The Development of AntiRetroviral Therapy in Africa (DART) trial

Risk of WHO 4 events and death by current CD4 on ART in the DART trial: the impact of CD4-dependent reporting bias

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Background

- In resource-rich countries, standard of care on ART includes routine laboratory monitoring for:
  - toxicity (haematology, biochemistry)
  - efficacy (CD4 cell count, viral load)
- In Sub-Saharan Africa, laboratory monitoring:
  - is not widely available (infrastructure, personnel etc)
  - is costly to maintain (reagents, quality control etc)

- DART Trial objective: to evaluate the need for on-ART routine laboratory monitoring for toxicity and CD4 cell counts in African adults starting ART having fulfilled clinical and CD4 criteria for ART initiation
3316 ART-naive adults with stage WHO 2, 3 or 4 HIV disease, CD4<200 cells/mm$^3$ (median 86 cells/mm$^3$) 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/mm$^3$

**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 (not CD4) & 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
New WHO 4 event or death (co-primary endpoint) and death (secondary endpoint)

![Graph showing the proportion of patients alive and alive without a new WHO 4 event over time.](image)

- **Alive:**
  - LCM/CDM: 0.95/0.94
  - Proportion: 1.0

- **Alive without a new WHO 4 event:**
  - LCM/CDM: 0.88/0.88
  - Proportion: 1.0

**Years from randomisation (ART initiation):**

<table>
<thead>
<tr>
<th>Years</th>
<th>LCM (in follow-up)</th>
<th>CDM (in follow-up)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1656</td>
<td>1660</td>
</tr>
<tr>
<td>1</td>
<td>1552</td>
<td>1542</td>
</tr>
<tr>
<td>2</td>
<td>1501</td>
<td>1494</td>
</tr>
<tr>
<td>3</td>
<td>1468</td>
<td>1445</td>
</tr>
<tr>
<td>4</td>
<td>1436</td>
<td>1395</td>
</tr>
<tr>
<td>5</td>
<td>796</td>
<td>749</td>
</tr>
</tbody>
</table>

**HR(CDM:LCM: death) = 1.35 (95% CI 1.10-1.65) p=0.004**

**Number needed to monitor for 1 year to prevent 1 death = 130**

**HR(CDM:LCM: WHO 4/death) = 1.31 (95% CI 1.14-1.51) p=0.0001**
DART trial results
(Lancet 2010;375:123-31)

• 5-year survival in 3316 participants with advanced HIV disease pre-ART (33% < 50 cells/mm$^3$) was excellent
  - loss to follow-up was very low (7% at 6 years; median 4.9 years FU)

• Routine 12-weekly laboratory monitoring for toxicity did not impact any adverse event outcome

• Routine 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
Objective

- To compare the risk of death and disease progression events between randomised groups at various CD4 counts
  - Poisson models, including multiple WHO 4 events (ie subsequent events after the first during the trial)

- Hypothesis: low CD4 in CDM may have more serious consequences because of clinicians not knowing this
Outcome ascertainment

- Clinicians were encouraged to report and investigate all potential WHO 4 events
  - patients not returning to clinic had home visits to ascertain deaths and other outcomes
- However, randomisation was open

  ➢ All reported WHO 4 events (and cause of death) were adjudicated against pre-specified protocol criteria by an Endpoint Review Committee with independent Chair and members, blinded to randomised group and to CD4 counts

  - 780/992 (79%) reported WHO 4 events met protocol criteria (“accepted” events)
  - most common reasons for rejecting events as endpoints were missing tests or other plausible diagnoses (Borok IAS 2009 TUPEB098)
Absolute change in CD4 over 5 years

Mean absolute CD4 (cells/mm³) (pointwise 95% CI)

Weeks from randomisation (ART initiation)

Global p = 0.02

NB: some participants were on STIs at weeks 60, 84 and 108
CD4 over follow-up time

0-<2 years after ART initiation

Most recent CD4

- **0-49**
- **50-99**
- **100-199**
- **200-349**
- **350-499**
- **500+**

33% <50 cells/mm³ pre-ART
CD4 over follow-up time

33% <50 cells/mm³ pre-ART

Note: LCM CD4 switch criteria was 100 cells/mm³ (confirmed) on ART

Most recent CD4

0-49, 50-99, 100-199, 200-349, 350-499, 500+
Risk of death by current CD4

- Median CD4 at death: 86, IQR 22-177; range 1-769
- Death rates per 100 PY:
  - LCM & CDM: 12.6 (215) events
  - Death: (382 deaths)

rates/100PY (events)

Most recent CD4
Risk of death by current CD4

- No difference between CDM/LCM in the risk of death at a given CD4 (p=0.54)

- Median CD4 at death: 86, IQR 22-177; range 1-769

- Death: LCM & CDM

Deatthe events:

- LCM&CDM: 12.6(215) 1.0(54) 0.9(23) 0.6(7) (382 deaths)
Risk by current CD4

Rates/100PY (events)
WHO 4 (acc)
CDM 27.5(268) 4.8(91) 2.3(65) 1.7(21) 1.1(6)
(452 events)
Death: LCM & CDM
LCM&CDM 12.6(215) 2.0(75) 1.0(54) 0.9(23) 0.6(7)
(382 deaths)

Death: LCM & CDM
WHO 4 accepted: CDM
Risk by current CD4

Rates/100PY (events)

WHO 4

<table>
<thead>
<tr>
<th>CDM</th>
<th>WHO 4 accepted: CDM</th>
<th>WHO 4 reported: CDM</th>
<th>Death: LCM &amp; CDM</th>
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<tbody>
<tr>
<td>27.5(268)</td>
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<td>1.7(21)</td>
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(452 events) (382 deaths)

Most recent CD4
WHO 4 events at high CD4s

- **CD4s at which WHO 4 event reported**
  - CDM: 33 (6%) events >350 cells/mm³ (max 895, 6 above 540)

- **CD4s at which WHO 4 event accepted**
  - CDM: 27 (6%) events >350 cells/mm³ (max 895, 4 above 540)
WHO 4 events at high CD4s

- **CD4s at which WHO 4 event reported**
  - **CDM:** 33 (6%) events >350 cells/mm$^3$  
    (max 895, 6 above 540)
  - **LCM:** 18 (4%) events >350 cells/mm$^3$  
    (max 540)

- **CD4s at which WHO 4 event accepted**
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  - **LCM:** 16 (5%) events >350 cells/mm$^3$  
    (max 540)
WHO 4 events at high CD4s

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- **CD4s at which WHO 4 event accepted**
  - CDM: 27 (6%) events >350 cells/mm$^3$  
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  - LCM: 16 (5%) events >350 cells/mm$^3$  
    (max 540)

- Risks of both reported and accepted WHO 4 events for a given CD4 differed significantly between CDM vs LCM (p=0.002 and p=0.02 respectively), **being greater in CDM only at higher CD4 where most time was spent**
### Risk by current CD4

#### Heterogeneity between LCM & CDM in risk of WHO 4 events for given CD4

- **p=0.02**

#### Rates/100PY (events)

<table>
<thead>
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<th>WHO 4 accepted</th>
<th>Most recent CD4</th>
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<tr>
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<td>LCM &amp; CDM</td>
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#### Death LCM & CDM

- **24.9(184)**
- **27.5(268)**
- **12.6(215)**
Possible explanation

• In CDM, the clinician does not know the CD4 count

• Any serious clinical episode could be a WHO 4 event because the patient could have a low CD4 count without the clinician knowing
  - full work up, diagnostic tests, event reported on CRFs etc
  ⇒ identify WHO 4 events which can occur at high CD4 counts (hence interest in “when to start ART” at high CD4 counts)

• In LCM, the clinician “knows” the episode cannot be a WHO 4 event, because the patient has a high CD4 count
  - no work up, event not reported
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    (hence interest in “when to start ART” at high CD4 counts)

- In LCM, the clinician “knows” the episode cannot be a WHO 4 event, because the patient has a high CD4 count
  - no work up, event not reported

Predicting the expected number of events
given observed CD4s in LCM
suggests 40 missed LCM WHO 4 events at CD4>200 cells/mm³
Conclusions

• Despite numerous strategies to reduce bias (standardised follow-up schedule, home visits, objective criteria, blinded ERC etc), open randomisation likely led nevertheless to CD4-dependent reporting bias in WHO 4 events
  - under-reporting and under-investigation of potential WHO 4 events at higher CD4 in LCM

• 356 LCM vs 459 CDM primary endpoints (Δ=103)
  - estimate 40 missed LCM events but as primary endpoint was first new WHO 4/death impossible to predict number of missed endpoints

• True differences between CDM/LCM in time to WHO 4/death, but not death, may be smaller than estimated

• Implications for open trials with clinical endpoints (let alone observational studies)
Acknowledgments

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