The Scope of the Global HIV/AIDS Pandemic – Current Estimates

- Cumulative HIV infections: 65 million
- People living with HIV/AIDS: 34 million
- New HIV infections in 2009: 2.6 million
- Deaths due to AIDS in 2009: 1.8 million
- Cumulative AIDS deaths: ~30 million

Source: UNAIDS, 2011
Predicted Survival if HIV+ at age 25 years

US military cohort (n = 2327, mean age 35) who started ART after 2000, 5-year mortality 0.3%

Marconi 2010

Two-Pronged Approach

Combination HIV Prevention

Reduce the number of new HIV infections

Treatments that clear Infection

Reduce the number of HIV-infected people
Last public appearance of the entire AIDS Quilt, 1996

Why Try To Cure HIV?
Which would you rather take?
Different “Cure” Objectives

**Eradication Cure**
- No functional HIV
- Effective immune response or ART not needed
Different “Cure” Objectives

Eradication Cure
No functional HIV
Effective immune response or ART not needed

Functional Cure
Control of HIV without ART or deleterious immunologic effects

Different “Cure” Objectives

Eradication
No functional HIV
Effective immune response or ART not needed

Hybrid
Reduced functional reservoirs & improve immune control without ART

Functional Cure
Control of HIV without ART or deleterious immunologic effects
Different “Cure” Objectives

**Eradication Cure**
No functional HIV
Effective immune response or ART not needed

Generation of latently infected cells is probably the result of transcriptional silencing during memory cell differentiation

- Naïve T-cell
- Activated T-cell
- Proliferating effector cells
- Resting memory T-cell
- Resting memory T-cell with latent HIV provirus

Antigen

HIV infection
Why does infection persist despite ART: 
Part 1: Resting CD4+ cell infection

Time to eradication > 73.4 years

Residual Virus Reservoirs

- Resting CD4 cells
- Other cellular compartments?
- Protected anatomical sites?

Chun TW, et al. PNAS. 1997;94:13193-13197
Primary strategy to eliminate latent HIV infection

Other Challenges:
• Clearance of infected cells
• Clearance of virions
• Complete block of new infection

The New York Times

2008

AIDS Patient Is Reported Cured in Berlin With a Rare Treatment

BY DONALD G. MCNEIL JR.

Dr. Greve and his colleagues say they believe they have cured a woman of AIDS by giving her a modified version of interferon alfa, a key antiviral drug that attacks the virus directly.

The woman, a 55-year-old American resident in Kenya, was infected with HIV while living in the United States. She began taking antiretroviral drugs, but the virus continued to replicate. In February 2008, she was prescribed a drug called pegylated interferon alfa-2b, which is used to treat chronic hepatitis C. The drug was given at a dosage of 4.5 million units per day for 6 months.

The woman was monitored closely for 2 years after treatment ended, and her HIV viral load remained undetectable. The study was published in the journal Nature.

The researchers concluded that pegylated interferon alfa-2b was effective in curing the woman of her HIV infection.
Patient No More

How was Tim Brown cured?

- Cytotoxic chemotherapy?
  - Modest to no long-term effects on HIV reservoirs
    - Cillo PLoS 2014 (in press); Henrich #418 CROI 2014 (Session TD14)

- Hematopoietic stem cell transplantation?
  - Autologous transplantation ineffective despite cART
    - Cillo JAIDS 2013; Mavigner #416 CROI 2014 (Session TD14)

- Allogeneic CCR5 Δ32/Δ32 stem cell transplant
  - Replacement of host hematopoietic and immune system
  - Donor cells resistant to infection by CCR5 tropic virus

- High risk (7-25% mortality)
  - Last resort for specific cancers
  - Primarily inspiration!
Long-term control of HIV by CCR5 Δ32/Δ32 stem cell transplantation: T. Brown, the Berlin Patient

Donor

CCR5−

HIV-1+
AML

CCR5+/

Substantial graft vs.
host disease

CCR5−

HIV-1−

Chemotherapy (x4)
Total-body irradiation (x2)

tscBMT
(X2)

off ART
no viral rebound

Courtesy of J Martinez Picado

Hütter. NEJM. 2009; Allens. Blood. 2010

Tim Brown: Eradication Cure

Stochastic Reversal of Latency

CCR5 −/−

TBI
GvH
ATG

Chronically producing cell
### Boston Patients (Henrich #144 LB; Session O-12)

<table>
<thead>
<tr>
<th>HSCT/Patient Factor</th>
<th>Patient A</th>
<th>Patient B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of acquisition</td>
<td>Perinatal</td>
<td>Sexual (adult)</td>
</tr>
<tr>
<td>CCR5 genetics</td>
<td>Δ32 Heterozygous</td>
<td>Δ32 Heterozygous</td>
</tr>
<tr>
<td>Favorable HLA alleles?</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Pre-HSCT HIV-1 DNA</td>
<td>144 copies/10⁶ PBMC</td>
<td>96 copies/10⁶ PBMC</td>
</tr>
<tr>
<td>Type of Allogeneic HSCT</td>
<td>HLA C-mismatched unrelated; CCR5&lt;sup&gt;wt/ wt&lt;/sup&gt;</td>
<td>Matched related donor; CCR5&lt;sup&gt;wt/ wt&lt;/sup&gt;</td>
</tr>
<tr>
<td>HSCT Conditioning</td>
<td>Reduced intensity</td>
<td>Reduced intensity</td>
</tr>
<tr>
<td>GVHD</td>
<td>Chronic, mild (skin)</td>
<td>Chronic, mild (skin)</td>
</tr>
<tr>
<td>Length of ART post-HSCT</td>
<td>4.5 years</td>
<td>2.8 years</td>
</tr>
<tr>
<td>Chimerism</td>
<td>&lt;0.001% host PBMC</td>
<td>&lt;0.001% host PBMC</td>
</tr>
<tr>
<td>Post-HSCT HIV-1 DNA</td>
<td>undetectable</td>
<td>undetectable</td>
</tr>
</tbody>
</table>

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**Relapse of 'cured' HIV patients spurs AIDS science on**

By **Kate Kelland**, Health and Science Correspondent

LONDON Thu Jan 2, 2014 5:21am EST

(Reuters) - Scientists seeking a cure for AIDS say they have been inspired, not crushed, by a major setback in which two HIV positive patients believed to have been cured found the virus re-invading their bodies once more.
The Second Cure?

- Infant born at U. Miss Medical Center
- Mother HIV+ (EIA, WB); no prenatal care
- Maternal VL: 2,423 c/mL, CD4 644/mm³
  - Infant born 35 weeks; NSVD
  - Rapid test HIV+ in neonate
- Standard testing of exposed infants: 2 HIV+ tests from 2 samples

<table>
<thead>
<tr>
<th>Sample</th>
<th>Age</th>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>30 hours</td>
<td>HIV DNA</td>
<td>positive</td>
</tr>
<tr>
<td>Blood</td>
<td>31 hours</td>
<td>HIV RNA</td>
<td>19,812 c/mL</td>
</tr>
</tbody>
</table>

Persaud D, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 46LB.
Virologic Response to HAART Regimen

- Mother stops ART about month 18 – LTFU until month 23
- HIV testing of infant done before restarting ART

Persaud D, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 48LB.

Sustained HIV-1 Remission (23 months off cART)

Remains under the care of Dr. Hannah Gay of the University of Mississippi Medical Center
Absent Residual Viremia and Replication-Competent Resting CD4+ T Cell Latent Reservoir

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Age at Testing (months)</th>
<th>Months Post-cART cessation</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residual Viremia (copies/mL)</td>
<td>24</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>8</td>
<td>&lt;2</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>15</td>
<td>&lt;1</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>18</td>
<td>&lt;1</td>
</tr>
<tr>
<td></td>
<td>39</td>
<td>21</td>
<td>&lt;1</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>22</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Infectious Virus Recovery (Infectious units per Million Resting CD4+ T cells)</td>
<td>24</td>
<td>6</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>15</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>18</td>
<td>&lt;0.03</td>
</tr>
</tbody>
</table>

Very Early Treatment of a Second Perinatally HIV-1 Infected Infant (4 Hours of Age)

High risk exposure: untreated maternal infection Maternal VI, near delivery =138,811 copies/mL, CD4=70 cells/mm³

Miller Children’s Hospital, LA County, Deveikis A, et al.
## Rapid Loss of Detection of HIV-1 Infection

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Age at Testing (months)</th>
<th>cART Duration (months)</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma viral load (copies/ml)</td>
<td>0.36 (11 days)</td>
<td>0.36</td>
<td>&lt;20</td>
</tr>
<tr>
<td></td>
<td>1.6</td>
<td>1.6</td>
<td>&lt;20</td>
</tr>
<tr>
<td></td>
<td>2.2</td>
<td>2.2</td>
<td>&lt;20</td>
</tr>
<tr>
<td></td>
<td>4.6</td>
<td>4.6</td>
<td>&lt;20</td>
</tr>
<tr>
<td></td>
<td>6.2</td>
<td>6.2</td>
<td>&lt;20</td>
</tr>
<tr>
<td></td>
<td>9.5</td>
<td>9.5</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Proviral DNA (Clinical Assay)</td>
<td>0.2 (6 days)</td>
<td>0.2 (6 days)</td>
<td>negative</td>
</tr>
<tr>
<td></td>
<td>1.6</td>
<td>1.6</td>
<td>negative</td>
</tr>
<tr>
<td></td>
<td>2.2</td>
<td>2.2</td>
<td>negative</td>
</tr>
<tr>
<td>Infectious Virus Recovery (IUPM)</td>
<td>1</td>
<td>1</td>
<td>&lt;0.13</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>3</td>
<td>&lt;0.20</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>9</td>
<td>&lt;0.15</td>
</tr>
</tbody>
</table>

## Strategies to reduce and/or control HIV reservoirs

- **Spontaneous or Induced Reversal of Latency**
  - Elimination of expressing cells
- **Stimulation and recruitment of immune effector cells**
- **Targeted antibody or antibody-drug conjugate delivery**
  - No infection of CD4+ T-cells

*Modified from Romas Geleziunas et al.*
HIV lives within chromatin: tipping the balance towards acetylation removes a restriction at the initiation of proviral expression

“Closed” Nucleosome
Transcription Repressed

“Open” Histones
Transcription Active

Activation of HIV-1 Gene Expression Correlates with HDAC1 inhibition

Archin AIDS 2009
Vorinostat:
Suberoylanilide hydroxamic acid (SAHA), a histone deacetylase inhibitor with nanomolar potency licensed for the treatment of cutaneous T cell lymphoma

Inhibits HDACs 1, 2, 3, and 8 (class I) and HDAC 6 (class II)

Archin ARHR 2009
Contreras JBC 2009

Measures of persistent HIV in fully suppressed patients on ART

Low-level Plasma HIV RNA

HIV DNA
Cell-associated HIV RNA in resting CD4+ T cells

Resting CD4+ T cell
Single dose proof-of-concept pilot study with vorinostat

Stable cART >6 months; HIV RNA<50 c/ml; CD4>300 cells/µl

Hypothesis:
• HIV RNA expression in circulating resting CD4 T cells will be increased during the period of VOR intracellular effect
• VOR will disrupt latency in vivo

Single 400 mg VOR dose:
Remeasure resting CD4+ T cell HIV RNA expression. Define potential for VOR to disrupt latency

- Mean 5.2-fold induction (range 1.5- to 10-fold)
- All increases significant ($p < 0.01$)
- No AE > Grade I
- No AE due to VOR
What we have found so far:

- A single dose of VOR induces expression of full-length HIV RNA within latently infected resting CD4+ T cells.
- This is the first direct measurement of disruption of latent HIV infection in vivo.
- The optimal dosing schedule of VOR, and its ability to repeatedly and completely perturb latency in all relevant infected cells, must be established.
- Separately, the potential for VOR to deplete (some or all) latently infected cells must be established.

What if disrupting latency is not enough?

When latency is disrupted, mechanisms to kill virus expressing cells may be needed:

- Augment HIV-1 specific immune response with HIV-1 vaccine prior to “kick”
- Improve HIV-1 specific CD8 response through ex vivo manipulation
  - TCR enhancement
- Infuse broadly neutralizing antibody or antibody primed for ADCC
- Wake up “exhausted” HIV-1 specific cells
  - Anti PD1 or Anti PD-L1
Objective

Functional Cure
Control of HIV without ART or deleterious immunologic effects

Post-Treatment HIV-1 Controllers with a Long-Term Virological Remission after the Interruption of Early Initiated Antiretroviral Therapy ANRS VISCONTI Study

Asier Sáez-Cirión¹, Charline Bacchus², Laurent Hocqueloux², Véronique Avettand-Fenoël³, Isabelle Girault⁴, Camille Lecuruix⁵, Valérie Potard⁶, Pierre Versmisse⁷, Adeline Melard⁸, Thierry Prazuck⁸, Benjamin Descours⁹, Julien Guergnon¹⁰, Jean-Paul Viard¹⁰, Faroudy Boufassa¹, Olivier Lambotte¹, Cécile Goujard¹, Laurence Meyer¹, Dominique Costagliola², Alain Venet², Gianfranco Pancino¹, Brigitte Autran², Christine Rouzioux¹, the ANRS VISCONTI Study Group²

B

Cell-associated HIV-1 DNA (Log copies/10⁶ PMNC)

Time after treatment interruption (months)

0 30 60 90 120 180 240 300 360

0 1 2 3 4
Acutely treated patients have significantly lower integrated HIV DNA in central memory CD4+ T cells
**Immune Control Approaches**

- **Antibodies**
  - Broadly-neutralizing MoAb (promote ADCC?)
  - Ab drug conjugates
  - Bispecific Ab (anti-HIV/anti-CD3)
  - Reverse immune exhaustion (anti-PD1/L1)*

- **Cellular therapies**
  - CD8+ T-cells with affinity enhanced TCRs or CARs (scFv)*
  - Activated NK cells

- **Therapeutic Vaccines**
  - Multiple approaches
  - Induction of de novo responses to epitope escape variants is key

*Succesful for cancer therapy*

---

**PD-L1 blockade in ARV suppressed SIVmac251-infected Rhesus Macaques**

**Hypothesis:**
- Treatment of ARV-suppressed SIV infected macaques with αPD-L1 should:
  - restore SIV-specific T cell function. Subsequently, this may:
    - reduce the latent SIV reservoir
    - lead to host control of virus following interruption of ARV

**Study design:**

- **SIV Infection** → **Start ARV** → **PD-L1 blockade** → **ARV** → **T1** → **Viral load rebound off ARV**

- **BMS-936559 (8)**
- **Isotype control (5)**
- **5 X 10mg/kg**

**Objectives:**
- Determine whether multiple doses of BMS-936559 affect:
  1. Virus-specific T cell functionality,
  2. Cell-associated viral DNA (latent reservoir) in tissues and periphery,
• Half of BMS-936559-treated animals had rebound similar to isotype-treated animals
• BMS-936559-responder group remained below 1000 cp/mL for >8 weeks
• Two had undetectable VL for 3-4 weeks

Strategic Objective

Host Modification
Confer resistance of cells to HIV
Gene Editing of CCR5 in Autologous CD4 T Cells of Persons Infected with HIV

Panel A depicts HIV viral loads (HIV RNA) for the six patients in cohort 1. SQ-282-T was initiated on day 0, day 28 (quasi-daily) treatment interruption (shaded areas) was initiated on day 28 and terminated on day 112. The treatment interruption was terminated prematurely on day 50 (Week 8 of the interruption period). In Patients 204 and 215, the dotted lines indicate reversion of highly active antiretroviral therapy (HAART). The historical HIV RNA set point (HIV RNA set point) and integrated vaginal set point viral load are plotted at 50 copies. Patient 209 was heterozygous for CCR5 alleles. Panel B shows the median CD4 T-cell, CD4 T-cell, and CCR5-modified T-cell counts in cohort 1 during the treatment interruption, as well as the viral load.
Ending AIDS

- Find patients earlier, bring treatment to them
- Develop ways to use ART as prevention
- Develop vaccines that substantially reduce the risk of transmission
- Build platforms to develop and test curative therapy
  - Perturb latency
  - Block all infection
  - Reach all relevant cells
  - Clear infected cells