Rationale for therapy at PHI

Immunological:
- Interfere with pathogenesis
- Preserve HIV-specific CD4+ T-help
- Reduce T-cell activation

Virological:
- Prevent or reduce seeding of reservoirs
- Affect viral set point

Epidemiological:
- Reduce infectivity and onward transmission
Natural history of HIV infection

- Acute:
  - Plasma viral load
  - HIV-specific CD8+ T cell response

- Chronic:
  - Peripheral blood CD4+ T cell count

Weeks

Years
Primming a T-cell response

- Antigen specific
- Activation threshold
- Effector responses
- Memory
- See antigen bound to self MHC by TcR
- Require cross linking of a minimum number of TcR-MHC-Ag complexes
Li et al., Nature 2005

"HIV swiftly guts the immune system"
Summary: Phylogenetic analysis of HIV-1 in early infection in the context of a model of random viral evolution allows for the identification of transmitted/early founder virus(es) responsible for productive clinical infection (Keele et al., PNAS 105: 7522, 2008).
Primary infection

Establishment of infection in lymphoid tissue

Lymph node

Massive viremia

Wide dissemination to lymphoid organs

HIV-specific immune response

Trapping of virus and establishment of chronic, persistent infection

Immune activation mediated by cytokines and HIV envelope-mediated aberrant cell signaling

Partial immunological control of virus replication

Accelerated virus replication

Rapid CD4+ T cell turnover

Destruction of immune system
Transit of HIV through the body

- Target cells CD4+ dendritic cells in genital tract mucosa
- Traffic to regional lymph nodes day 3
- Disseminate throughout body by 10 days
- Will infect and lie ‘dormant/latent’ for life span of that infected cell any CD4 bearing cell
Organs of the immune system:
Gut

HIV negative

60-80% loss memory
CD4+ T cells

Primary HIV
Green = memory CD4+ T cells
Red = Ki67+ cells

4 days after infection
10 days after infection

Li et al., Nature 2005

"HIV swiftly guts the immune system"
HIV pathogenesis

• CD4 T-cell help is required for optimal immune regulation and priming to new antigens (Kalams)
• HIV preferentially infects HIV-specific CD4+ T-cells (Douek)
• HIV-specific CD4+ T-cell function is lost early and not recovered despite immune reconstitution with later ART (Autran)
HIV-specific CD4+ T cells are preferentially infected by HIV.

Douek et al., Nature 2002

Frequency ratio between HIV and other memory CD4+ patient
Spontaneous loss of HIV-specific CD4+ T-helper cells at PHI

Fig. 1A

<table>
<thead>
<tr>
<th></th>
<th>S19A 16 DFOSx</th>
<th>S19B 22 DFOSx</th>
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<td>bac. ctrl.</td>
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(2.8x10^5/well)  (3.1x10^5/well)
Immune activation

Circulating CD4+ T-cells

Viremia

Mucosal CD4+ T-cells

4–8 weeks Acute
5–15 years Chronic
2–3 years AIDS

TRENDS in Microbiology
Can anything prevent/reverse this?

• ART intervention in PHI has been shown to induce vigorous HIV-specific CTL and CD4 T-cell responses which initially correlated with enhanced viraemic control and delayed immune destruction in an uncontrolled study (Rosenberg)

• BUT… the durability of this immune preservation is uncertain and the magnitude of such responses long-term did not predict viral control (N=14) (Kaufman)
Early highly active antiretroviral therapy for acute HIV-1 infection preserves immune function of CD8⁺ and CD4⁺ T lymphocytes


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Communicated by David Weatherall, University of Oxford, Oxford, United Kingdom, December 20, 1999 (received for review November 4, 1999)

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Immune control of HIV-1 after early treatment of acute infection


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What is the evidence?

- Randomised comparisons, \( n=5 \)
- Non-randomised comparisons, \( n=5 \)
- Uncontrolled studies, \( n=18 \)
- Rx at PHI vs chronic, \( n=3 \)
- Long term effect of Rx at PHI, \( n=2 \)
- Transient Rx at PHI, \( n=5 \)

D Smith, B Walker, D Cooper, E Rosenberg & J Kaldor. AIDS 2004; 18: 709-718
# Randomised trials at PHI

<table>
<thead>
<tr>
<th>PI</th>
<th>Regimen</th>
<th>n</th>
<th>f-up</th>
<th>VL</th>
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<tr>
<td>Placebo</td>
<td></td>
<td>38</td>
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<td>-0.85</td>
<td>+6</td>
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<td>Niu (1998)</td>
<td>ZDV</td>
<td>13</td>
<td>11.75</td>
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<td>+ &gt;200</td>
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<td>d4T,ddl,NVP</td>
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<td>PRIMO (2009)</td>
<td>TDF,FTC,EFV</td>
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<td>60</td>
<td></td>
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<tr>
<td>no treatment</td>
<td></td>
<td>23</td>
<td>60</td>
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D Smith et al., *AIDS* 2004
Limit disease progression
- the evidence

- Evidence
- Observational clinical trials (Kaufman, Walker, Smith, Fidler, Hecht, Jansen, Lampe, Streeck ACTGA57217) all have shown a trend towards enhanced CD4 count outcome off ART compared with no intervention but no significant viral load effect.

- RCT
  - Quest ART +/- vaccine showed no effect of vaccine enhancement,
  - SPARTAC 12, 48 weeks ART vs no therapy reports end 2010
  - PRIMO-semi randomised reported CROI 2009 enhanced CD4 benefit for 60 weeks after stopping ART

- No evidence of harm
- Rate of induced drug resistance within SPARTAC after ART in PHI is < 2%
When to treat?
How long after estimated HIV acquisition can ART help

- Early work focused on very acute HIV infection only (Rosenberg 2000, Kaufman 2004)

- More recent study compared acute (<14d) with early intervention (2-24 weeks) identified immunological benefit in both more if acute (Hecht 2006) these findings are supported by another study (Al-Harthi et al Clin Imm 2007 3 299-308)

- Primate models have suggested that very early ART could potentially delay the development of an HIV-specific immune response and could in fact be detrimental (Younes 2007)
Trial design

Randomisation

A 48 week long course ART (LCART)

B 12 week short course ART (SCART)

C No antiretroviral therapy

Main outcome: CD4 count <350 cells/µl on 2 occasions less than 4 weeks apart
Spartac Pilot: 2000-2004

Plan RCT of short course ART (SCART) at PHI, but....

• Is SCART safe? Tolerable? Adhered to?
• Will resistance be induced?
• How long is short?
• Does SCART need to reduce VL to <50 copies
• Which drugs?
• What happens when drugs are stopped?
• Will patients accept stopping SCART?
Pilot Study Endpoints

• **Primary Endpoint**
  • Measurement of HIV-specific CD4+ T-helper responses after SCART intervention up to 3 years off therapy

• **Secondary Endpoint**
  • Correlation between HIV-specific immune responses and clinical outcome
Pilot Study Results;
Cohort recruited

- n = 105 recruited 2000-2004 (St Mary’s Hosp)
- n = 15 untreated; n = 90 treated

- Median time from symptoms to diagnosis 78 range (12-98) days
- Median age 31 years (22-77)
- All UK acquired sexually transmitted infection
- 8% non-B clade
- Baseline CD4 550 (90-1480)
- Baseline viral load 4.94 log (1.78-7.20)
Cessation of HAART results in viral rebound
Viral rebound does not delete HIV-specific CD4+ T cells
Baseline prevalence of resistance

- $N = 105$
- Incidence dr-HIV 7%
  - Primary mutations in RT 4%
  - Primary mutations in PI 1%
  - MDR 2%
- Secondary mutations / polymorphisms mostly in protease $N = 58\%$ of these
  - $n = 4$ non-B clade ($n=2$ C, 1 A/G 1 A/E)
- Most commonly occurring polymorphism L63P, L10I, M36I,
- Majority persist > 6 months after diagnosis off SCART
- No increase in prevalence, 2000-2004
PHI resistance

N = 7/140  i.e. 5%
c.f. UK register, Brighton
Summary of Spartac Pilot

• Spartac pilot (n=105) suggests that:
  • SCART is safe, tolerable, acceptable
  • Preserves HIV-specific CD4+ T-cells
  • Does not induce resistance
  • Clinical significance uncertain

• Need for a RCT with no treatment arm….
Estimated average trends for CD4 cell count based on a common linear random effects model for CASCADE and SMH

All measurements censored until 6 months after stop of SCART
Estimated average trends for viral load levels on two separate nonlinear random effects models for CASCADE and SMH populations.

All SMH measurements prior to the end of SCART censored.
Primary study question

Does treatment of Primary HIV infection delay CD4 cell decline and consequently time to starting long-term anti-HIV therapy?
Secondary study questions

Does treatment of Primary HIV infection have an effect on:

- HIV-specific immune responses?
- Disease progression?
- Virological failure of long-term therapy?
- Drug resistance?
Immunology: protocol

- No HAART
- 12 weeks HAART
- 48 weeks HAART
The 5 criteria for PHI

1. HIV positive antibody test within 6-months of an HIV negative antibody test *(randomisation must take place within 6 months of previous negative test)*

2. HIV antibody negative with positive RT-PCR

3. Test “incident” at low level (<0.6) using detuned assay *(must be subtype B)*

4. Equivocal HIV antibody test supported by a repeat test within a 2-week period showing a rising optical density

5. Have clinical manifestations of symptomatic HIV seroconversion illness supported by antigen positivity and <4 bands positive on Western Blot
Clinical Sites and PIs

- **Rio de Janeiro, BR**: M Schechter
- **Sydney, Melbourne**: D Cooper
- **Cape Town**: D Woods
- **J'Burg**: H Rees
- **Durban**: G Ramjee
- **AC, KZN**: A-M Newell
- **AC, KZN**: A-M Newell
- **UK**: Sarah Fidler
- **Milan**: G Tambussi
- **Entebbe**: P Kaleebu
- **Spain**: Jose Melo
- **Dublin**: F Mulcahy
Fully recruited in 2008; 360 subjects
DSMB recommends study completes as planned
Minimum 3 years follow-up by end 2010
Unblinding planned for Q2, 2011
Only RCT of PHI still running.....
Principal Spartac UK Collaborators

**Imperial**
- Sarah Fidler
- Myra McClure

**Oxford**
- Rodney Phillips
- John Frater

**MRC CTU**
- Abdel Babiker
- Kholoud Porter