Effect on transmission of HIV-1 resistance of timing of implementation of viral load monitoring to determine switches from first to second line antiretroviral regimens in resource-limited settings.

Supplementary Results 1.

Synthesis model of progression of HIV and the effect of ART (V4a). Model fit. April 2009

The following provides some further details of the comparisons of the fit to observed data of the original model of HIV progression and the effect of ART. This original model was used to provide the part of the model relating to prognosis and the effect of ART.
Table 1. Incubation period to CD4 200, AIDS and death from seroconversion (no ART)

<table>
<thead>
<tr>
<th>Year from s/c</th>
<th>% with AIDS Observed(^1)</th>
<th>% died observed(^1)</th>
<th>% CD4 &lt; 200 observed(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.6</td>
<td>0.1</td>
<td>0.3</td>
</tr>
<tr>
<td>2</td>
<td>2.0</td>
<td>0.8</td>
<td>1.4</td>
</tr>
<tr>
<td>3</td>
<td>4.3</td>
<td>2.9</td>
<td>3.1</td>
</tr>
<tr>
<td>4</td>
<td>8.1</td>
<td>6.8</td>
<td>5.8</td>
</tr>
<tr>
<td>5</td>
<td>13.4</td>
<td>12.1</td>
<td>9.8</td>
</tr>
<tr>
<td>6</td>
<td>19.8</td>
<td>18.4</td>
<td>14.8</td>
</tr>
<tr>
<td>7</td>
<td>25.9</td>
<td>25.8</td>
<td>20.5</td>
</tr>
<tr>
<td>8</td>
<td>32.3</td>
<td>33.6</td>
<td>27.0</td>
</tr>
<tr>
<td>9</td>
<td>38.8</td>
<td>41.3</td>
<td>33.8</td>
</tr>
<tr>
<td>10</td>
<td>46.1</td>
<td>48.0</td>
<td>40.5</td>
</tr>
<tr>
<td>11</td>
<td>53.0</td>
<td>54.1</td>
<td>48.3</td>
</tr>
<tr>
<td>12</td>
<td>58.1</td>
<td>58.8</td>
<td>55.4</td>
</tr>
<tr>
<td>13</td>
<td>63.0</td>
<td>62.9</td>
<td>62.4</td>
</tr>
</tbody>
</table>

Table 2. Viral load set point and initial CD4 count (after primary infection)

<table>
<thead>
<tr>
<th></th>
<th>Observed(^3)</th>
<th>Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median VL set point:</td>
<td>4.5</td>
<td>4.0</td>
</tr>
<tr>
<td>Median CD4:</td>
<td>570</td>
<td>681</td>
</tr>
</tbody>
</table>

Table 3. Incubation period AIDS to death (pre-ART era)

<table>
<thead>
<tr>
<th>Years from AIDS diagnosis</th>
<th>% died observed(^4)</th>
<th>model</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40%</td>
<td>45%</td>
</tr>
<tr>
<td>3</td>
<td>84%</td>
<td>76%</td>
</tr>
</tbody>
</table>

median 17 mths 15 mths
Table 4. Association between viral load measured close to seroconversion (between 6-24 months) and risk of AIDS, adjusting for CD4 count and age. Observed data from ref 5.

<table>
<thead>
<tr>
<th>Observed Relative Hazard</th>
<th>Adjusted Relative Hazard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral load 1.87 (1.58 – 2.20)</td>
<td>1.76</td>
</tr>
<tr>
<td>(Per 0.5 log higher)</td>
<td></td>
</tr>
<tr>
<td>CD4 count 1.12 (1.02 – 1.24)</td>
<td>1.08</td>
</tr>
<tr>
<td>(Per 100 cells/mm³ higher)</td>
<td></td>
</tr>
<tr>
<td>Age 1.19 (0.96 – 1.47)</td>
<td>1.15</td>
</tr>
<tr>
<td>(Per 10 years older)</td>
<td></td>
</tr>
</tbody>
</table>

Table 5. Risk of AIDS by CD4 count and viral load and age over 6 years (pre-HAART)

<table>
<thead>
<tr>
<th>CD4</th>
<th>Observed⁶</th>
<th>Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 &lt; 350</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral load ≤ 1500 - (low n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1501- 7000</td>
<td>19</td>
<td>52</td>
</tr>
<tr>
<td>7001- 20000</td>
<td>42</td>
<td>72</td>
</tr>
<tr>
<td>20001- 55000</td>
<td>73</td>
<td>83</td>
</tr>
<tr>
<td>&gt; 55000</td>
<td>92</td>
<td>93</td>
</tr>
<tr>
<td>CD4 350-500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral load ≤ 1500 - (low n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1501- 7000</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>7001- 20000</td>
<td>40</td>
<td>50</td>
</tr>
<tr>
<td>20001- 55000</td>
<td>57</td>
<td>70</td>
</tr>
<tr>
<td>&gt; 55000</td>
<td>78</td>
<td>86</td>
</tr>
<tr>
<td>CD4 &gt; 500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral load ≤ 1500 - (low n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1501- 7000</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>7001- 20000</td>
<td>26</td>
<td>16</td>
</tr>
<tr>
<td>20001- 55000</td>
<td>48</td>
<td>38</td>
</tr>
<tr>
<td>&gt; 55000</td>
<td>67</td>
<td>69</td>
</tr>
</tbody>
</table>

* Viral load values used in MACS may need to be multiplied by ~ 2 to approximate to more commonly used Roche assay levels.
Table 6. Median CD4 count at diagnosis of AIDS and at death (pre-HAART era)

<table>
<thead>
<tr>
<th>AIDS</th>
<th>death</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observed:</strong></td>
<td>~ 40</td>
</tr>
<tr>
<td><strong>Model:</strong></td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>

Table 7. 3 year percent risk of AIDS after start of ART by baseline CD4 / viral load (age < 50, non-IDU, AIDS-free)

<table>
<thead>
<tr>
<th>Baseline viral load &lt; 100,000</th>
<th>Observed</th>
<th>Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline CD4 count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>50 - 99</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>100 - 199</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>200- 349</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>&gt; 350</td>
<td>3</td>
<td>8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline viral load ≥ 100,000</th>
<th>Observed</th>
<th>Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline CD4 count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>50 - 99</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>100 - 199</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>200- 349</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>&gt; 350</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 8. Effect of HAART vs no therapy on risk of AIDS and death

Simulated trial with 5 years follow up
Relative hazard of AIDS (HAART vs no therapy)

<table>
<thead>
<tr>
<th>Observed</th>
<th>Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.10</td>
<td>0.11</td>
</tr>
</tbody>
</table>
Table 9. % with virologic failure (viral load > 500 copies/mL / on ART) by time from start of HAART (patients starting with PI/r or NNRTI regimen). Observed data from ref 10.

<table>
<thead>
<tr>
<th>Years from start of HAART</th>
<th>obs</th>
<th>mod</th>
<th>obs</th>
<th>mod</th>
<th>obs</th>
<th>mod</th>
<th>obs</th>
<th>mod</th>
<th>obs</th>
<th>mod</th>
<th>obs</th>
<th>mod</th>
<th>obs</th>
<th>mod</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7%</td>
<td>8%</td>
<td>14%</td>
<td>15%</td>
<td>18%</td>
<td>20%</td>
<td>21%</td>
<td>23%</td>
<td>23%</td>
<td>25%</td>
<td>26%</td>
<td>28%</td>
<td>27%</td>
<td>29%</td>
</tr>
</tbody>
</table>

*Observed data may be overestimates due to some unrecognised stopping of ART

Table 10. Rate of viral rebound in people on 1st line HAART and with viral load < 50 copies/mL

<table>
<thead>
<tr>
<th>Rate per person year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed: 3-6</td>
</tr>
<tr>
<td>Model: 5.8</td>
</tr>
</tbody>
</table>

Table 11. Median CD4 count change at 3 years from start of HAART

| Observed: 273 |
| Model: 270 |

Table 12. Viral load response to second line HAART

% with virologic failure (viral load > 500 copies/mL and on ART)

<table>
<thead>
<tr>
<th>Years from start of second line HAART</th>
<th>obs</th>
<th>mod</th>
<th>obs</th>
<th>mod</th>
<th>obs</th>
<th>mod</th>
<th>obs</th>
<th>mod</th>
</tr>
</thead>
<tbody>
<tr>
<td>(modelled includes those with nucs before HAART)</td>
<td>32%</td>
<td>32%</td>
<td>42%</td>
<td>46%</td>
<td>49%</td>
<td>51%</td>
<td>56%</td>
<td>56%</td>
</tr>
</tbody>
</table>

Observed data from CHIC (unpublished)
### Table 13. Discontinuation of drugs in initial HAART regimen

Time from start of ART to discontinuation of at least one drug in initial regimen (discontinuation for any reason)

<table>
<thead>
<tr>
<th>Years from start of HAART</th>
<th>Observed Data</th>
<th>Modelled Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30%</td>
<td>32%</td>
</tr>
<tr>
<td>2</td>
<td>45%</td>
<td>47%</td>
</tr>
<tr>
<td>3</td>
<td>62%</td>
<td>59%</td>
</tr>
<tr>
<td>4</td>
<td>73%</td>
<td>67%</td>
</tr>
</tbody>
</table>

### Table 14. Percent with triple class virologic failure by years from start of HAART (patients naïve before HAART)

Observed data from ref 14. Modelled estimates based on ART start years 1997-2003 inclusive

<table>
<thead>
<tr>
<th>Years from start of HAART</th>
<th>Observed Data</th>
<th>Modelled Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>3</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>4</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>5</td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td>6</td>
<td>12%</td>
<td>10%</td>
</tr>
</tbody>
</table>

### Table 15. Triple class failure (those with triple class failure before 2001, as in PLATO paper)

% ever previously with viral load < 500

<table>
<thead>
<tr>
<th>% ever previously with viral load &lt; 500</th>
<th>Observed</th>
<th>Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed&lt;sup&gt;15&lt;/sup&gt;</td>
<td>50%</td>
<td>67%</td>
</tr>
</tbody>
</table>

At time of triple class failure:-

<table>
<thead>
<tr>
<th>At time of triple class failure:</th>
<th>Observed&lt;sup&gt;15&lt;/sup&gt;</th>
<th>Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (IQR) viral load:</td>
<td>4.5 (3.9 - 5.0)</td>
<td>4.2 (3.6 - 4.7)</td>
</tr>
<tr>
<td>Median (IQR) CD4:</td>
<td>199 (97 - 340)</td>
<td>137 (44 - 259)</td>
</tr>
<tr>
<td>Median (IQR) CD4 nadir:</td>
<td>65 (17 - 169)</td>
<td>41 (0 - 98)</td>
</tr>
<tr>
<td>Duration of ART (years):</td>
<td>4.7 (3.2 - 6.7)</td>
<td>5.5 (4.3 - 8.0)</td>
</tr>
<tr>
<td>% starting ART with &gt; 3 drugs</td>
<td>15%</td>
<td>22%</td>
</tr>
</tbody>
</table>
Table 16. Risk of resistance mutations (and virologic failure) after start of ART (patients starting with PI/r or NNRTI regimen)

<table>
<thead>
<tr>
<th>Years from start of HAART</th>
<th>% with at least one resistance mutation (and virologic failure)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>observed data from ref 10.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Observed data underestimates because resistance tests not always performed at virologic failure.</td>
</tr>
</tbody>
</table>

Table 17. % with at least one resistance mutation for all three main classes (and virologic failure)

<table>
<thead>
<tr>
<th>Years from start of HAART</th>
<th>% with at least one resistance mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>observed data from ref. 16.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 18. Risk of resistance mutations after start of ART *

<table>
<thead>
<tr>
<th>% with at least one resistance mutation</th>
<th>Years from start of HAART</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 obs</td>
</tr>
<tr>
<td>M184V mutation (in those starting with 3TC)</td>
<td>6%</td>
</tr>
<tr>
<td>TAM (in those starting with zdv or d4T)</td>
<td>4%</td>
</tr>
<tr>
<td>PI mutation (in those starting with boosted PI regimen)</td>
<td>3%</td>
</tr>
<tr>
<td>NNRTI mutation (in those starting with NNRTI regimen)</td>
<td>8%</td>
</tr>
</tbody>
</table>

*Observed data are likely to be under-estimates as resistance testing is not always performed at virologic failure.
Table 19. Risk of death after triple class resistance

% dead by 3 years (for people with TCR up to 2004.5)

<table>
<thead>
<tr>
<th></th>
<th>Observed</th>
<th>model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12%</td>
<td>20%</td>
</tr>
</tbody>
</table>

Table 20. Risk of death after triple class virologic failure
(observed data from ref. 15).

Years from triple class failure (Triple class failure occurring before 2002)

<table>
<thead>
<tr>
<th></th>
<th>1 obs</th>
<th>2 obs</th>
<th>3 obs</th>
<th>4 obs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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</tbody>
</table>

<p>| | | | | |</p>
<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>10%</th>
<th>17%</th>
<th>15%</th>
<th>21%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5%</td>
<td>9%</td>
<td>17%</td>
<td>24%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>27%</th>
</tr>
</thead>
</table>
REFERENCES


