TOWARDS A CURE:
WILL IT EVER BE TRULY ACHIEVABLE?

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HIV if untreated can lead to AIDS
Evolution of HIV Treatment

ART works by blocking new virus production.
HOW DID WE STOP AIDS? ANTIRETROVIRAL THERAPY

IT WORKS!!

Haitian Patient, before and after receiving free treatment for HIV infection and Tuberculosis. The photograph on the left was taken in March 2003, and that on the right in September 2003. Many impoverished patients in rural Haiti and Rwanda now receive comprehensive medical care through public-private partnerships.

ART has had the most dramatic change to survival for people living with HIV

Number of people receiving ART and percentage of all people living with HIV receiving ART in low- and middle-income countries overall and by WHO region, 2013*

*Country income classification by the World Bank at the time of the 2011 Political Declaration on HIV and AIDS.

Strategic Timing of AntiRetroviral Treatment: START study

When to Start Therapy: Balance Now Favors Earlier ART

- Drug toxicity
- Preservation of limited Rx options
- Risk of resistance (and transmission of resistant virus)

- Potency, durability, simplicity, safety of current regimens
- Emergence of resistance
- Toxicity with earlier therapy
- Subsequent treatment options
- Risk of uncontrolled viremia at all CD4 levels
- Transmission

Delayed ART  Early ART

Why can’t ART cure HIV?

HIV Infection in Target T cells

Latent infection

Active infection

1. Transcription of proviral DNA
2. Synthesis of viral components
3. Assembly of viruses
4. Budding of viruses from the host cell

Viral RNA

mRNA
How could we consider a “Cure” for HIV?

<table>
<thead>
<tr>
<th>Functional cure or remission</th>
<th>Sterilising Cure</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No viral replication off antiretroviral therapy</td>
<td>• No latently infected cells and so no detectable virus DNA AND RNA</td>
</tr>
<tr>
<td>• There may be the occasional latently infected cells, (Detectable viral DNA) but no/little evidence of viral transcription or replication</td>
<td>• No detectable viral reservoir</td>
</tr>
<tr>
<td>• No risk of onward transmission</td>
<td>• No detectable viral transcription</td>
</tr>
<tr>
<td>• No ongoing immunological damage</td>
<td>• Timothy Brown</td>
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The HIV reservoir

What is it? Where is it? Why is it a problem?

The HIV reservoir is like a needle in a haystack, if we can’t find - is it not there?
What assays should be used to measure the reservoir/determine “cure”?

- Viral outgrowth assays?
- T-cell activation assays?
- q-PCR-based assays?

Anatomical reservoirs
Bridging the gap from current cART to cure

CURE!

What if we give ART VERY early?

3 DAYS
Has one Baby been “cured” by early ART?

Is the baby cured?

- Unfortunately no

- Age 4 – Routine F/U
  - VL 16,750 copies/ml
  - Decreasing concentrations of CD4+
  - Detectable antibodies against HIV

- Sequencing – same strain as Mother’s
<table>
<thead>
<tr>
<th>Trials</th>
<th>VL &lt; 50 after no ART</th>
<th>AHI stage</th>
<th>Time at ART</th>
<th>ART duration before interruption</th>
</tr>
</thead>
<tbody>
<tr>
<td>VISCONTI</td>
<td>15.6%</td>
<td>Fiebig II to V</td>
<td>2.2 months from diagnosis</td>
<td>5 years</td>
</tr>
<tr>
<td>Swiss 1</td>
<td>9%</td>
<td>Fiebig I to VI</td>
<td>≤ 4 months from infection onset</td>
<td>1.5 years</td>
</tr>
<tr>
<td>Primo-SHM</td>
<td>5%</td>
<td>70% F I to IV 30% F V-VI</td>
<td>2 months from diagnosis</td>
<td>0.5 years or 1.5 years</td>
</tr>
<tr>
<td>ANRS CO6 PRIMO</td>
<td>11%</td>
<td>Fiebig I to VI</td>
<td>3.1 months from infection onset</td>
<td>1.5 years</td>
</tr>
<tr>
<td>CASCADE</td>
<td>8.2%</td>
<td>Fiebig I to VI</td>
<td>≤ 3 months from seroconversion</td>
<td>1 year</td>
</tr>
<tr>
<td>Trials without post-treatment controllers SPARTAC</td>
<td>Fiebig I to VI</td>
<td>2-6 months from diagnosis</td>
<td>1+ year</td>
<td></td>
</tr>
</tbody>
</table>

Functional cure: post ART controllers – The Visconti Cohort

Post-treatment controllers (PTC): infected individuals controlling HIV-1 infection after interruption of cART

14 patients
- Months on cART: 36.5 (12-92)
- Months post-cART: 89 (48-115)

Therapy started within 10 weeks following Primary Infection (median 39 days p.i.)

Saez-Cirion et al PLoS Path 2013
Different ideas on how to cure HIV

- **Inhibit residual replication**
  - Enhanced cART: novel drug classes/treatment intensification

- **‘Shock and kill’**
  - Induce HIV re-activation plus intensive cART*: valproic acid, vorinostat, panobinostat, disulfiram, phorbol ester derivatives, cytokines, immunotoxins

- **Immune stimulation**
  - Cytokines: IL-2, IL-7, IL-21
  - Therapeutic vaccines
  - Anti-PD-1, anti-PD-L1

- **Gene therapy**
  - Replace or silence
  - CCR5 knock-down; siRNA/short hairpin RNA

*Some treatment examples are not licensed for this indication


Activating latent virus is a necessary step in many HIV cure strategies

Timothy Brown/The Berlin patient: Example of a sterilizing cure?

- Treated for acute myelogenous leukemia by BMT
- Donor was homozygous for CCR5 gene deletion
- Interruption of ARVs
- No detectable HIV RNA for over 7 years

Research challenges

- Long term!
- Risk vs benefit
- Reactivation
- Removal of activated cells *in vivo*
- Ongoing replicative activity
- Toxicity?
- No uniform or validated assays

Current and planned HIV Cure research in the UK

**Clinical Cohorts in Development**

**Observational cohorts**
- ART + Chemotherapy in HIV+ on ART
- Viral reservoir characterization
- SPARTAC study
- CHERUB-yc: HIV research in young people and children with perinatally acquired HIV
- HEATHER:
  - A: Prospective cohort of ART treated PHI
  - B: Suppressed since HIV seroconversion on ART for > 2 years

**Intervention trials**
- ART in PHI +/- IVIG
- River Study
Dr. Sarah Fidler
• Chief Investigator
  • Imperial College London, HIV Clinical Trials Unit

• Two-arm (proof of concept) randomised phase II trial

• ARM A (Control):
  • 4-drug cART including Raltegravir

• ARM 2:
  • 4-drug cART including Raltegravir plus ChAd prime and MVA boost vaccines; followed by a 28-day course of vorinostat (10 doses in total)
Conclusions towards a cure for HIV

- ARV during acute HIV infection (AHI)
- Post treatment controllers (PTC) = >3 yrs treatment during AHI
- Predictors for PTC
  - short interval from HIV onset to ARV initiation
  - long duration of ARV
  - low HIV DNA and high CD4+ counts prior to interruption
- Combined interventions of ARV + therapeutic HIV vaccines + reservoir activators (+ early ARV at AHI)
Summary

- New ideas to cure HIV
- Will it work on a global scale?
- Will people get re-infected?
- How toxic are the drugs?
- How much will this cost?

Ethics of cure research

- Social/ethical implications of HIV cure research

  - Patient conceptions of "cure"

  - What is the duration of "cure"?

  - Concerns or issues of beneficence/justice

  - Therapeutic misconception
Thank You

• Dr. Sarah Fidler and Dr. John Thornhill

• Kristin Kuldanek and Kanta Mahay

• NHIVNA & European HIV Nursing Network

• Clinical Trials Participants

* …and you.

References


• McCarthy, M.. (2014). HIV is detected in child thought to have been cured. *British Medical Journal*. 349 (g4614).


