Community feedback: START study

Simon Collins
HIV i-Base
www.i-Base.info
Type of evidence

• Observational databases
  Can report associations but not prove that one thing is the cause of another.
  Can never fully account for “confounding” – where something that is either known or not known might explain the results.

• Randomised controlled trials
  The randomisation equally distributes known and unknown factors linked to the outcome.
HIV positive people, ART-naïve with CD4+ count > 500

Early ART
Initiate ART immediately following randomization (N=2,000)

Deferred ART
Defer ART until the CD4+ count declines to < 350 or AIDS (N=2,000)

Follow until 370 endpoints reached
START timeline

Dec 2009 – First US patients enrol (pilot)
April 2010 – Broader enrollment
2009-2015 – 10 Annual DSMB safety reports
https://insight.ccbr.umn.edu/start/index.php
May 2013 – Events reduced from 370 to 213
plus 600 more pts aged > 45 yo.
April 2014 – Fully enrolled
Dec 2016 – Expected close date
May 2015 – Study stopped – after 127 events
START key results

• ART was safe at high CD4 counts. Many people (20%) had CD4 >800.
• Early ART reduced serious AIDS-related illnesses, even at high CD4 counts.
• Little impact on heart, liver, kidney disease and non-AIDS cancers.
• Similar results in both low- and high-income countries.
• Dataset and sub studies will follow.
Combined endpoints

START had three ways of defining serious AIDS and non-AIDS events.
1. The combined endpoint of AIDS, serious non-AIDS or death.
2. The combined endpoint of AIDS or death.
3. The combined endpoint of serious non-AIDS events or non-AIDS related deaths.
Primary endpoints.1

Table 1a. Number of primary endpoints in each arm (15 May 2015)

<table>
<thead>
<tr>
<th>Category</th>
<th>Early arm (A)</th>
<th>Later arm (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1: AIDS, serious non-AIDS, or death (primary).</td>
<td>41</td>
<td>86</td>
</tr>
<tr>
<td>Category 2: AIDS or AIDS death.</td>
<td>14</td>
<td>46</td>
</tr>
<tr>
<td>Category 3: Serious non-AIDS or non-AIDS death.</td>
<td>28</td>
<td>41</td>
</tr>
</tbody>
</table>

* PY = patient years, ** NS = not statistically significant
### Primary endpoints.2

<table>
<thead>
<tr>
<th>Category 1: AIDS, serious non-AIDS, or death (primary).</th>
<th>Rate per 100 PY</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early arm (A)</td>
<td>0.60</td>
<td>0.47 (0.32 to 0.68)</td>
</tr>
<tr>
<td>Late arm (B)</td>
<td>1.25</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category 2: AIDS or AIDS death.</th>
<th>Rate per 100 PY</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early arm (A)</td>
<td>0.20</td>
<td>0.30 (0.17 to 0.55)</td>
</tr>
<tr>
<td>Late arm (B)</td>
<td>0.66</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category 3: Serious non-AIDS or non-AIDS death.</th>
<th>Rate per 100 PY</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early arm (A)</td>
<td>0.41</td>
<td>0.67 (0.42 to 1.09)</td>
</tr>
<tr>
<td>Late arm (B)</td>
<td>0.59</td>
<td>NS **</td>
</tr>
</tbody>
</table>

* PY = patient years, ** NS = not statistically significant
Who was in START

- 1685 people in 35 countries at 211 sites
- Median age 36 (IQR: 29 to 41), range 18 to 81.
- ~ 25% women and ~ 50% gay men
- 33% of participants in Europe, 25% in South America or Mexico, 21% in Africa, 11% in the US, 8% in Asia and 2% in Australia.
- Med CD4: 651 (IQR: 584-765; range 503 to 2296).
- Med VL: 12,000 c/mL (IQR: 3,000 to 40,000), 8% <400 copies/mL.
Medical at baseline

- ~30% were current smokers
- ~50% had half had at least one cardiovascular risk based on the Framingham calculator
- ~20% hypertension or HT treatment treatment
- 8% either had high blood lipids treatment.
- 3% had diabetes or related.
- 2.9% HBV and 3.7% HCV.
- 3% alcohol or substance use issues
- 6% had a psychiatric diagnosis (including depression, bipolar and other conditions).
Sub studies

• Neurological function
• Bone health
• COPD (chronic obstructive pulmonary disease).
• Genomics – single sample
• Arterial elasticity
• Liver fibrosis

Also:
• Monitoring (sites)
• Informed consent (short vs long)
Implications

- CD4 threshold is no longer criterion for ART.
- How to interpret absolute risk when resources are limited.
- Linking treatment and TasP
- Already included in draft BHIVA guidelines
- Potential in WHO guidelines
- Your conclusions?
BHIVA guidelines

• Comments back by Friday 17 July
• When to start: irrespective of CD4
• What to start – changes for efavirenz, Atripla, rilpivirine, Eviplera, lopinavir, fosamprenavir, nevirapine etc. 3TC vs FTC.
• Primary HIV infection
• When to change
• Special populations
Thanks