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Reduction of early mortality in HIV-infected African adults and children starting antiretroviral therapy

Submission date
28/09/2011

Recruitment status
No longer recruiting

Registration date
18/10/2011

Overall study status
Completed

Last Edited
01/07/2024

Condition category
Infections and Infestations

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

Plain English summary of protocol

Background and study aims
At the moment, there is no cure for HIV, the virus that causes AIDS, but there are medicines called anti-retrovirals (ARVs) that can control HIV and keep people well for a long time. Unfortunately in many African countries patients only come for treatment when they are very sick and HIV has already had a big effect on their bodies. Often patients have malnutrition, diarrhoea, infections such as tuberculosis, serious lung infections (pneumonia) and other severe infections. This means that many more people die during the first 3 months after starting ARVs compared to richer countries. The aim of this study is to find out whether or not giving extra treatments during the first 3 months of taking ARVs will help sick people with HIV and prevent some of them from dying early, or whether giving extra treatments doesn't make any difference and makes it harder to take ARVs. The extra treatments are:
1. An extra ARV drug added to the three standard ARVs (i.e., four ARVs in total)
2. A single pill containing cotrimoxazole (septrin) and isoniazid (to fight TB), plus fluconazole (to fight thrush) and azithromycin (to fight bacterial infections) and albendazole (to kill worms). All of these are medicines which fight against common infections in sick people with HIV
3. Extra food supplements to provide high energy food

Who can participate?
People aged 5 years and older who are HIV positive and also have low immunity measured by a blood test called the CD4 count, and therefore have a higher risk of getting sick.

What does the study involve?
Participants receive three ARVs and cotrimoxazole, together with any other medicines they are already taking or need for treatment of any infections. In addition, they are randomly allocated to receive or not receive each of the three extra treatments (ARVs, medicines to fight other infections, and nutritional supplements) for the first 3 months. After the first 3 months they continue to take three standard ARVs to fight HIV, cotrimoxazole (septrin) to help to protect against infections long-term, and isoniazid to protect against TB. Participants have regular clinic visits to see a nurse and a doctor and blood samples are taken to check for any side effects of the medicines. They are followed carefully for any side effects and responses to the treatments.

Some of the blood is used to work out how much of the ARVs are actually getting into their blood where they can fight the HIV virus. After almost 1 year (48 weeks), participants leave the study and their care is provided by their country's national health system, including provision of ARVs in line with the national programme.

What are the possible benefits and risks of participating?
Studies in rich countries have shown that taking four ARVs produces a very strong response to HIV so we want to see if taking an extra fourth ARV for the first 3 months of treatment reduces the risk of dying after people start ARVs. The risks are that there could be side-effects to this extra medicine, or that taking four medicines may be more difficult than three – if people don't take all their ARVs all the time, the HIV virus can develop resistance to the drugs which stops them working over the longer term. The potential benefits are that the immune system may respond better both initially and over the long term if a fourth ARV is used in the first 3 months. Similarly, whilst adding other extra medicines to fight infections could reduce the risk of dying from these infections, it might also increase the risk of other side-effects, some of which can be serious, and might also make it harder to take all the ARVs. This study is designed to find out whether the potential benefits outweigh the potential risks.

Where is the study run from?
The study will enrol 1800 people in four countries: Kenya, Malawi, Uganda and Zimbabwe. It is co-ordinated by the Medical Research Council in London (UK)

When is the study starting and how long is it expected to run for?
September 2012 to August 2015

Who is funding the study?
The study is funded by the UK Medical Research Council, the Department for International Development and the Wellcome Trust (UK)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
NCT01825031

Protocol serial number
G1100693

Study information

Scientific Title
Reduction of Early mortALITY in HIV-infected African adults and children starting antiretroviral therapy: a randomised controlled trial

Acronym
REALITY

Study objectives
To identify effective, safe and acceptable interventions to reduce early mortality in HIV-infected adults, adolescents, and older children (5 years or more) initiating antiretroviral therapy (ART).

Hypotheses:
1. Addition of 12 weeks of an integrase inihibitor (raltegravir) to initial antiretroviral therapy will reduce mortality, compared to standard of care first-line 3-drug 2-class ART.
2. Addition of enhanced OI prophylaxis with immediate isoniazid/pyridoxine (and cotrimoxazole), 12 weeks fluconazole, plus single-dose albendazole and 5 days of azithromycin at ART initiation, will reduce mortality, compared to standard of care cotrimoxazole prophylaxis plus continuation of any pre-existing prophylaxis (i.e. only starting cotrimoxazole) for the first 12 weeks followed by isoniazid prophylaxis from 12 weeks onwards.
3. Supplementation with Ready-to-Use Supplementary Food (RUSF) will reduce mortality, compared to standard of care nutritional support to those with poor nutritional status according to local guidelines

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethical approval was granted by the appropriate national ethics committees in Kenya, Malawi, Uganda and Zimbabwe as well as University College London Ethics Committee (UK)

Study design
2x2x2 open-label factorial multi-centre randomized controlled trial conducted in four countries

Primary study design
Interventional

Study type(s)

Treatment

Health condition(s) or problem(s) studied
Human Immunodeficiency Virus (HIV)

Interventions
Three methods to reduce early mortality following antiretroviral therapy (ART) initiation:
1. Increasing the potency of ART with a 12 week induction period using 4 antiretroviral drugs from 3 classes
2. Augmented prophylaxis against opportunistic/bacterial infections and helminths for 12 weeks
3. Macronutrient intervention using ready-to-use supplementary food for 12 weeks

Each intervention will be compared with standard care, which in previously untreated patients presenting late with very low CD4 counts is to initiate ART with 3 drugs from 2 classes, together with cotrimoxazole prophylaxis and macronutrient intervention only for those with low BMI (or low weight-for-height/mid-upper arm circumference in children).

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Albendazole, azithromycin, cotrimoxazole, fluconazole, isoniazid, pyridoxine, raltegravir

Primary outcome(s)
Mortality over the first 24 weeks after starting anti-retroviral therapy

Key secondary outcome(s))
1. Mortality in 48 weeks after starting anti-retroviral therapy
2. Safety:
2.1. Serious adverse events
2.2. Grade 4 adverse events
2.3. Adverse events leading to modification of ART or other study drugs
3. Endpoints relating to the specific mechanisms of action of each intervention
3.1. Anti-HIV: CD4 levels
3.2. Anti-infection: incidence of tuberculosis, cryptococcal and candida disease, severe bacterial infections
3.3. Nutritional: body mass index (BMI), weight and body fat assessed by bioimpedance analysis (BIA), height (in children), grip strength
4. Hospital inpatient episodes and total days admitted
5. Adherence to ART and acceptability of each strategy measured by pill counts and questionnaire

Completion date
31/08/2015

Eligibility

Key inclusion criteria
1. Aged 5 years or older (the lower age limit is because CD4 counts are less reliable predictors of immunodeficiency under 5 years: CD4 counts are recommended by WHO guidelines in older children)
2. Documented HIV infection by HIV ELISA
3. Naive to ART except for drugs given or received to prevent mother-to-child transmission
4. CD4 T-cell count <100 cells/mm3 on blood test taken at screening for REALITY
5. Results of screening haematology and biochemistry tests available
6. Patient/carer provide informed consent (and children <18 years assent, as appropriate according to their age and knowledge of HIV status)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
5 years

Sex
All

Total final enrolment
1805

Key exclusion criteria
1. Contraindications to any proposed antiretroviral drugs (including integrase inhibitors), isoniazid, fluconazole, albendazole or azithromycin
2. Pregnant or breastfeeding or intending to become pregnant during the first 12 weeks of the study

Date of first enrolment
18/06/2013

Date of final enrolment
10/04/2015

Locations

Countries of recruitment
Kenya

Malawi

Uganda

Zimbabwe

Study participating centre
Joint Clinical Research Centre
Fort Portal
Uganda
-

Study participating centre
Joint Clinical Research Centre
Mbarara
Uganda
-

Study participating centre
Joint Clinical Research Centre
Mbale
Uganda
-

Study participating centre
Joint Clinical Research Centre
Gulu
Uganda
-

Study participating centre
University of Zimbabwe Clinical Research Centre (UZCRC)
Harare
Zimbabwe
-

Study participating centre
University of Malawi
Department of Medicine
Blantyre
Malawi
-

Study participating centre
Moi University Clinical Research Centre (MUCRC)
Eldoret
Kenya
-

Study participating centre
KEMRI Wellcome Trust Centre
Kilifi
Kenya
-

Sponsor information

Organisation
Medical Research Council (UK)

ROR
https://ror.org/03x94j517

Funder(s)

Funder type
Government

Funder Name
Global Health Trials Scheme [Department for International Development, Medical Research Council & Wellcome Trust] (UK) ref: G1100693/1

Results and Publications

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?

Results article		20/07/2017		Yes	No
Results article		01/05/2018		Yes	No
Results article		04/12/2018		Yes	No
Results article		04/03/2018	01/10/2019	Yes	No
Results article		04/03/2018	01/10/2019	Yes	No
Other publications	Calprotectin as a biomarker	27/11/2020	21/12/2020	Yes	No
Other publications	Biomarkers of mortality	28/06/2024	01/07/2024	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes