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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

Submission date
18/10/2000

Registration date
18/10/2000

Last Edited
27/02/2017

Recruitment status
No longer recruiting

Overall study status
Completed

Condition category
Infections and Infestations

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol
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

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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/mm3 or above (after 24 or 48 weeks on ART) [updated June 2006 from 300 cells/mm3 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 ≥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 ≥18 years
3. Symptomatic WHO stage 2, 3 or 4 HIV disease and CD4 <200 cells/mm3
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 10^9/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
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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?
Other publications	publication on prevalence, incidence and predictors of severe anaemia	01/06/2006		Yes	No
Other publications	publication on virological response	26/06/2006		Yes	No
Results article	results of pharmacokinetic sub-study	30/03/2007		Yes	No
Results article	results on interupted versus continous therapy	11/01/2008		Yes	No
Results article	results on demographics of poor adherence	01/08/2008		Yes	No
Results article	results on routine versus laboratory monitoring	09/01/2010		Yes	No
Results article	results of observational analysis	10/04/2010		Yes	No
Other	cost -effectiveness of routine versus laboratory monitoring	01/04		Yes	No

publications		/2012		
Results article	results on pregnancy and infant outcomes	01/04 /2012	Yes	No
Results article	secondary analysis results	02/10 /2013	Yes	No
Results article	retrospective analysis results	13/03 /2014	Yes	No
Results article	retrospective analysis results	21/02 /2017	Yes	No