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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

A Reid*[1], P Munderi[2], C Kityo Mutuluuza[3], D Gibb[4], E Katabira[5],
J Hakim[1], H Grosskurth[2], P Mugyenyi[3], J Darbyshire[4] and C Gilks[6] on behalf of the DART Trial

[1]University of Zimbabwe, Harare, Zimbabwe; [2]MRC/UVRI Programme on AIDS, Entebbe, Uganda; [3]Joint Clinical Research Centre, Kampala, Uganda;
[4] MRC Clinical Trials Unit, London, UK; [5]Academic Alliance, Mulago, Uganda; [6]Imperial College, London, UK

***Contact details:**
Department of Clinical Pharmacology
University of Zimbabwe, PO Box A178
Avondale, Harare
Zimbabwe
Tel: +263 4 791 631 #2227
Fax: +263 4 705 995
Email: reid@uzcrc.co.zw

MRC Clinical Trials Unit
222 Euston Road, London, NW1 2DA
Tel: +44 20 7670 4894
Fax: +44 20 7670 4818
Email: sarah.walker@ctu.mrc.ac.uk

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ABSTRACT

Background: DART (**D**evelopment of **A**nti-**R**etroviral **T**herapy 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.

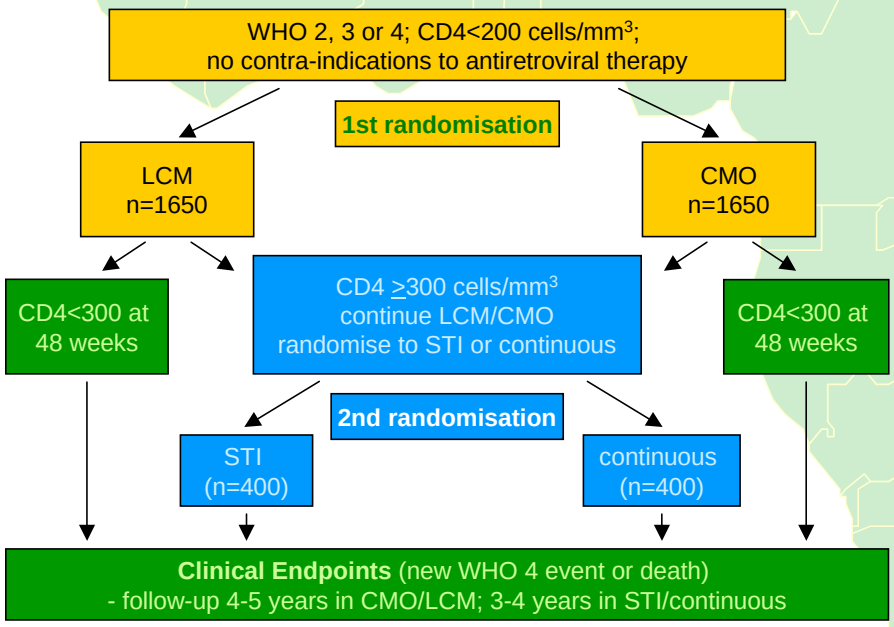
Methods: 3300 symptomatic ART-naive adults from 3 sites (2 Uganda, 1 Zimbabwe) with CD4 <200 cells/mm^3 will receive 3-drug ART (first and second-line) and be followed for up to 5 years. The primary outcome is WHO stage 4 disease or death. A second randomisation will assess the potential benefits and 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^3 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^3 (34% <50 cells/mm^3, 24% 50-99 cells/mm^3), 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^3 (median increase 86, IQR 41-141) and 38% have achieved a CD4 ≥200 cells/mm^3. 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.

DART: RATIONALE and DESIGN

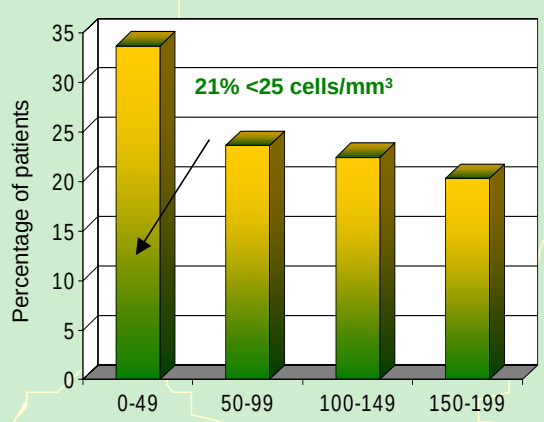
- Routine laboratory monitoring of ART for toxicity (haematology, biochemistry) and efficacy (T cell subsets, viral load) is standard of care in industrialised countries, but its need has never formally been assessed
- Providing such intensive laboratory monitoring in Africa requires infrastructure which is not widely available, is costly, and has issues with quality control
- **DART is asking: 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**)
  - clinicians can request toxicity results for **CMO** patients if clinically indicated
- Structured Treatment Interruptions (STIs) are a potential strategy for reducing ART exposure
- **DART is also asking: 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^3 at 48 weeks



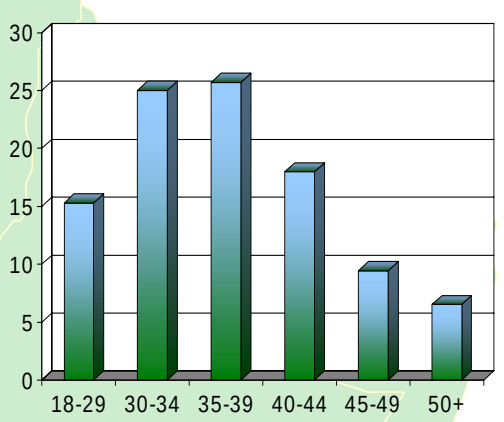
OVERVIEW of PATIENTS ENROLLED in DART

- 64% are women
  - 52 women (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 (see Figure below)
- 30% have been enrolled from the MRC Progamme 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
- 25% had WHO stage 4, 55% WHO stage 3 and 21% WHO stage 2 disease
- median CD4 was 85 cells/mm^3 (IQR 31 to 140: range 1 to 199) (see Figure below)
- all patients started ART with combivir (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 switched ZDV to D4T for toxicity (anaemia and/or neutropenia in the majority)

Baseline CD4 count



Age at randomisation



ADHERENCE to ART in DART

- Patients are prescribed 28 days ART (until their next 4-weekly clinic visit)
- Patients complete an adherence questionnaire at each clinic visit
- 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
  - 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, running out of pills, simply forgetting, feeling sick, being busy and wanting to avoid side effects

FOLLOW-UP in DART

2701 patients have been randomised to **17 May 2004** (53% of those screened)

- 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^3		Absolute CD4 ≥200 cells/mm^3	
Week 12 (N=2032)	+74 cells/mm^3 (IQR +33 to +126)	737	(36%)	720	(35%)
Week 24 (N=1552)	+86 cells/mm^3 (IQR +41 to +141)	674	(43%)	596	(38%)

Note: at randomisation, median CD4 was 85 cells/mm^3 (IQR 31 to 140: range 1 to 199)

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 similar to those 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^3 at 24 weeks**
- **A substudy assessing virological suppression with ZDV/3TC/TDF is underway**
- **DART will assess whether routine laboratory monitoring is necessary for effective ART use**
- **Follow-up in DART is planned to continue until the end of 2007**

COLLABORATORS and ACKNOWLEDGEMENTS

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Trial Steering Committee: I Weller (Chair), A Babiker, S Bahendeka, M Bassett, A Chogo Wapakhabulo, J Darbyshire, B Gazzard, C Gilks, H Grosskurth, J Hakim, A Latif, E Loeliger (observer), M Imperiale (observer), O Mugurungi, P Mugyenyi, P Naidoo (observer), M Palmer (observer), J Rooney (observer), J-M Steens (observer). **Data and Safety Monitoring Committee:** A McLaren (Chair), D Serwadda, J Matenga, C Hill, A Pozniak. **Endpoint Review Committee:** T Peto (Chair), E Katabira, M Borok, A Palfreeman, C Kityo, A Reid, P Munderi, D Gibb, C Puddephatt.

Joint Clinical Research Centre, Kampala, Uganda: P Mugyenyi, C Kityo, D Tumukunde, F Ssali, D Atwine, G Mulindwa, G Kabuye, R Byaruhanga, T Bakeimyaga-Grace, H Katabira, E Nimwesiga, G Barungi, S Atwiine, F Ahimbisibwe, S Tugume, T Otim, J Takubwa, M Mulindwa, S Murungi, J Tukamushaba, D Muebesa, H Kyomugisha, J Kagina. **University of Zimbabwe, Harare, Zimbabwe:** A Latif, J Hakim, V Robertson, A Reid, A Jamu, S Makota, G Musoro, N Ngorima, M Pascoe, F Taziwa, L Chakonza, E Chidziva, H Chirairo, S Chitsungo, F Mapinge, A Mawora, C Muvirimi, G Tinago, J Chimanzi, J Machingura, C Maweni, S Mutsai, R Warara, M Matongo, N Mdege, S Mudzingwa, M Jangano, I Machingura, K Moyo, L Vere, E Chigwedere, M Phiri. **MRC Programme on AIDS/Uganda Virus Research Institute, Entebbe, Uganda:** H Grosskurth, P Munderi, K Wangati, D Kajungu, B Amuron, D Nsibambi; R Kasirye, E Zalwango, M Nakazibwe, B Kikaire, G Nassuna, R Massa, K Fadhiru, M Namyalo, A Zalwango, L Generous, P Khauka, N Rutikarayo, W Nakahima, J Nakiyingi, P Hughes. **The AIDS Support Organisation (TASO), Uganda:** A Coutinho, B Etukoit. **Academic Alliance, Mulago Hospital, Uganda:** E Katabira, J Oyugi, A Ronald, A Kambungu, J Martin, R Nalumenya, R Nairubi, E Bulume, M Teopista, C Twijukye, F Sematala. **Imperial College, London, UK:** C Gilks, L Colquhoun, C Puddephatt, K Boocock. **MRC Clinical Trials Unit, London, UK:** J Darbyshire, DM Gibb, A Burke, D Bray, A Babiker, AS Walker, H Wilkes, P Kelleher.

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