Early diagnosis and Primary HIV Infection

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MRC Clinical Trials Unit
Early HIV infection

- Active HIV replication at site of transmission
- Rapid dissemination to local lymphoid tissues
- Subsequent trafficking of HIV to gut-associated lymphoid tissue and entire body
- Resulting in high levels of HIV virions circulating in plasma rapidly disseminating to sanctuary reservoirs
- Control of HIV-specific immune response follows
**Definitions**

- **Acute infection**: until control of viraemia
  - ~4-6 weeks from infection
- **PHI**: within 6 months of SC??
- **Early infection**: within 12 months of SC
Importance of PHI

• Intervention at time may be best hope of long-lasting viral control
  ▪ Observational studies disagree on findings
  ▪ Two RCTs with viral set-point as end point abandoned
    ▪ SPARTAC (RCT of no Rx vs. 12 weeks vs. 48 weeks)

• Contribution to propagation of epidemic
  ▪ Extremely high viral load
  ▪ Characteristics of viral variants in PHI may be easier to transmit
  ▪ Lack of awareness of infection
CD4 cell decline following stopping 12-week cART (SMH)
HIV RNA changes following stopping 12-week cART (SMH)
Importance of PHI

• Intervention at time may be best hope of long-lasting viral control
  ▪ Observational studies disagree on findings
  ▪ Two RCTs with viral set-point as end point abandoned
  ▪ SPARTAC (RCT of no Rx vs. 12 weeks vs. 48 weeks)

• Contribution to propagation of epidemic
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  ▪ Characteristics of viral variants in PHI may be easier to transmit
  ▪ Lack of awareness of infection
HIV transmission rate by HIV RNA level of positive partner

![Graph showing transmission rate by HIV RNA level for different transmission types.](image)

**UK CAB Meeting**

**9th July 2010**
Log HIV RNA at first presentation by time since seroconversion

Time from seroconversion to first viral load test:

- 0-1 week (n=95)
- 1 week - 1 month (n=90)
- 1-3 months (n=197)
- 3-6 months (n=277)
- 6-12 months (n=231)
- Over 12 months (n=129)
- Overall (n=1019)

Legend:
- <2.7 (undetectable)
- 2.69-3.99
- 4.00-4.69
- 4.70-4.99
- ≥ 5.00
HIV RNA levels upon cessation of cART in PHI and CHI

Median VL, log10 copies/ml (IQR; log scale)

Time since ART stop, weeks

Pre ART 0 8 16 24 32 40 48

CHI (SMART)

PHI (SPARTAC)
Why Seroconverters?

- Follow-up data allow us to relate events to the same time since an individual first became infected with HIV
- A unique opportunity to study HIV throughout its whole infection period
- Allow us to examine characteristics of recently acquired HIV infection in population, and changes to this over time
- Aiming towards early diagnosis: seroconverters represent what may be achieved optimally
- Relatively few in any one clinic/study- ideal for collaboration
UK Register of HIV Seroconverters and CASCADE

- **UK Register**
  - >2500 individuals with well-estimated dates of HIV seroconversion from 116 UK clinics
  - MRC baseline funding

- **CASCADE**
  - Collaboration of 25 partner organisations from 15 European countries, Australia and Canada
  - EU FP7 funding of EuroCoord NoE (5 years)
CASCADE partner countries
## Estimated adult (15-49 years) HIV prevalence

<table>
<thead>
<tr>
<th>Country</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ukraine, Estonia, Russia</td>
<td>1.1 - 1.4</td>
</tr>
<tr>
<td>Italy, Spain</td>
<td>0.5 - 0.6</td>
</tr>
<tr>
<td>France, Portugal, Switzerland</td>
<td>0.4</td>
</tr>
<tr>
<td>UK, Greece, Denmark, Netherlands</td>
<td>0.2</td>
</tr>
<tr>
<td>Germany, Norway, Poland</td>
<td>0.1</td>
</tr>
<tr>
<td>Canada</td>
<td>0.3</td>
</tr>
<tr>
<td>Australia</td>
<td>0.1</td>
</tr>
</tbody>
</table>
## Participating cohorts

<table>
<thead>
<tr>
<th>Sydney AIDS Prospective Study</th>
<th>German Cohort</th>
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<tbody>
<tr>
<td>Sydney Primary HIV Infection cohort</td>
<td>Danish HIV Cohort</td>
</tr>
<tr>
<td>Greek Haemophilia Cohort</td>
<td>Aquitaine Cohort</td>
</tr>
<tr>
<td>Italian Seroconversion Study</td>
<td>SEROCO Cohort</td>
</tr>
<tr>
<td>Oslo and Ulleval Hospital Cohorts</td>
<td>Madrid Cohort</td>
</tr>
<tr>
<td>Lyon Primary Infection Cohort</td>
<td>Valencia IDU Cohort</td>
</tr>
<tr>
<td>French Hospitals Database on HIV</td>
<td>Swiss HIV Cohort Study</td>
</tr>
<tr>
<td>Amsterdam Cohort Studies</td>
<td>Barcelona IDU Cohort</td>
</tr>
<tr>
<td>Edinburgh Hospital Cohort</td>
<td>Primo Cohort</td>
</tr>
<tr>
<td>Badalona IDU Hospital Cohort</td>
<td>IcONA cohort</td>
</tr>
<tr>
<td>Royal Free Haemophilia Cohort</td>
<td>UK Register of HIV Seroconverters</td>
</tr>
</tbody>
</table>
Estimated HIV survival 1979-1996

By age at seroconversion

CASCADE. Lancet 2000;355:1131-7
CD4 and HIV RNA by time since HIV seroconversion

Touloumi G et al. AIDS 2004;18:1697-1705
## Average CD4 loss over time since HIV seroconversion

<table>
<thead>
<tr>
<th>Age at SC CD4</th>
<th>2 yrs</th>
<th>5 yrs</th>
<th>5 yrs</th>
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<tbody>
<tr>
<td>loss/yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-20</td>
<td>500</td>
<td>350</td>
<td>50</td>
</tr>
<tr>
<td>21-30</td>
<td>490</td>
<td>310</td>
<td>60</td>
</tr>
<tr>
<td>31-40</td>
<td>470</td>
<td>270</td>
<td>65</td>
</tr>
<tr>
<td>&gt;40</td>
<td>440</td>
<td>250</td>
<td>63</td>
</tr>
</tbody>
</table>
Mean HIV-RNA trajectories by sex and exposure group

HIV RNA levels (log10 copies/ml) vs. Years since seroconversion

- Homosexual men
- Heterosexual & IDU men
- Haemophiliacs
- Heterosexual women
- IDU women

AIDS 2004;18:1697-1705
Changes in risk of death following HIV seroconversion in UK

Ewings F et al. AIDS 2008;22:89-95
Proportion surviving 10 years following SC 2002-2006 in UK

Years since seroconversion

Proportion surviving

Age (yrs) Proportion surviving 10 yrs from SC

15 - 24 0.94
25 - 34 0.95
35 - 44 0.93
45+ 0.83

Ewings F et al. AIDS 2008;22:89-95
### Excess deaths over calendar time

<table>
<thead>
<tr>
<th>Calendar period</th>
<th>Person-years of follow-up</th>
<th>Observed deaths (n=2475)</th>
<th>Expected deaths (n=226)</th>
<th>Excess deaths</th>
<th>Mortality rate/1000 PY</th>
<th>Excess mortality rate/1000 PY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-1996</td>
<td>30 228</td>
<td>1290</td>
<td>54.3</td>
<td>1235.7</td>
<td>42.7</td>
<td>40.9</td>
</tr>
<tr>
<td>1996-97</td>
<td>13 978</td>
<td>463</td>
<td>27.5</td>
<td>435.5</td>
<td>33.1</td>
<td>31.2</td>
</tr>
<tr>
<td>1998-99</td>
<td>16 136</td>
<td>220</td>
<td>32.2</td>
<td>187.8</td>
<td>13.6</td>
<td>11.6</td>
</tr>
<tr>
<td>2000-01</td>
<td>17 613</td>
<td>205</td>
<td>37.7</td>
<td>167.3</td>
<td>11.6</td>
<td>9.5</td>
</tr>
<tr>
<td>2002-03</td>
<td>16 679</td>
<td>180</td>
<td>39.5</td>
<td>140.5</td>
<td>10.8</td>
<td>8.4</td>
</tr>
<tr>
<td>2004-06</td>
<td>13 695</td>
<td>117</td>
<td>35.1</td>
<td>81.9</td>
<td>8.5</td>
<td>6.0</td>
</tr>
</tbody>
</table>

Bhaskaran B et al. — *JAMA* 2008;300:51-9
All-cause mortality pre-1996 and 2004-06 (sexual exposure only)

Estimated cumulative mortality

Time since seroconversion (years)

Pre-1996 (HIV infected)

2004-2006 (HIV infected)

2004-2006 (uninfected)

<45 years at seroconversion

45+ years at seroconversion

Bhaskaran B et al. JAMA 2008;300:51-9
Should a clinician take account of CD4 decline when initiating cART?

• Treatment guidelines recommend initiating at CD4 350 (USA >500)

• Initiate earlier if CD4 decline rapid:
  ▪ >100 cells/year lost (IAS)
  ▪ >50-100 cells/year lost (EACS)
Abstract

Background: CD4 cell count is a strong predictor of the subsequent risk of AIDS or death in HIV-infected patients initiating combination antiretroviral therapy (cART). It is not known whether the rate of CD4 cell decline prior to therapy is related to prognosis and should, therefore, influence the decision on when to initiate cART.

Methods and Findings: We carried out survival analyses of patients from the 23 cohorts of the CASCADE (Concerted Action on SeroConversion to AIDS and Death in Europe) collaboration with a known date of HIV seroconversion and with at least two CD4 measurements prior to initiating cART. For each patient, a pre-cART CD4 slope was estimated using a linear mixed effects model. Our primary outcome was time from initiating cART to a first new AIDS event or death. We included 2,820 treatment-naïve patients initiating cART with a median (interquartile range) pre-cART CD4 cell decline of 51 (46–61) cells/µl per year; 255 patients subsequently experienced a new AIDS event or death and 125 patients died. In an analysis adjusted for established risk factors, the hazard ratio for AIDS or death was 1.01 (95% confidence interval 0.97–1.04) for each 10 cells/µl per year reduction in pre-cART CD4 cell decline. There was also no association between pre-cART CD4 cell slope and survival. Alternative estimates of CD4 cell slope gave similar results. In 1,731 AIDS-free patients with >350 CD4 cells/µl from the pre-cART era, the rate of CD4 cell decline was also not significantly associated with progression to AIDS or death (hazard ratio 0.99, 95% confidence interval 0.94–1.03, for each 10 cells/µl per year reduction in CD4 cell decline).

Conclusions: The CD4 cell slope does not improve the prediction of clinical outcome in patients with a CD4 cell count above 350 cells/µl. Knowledge of the current CD4 cell count is sufficient when deciding whether to initiate cART in asymptomatic patients.

Please see later in the article for the Editors’ Summary.
### Specific causes and most recent CD4 and HIV RNA

<table>
<thead>
<tr>
<th></th>
<th>Cause specific relative hazard (95% CI)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AIDS-related malignancy</td>
<td>Non-AIDS related malignancy</td>
</tr>
<tr>
<td>Pre-HAART CD4</td>
<td>0.80 (0.77- 0.83)</td>
<td>0.89 (0.85- 0.94)</td>
</tr>
<tr>
<td>Post HAART CD4</td>
<td>0.81 (0.77- 0.86)</td>
<td>0.86 (0.81- 0.92)</td>
</tr>
<tr>
<td>Pre-HAART HIV RNA</td>
<td>1.26 (0.64- 2.45)</td>
<td>1.38 (0.62- 3.09)</td>
</tr>
<tr>
<td>Post HAART HIV RNA</td>
<td>1.70 (1.20- 2.42)</td>
<td>1.27 (0.91- 1.78)</td>
</tr>
</tbody>
</table>

 CASCADE. AIDS 2006;20:741-9
Association between risk of death and CD4 cell count

- All causes of death: 0.36 (0.31-0.42)
- AIDS-defining: 0.68 (0.56-0.82)
- Non-AIDS infection: 0.68 (0.56-0.82)
- Liver disease: 0.67 (0.54-0.82)
- Non-AIDS cancer: 0.66 (0.55-0.79)
- Cardiovascular disease: 0.86 (0.73-1.02)
- Violent cause: 1.10 (1.00-1.20)
- Substance abuse: 0.77 (0.64-0.94)
- Respiratory Disease: 0.56 (0.41-0.76)
- Other medical cause: 0.69 (0.58-0.83)

Marin B et al. AIDS 2009;23:1743-53

UK CAB Meeting

9th July 2010
Future plans
CASCADE research focus

- Addressing areas related to early infection and research questions requiring knowledge of time of HIV seroconversion
  - Detection of early infection
  - Characterisation of newly-infected populations
  - Monitoring outcome
  - Assessing determinants of outcome
    - HIV-related
    - Host-related (including genetic)
    - HCV
    - Socio-economic factors
Detecting early infection

- Work being undertaken in collaboration with HPA, UCL and partners in Ukraine, Estonia and Poland
- Developing transferable assay for differentiating incident from chronic infection
- Assessing its performance in population and in pregnant women
- Estimating HIV incidence
- Assessing factors related to seroconversion in pregnancy
Characterising new infections

Phylogenetic analyses of pol sequences linking with CHAIN:
• Provide picture of new infections across Europe
• Assess extent to which new infections occur within transmission networks and characterise
• Assess differences between clustered and non-clustered individuals
• Assess proportion of acutely infected involved in ongoing transmission

Why important?
• insight into factors responsible for spread of epidemic and characteristics within clusters
• crucial to design of effective prevention strategies
• prerequisite to considering whether to intervene during primary infection is an effective public health strategy
Outcome and its determinants

- Ongoing monitoring of changes in survival as new regimens and strategies introduced
- Impact of viral tropism of strains in PHI on disease course and factors related to co-receptor usage
- GWA study to identify host factors related to outcome
- Examine and compare associations for people infected in different calendar periods
- Compare disease progression between Europeans and: Africans in Europe, Africans in Africa
- Effect of HCV on HIV progression- HIV predating HCV seroconversion
UK Register directions

- Monitor survival and outcome: what can be achieved optimally
- Consequences of initiating cART in PHI
- Changes in behaviour and attitudes to therapy over time following seroconversion: altruistic acceptability of starting cART
- Devising predictions of who will do well-monitoring frequency
- New intervention studies in PHI?
Thank you- UK Register

- **Steering Committee**: A Phillips (Chair), A Babiker, R Brettle, J Darbyshire, V Delpech, P Easterbrook, S Fidler, M Fisher, R Gilson, D Goldberg, D Hawkins, H Jaffe, A Johnson, K McLean, D Pillay

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- **Clinical Advisory Board:** Heiner Bucher, Andrea de Luca, Martin Fisher, Roberto Muga

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