The Development of Antiretroviral Therapy in Africa (DART) trial

Design and key substudy results

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on behalf of the DART Trial Team
In resource-rich countries, standard of care on ART includes routine laboratory monitoring for:
- toxicity (haematology, biochemistry)
- efficacy (CD4 cell count, viral load)

The level of monitoring required has never been established.

In Africa, laboratory monitoring:
- is not widely available (infrastructure, personnel etc)
- is costly to maintain (reagents, quality control etc)

Question: can ART be given safely with clinically driven, rather than routine, laboratory monitoring?
Main objectives of DART

- To evaluate the need for routine laboratory monitoring of ART in African adults starting ART having fulfilled clinical and CD4 criteria for ART initiation

- To evaluate 12 week cycles of structured treatment interruptions (STIs) in patients with CD4 ≥300 cells/mm³ at 48/72 weeks (stopped March 2006)

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

- Cost-effectiveness analysis

1 DART Trial Team *AIDS* 2008;22(2):237-47
3316 ART-naive adults with stage WHO 2, 3 or 4 HIV disease, CD4<200 cells/mm³ initiating 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
Why was DART so large and long?

• Designed with sufficient power to determine whether CDM was non-inferior to LCM
  - defined as no more than a very small increase in event rate from 10/100 PY in LCM to 11.8/100 PY in CDM
  - this small difference was considered acceptable, given potential benefits of CDM in terms of costs, access to and ease of decentralised ART delivery and hence wider rollout

• Long follow-up was essential as any differences between laboratory and clinical monitoring may only emerge, or may become more apparent, over time
  - patients will be on ART for life, not just for 2-3 years
ART regimens

- First-line regimens based on ZDV+3TC (as Combivir)
  - 2469 (74%) ZDV+3TC+TDF
  - 300 (9%) ZDV+3TC+bABC (open label after 24 weeks)
  - 300 (9%) ZDV+3TC+bNVP (open label after 24 weeks)
  - 247 (7%) ZDV+3TC+NVP

- Different regimens increases generalisability

- Second-line regimens based on boosted PI
  - LPV/r+NNRTI±NRTI if 3NRTIs as first-line
  - LPV/r+2NRTIs if NNRTI+2NRTIs as first-line
Wider contributions to the evidence base for ART in Africa

DART is more than a trial - it has become a major research programme

- First-line NORA randomisation, and second-line pilot randomisations to optimise NRTIs and evaluate PI monotherapy

- HIV virology/resistance project (stored samples)
  - majority of laboratory work conducted in Africa

- Other projects in key clinical areas
  - 9 peer reviewed articles and 29 conference presentations with key findings for ART management in resource-limited settings:
    - very low levels of renal impairment with tenofovir DF to 2 years
    - safe strategies for stopping nevirapine (pharmacokinetics)
    - lower than expected rate of HSR with abacavir; absence of HLAB-5701
  - Other areas include toxicity, pharmacokinetics, adherence, health-related quality of life, clinical/immunological outcomes, including OIs and tuberculosis, pregnancy and infant follow-up, survival on ART vs pre-ART
• MOPEB003: Impact of different WHO 3/4 events on ART on subsequent survival

• MOPEB020: Impact of cotrimoxazole in patients on ART

• MOPEB057: 5 year follow-up of participants initiating ART with Combivir plus nevirapine or abacavir (randomised)

• TUPEB098: Assigning clinical endpoints in clinical trials in resource limited settings

• TUPDB104: Impact of ART on incidence of malaria in Uganda

• TUPEB184: 5 year follow-up of creatinine and estimated GFR in patients receiving and not receiving TDF first-line

• WEPEB261: Pregnancy outcomes in women in DART
Impact of cotrimoxazole prophylaxis in patients on ART

**MOPEB020**

- Key findings (I)
  - Cotrimoxazole prophylaxis (CTX) decreases mortality by 50% in the first 72 weeks on ART
    - independently of current CD4
    - no effect after 72 weeks
  
  By current CD4: not on CTX
  - CD4<200, <72 wks ART, on CTX
    - OR: 0.48 (95% CI: 0.33 - 0.5)
  - CD4>200, <72 wks ART, on CTX
    - OR: 0.57 (95% CI: 0.5 - 0.6)
  - CD4<200, >72 wks ART, on CTX
    - OR: 0.99 (95% CI: 0.98 - 1)
  - CD4>200, >72 wks ART, on CTX
    - OR: 1.17 (95% CI: 1.15 - 1.19)
Impact of cotrimoxazole prophylaxis in patients on ART

MOPEB020

- Key findings (II)
  - 4 year survival for adults initiating ART and taking/not taking cotrimoxazole
    - 94% vs 92% with pre-ART CD4 150 cells/mm³
    - 87% vs 81% with pre-ART CD4 15 cells/mm³
5 year follow-up of Combivir plus nevirapine or abacavir (randomised)

MOPEB057

- Key findings:
  - At 5 years, 91% participants alive in both groups (81% alive without new WHO 4 events)
  - Clear VL and CD4 advantages to NVP

![Graph showing survival rates](image)
Key findings

- Low incidence of renal impairment on all regimens (TDF and non-TDF): overall
  - 2.9% eGFR ever <30 ml/min/1.73m²
  - 5.0% confirmed eGFR <60 ml/min/1.73m²
  - 2.9% confirmed 25% decrease from baseline eGFR

- No difference between LCM and CDM in incidence of confirmed eGFR decrease

- Renal disease contributed to death in a minority of patients (n=16, 0.5%) and was generally related to intercurrent disease
Pregnancy outcomes in DART

WEPEB261

• Key findings

- 378 pregnancies in 299/1867 (16%) women of child-bearing age at ART initiation
  - 4.83/100 woman-years
  - 60% on combivir+tenofovir DF
- 57% livebirths, 6% stillbirths and 36% terminations/miscarriage
- No excess congenital abnormalities vs pregnancy register - 3.0%
  - 3 club foot, 1 skin tag, 1 undescended testes, 1 hydrocephalus, 1 cardiac (PDA & ASD)
- No reported HIV-infected babies to date
Looking forward

- Second-line studies - ART (OHFS) & bPI monotherapy (SARA)
- HIV virology/resistance project (stored samples)
- Hepatitis B virology project (stored samples)
- Follow-up of infants born to mothers in DART
- Impact of ART on disclosure and sexual behaviour
- Toxicity on first- and second-line ART
- Non-randomised comparison of first-line regimens
- Prevalence and impact of immunological non-response
- Optimising “when to switch” (using causal models)
- Relationship between (minor) symptoms and ART failure

- Maintenance of the DART cohort long-term
- EARNEST: a large (1200 participant) RCT of second-line ART
DART partners

Support:

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

MRC Clinical Trials Unit, UK
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MRC/UVRI Uganda Research Unit on AIDS, Entebbe, Uganda
- TASO, Uganda

University of Zimbabwe, Harare, Zimbabwe

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- Gilead Sciences
- Boehringer-Ingelheim
- Abbott