The Development of AntiRetroviral Therapy in Africa (DART) trial

Comparison of routine vs clinically driven laboratory monitoring in HIV-infected African adults over 5 years on ART: Final results of the DART trial

Peter Mugyenyi on behalf of the DART Trial Team
Main objective of DART

• To evaluate the need for routine laboratory monitoring of ART
  - in African adults who fulfilled clinical and CD4 criteria for ART initiation
  - in terms of clinical effectiveness, safety and costs

• Primary endpoints
  - **Efficacy**: new WHO stage 4 HIV event (AIDS) or death
  - **Safety**: any Serious Adverse Event which is not only HIV-related
Trial design

3316 ART-naive adults with stage WHO 2, 3 or 4 HIV disease, CD4<200 cells/mm³ initiating triple drug ART

Laboratory and Clinical Monitoring (LCM)
12 weekly biochemistry, FBC & CD4

Other investigations & concomitant medications if clinically indicated

Switch to second-line for
- new/recurrent WHO 4
  (or multiple WHO 3)
- CD4<100 cells/mm³

Clinically Driven Monitoring (CDM)
12 weekly biochemistry, FBC & CD4,
FBC & biochemistry only returned if clinically indicated
(or grade 4 toxicity);
CD4 never returned

Other investigations & concomitant medications if clinically indicated

Switch to second-line for new/recurrent WHO 4
(or multiple WHO 3)

As per WHO guidelines, switching before 48 weeks discouraged in both arms
Trial status

- 6578 patients screened
- 3316 patients randomised to CDM or LCM
  - between 15 January 2003 and 28 October 2004

- Final data to 31 December 2008 (max 6, median 4.9 years)
  - during Jan 2009, all laboratory tests returned to CDM participants
  - participants transitioned care into Ugandan and Zimbabwean national ART programmes (except those in second-line studies)
  - results of second-line studies expected early 2010
# Characteristics at baseline (ART initiation)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LCM N=1656</th>
<th>CDM N=1660</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>1092  66%</td>
<td>1064  64%</td>
</tr>
<tr>
<td>Age (years) median (range)</td>
<td>36  (18-67)</td>
<td>36  (18-73)</td>
</tr>
<tr>
<td>CD4 count (cells/mm³) median</td>
<td>86  (0-199)</td>
<td>86  (1-199)</td>
</tr>
<tr>
<td>&lt;50 cells/mm³</td>
<td>554   33%</td>
<td>555   33%</td>
</tr>
<tr>
<td>HIV-1 RNA (log₁₀ copies/ml) mean (SD)*</td>
<td>5.4  (0.7)</td>
<td>5.4  (0.7)</td>
</tr>
<tr>
<td>WHO stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>363   22%</td>
<td>310   19%</td>
</tr>
<tr>
<td>3</td>
<td>916   55%</td>
<td>948   57%</td>
</tr>
<tr>
<td>4</td>
<td>377   23%</td>
<td>402   24%</td>
</tr>
<tr>
<td>On cotrimoxazole before/at ART initiation</td>
<td>1014  61%</td>
<td>1034  62%</td>
</tr>
<tr>
<td>ART: ZDV+3TC plus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF</td>
<td>1232   74%</td>
<td>1237   75%</td>
</tr>
<tr>
<td>ABC</td>
<td>150    9%</td>
<td>123    9%</td>
</tr>
<tr>
<td>NVP</td>
<td>274    16%</td>
<td>273    16%</td>
</tr>
<tr>
<td>Identified at any time (including post-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline) as having previously received</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ART</td>
<td>65    4%</td>
<td>65    4%</td>
</tr>
<tr>
<td>Previous ART for MTCT (% of women)</td>
<td>23    2%</td>
<td>38    4%</td>
</tr>
</tbody>
</table>

* assayed in a subset (N=968) at baseline only
Follow-up

- Median follow-up to 31 December 2008 4.9 years (IQR 4.5-5.3)
  - 14,937 person-years
  - 236 (7%) lost to follow-up
  - 98% and 99% of expected nurse and doctor visits attended
  - high patient-reported adherence

Blinding of laboratory test results in the CDM arm

- Few CDM participants sought external CD4 counts
  - clinicians remained blinded
  - at DART exit, 81/1281 (6%) reported having CD4s done privately
    - 43/81 had 1 CD4 test only
    - 3/81 had 6 or more
Adverse events

Proportion event-free

Years from randomisation (ART initiation)

SAE p=0.20
ART-modifying AE p=0.85
Grade 4 AE p=0.18
Grade 3/4 AE p=0.52

IAS July 2009
## Antiretroviral therapy

### At last follow-up/31 December 2008

<table>
<thead>
<tr>
<th></th>
<th>LCM N=1656</th>
<th>CDM N=1660</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Remained on first-line</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- still taking original first-line regimen</td>
<td>1014 (61%)</td>
<td>1059 (64%)</td>
</tr>
<tr>
<td>- substituted CBV only</td>
<td>113 (7%)</td>
<td>98 (6%)</td>
</tr>
<tr>
<td>- substituted third drug (±CBV)</td>
<td>162 (10%)</td>
<td>179 (11%)</td>
</tr>
<tr>
<td>- off ART for &gt;90 days</td>
<td>6 (0.4%)</td>
<td>10 (0.6%)</td>
</tr>
<tr>
<td><strong>Had switched to second-line</strong></td>
<td>361 (22%)</td>
<td>314 (19%)</td>
</tr>
</tbody>
</table>
Switch to second-line

Proportion switched to second-line (cumulative incidence)

HR(CDM:LCM) = 0.84 (95% CI 0.72-0.98), p=0.03

HR(CDM:LCM) 0.48 0.77 0.90 1.35 1.10
heterogeneity p=0.001

Years from randomisation (ART initiation)
Progression to new WHO 4 event or death (primary endpoint)

Proportion alive without a new WHO 4 event

Years from randomisation (ART initiation)

LCM: n= 1656, 1438, 1364, 1306, 1255, 682
CDM: n= 1660, 1443, 1354, 1262, 1184, 613

356 events LCM: 5.2/100 PY
459 events CDM: 6.9/100 PY
Progression to new WHO 4 event or death (primary endpoint)

HR(CDM:LCM) = 1.31 (95% CI 1.14-1.51) p=0.0001

Proportion alive without a new WHO 4 event

Years from randomisation (ART initiation)

356 events
LCM: 5.2/100 PY
CDM: 6.9/100 PY
459 events

LCM: n= 1656 1438 1364 1306 1255 682
CDM: n= 1660 1443 1354 1262 1184 613
Survival

Years from randomisation (ART initiation)

Proportion alive

HR(CDM:LCM) = 1.35 (1.10-1.65) p=0.004

Number needed to monitor for 1 year to prevent 1 event = 130

164 events
LCM: 2.2/100 PY
CDM: 2.9/100 PY

218 events

<table>
<thead>
<tr>
<th>Year</th>
<th>LCM</th>
<th>CDM</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>1640</td>
<td>1542</td>
</tr>
<tr>
<td>4</td>
<td>1575</td>
<td>1445</td>
</tr>
<tr>
<td>3</td>
<td>1501</td>
<td>1494</td>
</tr>
<tr>
<td>2</td>
<td>1468</td>
<td>1395</td>
</tr>
<tr>
<td>1</td>
<td>1436</td>
<td>1395</td>
</tr>
<tr>
<td>0</td>
<td>796</td>
<td>749</td>
</tr>
</tbody>
</table>
Survival

Entebbe Cohort (Uganda): pre-ART 1996-2000, median CD4 75 at enrolment: 57.7/100 PY
Survival

Entebbe Cohort (Uganda): pre-ART 1996-2000, median CD4 75 at enrolment: 57.7/100 PY

Proportion alive

Years from enrolment

CDM: 2.9/100 PY
218 events
Survival

Entebbe Cohort (Uganda):
pre-ART 1996-2000, median CD4 75 at enrolment:
57.7/100 PY

Proportion alive

Years from enrolment

0.95
0.94
0.92
0.90
0.87
0.55
0.18
0.08

164 events
LCM: 2.2/100 PY
CDM: 2.9/100 PY
218 events
Absolute event rates over time on ART

New WHO 4/death (PRIMARY) vs Death

Predicted rate of new WHO4/death in LCM

Rate per 100 PY (95% CI)

LCM 0-<2 years
CDM 0-<2 years
Absolute event rates over time on ART

predicted rate of new WHO4/death in LCM

Death

New WHO 4/death (PRIMARY)

Rate per 100 PY (95% CI)

LCM 0-<2 years
CDM 0-<2 years
LCM 2-6 years
CDM 2-6 years
Absolute event rates over time on ART

Predicted rate of new WHO4/death in LCM

Death

New WHO 4/death (PRIMARY)

New severe WHO 4/death

Rate per 100 PY (95% CI)

LCM 0-<2 years
CDM 0-<2 years
LCM 2-6 years
CDM 2-6 years

EXCLUDING oesophageal candidiasis
Main Finding

• There is a small but statistically significant difference in mortality and disease progression between the two arms only from the third year on ART

• What causes this?
Explanation

- There is a small but statistically significant difference in mortality and disease progression between the two arms only from the third year on ART

- What causes this?

  - Slightly later switching to second-line therapy in CDM leading to a few more patients in CDM living with lower CD4 counts on first-line and at increased risk of clinical events
Most recent CD4 on first-line

Median

Last CD4 (cells/mm³)

LCM
CDM

Last seen alive on first-line

IAS July 2009
Most recent CD4 on first-line

Median

Last CD4 (cells/mm$^3$)

LCM

CDM

Last seen alive
on first-line

IAS July 2009

372

338

75%

70%

1%

3%

1%

4%
Most recent CD4 on first-line

Median

Last CD4 (cells/mm³)

LCM

CDM

Last seen alive on first-line

Died on first-line
Most recent CD4 on first-line

<table>
<thead>
<tr>
<th>LCM</th>
<th>CDM</th>
<th>LCM</th>
<th>CDM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>372</td>
<td>338</td>
<td>100</td>
</tr>
<tr>
<td>75%</td>
<td>70%</td>
<td>19%</td>
<td>9%</td>
</tr>
<tr>
<td>1%</td>
<td>1%</td>
<td>3%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Last seen alive on first-line

Died on first-line
Most recent CD4 on first-line or at switch

<table>
<thead>
<tr>
<th>Last CD4 (cells/mm³)</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>372</td>
</tr>
<tr>
<td></td>
<td>338</td>
</tr>
<tr>
<td></td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>56</td>
</tr>
</tbody>
</table>

Last seen alive on first-line:
- LCM: 1%
- CDM: 1%
- LCM: 3%
- CDM: 4%
- LCM: 19%
- CDM: 32%

Died on first-line:
- LCM: 20%
- CDM: 46%

Switched to second-line:
- LCM: 38%
- CDM: 40%

IAS July 2009
Most recent CD4 on first-line or at switch

<table>
<thead>
<tr>
<th>Median</th>
<th>372</th>
<th>338</th>
<th>100</th>
<th>60</th>
<th>63</th>
<th>56</th>
</tr>
</thead>
<tbody>
<tr>
<td>Last CD4 (cells/mm$^3$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>800</td>
<td>700</td>
<td>600</td>
<td>500</td>
<td>400</td>
<td>300</td>
<td>200</td>
</tr>
<tr>
<td>75%</td>
<td>70%</td>
<td>19%</td>
<td>9%</td>
<td>2%</td>
<td>2%</td>
<td>20%</td>
</tr>
<tr>
<td>1%</td>
<td>3%</td>
<td>18%</td>
<td>20%</td>
<td>38%</td>
<td>16%</td>
<td>48%</td>
</tr>
</tbody>
</table>

Last seen alive on first-line

died on first-line

switched to second-line

IAS July 2009
Absolute change in CD4 over 5 years

Mean absolute CD4 (cells/mm$^3$) (pointwise 95% CI)

Weeks from randomisation (ART initiation)

LCM
CDM

NB: some participants were on STIs at weeks 60, 84 and 108

Global p = 0.02
Conclusions

- 5-year survival in 3316 participants with advanced HIV disease pre-ART was excellent (CDM 87%, LCM 90%)
- Loss to follow-up was very low
- Routine laboratory monitoring for toxicity did not impact adverse events or substitutions in first-line
- 12-weekly CD4 monitoring had no impact on disease progression during the first 2 years on ART
  - after 2 years, a small but significant impact on clinical disease progression favouring LCM appeared to be driven by later switch to second-line ART in CDM
  - there may be a role for targeted, as opposed to routine, CD4 monitoring from the second year on ART