The Development of AntiRetroviral Therapy in Africa (DART) trial

Design and key substudy results

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Background & rationale

- 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/mm^3 at 48/72 weeks (stopped March 2006[1])*
- 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

Trial Design

3316 ART-naive adults with stage WHO 2, 3 or 4 HIV disease, CD4<200 cells/mm^3 initating ART

randomise

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 & 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

randomised blinded NORA substudy in Uganda

- 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

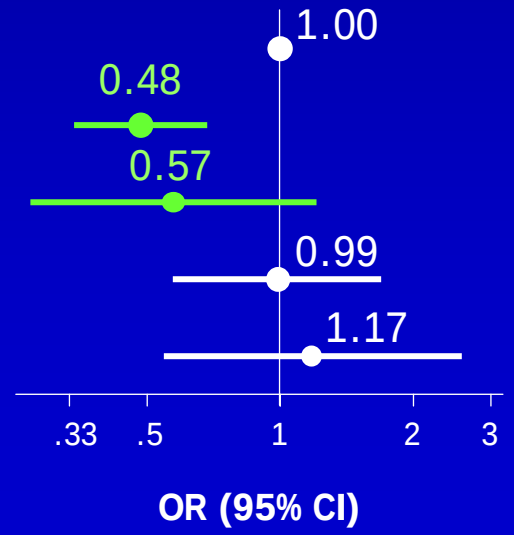
IAS poster presentations

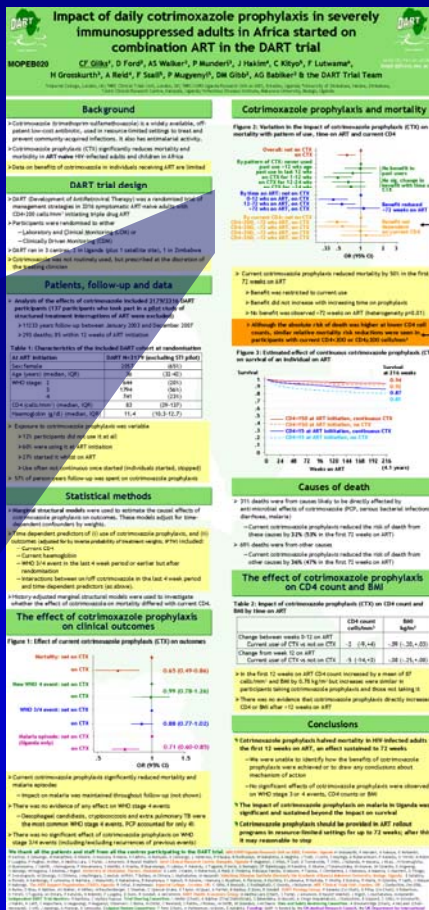
- MOPEB003: Impact of different WHO 3/4 events on ART on subsequent survival
- MOPEB020: Impact of cotrimoxazole in patients on ART
- MOPEB057: 5 year follow-up of participants initiating ART with Combivir plus nevirapine or abacavir (randomised)
- TUPEB098: Assigning clinical endpoints in clinical trials 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

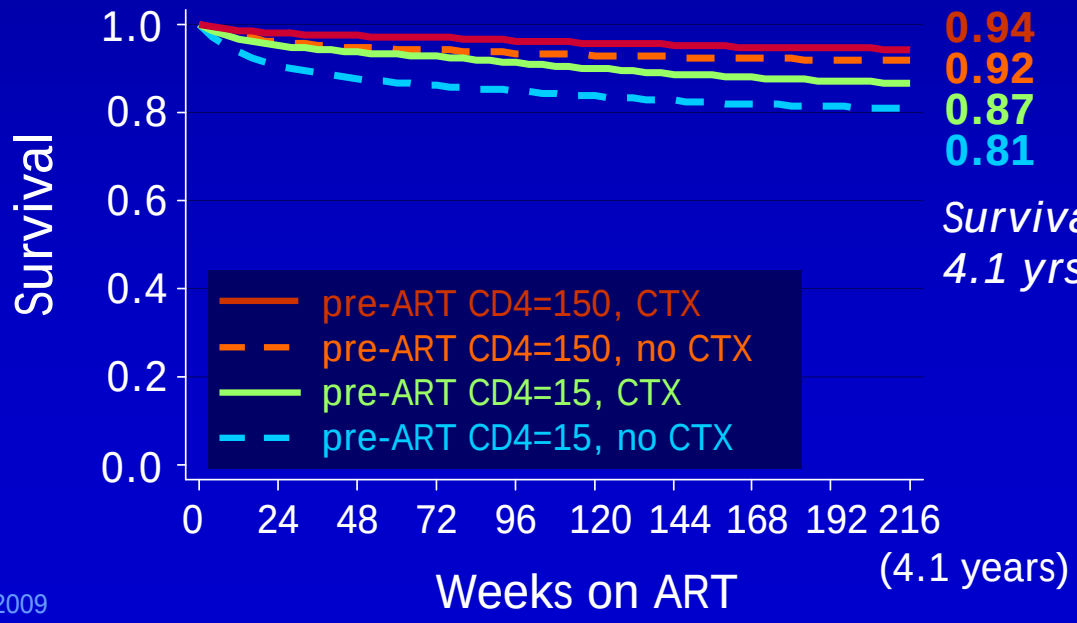


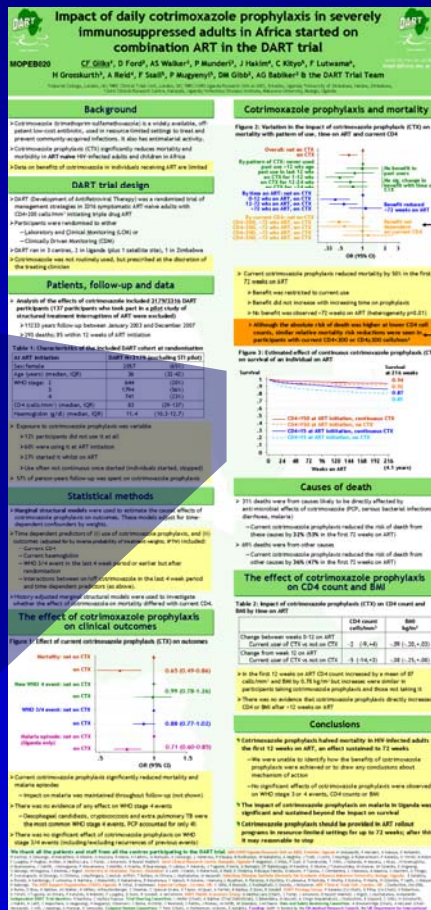


Impact of cotrimoxazole prophylaxis in patients on ART

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/mm^3
    - **87%** vs **81%** with pre-ART CD4 15 cells/mm^3

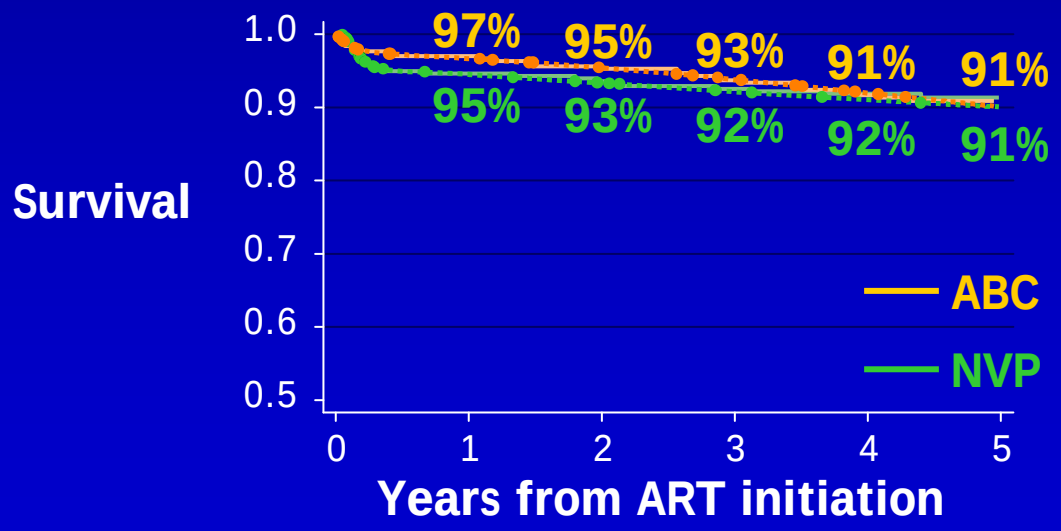


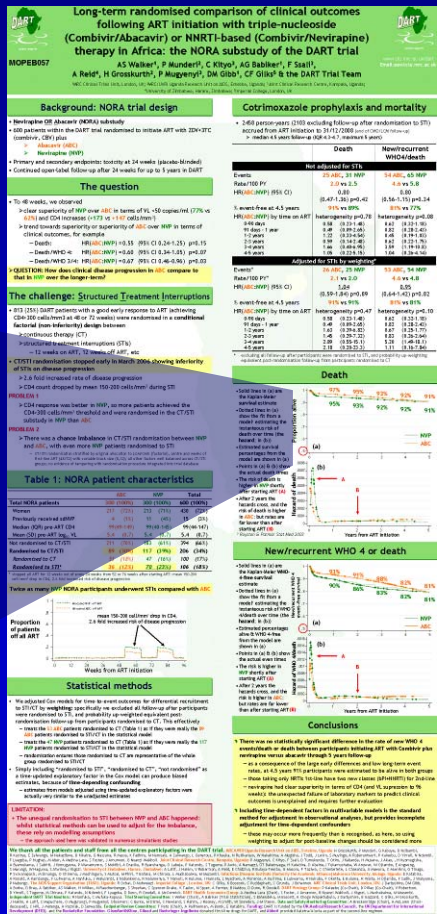


5 year follow-up of Combivir plus nevirapine or abacavir (randomised)

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

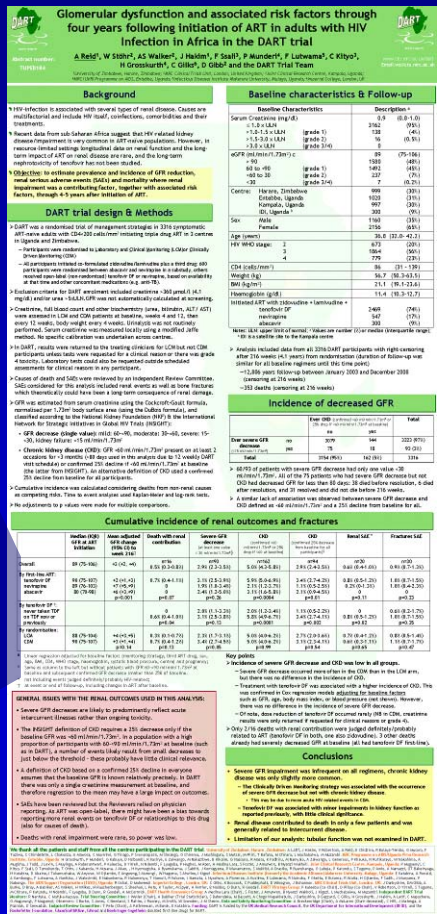




5 year follow-up of estimated GFR in patients initiating ART

TUPEB184

- 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


Glomerular dysfunction and associated risk factors through four years following initiation of ART in adults with HIV infection in Africa in the DART trial

Background

DART trial design & Methods

Baseline characteristics & Follow-up

Incidence of decreased GFR

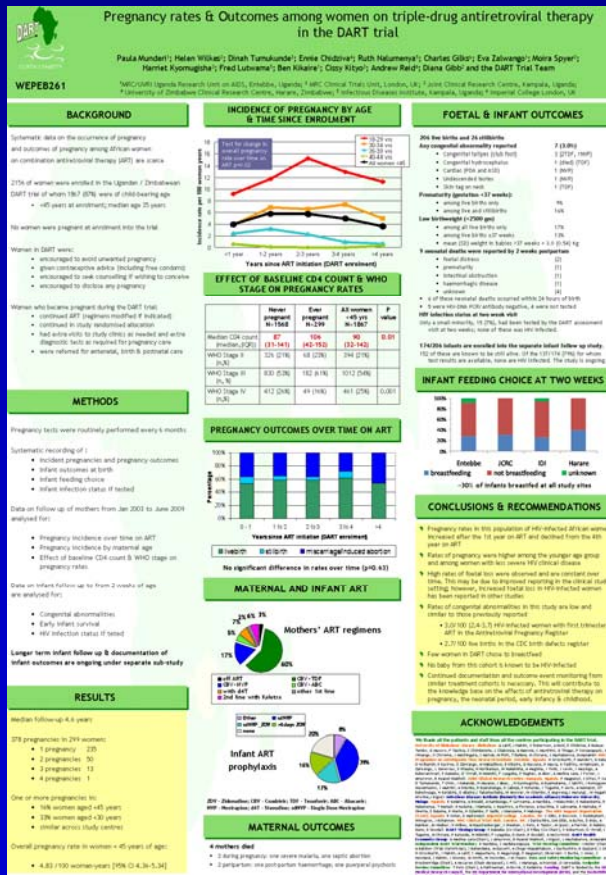
Cumulative incidence of renal outcomes and fractures

Conclusions

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

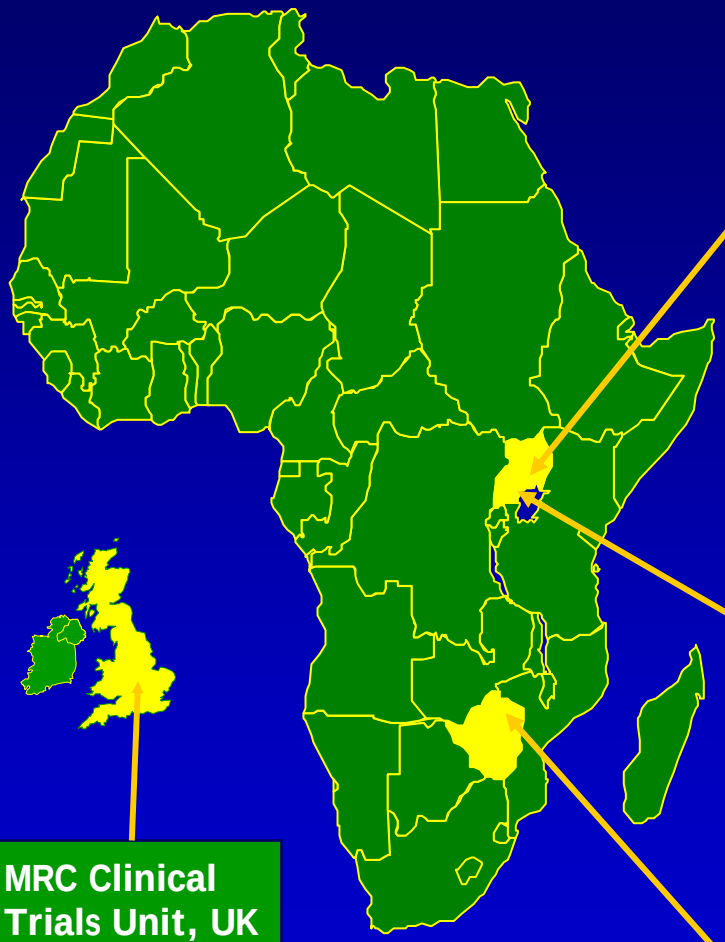
- Second-line studies - ART (OHFS) & bPI monotherapy (SARA)
- HIV virology/resistance project (stored samples)
- Hepatitis B virology project (stored samples)
- Follow-up of infants born to mothers in DART
- Impact of ART on disclosure and sexual behaviour
- Toxicity on first- and second-line ART
- Non-randomised 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



- 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


DART