HIV cure strategies: interventions, endpoints and ethics

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Competing interests disclosure

Pecuniary interests
• Consultancy work – Viiv, BMS, Merck, Abivax, Tetralogic
• Grant support – Viiv, Merck, Gilead

Non-pecuniary interests
• Member, Governing Council, International AIDS Society, July 2016-July 2020
• Chair, Ministerial Advisory Committee for Blood Borne Viruses and Sexually Transmitted Infections, Commonwealth of Australia, November 2014 – November 2017
• Member, National Health and Medical Research Council of Australia, July 2015-July 2018
Professor David Cooper AO
19 April 1949 – 18th March 2018
Commonwealth Games: Scotland's Duncan Scott emerges as new swimming star after 100m win

by James Maasdorp on the Gold Coast
Updated 9 Apr 2018, 10:22am
## Commonwealth Games Medal Tally

<table>
<thead>
<tr>
<th>Country</th>
<th>Gold</th>
<th>Silver</th>
<th>Bronze</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>80</td>
<td>59</td>
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<tr>
<td>England</td>
<td>45</td>
<td>45</td>
<td>46</td>
</tr>
<tr>
<td>India</td>
<td>26</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Canada</td>
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<td>40</td>
<td>27</td>
</tr>
<tr>
<td>New Zealand</td>
<td>15</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>South Africa</td>
<td>13</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Wales</td>
<td>10</td>
<td>12</td>
<td>14</td>
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<tr>
<td>Scotland</td>
<td>9</td>
<td>13</td>
<td>22</td>
</tr>
<tr>
<td>Nigeria</td>
<td>9</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Cyprus</td>
<td>8</td>
<td>1</td>
<td>5</td>
</tr>
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</table>
A short history of HIV cure research: a shift from cure to remission but a long way to go

- **1997**: HIV latency identified
- **2009**: The Berlin patient
- **2010**: Post treatment control
- **2014-now**: Case reports of remission

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Use of Real-Time PCR and Molecular Beacons To Detect Virus Replication in Human Immunodeficiency Virus Type 1-Infected Individuals on Prolonged Effective Antiretroviral Therapy


Aaron Diamond AIDS Research Center, New York, New York 10016

Received 25 November 1998/Accepted 5 March 1999

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Nature Medicine

A global scientific strategy to eliminate HIV
Reward system activation boosts immunity
Targeting stem cell aging to improve muscle regeneration

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POZ Magazine

The Man Who Once Had HIV

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CURE HIV
What should a cure look like in the era of single tablets, long acting agents, reducing cost of ART and U=U?

**Efficacy:** aviremia in absence of ART for at least 2 years; early failure is tolerable, late failures must be rare

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

**Target Population:** effective for ART initiated at any stage and in all populations (gender, subtype)

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

**Cost:** < $1400 USD (resource limited settings)
Outline

• Clinical strategies and what’s in the pipeline
• Endpoints of cure studies and biomarkers
• Ethical considerations of cure studies
Clinical strategies to achieve remission off ART
Virus elimination
Virus elimination

- Very early ART
- Latency reversal or “shock and kill”
- Permanent silencing or “block and lock”
- Immunotoxins
- Gene editing
- Transplantation
Early ART leads to a decrease in the reservoir and a delay in viral rebound but no cure.

Fiebig I rebound range: 13-48 days
Fiebig III-IV rebound range: 14-77 days
Chronic rebound range: 5-29 days

Chronic infection (n=14); Median 14 days
Fiebig III-IV (n=14); Median 22 days
Fiebig I (n=8); Median 26 days

Late rebound out to >24 months described following very very early ART

Latency reversal: shock and kill

Latency reversing agent

Latent infection → Productive infection

Immune mediated killing or Pro-apoptotic drugs

Cell death
Multiple latency reversal agents active in vitro

- Latency reversal possible in vivo
- No induction of cell death
- Future studies need more potent LRAs and/or combinations

Kim, Anderson and Lewin. Cell Host Microbe 2018
Latency reversal requires multiple steps in RNA production – multiple blocks present in a resting cell

Yukl et al., Science Translational Med 2018
No residual virus replication on ART: ART intensification with dolutegravir

- Multi site, randomized placebo-controlled, double blind study (n=40)
- No significant change in 2LTR, total DNA, integrated DNA, cell associated or plasma RNA or markers of immune activation

Rasmussen et al., Lancet HIV 2018
Boosting Immunity
Boosting immunity

• Broadly neutralising antibodies
• T-cell vaccines
• T-cell immunotherapy
• Reduce inflammation
• Alter T-cell trafficking
Broadly neutralising antibodies (bNABs) have multiple potential roles in HIV prevention and cure.
bNABs can delay time to rebound off ART, can eliminate infected cells and may even boost T-cell function

Similar results for:
- **VRC01**
  - Crowell, 7th IAS *Science*, Paris
- **10-1074**

But longer delay to rebound with **3BNC1017+10-1074**
- Nussenweig, 7th IAS *Science*, Paris

bNAbs + TLR7 agonist induces remission in a monkey model – human studies awaited

- SHIV infected rhesus macaques
- early ART
- high frequency of controllers?
- role of TLR7 agonist?

PGT121 = broadly neutralising antibody; TLR = toll like receptor

Vesatolimod (formerly GS-9620, TLR7 agonist) at escalating, multiple doses in HIV-1 infected individuals (n=72) completely recruited

Barouch et al., CROI 2018
T cell vaccines + TLR7 agonists also look good in a monkey model - human studies awaited

Ad26 = adenovirus 26; MVA = modified Vaccinia Ankara; TLR = toll like receptor

RV405 Bangkok: HIV+ participants treated during acute infection, on ART 24 months and randomised to Ad26/MVA (n=18) or placebo (n=9) followed by ART interruption

Immunotherapy: immune checkpoint blockers and chimeric antigen receptor (CAR) T-cells

Potential role in boosting HIV-specific T cell immunity
Some concerns around safety and toxicity

Wykes M and Lewin SR, Nat Rev Immunol 2017
CITN-12: Anti-PD-1 (pembrolizumab) in HIV and cancer

- Multicentre study of HIV and advanced cancers (n=36)
- Pembrolizumab 200mg IV every 3 weeks for 2 years
- Recruitment in 3 cohorts of different CD4 counts
- Safety and AEx similar to HIV negative cohorts

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Total N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroidism</td>
<td>2</td>
<td>4</td>
<td></td>
<td>6 (35.3)</td>
</tr>
<tr>
<td>ALT increased</td>
<td>1</td>
<td></td>
<td>1</td>
<td>2 (17.6)</td>
</tr>
<tr>
<td>Joint stiffness</td>
<td>1</td>
<td></td>
<td></td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>1</td>
<td>2</td>
<td></td>
<td>3 (11.8)</td>
</tr>
</tbody>
</table>

Uldrich T, CROI2018, March 2018, Boston
Endpoints of clinical studies and biomarkers that predict cure
Treatment interruption is the only way to determine if an intervention is successful.

No biomarker available that can predict time to rebound or post treatment control.
Large increase in studies with treatment interruptions for cure: adverse events rare

Systematic review of 101 clinical trials with a treatment interruption, 42 cure related studies, >1000 participants, adverse events very rare post 2014

Lau, Lewin, Smith and McMahon
Treatment interruption seems to not change the size of the reservoir.

**Optimising Pediatric HIV Treatment study**: HIV-infected infants (n=14) in Kenya with treatment interruption after 24 months of ART and re-initiation based on CD4 decline.

Pankau et al., OFID 2018
Post treatment control is common depending on definition and duration of follow up

<table>
<thead>
<tr>
<th>HIV pDNA/IL-12 or placebo</th>
<th>rVSV gag or placebo</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
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<tr>
<td>12</td>
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<td>56</td>
<td>72</td>
</tr>
<tr>
<td>72</td>
<td>96</td>
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Vaccination/ART phase (48 weeks) | ART treatment interruption phase (16 weeks) | Follow-up/ART phase (24 weeks)

- Restart ART before 16 weeks if VL > 50,000 copies/ml x 4 weeks
- >30% decline CD4 count
- CD4 < 350/mm³
- Acute retroviral syndrome

Post treatment control at 4 months post ART cessation (n=15)
- <40 RNA copies/ml ~ 20% of subjects
- <400 RNA copies/ml ~ 27% of subjects
- <2000 RNA copies/ml ~ 40% of subjects

Sneller MC, Science Transl Med 2017
Ethical issues in cure research
Current ethical issues

- Risk benefit relationship of any intervention
- Seroconversion (for people who initiate ART very early)
- Availability of cure studies for some populations: women, rural, low income, co-infections
- Safety and acceptability of a treatment interruption
  - How long?
  - Viral load endpoint?
  - Frequency of monitoring?
  - PREP for partners?
  - Placebo or not?
## Acceptability of treatment interruption for cure

<table>
<thead>
<tr>
<th></th>
<th>Community (n=442)</th>
<th>Providers (n=140)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV cure achievable in next 10 years</td>
<td>55%, 226/410</td>
<td>19%, 26/140</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HIV cure not achievable in lifetime</td>
<td>14% 56/410</td>
<td>16% 23/140</td>
<td>0.4</td>
</tr>
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Jill Lau and James McMahon
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