infected cells
- Inhibit histone deacetylase
- Inhibit bromodomain extraterminal
- Activate toll-like receptors
- Activate protein kinase C

**KILL**
Viral clearance by the immune system
- Broadly neutralizing antibodies
- Therapeutic HIV vaccines
- Anti programmed cell death (PD)1
- Anti PD ligand 1

**HIV RESISTANT CELLS**
Transfusing cells without CCR5 gene
- Gene-editing therapy
- Bone marrow or cord blood transplantation

**Combination Cure**
HIV Cure and Cure Research: Social and Ethical Considerations
Societal and Individual Expectation

- Eradicated = normal or free of disease or healed
- Long-term adverse consequences of HIV
  - New normal
- Long-term monitoring of viral load
- Stigma and discrimination
- When to call someone “cured”?\(^1\)
  - Best measure of reservoir is not known
  - HIV remission
    - \( VS_{LLD, OT_{time}} \) = Viral Suppression Off ART

\(^1\)Forum Cure Project (V. Miller)
Australian Participants’ Priorities on Outcomes of Cure Research

20 participants with chronic HIV infection in vorinostat (HDACi) trial

- Not passing virus onto others
- Not getting HIV a second time
- Being considered as a person not infected with HIV
- Stopping HIV medications
- No longer needing to see a doctor

Ethics of HIV cure

- Ideal candidates are persons who are well with viral suppression
- Potentially toxic interventions
- ART interruption
- Cost and accessibility

What might the future look like?

Preventive HIV Vaccine
- Prevent infection
- Modulate immunity to limit viral reservoir

Early Diagnosis
Early Treatment
- Limit HIV reservoir and replication

Novel Therapy
- Eliminate all cells capable of producing HIV
Acknowledgements

Study Volunteers and Research Teams
RV254/SEARCH010 acute HIV and HIV-NAT 194/pediatric reservoir

Thai Red Cross AIDS Research Center
Praphan Phanuphak
Nittaya Phanuphak
Suteeraporn Pinyakorn

Monash University
Sharon Lewin

NIAID, NIH
Anthony Fauci

Northwestern University
Ellen Chadwick

NICHHD, NIH
Lynne Mofenson

Johns Hopkins University
Robert Siliciano
Deborah Persaud
Alison Hill

US Military HIV Research Program
Nelson Michael
Jerome Kim
Merlin Robb
Lisa Reilly

University of Pennsylvania
Pablo Tebas

Aarhus University
Lars Ostergaard

Oregon Health Science University
Louis Picker

University of Pittsburgh
John Mellors

UCSF
Steve Deeks

Harvard University
Dan Barouch

Purple Haze
Tarandeep Anand

Institut Pasteur
Asier Saez-Cirion

Vaccine and Gene Therapy Institute-Florida
Nicolas Chomont

Funding for Acute Infection Study RV254 provided by U.S NIH, U.S. DoD and amfAR