

# Development of AntiRetroviral Therapy in Africa - a randomised trial of monitoring practice and structured treatment interruptions in the management of antiretroviral therapy in adults with HIV infection in Africa

<b>Submission date</b> 18/10/2000	<b>Recruitment status</b> No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered
		<input type="checkbox"/> Protocol
<b>Registration date</b> 18/10/2000	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan
		<input checked="" type="checkbox"/> Results
<b>Last Edited</b> 27/02/2017	<b>Condition category</b> Infections and Infestations	<input type="checkbox"/> Individual participant data

## Plain English summary of protocol

[http://www.ctu.mrc.ac.uk/research\\_areas/study\\_details.aspx?s=12](http://www.ctu.mrc.ac.uk/research_areas/study_details.aspx?s=12)

## Study website

<http://www.ctu.mrc.ac.uk/dart>

## Contact information

### Type(s)

Scientific

### Contact name

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### Contact details

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## Additional identifiers

EudraCT/CTIS number

**IRAS number**

**ClinicalTrials.gov number**

**Secondary identifying numbers**

G0000068

## **Study information**

### **Scientific Title**

Development of AntiRetroviral Therapy in Africa - a randomised trial of monitoring practice and structured treatment interruptions in the management of antiretroviral therapy in adults with HIV infection in Africa

### **Acronym**

DART

### **Study objectives**

To compare, in terms of clinical HIV disease progression or death:

1. Clinical monitoring only (CMO) versus routine regular laboratory and clinical monitoring (LCM)
2. Structured Treatment Interruptions (STIs: 12 weeks on, 12 weeks off therapy) versus continuous ART, initiated if the CD4 count has increased to 200 cells/mm<sup>3</sup> or above (after 24 or 48 weeks on ART) [updated June 2006 from 300 cells/mm<sup>3</sup> or above (after 48 or 72 weeks on ART)]

The hypothesis is that CMO will result in similar outcomes to LCM, and that ART administered as pulse therapy (STI) will result in similar outcomes to continuous ART, in terms of progression of clinical HIV disease or death.

STI Pilot Study Objectives: The initial non-randomised pilot study of STIs will inform on the safety of the 12 weeks on, 12 weeks off STI strategy and only after the completion of this substudy will the second randomisation commence.

Abacavir Safety Substudy Nevirapine OR Abacavir (NORA) Substudy Objectives: This randomised sub-study of 600 patients will address issues of safe administration of Abacavir in resource poor settings and will compare the safety of Abacavir with that of Nevirapine when used in combination with Combivir.

### **Ethics approval required**

Old ethics approval format

### **Ethics approval(s)**

Protocol approved in Uganda, Zimbabwe and United Kingdom

### **Study design**

Randomised controlled trial

### **Primary study design**

Interventional

### **Secondary study design**

Randomised controlled trial

**Study setting(s)**

Not specified

**Study type(s)**

Treatment

**Participant information sheet**

Patient information can be found at: <http://www.ctu.mrc.ac.uk/dart/faq.asp>

**Health condition(s) or problem(s) studied**

Human Immunodeficiency Virus (HIV), Acquired Immunodeficiency Syndrome (AIDS)

**Interventions**

Randomisation to Clinical Monitoring Only (CMO) or Laboratory and Clinical Monitoring (LCM): 3300 patients will be randomised to CMO or LCM over a period of 1-2 years. Randomisation will be stratified by CD4 count (0-99, 100-199) clinical site and by third drug (Tenofovir DF, Nevirapine or NORA substudy).

**Structured Treatment Interruptions (STI):**

Because there were no data on STI in the African setting, where patients are likely to have low CD4 cell counts before starting ART, a non-randomised pilot study of the first 100 patients eligible for the STI randomisation was undertaken. Following the successful completion of this pilot a randomisation to STI or continuous antiretroviral therapy (ART) was opened to patients when they reached 52 or 76 weeks of DART if they had a CD4 count of  $\geq 300$  at week 48 or 72.

**NORA substudy:**

A randomised, double-blind, phase II (substudy) trial to evaluate the toxicity of Abacavir compared with Nevirapine, both in combination with Ziduvudine + Lamivudine (Combivir), as first-line antiretroviral therapy in patients participating in the DART trial.

**Intervention Type**

Drug

**Phase**

Not Applicable

**Primary outcome measure**

1. Efficacy: Progression to a new WHO stage 4 HIV event or death
2. Safety: Any serious adverse event, which is not HIV related

**Secondary outcome measures**

1. Progression to a new or recurrent WHO stage 4 HIV event or death
2. Progression to a new WHO stage 4 HIV event or death from 6 weeks after randomisation
3. Progression to a new or recurrent WHO stage 4 HIV event or death from 6 weeks after randomisation
4. Any grade 3 or 4 adverse events
5. Number and class of anti-HIV drugs received by 3 years
6. Time to cessation of first-line regimen for failure
7. Adherence as measured by questionnaire and pill counts
8. CD4 count at 3 years (provided that it is at least 2 months after restarting ART for those in the STI group)

9. HIV RNA viral load (performed retrospectively) at 3 years (providing that it is at least 2 months after restarting ART for those in the STI group)
10. HIV resistance profiles at 3 years in those with detectable viral load (providing that it is at least 2 months after restarting ART for those in the STI group)

**Overall study start date**

15/01/2003

**Completion date**

31/12/2007

## Eligibility

**Key inclusion criteria**

1. Documentation of HIV-1 infection: antibody positive serology by enzyme-linked immunosorbent assay (ELISA) test (confirmed by licensed second ELISA or Western Blot)
2. Age  $\geq 18$  years
3. Symptomatic WHO stage 2, 3 or 4 HIV disease and CD4  $< 200$  cells/mm<sup>3</sup>
4. ART naïve (except for ART use during pregnancy for the prevention of mother-to-child HIV transmission)
5. Agreement and documented informed consent to be randomised to CMO or LCM and to STI or continuous ART, if eligible
6. Life expectancy of at least 3 months

**Participant type(s)**

Patient

**Age group**

Adult

**Lower age limit**

18 Years

**Sex**

Both

**Target number of participants**

3300

**Key exclusion criteria**

1. Cannot or unlikely to attend regularly (e.g. usual residence too far from Study Centre)
2. Likelihood of poor compliance
3. Presence of acute infection (e.g. malaria, acute hepatitis, pneumococcal pneumonia, non-typhoid salmonella septicaemia, cryptococcal meningitis). Patients may be admitted after recovery of an acute infection. Patients with tuberculosis (TB) will not be enrolled while on the intensive phase of anti-tuberculosis therapy, but should be re-evaluated after the intensive phase and a decision made then about starting ART. Patients starting ART whilst on anti-tuberculosis therapy after the intensive phase will not receive NVP, nor will they be randomised into the NORA substudy.

4. On chemotherapy for malignancy
5. Laboratory abnormalities which are a contraindication for the patient to start ART (e.g. haemoglobin <8 g/dl, total white blood cell count [WBC] <0.75 x 10<sup>9</sup>/l, aspartate aminotransferase [AST] or alanine aminotransferase [ALT] >5 x the upper limit of normal [ULN], grade 3 renal dysfunction - creatinine >360 µmol/l and/or urea >5 x ULN)
6. Pregnancy or breastfeeding

**Date of first enrolment**

15/01/2003

**Date of final enrolment**

28/10/2004

## Locations

**Countries of recruitment**

England

Uganda

United Kingdom

Zimbabwe

**Study participating centre**

**MRC Clinical Trials Unit**

London

United Kingdom

NW1 2DA

## Sponsor information

**Organisation**

Medical Research Council (MRC) (UK)

**Sponsor details**

Clinical Trials Unit

222 Euston Road

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**Sponsor type**

Research council

**Website**

<http://www.ctu.mrc.ac.uk/>

**ROR**

<https://ror.org/03x94j517>

## **Funder(s)**

### **Funder type**

Government

### **Funder Name**

Medical Research Council (UK)

### **Alternative Name(s)**

Medical Research Council (United Kingdom), UK Medical Research Council, MRC

### **Funding Body Type**

Government organisation

### **Funding Body Subtype**

National government

### **Location**

United Kingdom

### **Funder Name**

Department for International Development

### **Alternative Name(s)**

Department for International Development, UK, DFID

### **Funding Body Type**

Government organisation

### **Funding Body Subtype**

National government

### **Location**

United Kingdom

### **Funder Name**

Rockefeller Foundation (USA)

**Alternative Name(s)**

The Rockefeller Foundation, Rockefeller Fdn, RF

**Funding Body Type**

Private sector organisation

**Funding Body Subtype**

Trusts, charities, foundations (both public and private)

**Location**

United States of America

**Funder Name**

Antiretroviral drugs donated by Gilead (USA), GlaxoSmithKline (UK), Boehringer-Ingelheim (Germany)

## Results and Publications

**Publication and dissemination plan**

Not provided at time of registration

**Intention to publish date****Individual participant data (IPD) sharing plan****IPD sharing plan summary**

Not provided at time of registration

**Study outputs**

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">Other publications</a>	publication on prevalence, incidence and predictors of severe anaemia	01/06/2006		Yes	No
<a href="#">Other publications</a>	publication on virological response	26/06/2006		Yes	No
<a href="#">Results article</a>	results of pharmacokinetic sub-study	30/03/2007		Yes	No
<a href="#">Results article</a>	results on interrupted versus continuous therapy	11/01/2008		Yes	No
<a href="#">Results article</a>	results on demographics of poor adherence	01/08/2008		Yes	No
<a href="#">Results article</a>	results on routine versus laboratory monitoring	09/01/2010		Yes	No
<a href="#">Results article</a>	results of observational analysis	10/04/2010		Yes	No
<a href="#">Other</a>	cost-effectiveness of routine versus laboratory monitoring	01/04		Yes	No

<a href="#">publications</a>		/2012		
<a href="#">Results article</a>	results on pregnancy and infant outcomes	01/04 /2012	Yes	No
<a href="#">Results article</a>	secondary analysis results	02/10 /2013	Yes	No
<a href="#">Results article</a>	retrospective analysis results	13/03 /2014	Yes	No
<a href="#">Results article</a>	retrospective analysis results	21/02 /2017	Yes	No