

# A randomised trial of monitoring practice and structured treatment interruptions in the management of antiretroviral therapy in adults with HIV Infection in Africa: the DART Trial



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## ABSTRACT

**Background:** DART (Development of Anti-Retroviral Therapy in Africa) is an open label randomised trial assessing feasible therapeutic approaches for resource poor settings: clinical monitoring only versus CD4 plus laboratory plus clinical monitoring, and structured treatment interruptions (STI) versus continuous therapy.

**Methods:** 3300 symptomatic ART-naive adults from 3 sites (2 Uganda, 1 Zimbabwe) with CD4 <200 cells/mm<sup>3</sup> will receive 3-drug ART (first and second-line) and be followed for up to 5 years. The primary outcome is WHO stage 4 disease or death. A second randomisation will assess the potential benefits and risks of STI in patients with good CD4 responses, following a 100 patient pilot (12 weeks on, 12 weeks off) in those achieving CD4 >250 cells/mm<sup>3</sup> after 24 weeks of continuous ART.

**Results (updated):** Recruitment started in January 2003: to date, 5243 and 2701 adults have been screened and randomised respectively. 64% of those randomised are women, 52 of whom (3%) received prior ART to prevent mother-to-child HIV transmission. The median age is 37 years, with 16% over 45. Most have advanced HIV disease (25%, 55% and 21% WHO stage 4, 3 and 2 respectively), with median CD4 85 cells/mm<sup>3</sup> (34% <50 cells/mm<sup>3</sup>, 24% 50-99 cells/mm<sup>3</sup>), and median weight 57 kg (IQR 51-64). Thus 2326 patients initiated ZDV/3TC/TDF as first line ART, 138 ZDV/3TC/NVP and 237 ZDV/3TC plus blinded NVP or ABC; 5% have substituted d4T for ZDV for toxicity. 43% of 1552 patients at 24 weeks have increased CD4 by at least 100 cells/mm<sup>3</sup> (median increase 86, IQR 41-141) and 38% have achieved a CD4 ≥200 cells/mm<sup>3</sup>. 95% adherence questionnaires to 24 weeks reported no missed pills in the last 4 days; 64% patients never missing a dose through this period.

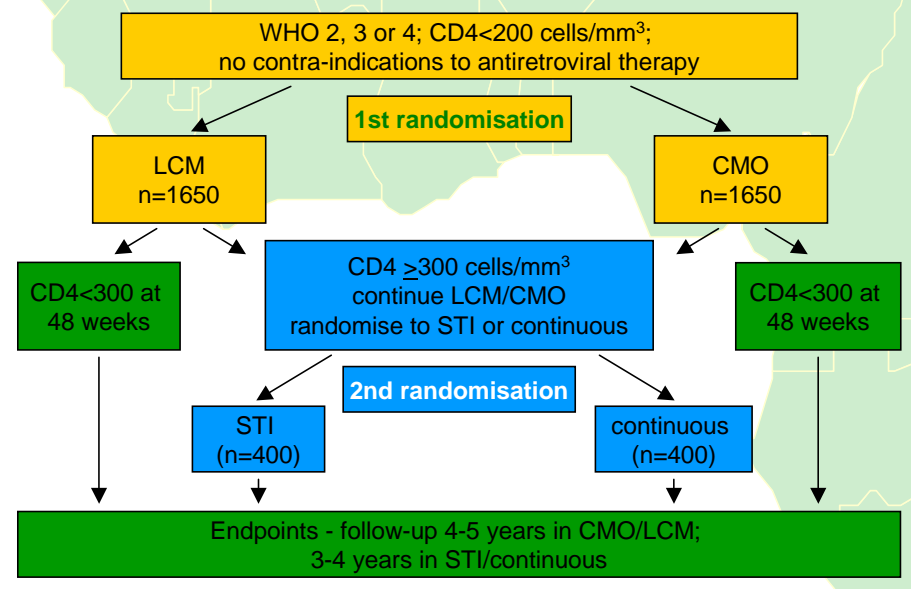
**Discussion:** Obstacles to widespread ART introduction in developing countries include drug costs, and the need for infrastructure to administer and monitor ART and ensure long-term adherence. DART will assess whether laboratory monitoring is necessary for effective ART use, and whether toxicity can be reduced by STI without compromising efficacy.

## SUMMARY

- ↳ Enrolment into DART has been good: recruitment to the main LCM/CMO comparison will be completed by end of September 2004
- ↳ Follow-up has been excellent
- ↳ The CD4 increases observed are in line with those obtained in patients with low CD4 counts in industrialised countries
- ↳ Given the low CD4 counts at ART initiation, a substantial proportion of patients still have CD4 counts below 200 cells/mm<sup>3</sup> at 24 weeks
- ↳ A substudy assessing virological suppression with ZDV/3TC/TDF is underway
- ↳ DART will assess whether laboratory monitoring is necessary for effective ART use
- ↳ Follow-up in DART is planned to continue until the end of 2007

## DART: RATIONALE and DESIGN

- ↳ ART use requires laboratory monitoring for toxicity (haematology, biochemistry) and efficacy (T cell subsets, viral load)
- ↳ Intensive laboratory monitoring in Africa requires infrastructure which is not widely available, is costly, and has issues with quality control
- ↳ **Can ART be given safely with minimal monitoring?**
  - ↳ randomise between routine **L**aboratory and **C**linical **M**onitoring (**LCM**) versus **C**linical **M**onitoring **O**nly (**CMO**)
- ↳ **Can STI reduce toxicity and time spent on ART without compromising efficacy?**
  - ↳ randomise between **C**ontinuous **T**herapy (**CT**) versus **S**tructured **T**reatment **I**nterruption (**STI**) (12 weeks on, 12 weeks off) in those with CD4 ≥300 cells/mm<sup>3</sup> at 48 weeks



## FOLLOW-UP in DART

- ★ Total 1238 person years of follow-up (minimum 0 years, maximum 1.3 years per patient)
- ★ 7 (0.3%) patients not known to have died were definitely known to be lost to follow-up
- ★ 74 (3%) patients not known to have died were last seen alive more than 3 months ago

## OVERALL CD4 INCREASES in DART

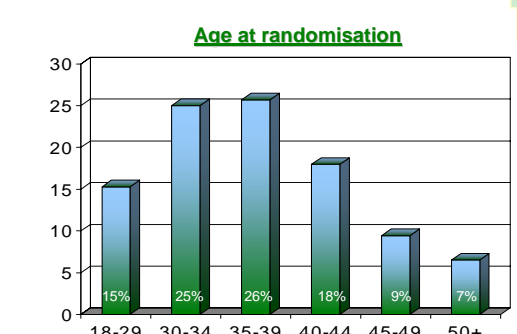
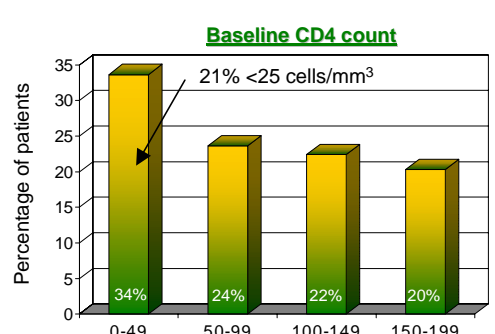
	Median CD4 increase (IQR)	CD4 increase ≥100 cells/mm <sup>3</sup>	Absolute CD4 ≥200 cells/mm <sup>3</sup>
<b>Week 12 (N=2032)</b>	74 cells/mm <sup>3</sup> (IQR 33 to 126)	737 (36%)	720 (35%)
<b>Week 24 (N=1552)</b>	86 cells/mm <sup>3</sup> (IQR 41 to 141)	674 (43%)	596 (38%)

## ADHERENCE to ART in DART

- ★ Patients are prescribed 28 days ART (until their next clinic visit)
- ★ Patients complete an adherence questionnaire at clinic visits every 4 weeks
- ★ Over the first 24 weeks in DART, 9538 questionnaires have been completed
  - ↳ 98% questionnaires reported attending clinic visit on time or early
  - ↳ 95% questionnaires reported missing no pills in the last 4 days
  - ↳ the percentage reporting never having missed a pill dropped over time as expected
    - from 80% at 4 weeks to 76%, 73%, 68%, 65% and 64% at 8, 12, 16, 20 and 24 weeks respectively
  - ↳ at 24 weeks (N=1069)
    - 64% reported they had never missed a pill
    - 9% reported they last missed a pill more than 3 months ago
    - 15% reported they last missed a pill 1-3 months ago
    - 5% reported they last missed a pill 2-4 weeks ago
    - 3% reported they last missed a pill 1-2 weeks ago
    - 4% reported they last missed a pill in the last week
  - ↳ most frequent reasons for missing doses were being away from home, simply forgetting, running out of pills, feeling sick, being busy and wanting to avoid side effects

## OVERVIEW of PATIENTS ENROLLED in DART

- 2701 patients** have been randomised to 17 May 2004 (53% of those screened)
- ★ 64% are women
    - ↳ 52 women (2% of total, 3% of women) had previously received ART for prevention of mother-to-child transmission. This was single dose nevirapine in 89% of cases
  - ★ median age is 37 years - 15% under 30 years and 16% over 45 years
  - ★ 30% have been enrolled from the MRC Programme on AIDS/Uganda Virus Research Institute (Uganda); 26% from the Joint Clinical Research Centre (Uganda); 11% from the Academic Alliance (Uganda); and 33% from the University of Zimbabwe (Zimbabwe)
  - ★ 98% acquired HIV through sex between men and women
  - ★ 52% were first diagnosed HIV positive when screened for entry to DART
    - ↳ those with a prior positive test had been diagnosed for median 1.1 years (IQR 0.4 to 3.5 years)
  - ★ 25% were WHO stage 4, 55% WHO stage 3 and 21% WHO stage 2
  - ★ median CD4 was 85 (IQR 31 to 140; range 1 to 199)
  - ★ all patients started ART with ZDV/3TC PLUS
    - ↳ tenofovir (TDF) n=2,326 (target 2500)
    - ↳ open label nevirapine (NVP) n= 138 (target 200)
    - ↳ blinded NVP or abacavir (ABC) [randomised NORA substudy] n= 237 (target 600)
  - ★ 134 patients (5%) have substituted ZDV for D4T for toxicity



## COLLABORATORS and ACKNOWLEDGEMENTS

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

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**Funding:** DART is funded by the UK Medical Research Council, the UK Department for International Development (DfID), and Rockefeller Foundation. First-line drugs are provided by GlaxoSmithKline, Gilead and Boehringer-Ingelheim.