HIV remission: viral suppression in the absence of ART

Sarah Fidler
Brian Gazzard Lecture
BHIVA 2016
U.K. Papers Erroneously Report, Yet Again, That an HIV Cure Is Near

The misreported news, which originated in The Sunday Times, concerns a “kick-and-kill” cure attempt that still requires years of follow-up.

October 3, 2016  •  By Benjamin Ryan

Why talk of a cure for HIV is premature
Summary of talk

• What is HIV remission?
• What are the pros and cons of “cure” research
• What is the evidence that PTC might work?
• How do we predict PTC?
What do we mean by ‘curing HIV’?
Clinically undetectable viraemia in the absence of ART

Sterilising Cure

INFECTION DISEASE MODEL
• The ‘Berlin’ patient
• Aviraemia; no transmission
• No replication competent virus
• No detectable HIV-infected cells

‘Functional’ Cure

REMISSION

“CANCER” MODEL
• No disease progression
• No CD4 cell loss
• No transmission
• But...no agreed duration
Antiretroviral therapy

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 does not eradicate HIV

HIV persists during ART
Why can't ART cure HIV?

(a) Latent infection

(b) Active infection
We need a balanced view on whether we should even try to HIV cure

**Pros**
- The chance it might work
- Could have time off ART
- Avoid drug toxicities

**Cons**
- Safety transmission
- Adverse events
- Reservoir seeding
- No viral rebound doesn’t necessarily mean no pathogenesis
Pros and cons of interrupting ART?

**Pros**

- The only way we currently have, to tell if a “cure” intervention has had an effect
- IF successful could limit exposure to lifelong ART
- Avoid the pressure of daily ART

**Cons**

- SMART trial showed increased all-cause mortality
- Unknown outcomes
- Potential risk of onward transmission
- Potential risk of reservoir seeding
- Potential inflammatory and general health risks
- We don’t know how to do it?
Barriers to HIV cure: viral latency and reservoirs

HIV infects CD4+ cells

Some become resting memory cells; ‘reservoir’

The HIV reservoir

What is it? where is it? why is it a problem?
Where is the viral reservoir?

If we can't find it, it doesn't mean it isn't there?
Tests that measure the viral reservoir

Latent infection

- HIV DNA
- 2-LTR circles
- Integrated DNA Infectious Units (IUPM)
- Cell associated RNA
  - US RNA and MS RNA
- HIV RNA (SCA)

Productive infection

Lewin and Rouzioux, AIDS 2011
The viral reservoir; If we can find it, what does it mean?
Trial schema & primary endpoint

Randomisation

- ART-48 (48 week ART)
- ART-12 (12 week ART)
- SOC (No ART)

Primary endpoint: confirmed CD4 count <350 cells/mm³ (within 4 weeks, and not within first 3 months) or initiation of long-term treatment

• Definition of PHI
  • laboratory evidence of infection within 6 months of a previous negative test, <3 bands WB, RITA incident, antibody negative PCR+
HIV-1 DNA at PHI predicts TRIAL endpoint in untreated participants


Untreated individuals from PHI:

Cox Model:

Univariable predictors:
- Total HIV-1 DNA: HR 4.16 (CI 2.10-8.26); p <0.0001*
- Int HIV-1 DNA: HR 5.41 (CI 1.65-18.04); p = 0.006
- Plasma VL: HR 1.74 (CI 1.13-2.68); p = 0.011

Multivariable analyses
- Total HIV-1 DNA: HR=3.57 (1.58-8.08); p=0.002
- CD4 count: HR=0.67 (0.53-0.84); p<0.001
- Not plasma viral load or Integrated DNA
If size matters....the hypothesis towards remission

• The longer people live with untreated HIV the larger the pool of latently infected cells

• If ART is started immediately around the time of diagnosis will it be possible to push the reservoir below a threshold enabling viral control off therapy?
Extremely Low HIV DNA Levels in Fiebig I Subjects

Updated from Ananworanich J, PLoS ONE 2012
Data provided by Nicolas Chomont, Claire Vandergeeten (VGTI-Florida)
Reservoir responses to ART initiated in acute and chronic stage infection

What happens if people treated early in PHI stop therapy?

- VISCONTI study identified 14 individuals treated in Acute infection for average 3.5 years who stopped ART and controlled viraemia for years after stopping.
- They did not share “protective” HLA alleles.
- Virus could be grown in vitro from blood samples.
- Did they control because their level of viral reservoir was below a certain threshold?
Clinical benefits of early ART: Visconti (ANRS)

- 14 post-treatment controllers from the ANRS/Visconti study
- ART started within 10 weeks after primary infection, for a median time of 3 years
- Virological control following ART cessation for an average time > 9 years

Post treatment controllers naturally “control” a reservoir of small magnitude

A. Saez-Cirion et al. PLoS Path 2013
Sustained remission off ART is rare but achievable.

- Viral load
- ART
- <2 months
- Boston A 3 months
- Boston B 8 months
- Mississippi child 28 months
- ART started early in infection
- Timothy Brown

References:
- Hütter et al. NEJM 2009
- D. Persaud et al. NEJM 2013
- K. Luzuriaga et al. NEJM 2015
- T. Henrich et al. JID 2013
- W. Stöhr et al. Plos One 2013
- L. Hocqueloux et al. AIDS 2010
- A. Saez-Cirion et al. Plos Path 2013
- Adapted from J. Cohen, Science 2015.
<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><strong>VISCONTI</strong> <em>(Hocqueloux L, 2010)</em></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><strong>Swiss 1</strong> <em>(Gianella S, 2011)</em></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><strong>Primo-SHM</strong> <em>(Grijsen ML, 2012)</em></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><strong>ANRS CO6 PRIMO</strong> <em>(Goujard C, 2012)</em></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><strong>CASCADE</strong> <em>(Lodi S, 2012)</em></td>
<td>8.2%</td>
<td>Fiebig I to VI</td>
<td>≤ 3 months from seroconversion</td>
<td>1 year</td>
</tr>
<tr>
<td><strong>Trials without post-treatment controllers SPARTAC</strong> <em>(von Wyl V 2011; Volberding P 2009; Rosenberg ES 2010; Fidler S 2011)</em></td>
<td></td>
<td>Fiebig I to VI</td>
<td>2-6 months from diagnosis</td>
<td>1+ year</td>
</tr>
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Is there a lowest level of viral “reservoir” below which we could stop ART?
HIV-1 DNA at Treatment Interruption predicts time to VL rebound

- Graph showing time to rebound to 400 copies per ml plasma with labels:
  - Percent without viral rebound
  - Time to rebound (weeks)

- Statistical significance: \( p = 0.0038 \)

- Curves for low and high total DNA levels:
  - Low total DNA: black line
  - High total DNA: red line
The size of the expressed HIV reservoir predicts timing of viral rebound after treatment interruption.

Summary of 6 ACTG TI studies amongst n = 235 study participants; n = 155 chronic infection, n = 32 acute infections
Viral rebound was considered > 200, or > 1000 copies HIV RNA/ml
For the majority viral load became detectable by week 4

‘Post-Treatment Control or Treated Controllers’?

- SPARTAC
- Identified ‘controllers’: >16 weeks of remission
- Regardless of treatment
- Do we see ‘remission’ in untreated patients that ‘mimics’ remission after TI?

'Post-Treatment Control or Treated Controllers' - analysis of SPARTAC

<table>
<thead>
<tr>
<th>Cohort description</th>
<th>ART12</th>
<th>ART48</th>
<th>No ART</th>
<th>Total</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of controllers (% total)</td>
<td>9 (7.9)</td>
<td>16 (13.4)</td>
<td>10 (7.8)</td>
<td>35 (9.7)</td>
<td>0.24</td>
</tr>
<tr>
<td>No. without rebound at end of follow up</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Duration of ART (weeks; mean [SD])</td>
<td>11.9 (0.5)</td>
<td>47.7 (0.7)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.96</td>
</tr>
<tr>
<td>Male</td>
<td>3</td>
<td>6</td>
<td>4</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>6</td>
<td>10</td>
<td>6</td>
<td>22</td>
<td></td>
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<tr>
<td>Duration of remission (weeks)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;26</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>26-52</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td></td>
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<tr>
<td>52-104</td>
<td>0</td>
<td>7</td>
<td>7</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>&gt;104 weeks</td>
<td>3</td>
<td>6</td>
<td>7</td>
<td></td>
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</table>
Conclusion

• Measures of CD4+ T-cell total HIV DNA predict rate of disease progression in PHI

• Total & integrated HIV DNA in CD4+ T-cell at treatment interruption predict time to VL rebound on stopping therapy but…

• BUT…. In other cases these measures were not predictive; Mississippi baby, Boston transplant patients,

• Even a short period of ART if started early after infection seems to confer an increased chance of PTC but still rare

• Increase sensitivity of predictive value by generating an “algorithm”
<table>
<thead>
<tr>
<th>Biomarker 'Class'</th>
<th>Biomarker</th>
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<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td>CD4 Cell Count</td>
</tr>
<tr>
<td></td>
<td>Plasma Viral Load</td>
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<tr>
<td></td>
<td>CD4/CD8 Ratio</td>
</tr>
<tr>
<td><strong>Viral nucleic acid</strong></td>
<td>HIV-1 DNA (Total)</td>
</tr>
<tr>
<td></td>
<td>HIV-1 DNA (Integrated)</td>
</tr>
<tr>
<td></td>
<td>Cell-Associated Unspliced HIV-1 RNA</td>
</tr>
<tr>
<td><strong>HIV-1 T cell immunity</strong></td>
<td>CD8 ELISpot</td>
</tr>
<tr>
<td></td>
<td>CD4 ELISpot</td>
</tr>
<tr>
<td><strong>T cell activation</strong></td>
<td>HLA-DR</td>
</tr>
<tr>
<td></td>
<td>CD38</td>
</tr>
<tr>
<td></td>
<td>CD25</td>
</tr>
<tr>
<td></td>
<td>CD69</td>
</tr>
<tr>
<td><strong>T cell exhaustion/ ‘immune checkpoint’</strong></td>
<td>PD-1</td>
</tr>
<tr>
<td></td>
<td>LAG-3</td>
</tr>
<tr>
<td></td>
<td>TIM-3</td>
</tr>
<tr>
<td><strong>Soluble markers</strong></td>
<td>IL-6</td>
</tr>
<tr>
<td></td>
<td>D-dimer</td>
</tr>
</tbody>
</table>
PD-1, Lag-3 and Tim-3 Predict Time to Rebound after TI

Biomarker expression on T cells | Unadjusted HR(CI) p-value | Adjusted for baseline HIV-1 DNA HR(CI) p-value
--- | --- | ---
PD-1 CD4+ | 1.35 [1.072-1.71] p=0.011 | 1.46 [1.06-1.85] p=0.016
PD-1 CD8+ | 1.15 [1.015-1.319] p=0.0293 | 1.37 [0.950-1.552] P=0.145
Tim-3 CD4+ | 1.25 [1.12-1.4] p<0.001 | 1.36 [1.16-1.597] P=0.009
Tim-3 CD8+ | 1.11 [1.04-1.2] p=0.0036 | 1.15 [1.06-1.32] p=0.0011
Lag-3 CD4+ | 1.08 [1.027-1.146] p=0.0036 | 1.082 [1.022-1.146] P=0.0066
Lag-3 CD8+ | 1.104 [1.025-1.19] p=0.0093 | 1.129 [1.097-1.280] P=0.056
HIV DNA is associated with “good prognosis” HLA class I alleles

Patients with ‘good’ Class I HLAs (n=20) red have lower HIV-1 DNA than ‘progressive’ HLA alleles blue (n=55); p<0.001. (3.46 vs 4.05 log\textsubscript{10} copies/million CD4 T cells)
CD4:CD8 ratio at seroconversion predicts time to VL rebound on stopping therapy

N=206 Spartac + UK register of HIV seroconverters

Thornhill et al.
Factors Associated with virological rebound

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio [95% Confidence Interval]</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (Female)</td>
<td>0.72 [0.27-1.96]</td>
<td>0.52</td>
</tr>
<tr>
<td>Enrolment from an African site</td>
<td>1.63 [0.80-3.29]</td>
<td>0.18</td>
</tr>
<tr>
<td>Days from seroconversion to ART Initiation</td>
<td>1.000 [0.999-1.001]</td>
<td>0.60</td>
</tr>
<tr>
<td>ART Initiation HIV Viral Load (per Log copy/ml increase)</td>
<td>1.22 [1.04-1.44]</td>
<td>0.02</td>
</tr>
<tr>
<td>Duration on ART (months)</td>
<td>0.96 [0.93-0.99]</td>
<td>0.05</td>
</tr>
<tr>
<td>ART initiation CD4/CD8 ≥ 1.2 compared to &lt;1.2*</td>
<td>0.586 [0.345-0.997]</td>
<td>0.049</td>
</tr>
</tbody>
</table>

Multivariable model adjusted for sex, age category, exposure category, enrolment from an African site, time from seroconversion to ART Initiation, HIV Viral Load (Log), Duration on ART, and Time from both viral load and CD4/CD8 measurement to ART Initiation

*Model for CD4/CD8 ratio as a continuous variable was not significant, a poorer model fit (as measured by AIC) and is not shown
The importance of viral blips and duration of therapy initiated in primary infection in maintaining viral control after stopping cART

Sarah Fidler\textsuperscript{1}, Ashley D. Olson\textsuperscript{2}, Julie Fox\textsuperscript{1}, Andrew Phillips\textsuperscript{2}, Charles Morrison\textsuperscript{3}, John Thornhill\textsuperscript{1}, Heiner C. Bucher\textsuperscript{4}, Roberto Muga\textsuperscript{5}, Kholoud Porter\textsuperscript{2} on behalf of CASCADE Collaboration in EuroCoord

\textsuperscript{1}Department of Genitourinary Medicine and Infectious Disease, Imperial College, London, UK; \textsuperscript{2}University College London, London, UK; \textsuperscript{3}Behavioral and Biomedical Research Division, Family Health International, Research Triangle Park, NC, USA; \textsuperscript{4}Basel Institute for Clinical Epidemiology University hospital Basel, CH; \textsuperscript{5}Department of Internal Medicine, Hospital Universitari Germans Trias i Pujol, Badalona, Spain
Association of viral blips with risk of viral rebound

- Each blip >400 copies HIV RNA/ml was associated with a 2 fold increased hazard of viral rebound
- PI regimens were associated with a 38% decreased hazard of viral rebound as was more recent year of cART initiation
- There was no association with time to viral rebound and CD4 cell count, SC age, risk group and sex
Treatment interruption algorithm

- Baseline HIV VL, CD4 count CD4:8 ratio
- Absence of viral blips > 400 copies HIV RNA/ml
- Markers of immune activation prior to TI
- Total HIV DNA at baseline and prior to TI
- Longer duration of ART started in PHI
- Shorter duration of infection pre-ART start
Summary

• Virological remission is real
• We don’t understand the pathological consequences
• We are starting to understand the role of ART
  • But will be difficult as no control groups
• There is an interplay between host immunity and stochastic reactivation
• We are starting to develop predictors of PTC, but need more to understand the mechanism
• Important to put all of this in the setting of excellent ART and outcomes to balance risk vs benefits
We need a balanced view; safety, good science and achievable goals
Thanks to all study participants
Community of people living with HIV; Simon Collins, Damien Kelly
CHERUB collaboration
John Frater, Jonathan Weber
Nicholas Chomont,
RIVER trial management team
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(MSD, GSK)