The Development of AntiRetroviral Therapy in Africa (DART) trial

What have we learnt?

James Hakim
on behalf of the DART Trial Team
What have we learnt? (I)

A trial provides an excellent way to build partnerships and teams
DART partners

Support:

- MRC, UK
- DFID, UK
- Rockefeller Foundation
- GlaxoSmithKline
- Gilead Sciences
- Boehringer-Ingelheim
- Abbott

Joint Clinical Research Centre, Kampala, Uganda
Infectious Diseases Institute, Makerere University, Uganda
MRC/UVRI Uganda Research Unit on AIDS, Entebbe, Uganda
TASO, Uganda
University of Zimbabwe, Harare, Zimbabwe

MRC Clinical Trials Unit, UK
Imperial College, UK
Disused clinic buildings were refurbished for the DART trial at Entebbe.

Extra space was needed at JCRC for the clinical work of DART.

... and Zimbabwe.
• Local trial centres and databases
• Local independent trial monitors
• Superb participant retention
  – 7% lost to follow-up at 5 yrs
Capacity development

- IT, pharmacy, laboratory development
- Training & mentoring
  - clinicians, nurses, counsellors
  - pharmacists
  - trial & data managers
  - statisticians
  - health economists
- Masters in Biostatistics (3), Epidemiology (1); PhDs in Biostatistics (1), Epidemiology (1)

www.ctu.mrc.ac.uk/dart
Community involvement

- Partnership with the DART participant community
  - annual participant days
- Grassroots community activism from clinic “days”
  - encouragement for adherence
  - micro-economic projects
  - family support groups
- Advocacy for prevention and against stigma led by DART participants
What have we learnt? (II)

DART results provide evidence to inform ART policy & delivery
Overall results

Overall survival at 5 years in 3316 participants with advanced HIV disease pre-ART was excellent (CDM 87%, LCM 90%)

- Retention was very high
- Survival was better than predicted, given advanced disease stage at enrolment
  - emphasises the importance of excellent clinical care including access to concomitant medications & diagnostics
- ART can be given wherever people live: next steps
  - widening distribution of drugs
  - focussing resources on strengthening healthcare systems and training HCWs to deliver life-saving treatment
    - benefits health infrastructure for everyone
Toxicity monitoring

Routine laboratory monitoring for toxicity did not impact adverse events or substitutions in first-line

- Differences between arms are driven by HIV events
- More tests done in LCM
  - routine monitoring does not prevent extra tests being requested
- Routine laboratory tests for toxicity were the most costly part of ART provision in DART
- Laboratories are still needed
  - eg screening; diagnosis and management of acute illnesses
12-weekly CD4 monitoring had no impact on disease progression during the first 2 years on ART: after this, a small impact on clinical disease progression appeared to be driven by later switch to second-line in CDM

- Targeted CD4 monitoring from the 2nd year on ART may be clinically useful for decisions about switching ART
  - further research is needed to explore
    - the minimum frequency of CD4 monitoring required
    - the impact of different switching criteria
  - those initiating ART with higher CD4 counts may be able to defer CD4 monitoring for longer than 12-18 months
  - economic considerations are important for implementation
    - e.g. availability of cheaper and simpler CD4 monitoring tests
Cost-effectiveness

• Cost per life-year gained of $9,016 in LCM arm
  - 7-fold higher than WHO/CMH threshold for cost-effectiveness

• Finances are limited and priorities need to be set
  - e.g. balancing resource use to monitor patients on ART versus initiating more patients on therapy

• For CD4 monitoring to be cost effective, the cost needs to fall below $3.80
What have we learnt? (III)

The wider context
Survival

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

DART
LCM: 2.2/100 PY
CDM: 2.9/100 PY
Resource allocation

- 6.7 million adults and children in Sub-Saharan Africa were estimated to need ART in December 2007
  - only 2.2 million were receiving ART

- Global economic crisis is threatening programme funding

- Using DART to help resource allocation
  - what could be achieved in an ART programme with $1,000,000 over 5 years...
For $1,000,000 over 5 years

Mean cost/patient: LCM $3,425, CDM $2,493

LCM: TREAT 292

CDM: TREAT 401 (extra 109)

Assuming cost of patients not treated is $0. Based on difference in life-years from CEA.
**Survival**

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

**DART**
- LCM: 2.2/100 PY
- CDM: 2.9/100 PY
For $1,000,000 over 5 years

Mean cost/patient: LCM $3,425, CDM $2,493

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>LCM: TREAT 292</th>
<th>CDM: TREAT 401 (extra 109)</th>
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<tr>
<td>treated, alive</td>
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<td>35</td>
</tr>
<tr>
<td>treated, died</td>
<td>73</td>
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<tr>
<td>not treated, died</td>
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<tr>
<td>not treated, alive</td>
<td>271</td>
<td>366</td>
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Total deaths: 94 from Entebbe Cohort data

Assuming cost of patients not treated is $0. Based on difference in life-years from CEA.
Excluding routine toxicity tests in LCM

Mean cost/patient: LCM $2,726, CDM $2,493

LCM: TREAT 367
CDM: TREAT 401 (extra 34)

Number of patients

Assuming cost of patients not treated is $0. Based on difference in life-years from CEA.
Other aspects of healthcare delivery

- DART focused on the contribution of routine laboratory testing to benefits and costs of ART provision.

- However, other aspects of service delivery are also key to sustainability, benefits and costs:
  - local health centre vs hospital based service provision
    the JINJA trial [MOAD101]
  - nurse vs doctor led service provision
    the CIPRA-SA-1 trial [http://www.cipra-sa.com/project1.asp]
Conclusion

• DART provides clear evidence to help governments and policymakers determine priorities for ART programmes

• DART adds to the evidence base for ART in Africa in ways beyond those originally anticipated

• DART created highly skilled teams of ART clinical trialists and centres of ART and research excellence in Uganda and Zimbabwe

• Partnerships have been developed, additional resources leveraged and a broader scientific agenda realised
Acknowledgments

We thank all the patients and staff from all the centres participating in the DART trial.