PROSPECTS FOR HIV CURE IN ADULTS
Scientists on brink of HIV cure

Researchers believe that there will be a breakthrough in finding a cure for HIV “within months”.

With modern HIV treatment if medication is stopped, HIV reservoirs become active and start to produce more of the virus. Photo: Alamy

By Jake Wallis Simons
6:30PM BST 27 Apr 2013

Danish scientists are expecting results that will show that “finding a mass-distributable and affordable cure to HIV is possible”.

April 29th 2013; Telegraph online
Gambian President Yahya Jammeh has again stirred controversy for claiming that he has a “natural cure” for HIV and that he has now successfully treated over 68 patients.
What is ‘cure’?

Issues to consider:

- Post treatment control – the benefit of treating early
- Anti-latency agents to activate the reservoir
- A role for immunotherapy
The Problem: Barriers to an HIV Cure

HIV infects CD4+ cells. ‘Reservoir’ created

Reservoir size impacts clinical progression

Latently infected cell | Productively infected cell

? Can we target ‘latent’ cells with new therapies?

? How do we measure the reservoir?

? Can we identify those patients most amenable to cure?
What is ‘cure’?

Issues to consider:

- Post treatment control – the benefit of treating early
- Anti-latency agents to activate the reservoir
- A role for immunotherapy
**WHAT DO WE MEAN BY ‘CURING HIV’?**

<table>
<thead>
<tr>
<th>Sterilising Cure vs ‘Functional’ Cure</th>
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<tbody>
<tr>
<td><strong>INFECTION MODEL</strong></td>
</tr>
<tr>
<td>The ‘Berlin’ patient</td>
</tr>
<tr>
<td>Aviraemia – plasma viral load &lt;1 copy/ml</td>
</tr>
<tr>
<td>No replication competent virus</td>
</tr>
<tr>
<td>No detectable HIV-infected cells</td>
</tr>
<tr>
<td><strong>“CANCER” MODEL</strong></td>
</tr>
<tr>
<td>Clinically undetectable viraemia in absence of ART</td>
</tr>
<tr>
<td>No disease progression</td>
</tr>
<tr>
<td>No CD4 cell loss</td>
</tr>
<tr>
<td>No transmission</td>
</tr>
<tr>
<td>But...no agreed duration</td>
</tr>
</tbody>
</table>
‘Sterilising’ cure – The Berlin Patient
What is ‘cure’?

Issues to consider:

- Post treatment control – the benefit of treating early
- Anti-latency agents to activate the reservoir
- A role for immunotherapy
Early ART impacts the reservoir

Hocqueloux et al., *AIDS* 2010; 24:1598

SPARTAC Trial

**Log HIV DNA copies / million cells**

- **Chronic infection (n=135)**
- **Acute infection (n=22)**

**Time on HAART (years)**

**log_{10}(Copies total HIV) per million CD4+ T cells**

- **SOC (WK0)**
- **ART-12 (WK12)**
- **ART-48 (WK48)**

- **p < 0.0001**
- **p < 0.0001**
- **p = ns**
Evidence for ‘Post-treatment control’

- The Original ‘Berlin Patient’ (NEJM, 1999)
- Rosenberg (Nature 2000)
- Hocqueloux et al (AIDS 2010)
- Goujard et al (Antivir Ther 2012)
- Lodi et al (Arch Intern Med 2012)
- Saez-Cirion et al (Plos Path 2013 VISCONTI)
- Stöhr et al (Plos One 2013; SPARTAC)
French ANRS cohort study:

- ART initiation within 10 weeks after acute infection
- ART for (at least) one year
- Undetectable VL on treatment
- VL remaining <400 cp/mL for (at least) 12 months after treatment interruption
<table>
<thead>
<tr>
<th>Code</th>
<th>Sex</th>
<th>Year of diagnosis</th>
<th>PHI</th>
<th>Fiebig ART initiation</th>
<th>ART combination</th>
<th>Time on cART (months)</th>
<th>Time since interruption (months)</th>
<th>CD4 T-cell counts (cells/µL)</th>
<th>First PHI PHIL</th>
<th>PHII ART initiation</th>
<th>ART combination</th>
<th>Time on cART (months)</th>
<th>Time since interruption (months)</th>
<th>HIV-1 DNA VL during follow-up (c/mL)</th>
<th>HIV-1 RNA VL since treatment interruption (c/mL)</th>
<th>HIV-1 RNA VL since treatment interruption (c/mL)</th>
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<td>OR1</td>
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<td>Sympt</td>
<td>V</td>
<td>2 NRTI</td>
<td>81</td>
<td>82</td>
<td>416</td>
<td>81</td>
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<td></td>
<td></td>
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<td>V</td>
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<td>955</td>
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<td>92</td>
<td>107</td>
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<td></td>
<td></td>
<td>91</td>
<td>18/2</td>
<td>10/2</td>
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<tr>
<td>OR8</td>
<td>M</td>
<td>1998</td>
<td>Sympt</td>
<td>III</td>
<td>2 NRTI+PI→3NRTI</td>
<td>60</td>
<td>72</td>
<td>502</td>
<td>60</td>
<td>72</td>
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<td></td>
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<td>224</td>
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<td>397</td>
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<td>371</td>
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<td>36.5</td>
<td>89</td>
<td>5.0 (VL &lt; 50)</td>
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<td>59</td>
<td>489</td>
<td>31</td>
<td>59</td>
<td></td>
<td></td>
<td></td>
<td>&lt;20</td>
<td>11/1</td>
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<tr>
<td>LY1</td>
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<td>III</td>
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<td>84</td>
<td>455</td>
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<td>84</td>
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<td></td>
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<td>48</td>
<td>93</td>
<td>580</td>
<td>48</td>
<td>93</td>
<td></td>
<td></td>
<td></td>
<td>5</td>
<td>13/1</td>
<td>1/4</td>
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<td>Sympt</td>
<td>V</td>
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<td>113</td>
<td>822</td>
<td>34</td>
<td>113</td>
<td></td>
<td></td>
<td></td>
<td>5</td>
<td>13/1</td>
<td>1/14</td>
</tr>
<tr>
<td>MEDIAN</td>
<td></td>
<td>1999</td>
<td>Sympt</td>
<td>V</td>
<td></td>
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<td>89</td>
<td>502</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;20</td>
<td>1/4</td>
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3538 patients <6 months of PHI
756 patients treated within 6 months and at least for a year
74 patients with VL<50 RNA copies/ml who stop (ie only 2% of PHI patients

Probability of control at 24 months: **15.7%** [6.5-28.5]
Objective: to determine the effect of short course ART compared with no ART in primary HIV infection (PHI)

PHI: <6 months since estimated date of seroconversion

N=371; Randomised to 3 arms
- 48-weeks ART (ART-48)
- 12-weeks ART (ART-12)
- No therapy (Standard of Care, SOC)

Primary endpoint
- Time to CD4 < 350 cells/mm³ or long-term ART initiation

THE SPARTAC TRIAL; HIV RNA REBOUND FOLLOWING ART INTERRUPTION

Change in log10 HIV RNA from baseline

Weeks from ART interruption or randomisation (SOC)

SOC
ART-12
ART-48

Fidler et al, NEJM, 2013
**Patient demographics**

<table>
<thead>
<tr>
<th></th>
<th>n = 165</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>110 (67)</td>
</tr>
<tr>
<td>Female</td>
<td>55 (33)</td>
</tr>
<tr>
<td><strong>Age, median (IQR)</strong></td>
<td>34 (27–41)</td>
</tr>
<tr>
<td><strong>Risk, n</strong></td>
<td></td>
</tr>
<tr>
<td>MSM</td>
<td>101</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>62</td>
</tr>
<tr>
<td>Not Known</td>
<td>2</td>
</tr>
<tr>
<td><strong>Estimated time since seroconversion, days (IQR)</strong></td>
<td>85 (60–101)</td>
</tr>
<tr>
<td><strong>CD4 cell count, cells/µL (IQR)</strong></td>
<td>565 (463–707)</td>
</tr>
<tr>
<td><strong>Plasma HIV-1 VL, RNA c/mL (IQR)</strong></td>
<td>24,293 (4540–108,928)</td>
</tr>
<tr>
<td><strong>Median follow-up, weeks (IQR)</strong></td>
<td>167 (108–199)</td>
</tr>
</tbody>
</table>

**SPARTAC: SUB-ANALYSIS**

Of the 165 participants:
- 161 had viral rebound (> 400 RNA c/mL)*
  - The majority had VL rebound within 12 weeks of stopping ART
  - Four participants maintained VL < 400 c/mL for 164–202 weeks
- Are they PTCs?

*On two separate occasions. Two had only one VL ≥ 400 c/ml followed by initiation of long-term ART or loss to follow-up
IMPACT OF ART DURATION: <12 VS > 12 WEEKS

Probabilities of remaining undetectable (<400 copies/ml)

<table>
<thead>
<tr>
<th></th>
<th>12 weeks</th>
<th>52 weeks</th>
<th>104 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>ART &gt;12 weeks</td>
<td>32%</td>
<td>14%</td>
<td>5%</td>
</tr>
<tr>
<td>ART &lt;12 weeks</td>
<td>21%</td>
<td>4%</td>
<td>4%</td>
</tr>
</tbody>
</table>
MUTATED VIRAL GENOMES DOMINATE THE RESERVOIR

- 32.4% Hypermutation
- 11.7% Intact genome
- 45.5% Large internal deletion
- Ψ/MSD deletion/or mutation 6.5%
- Nonsense mutations/INDEL 3.8%
What is ‘cure’?

Issues to consider:

- Post treatment control – the benefit of treating early
- Anti-lactency agents to activate the reservoir
- A role for immunotherapy
‘ANTI-LATENCY AGENTS’

- PMA – Protein Kinase C agonist
- TNFa – MAPK / NFkB signalling
- Methylation inhibitors
  - 5-aza-2’-deoxycytidine (5-aza-dC)
- Prostratin – Protein Kinase C agonist
- Histone Deacetylase Inhibitors (HDACi)
  - Sodium valproate
  - Disulfiram
  - Vorinostat (Class 1 and 2 inhibitor 1,2,3,4,5,6,7,8,9,10)
  - Panobinostat (Pan HDACi)
  - Romidepsin (Class 1 and 2)
HDACI ACTIVITY - U1 CELL LINE

Graph showing % Live U1 cell p24 expression (background subtracted) against Concentration / uM. The graph includes data for different compounds such as Romidepsin, Prostratin, SAHA, Valproic Acid, and Panobinostat at different concentrations and time points (Day 1 and Day 2).
HDAC INHIBITORS – EASY
HDAC INHIBITORS – COMPLEX

A

B

nuc-0

nuc-1

TFII

USF-1/2

CBF-1

CTIP-2

YY1

+1

LSF

HATs

GR

USF

LEF-1

p50/p65

Sp1

AP-4

+1

LSF

TAR

Tat

YY1

+
Administration of vorinostat disrupts HIV-1 latency in patients on antiretroviral therapy

N. M. Archin¹, A. L. Liberty¹, A. D. Kashuba¹, S. K. Choudhary¹, J. D. Kuruc¹, A. M. Crooks¹, D. C. Parker¹, E. M. Anderson², M. F. Kearney², M. C. Strain³, D. D. Richman³, M. G. Hudgens¹, R. J. Bosch⁴, J. M. Coffin², J. J. Eron¹, D. J. Hazuda⁵ & D. M. Margolis¹
Safety and Effect on HIV Transcription of Vorinostat in Patients Receiving Suppressive Combination Anti-Retroviral Therapy


20th Conference on Retroviruses and Opportunistic Infections, Atlanta, GA, March 3-6, 2013
Significant increase in cell associated US HIV RNA on and post drug

Mean fold increase in US HIV RNA
- Pre to on treatment = 2.65 (95% CI 1.76, 3.52, p=0.023)
- Pre to off treatment = 3.00 (95% CI 2.16, 3.84, p=0.018)

GEE analysis grouping all “on drug” and “post drug” data points and adjusting for CV of the assay.

Unpublished: Slide courtesy of Sharon Lewin
What is ‘cure’?

Issues to consider:
- Post treatment control – the benefit of treating early
- Anti-latency agents to activate the reservoir
- A role for immunotherapy
DO LATENT CELLS PRODUCE ANTIGEN?

Directly Infected Resting CD4+T Cells Can Produce HIV Gag without Spreading Infection in a Model of HIV Latency

Matthew J. Pace¹, Erin H. Graf¹, Luis M. Agosto¹, Angela M. Mexas¹, Frances Male², Troy Brady², Frederic D. Bushman², Una O’Doherty¹*

¹ Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, United States of America, ² Department of Microbiology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, United States of America

Abstract

Despite the effectiveness of highly active antiretroviral therapy (HAART) in treating individuals infected with HIV, HAART is not a cure. A latent reservoir, composed mainly of resting CD4+T cells, drives viral rebound once therapy is stopped. Understanding the formation and maintenance of latently infected cells could provide clues to eradicating this reservoir. However, there have been discrepancies regarding the susceptibility of resting cells to HIV infection in vitro and in vivo. As we have previously shown that resting CD4+T cells are susceptible to HIV integration, we asked whether these cells were capable of producing viral proteins and if so, why resting cells were incapable of supporting productive infection. To answer this question, we spinoculated resting CD4+T cells with or without prior stimulation, and measured integration, transcription, and translation of viral proteins. We found that resting cells were capable of producing HIV Gag without supporting spreading infection. This block corresponded with low HIV envelope levels both at the level of protein and RNA and was not an artifact of spinoculation. The defect was reversed upon stimulation with IL-7 or CD3/28 beads. Thus, a population of latent cells can produce viral proteins without resulting in spreading infection. These results have implications

Pace et al, 2013 Plos Pathogens 8(7): e1002818
What is the interaction between the new ‘anti-latency drugs’ and the immune response?

Vorinostat does not reliably lead to CD8 T cell induced cell killing

Shan et al. Immunity 2012
UK-based trial:
- recruiting 2014
- Managed by CHERUB
- 3 interventions:
  - Early ART
  - Vaccination
  - HDACi

Primary Outcome:
- Change in Reservoir Size

THE SOLUTION?: PHI + HDACi + VACCINE
CHERUB
Collaborative HIV Eradication of Reservoirs: UK Biomedical Research Centres
The CHERUB collaboration

CHERUB (Collaborative HIV Eradication of Viral Reservoirs: UK BRC) is a new approach to HIV therapeutics in the UK. CHERUB will be the first pan-BRC cooperative project to compete internationally in one of the most exciting new fields of biomedical research.

Internationally recognised researchers from five BRCs are working together to provide a unique experimental medicine approach to new HIV therapeutic strategies. CHERUB will be the UK’s flagship in this field, bringing together, amongst others, clinicians, virologists, immunologists, molecular biologists and mathematical modellers under the NIHR umbrella.

The aim of the CHERUB collaboration is to:
- Develop and promote a coordinated NIHR-funded UK-wide response to the need to explore strategies targeting HIV eradication and remission.
- Create a NIHR-funded biobank of samples for use in scientific research by the collaborative CBRC parties, according to agreed study protocols.
- Undertake internationally competitive clinical and scientific research within a CBRC framework for sharing of data, resources and consumables.
- Seek external funding to support projects within CHERUB.

Follow CHERUB on Twitter: @ukcherub

Recent Posts
- Report in the Daily Telegraph on the Danish Panobinostat Study
- Towards an HIV cure: a global scientific strategy
- New approaches in HIV eradication research

Tweets from CHERUB

- “Cured of AIDS”? Not Yet. http://t.co /eHf4aceojg about 20 hours ago from Tweet Button
- CHERUB in the news: http://t.co /eAqg4vK2B8 about 1 day ago from web
- CHERUB at BHRVA2013 about 1 week ago from web
- We will be at the BHIVA annual meeting tomorrow in Manchester to discuss with UK clinicians how to advance HIV Cure research in the UK. about 2 weeks ago from web
- Fantastic to have held our first satellite meeting at BHIVA, and to be able to push forward the UK HIV cure agenda with this group. about 6 months ago from web
Acknowledgements

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• Kholoud Porter

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• The SPARTAC trial Investigators

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