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The Myth or reality of an HIV Cure

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Viruses, Vaccines and Eradication
Disclosures

• Nothing to disclose
HIV infects CD4+ cells

Some CD4+ T-cells become resting memory cells; ‘reservoir’

Larger reservoir size accelerates clinical progression & predicts time to viral rebound

HIV reservoirs

- Lymph nodes
- Blood
- CNS Brain
- Gut associated lymphoid tissue
- Genital tract
Two types of HIV “Cure”

**Sterilising cure**
- Replication-competent virus eliminated?
- Extremely difficult to achieve

**Functional cure**
- Host control of viral replication without continued treatment
- Immune function restored and stabilised
- HIV-induced inflammation reduced
- Risk of transmission to others reduced (if low viral load)
- More plausible?
HIV cure is possible

Timeline for the Berlin patient: the first and longest duration clinical cure case

AML, acute myeloid leukaemia; cART, combination antiretroviral therapy; CCR5, chemokine (C-C motif) receptor 5.

HIV-1 remission following CCR5Δ32/Δ32 haematopoietic stem-cell transplantation

Ravindra K Gupta, Sultan Abdul-jawad, Laura E McCoy, Hoi Ping Mok, Dimitra Peppa, Maria Salgado, Javier Martinez-Picado, Monique Nijhuis, Annemarie M.J. Wensing, Helen Lee, Paul Grant, Eleni Nastouli, Jonathan Lambert, Matthew Pace, Fanny Salasc, Christopher Monit, Andrew Innes, Luke Muir, Laura Waters, John Frater, Andrew ML Lever, SG Edwards, Ian H Gabriel & Eduardo Olavarria
Case History

• HIV-1 Diagnosis 2003
• **2013**: Stage IVb Hodgkin lymphoma
  Atripla initiated. Viral suppression achieved
  Switch to TDF/FTC/Raltegravir (ABVD chemo)

• Failed multiple lines of chemotherapy and mobilisation for auto SCT
• Donor registry search for allo HSCT
  • Unrelated 9/10 HLA high-resolution match.
  • Donor homozygous CCR5-d32 mutation
<table>
<thead>
<tr>
<th>‘The London Patient’</th>
<th>‘The Berlin Patient’</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Homozygous for wild type CCR5</td>
<td>• Heterozygous for Δ32</td>
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<tr>
<td>• Infection with R5 using virus</td>
<td>• Infection with R5 using virus</td>
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<tr>
<td>• Hodgkin Lymphoma</td>
<td>• Acute Myelogenous Leukemia</td>
</tr>
<tr>
<td>• Single HSCT</td>
<td>• Two HSCT</td>
</tr>
<tr>
<td>• No irradiation</td>
<td>• Total Body Irradiation</td>
</tr>
<tr>
<td>• Reduced intensity conditioning</td>
<td>• Full intensity conditioning</td>
</tr>
<tr>
<td>• T cell depletion with aCD52</td>
<td>• T cell depletion with ATG</td>
</tr>
<tr>
<td>• Mild GVH</td>
<td>• Mild GVH</td>
</tr>
<tr>
<td>• 100% T cell donor chimerism</td>
<td>• 100% T cell donor chimerism</td>
</tr>
<tr>
<td>• 20 months off ART</td>
<td>• 12 years off ART</td>
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Summary of Stem cell transplantation

• This is not scalable
• Any HIV+ patient requiring BMT should receive d32 deletion donor wherever possible
• Better understanding of exact mechanisms may inform future less invasive interventions
Different approaches to cure HIV

1. Inhibit residual replication
   - Enhanced cART: novel drug classes/treatment intensification
   - Push viral reservoir levels to below a “threshold”
   - Enhanced tissue penetration of ART eg nanotechnology

2. Immune modulation
   - Therapeutic vaccines
   - Broadly Neutralising antibodies (Bnabs)
     - Anti-PD-1, anti-PD-L-1,
     - Cytokines: IL-2, IL-7, IL-21

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

4. Gene therapy
   - Replace or silence
   - CCR5 knock-down; siRNA/short hairpin RNA
     - Wei et al 3.6.2019 Nature Medicine 21% increase in all-cause mortality
   - CAR-T-cells
How to design an HIV remission/cure trial?

Measure the impact of an intervention on laboratory measures of HIV reservoir....
Total HIV DNA most well described but does not reflect replication competent virus
none have been validated to
none predict post-treatment control

Most clinically important outcome is **viral control OFF ART**
- time to viral rebound (> threshold)
- allow viral rebound and look for length of potential control
- allow to reach a new “set point”
Analytical Treatment Interruption designs

How to do ATI safely?

How frequently to test viral load?

How to test viral load?

Risks of viral transmission

How long to wait before treatment re-initiation?
1. Push viral reservoirs below a “threshold”

novel drug classes/treatment intensification (no effect)
Start ART very early after acute infection
Start ART; Very early, in acute infection

RV411 Study group Thailand
N = 8 individuals starting ART at Feibig I (first 2 weeks after infection)
On ART median 2.8 years
All experienced rapid viral rebound (>20 cpm x 2) by median 26 days following analytical treatment interruption
None controlled by week 24

Associations with time to viral rebound:
1. CD4:8 ratio <1 was associated with faster time to viral rebound
2. No association between pre-ATI HIV DNA and time to viral rebound

Colby et al Nature Medicine 2018 24 923-926
Summary

• Although the earlier ART is commenced the lower the size of the reservoir, for the majority of individuals interruption of ART leads to rapid viral rebound

• VERY early ART before antibody development maybe too early to allow time for HIV-specific immunity to develop

• There maybe a threshold of HIV reservoir below which post-treatment viral control will occur but this is uncertain and may differ for each individual.

• The risks of viral rebound for the individual are minimal, but the risks of inadvertent onward transmission maybe significant.
2. Immune modulation

- Therapeutic vaccines
- Broadly Neutralising antibodies (bNabs)
  - Anti-PD-1, anti-PD-L-1,
  - Cytokines: IL-2, IL-7, IL-21
Principle of immune potentiation

Restore immune function with therapeutic vaccines in HIV infection\(^1\)

Generate de novo or boost pre-existing HIV-specific T-cell responses\(^2\)

- Whole inactivated
- Live attenuated
- Synthetic peptides
- Recombinant subunit
- Recombinant viral vectors
- Recombinant bacterial vectors

Exhausted T cell → Immune intervention → Reinvigorated T cell

APC, antigen-presenting cell.
<table>
<thead>
<tr>
<th>Study Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>ERAMUNE 02</td>
<td>ART intensification (raltegravir or maraviroc) ± immunomodulation (DNA + HIV-rAd5 vaccine) did not significantly reduce the HIV DNA reservoir in blood or rectal tissue</td>
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<tr>
<td>RISVAC 03</td>
<td>MVA-B vaccination increased Gag- and Env-gp120-specific T-cell responses but had only marginal impact on VL rebound after cART interruption</td>
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<tr>
<td>ACTG A5197</td>
<td>rAd5 HIV-1 Gag vaccine showed positive correlation between Gag-specific cells and lower viral rebound during treatment interruption, although the effect decreased over time</td>
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<tr>
<td>NCT00659789</td>
<td>Vacc-4x, a p24Gag HIV-1 vaccine, lowered VL but did not affect the proportion of participants resuming cART before end of study or change in CD4 counts during treatment interruption</td>
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<tr>
<td>NCT00751595</td>
<td>HIV-1 Tat protein was safe, well tolerated and induced anti-Tat Abs in most patients. Vaccination promoted a durable and significant restoration of T, B, NK cells, and CD4+ and CD8+ central memory subsets. A significant reduction of blood proviral DNA was seen after Week 72</td>
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<tr>
<td>HVTN 090</td>
<td>rVSV vaccine recipients became seropositive for VSV after two vaccinations. Gag-specific T-cell responses were detected in 63% of participants by interferon-γ enzyme-linked immunospot at the highest dose postboost</td>
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Activating latent virus maybe a necessary step in many HIV cure strategies

Latently infected CD4⁺ T cell
- Anti-CD3 + anti-CD28 co-stimulation
- IL-2
- IL-7
- Prostratin
- HDAC inhibitors
- Other molecules

Productively infected CD4⁺ T cell
- Budding and maturation
- HIV Env
- Translation and virion assembly
- mRNA splicing and nuclear export
- Transcription
- HIV antigen loading into MHC class I

Cytoxic molecules induce cell lysis

HIV-specific cytotoxic CD8⁺ T cell

HDACi HIV latency reversing agents alone are not sufficient to confer remission off ART

Panobinostat, a histone deacetylase inhibitor, for latent-virus reactivation in HIV-infected patients on suppressive antiretroviral therapy: a phase 1/2, single group, clinical trial

Summary
Background Activating the expression of latent virus is an approach that might form part of an HIV cure. We assessed the ability of the histone deacetylase inhibitor panobinostat to disrupt HIV-1 latency and the safety of this strategy.

Activation of HIV Transcription with Short-Course Vorinostat in HIV-Infected Patients on Suppressive Antiretroviral Therapy

HIV Kick and Kill approach
A two-arm (proof of concept) randomised phase II trial

ART vs ART + Vorinostat + a prime boost HIV-1 Vaccine
Study design: 1:1 randomized control trial

Individual with defined PHI

Immediate standard ART (irrespective of CD4) + integrase inhibitor

Undetectable viral load

Randomisation

- ART only
- ART + V + V

Vaccines

HDACi

Primary outcome: total proviral DNA in CD4+ T cells

Secondary outcomes
No difference in total HIV DNA or viral outgrowth by study arm

 Primary endpoint: \( \log_{10} \) Total HIV DNA copies/million CD4+T cells
Difference (ART+V+V minus ART only) in mean averaged across PR weeks 16 and 18: 0.04 (95% CI: -0.03 to 0.11); p=0.26

qVOA No significant difference by study arm
Summary of Kick and Kill studies using LRA and T-cell vaccines

• One RCT (RIVER) shown no effect of HDACi (Vorinostat) + T-cell vaccine vs ART alone on measures of HIV reservoirs
• Latency reversal using this HDACi maybe inadequate or T-cell vaccine epitopes may not recognize the correct viral sequences
• There are other ways to induce the kick and kill under investigation
Broadly Neutralising antibodies (Bnabs)

- The antigen binding region is HIV envelope specific bNabs behave as antiviral agents
- The Fc region has other functions; ADCC and facilitates binding to APC to enhance T-cell function
- “Vaccinal” effect
- Next generation bNAbs have extended half-lives (up to 3-6 months)
5 key bNAb binding sites on HIV Env

Adapted from Burton et al, Science 2012
HIV-1 antibody 3BNC117 suppresses viral rebound in humans during treatment interruption

Johannes F. Scheid1,2*, Joshua A. Horwitz1*, Yotam Bar-On1, Edward F. Kreider3, Ching-Lan Lu4, Julio C. C. Lorenzi1, Anna Feldmann3, Malte Braunschweig3, Lilian Nogueira3, Thiago Oliveira3, Irina Shimeliovich3, Roshni Patel1, Leah Burke5, Yohuda Z. Cohen1, Sonya Hadrigan1, Allison Settler1, Maggi Witmer-Pack1, Anthony P. West Jr6, Boris Juclg7, Tibor Kecler8, Thomas Hawthorne8, Barry Zingman9, Roy M. Gulick10, Nico Pfeifer11, Gerald H. Lerner12, Michael S. Seaman10, Pamela J. Bjorkman13, Florian Klein13,14, Sarah J. Schlesinger1, Bruce D. Walker7,13, Beatrice H. Hahn3, Michel C. Nussenzweig13,14 & Marina Caskey1

July 2016

- N=13 with chronic HIV infection suppressed for >12 months
- Infusions of 3BNC117. TI 2 days later
- Up to 19 week delay in rebound vs historical controls (2.6 weeks)
- Rebound occurred with escape variants or once antibody levels had dropped
What next......?
Impact of Dual bNAb therapy given in treated HIV infection

Nussenzweig; AIDS, Amsterdam 2018
Human bNab studies

• The new innovation for prevention as well as remission
• long-acting function currently under investigation
• Combination approaches of 3 bNabs plus LRA + T-cell vaccination
• Safe, well tolerated and works with ART
• Now ongoing n = 14 proof of concept studies on combination bNabs in humans for cure
• A randomised placebo controlled trial of ART plus dual long-acting HIV-specific broadly neutralising antibodies (bNAb) vs ART-only in treated Primary HIV Infection on viral control off ART
Conclusion

• Multiple approaches towards HIV remission in addition to early or long-term ART to limit the size of the measured HIV reservoir look encouraging
• Will probably need a combination approach
• Important to balance risk vs benefits of each strategy
• May end up with induction then remission and maintenance therapy following a cancer treatment model and removing the need for daily ART
• When will there be a cure?
  • Post-treatment viral control maybe 5-10 years combination + ART
  • Sterilising Cure a Long time....
All the SPARTAC, RIVER and HEATHER study participants and collaborators

John Frater
Abdel Babiker
Julie Fox
Sabine Kinloch
Andrew Lever
Lucy Dorrell
Simon Collins Damian Kelly
CHERUB collaborators