

The DART trial:
Development of Anti-Retroviral Therapy in Africa
<http://www.ctu.mrc.ac.uk/dart>



Tuesday, 14 March, 2006

Embargo until 18:00 pm GMT

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DART trial moves patients from interrupted to continuous antiretroviral therapy (ART)

The Medical Research Council (MRC) today announced that patients enrolled into the structured treatment interruption (STI) arm in the DART study are being moved to continuous therapy (CT). The randomised trial of different strategies for the clinical management of ART, the main purpose of the DART trial, continues.

The decision to move patients to continuous therapy was made by the Trial Steering Committee following review of data by an independent Data and Safety Monitoring Committee (DSMC). The DSMC, charged with regularly reviewing trial progress and any safety issues during the five-year trial, conducted a review during early March. Interim data from 799 patients demonstrated a greater rate of clinical HIV-related disease in patients undergoing fixed length STIs (12 weeks on ART, 12 weeks off ART) compared to patients on the CT arm. All study physicians and participants are being notified of the findings and recommendations; all participants will continue to be followed up and receive ART within DART.

Although the relative difference in rates of HIV-related disease between the two arms was statistically significant, the absolute rates were relatively low at 2.0 per 100 person years in the CT arm versus 8.6 in the STI arm. Whilst most of these disease episodes in the STI arm were treatable and did not require hospitalisation, the differences between patients who interrupted therapy and patients who were treated with CT was considered clinically important. These data suggest that although many patients were able to take therapy intermittently, the strategy assessed in DART of 12 weeks off, 12 weeks on ART after 12-18 months of first starting therapy carries an increased risk of clinical symptoms in patients who have low pre-ART CD4 counts (below 200 cells/mm³) and multiple illnesses before starting treatment and cannot be recommended. Nevertheless, the need to interrupt therapy for multiple reasons, e.g. drug toxicity, is likely to remain an integral part of life-long treatment of HIV disease. Finding out how and when therapy can be interrupted safely and which patients may benefit from such strategies are still important questions and should be pursued in future trials.

Meanwhile, the DART trial is continuing with its primary objective to evaluate simplified monitoring of antiretroviral therapy in Africa.

DART is the largest trial of its kind in Africa, and one of Africa's first multi-centre, multi-country HIV treatment trials. It has recruited 3,300 volunteers at the Joint Clinical Research Centre (Kampala, Uganda), the MRC/UVRI Uganda Research Unit on AIDS (Entebbe), and the University of Zimbabwe College of Health Sciences (Harare). DART is funded by the MRC, the Rockefeller Foundation and DFID, and is coordinated by scientists from the three African sites, Imperial College London and the MRC Clinical Trials Unit. Other partners include the AIDS Support Organisation (TASO, Uganda) and The Infectious Diseases Institute in Mulago, Kampala (Uganda). The pharmaceutical companies GlaxoSmithKline, Gilead and Boehringer Ingelheim are donating antiretrovirals for the study.

DART trial design

The DART trial is an open, randomised trial set up to evaluate two strategic approaches for management of antiretroviral therapy (ART) in HIV infected adults in Africa: clinical monitoring only compared with laboratory plus clinical monitoring and structured treatment interruptions compared with continuous ART. The primary efficacy outcome measure is clinical disease progression. DART trial participants were recruited from eligible individuals who had taken no previous ART other than for the prevention of mother-to-child transmission of HIV and required ART because of the stage of their HIV disease (i.e. they had symptomatic disease (WHO clinical stage 2, 3 or 4) and a CD4 cell count below 200 cells/mm³). See: <http://www.ctu.mrc.ac.uk/dart> for more information.

Structured treatment interruption data in DART

Before patients were randomised between STI and CT, a pilot study was conducted within DART to inform the final design of the STI strategy, with the aim of minimising risk to patients subsequently randomised to STI. After the pilot study was completed, 799 patients who achieved a good immune response (CD4 \geq 300 cells/mm³ after 48 or 72 weeks of therapy) were randomised to structured treatment interruption (STI) or to continuous ART (CT). Patients in the STI arm had cycles of 12 weeks on treatment and 12 weeks off treatment, with an average of 40 weeks follow-up. The DSMC reviewed interim data available up to January 15 2006 from the 799 patients randomised to STI versus CT. Key results were as follows: there were two deaths, one in each arm; there was a higher rate of HIV-related disease in the STI arm but also a suggestion of higher antiretroviral-related toxicity rates in the CT arm. Full data will be submitted to the World AIDS conference 2006 in Toronto.

	CT	STI
Patients randomised	398	401
Number of deaths (rate per 100 person years)	1 (0.3)	1 (0.3)
Number of patients with HIV-related disease * (rate per 100 person years)	6 (2.0)	25 (8.6)
Number of patients with HIV-related disease excluding oesophageal candidiasis** (rate per 100 person years)	4 (1.3)	10 (3.3)
Number of patients with Grade 3 or 4 adverse events (rate per 100 person years)	9 (3.7)	5 (1.6)
Number of patients with toxicity-related ART changes (rate per 100 person years)	9 (3.3)	0 (0.0)

* Patients with at least one new or recurrent WHO stage 4 diagnosis (including two deaths, one in each arm)

** The most common illness was oesophageal candidiasis (thrush of the gullet), which is generally treatable without hospitalisation.