Outline

- Is HIV cure possible?
  - HIV persistence
- Cure Strategies
- Ethical and social considerations

*Short video on patients’ perspectives on cure*
# A Case of Cure

## The Berlin Patient

<table>
<thead>
<tr>
<th>Off ART</th>
<th>6 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment</strong></td>
<td><strong>CCR5-/- bone marrow transplant</strong></td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
<td>Make cells Resistant to HIV</td>
</tr>
<tr>
<td><strong>Lesson</strong></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>Treatment</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>Lesson</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 (in press); \(^3\)Persaud D, NEJM 2014
HIV Persistence

- Cell death
- Resting state
Measuring the HIV Reservoir

- Total HIV DNA
- Integrated HIV DNA
- Replication competent virus

HIV DNA (100%)
- Replication competent (0.1%)
- Intact, inducible (10%)

Ho, Cell, 2013; Cillo, PNAS 2014
Reservoir and Immunity

latent virus

immunity

Boston patients

Mississippi child
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

Hansen SG and Picker LJ, Nature 2013

No protection
but
Virus eradicated in 50%

Controllers (n=9)

Follow up discontinued

Non-controllers (n=7)

Plasma viral load (Log copy eq. per mL)
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 in Long-lived CD4+ T cell subsets (RV254/SEARCH010)

Nicolas Chomont (VGTI-Florida)
Updated from Ananworanich J, 2013 CROI
Early ART in Infants

Three US teenagers treated from infancy have no replication competent HIV

Luzuriaga K, JID 2014

Visconti post treatment controllers

Ananworanich J, AIDS 2014

Total HIV DNA (copies in $10^6$ CD4 T cells)
Shocked but not Killed

HDACi Panobinostat

n=16

Fold increase in CA-US RNA

Start Panobinostat
End Panobinostat

Replication competent virus did not decline

ANOVA p<0.0001

Rasmussen et al, 2014 CROI
Broadly Neutralizing Antibody

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

Cell death

Viral clearance

PGT121
Viral load suppression in macaques (n=3)

Barouch DH, Nature 2013
Gene therapy to eliminate CCR5

- Leukapharesis
- CD4+ T-cell isolation
- ZFN cut CCR5 gene
- Re-infuse

Tebas P, NEJM 2014
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
  - \( V_{S_{LLD}} O_{T_{time}} \) = 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
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“What does HIV cure mean to me?”