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Metformin treatment for diabetes prevention in Africa

Submission date	Recruitment status	[X] Prospectively registered
27/06/2020	No longer recruiting	[_] Protocol
Registration date	Overall study status	[_] Statistical analysis plan
09/07/2020	Ongoing	[_] Results
Last Edited	Condition category	[_] Individual participant data
17/01/2025	Nutritional, Metabolic, Endocrine	[X] Record updated in last year

Plain English summary of protocol

Background and study aims
The numbers of people with type 2 diabetes in Africa are rising rapidly. People who are living with HIV and have been on treatment for HIV seem to be at high risk for developing diabetes. We are looking for ways to prevent people who have already have raised blood sugar (called prediabetes), from going on to develop diabetes.
We will test a drug called metformin in HIV infected persons with pre-diabetes to see what effect, if any, it has on blood glucose. We will be testing whether Metformin can stop or delay a person developing diabetes. Metformin has been tested for this purpose in high-income countries, but not in Africa and not among those who are on HIV treatment. The study will be conducted in Tanzania.

Who can participate?
Adults over the age of 18, who are HIV-infected and have been stable on treatment for HIV-infection for a minimum of 6 months and who have pre-diabetes.

What does the study involve?
We will screen people in HIV treatment programmes to identify those who have prediabetes. Screening will be done using both the fasting glucose and the oral glucose tolerance tests. If patients agree to take part in the study, we will allocate them at random to one of two groups. One group will receive a slow-release preparation of metformin which only needs to be taken once a day; and the other group will receive a placebo that looks like the metformin and also is taken once a day. Neither the patient or the doctors will know who is receiving the drug and who is receiving the placebo (this is called a randomised double-blind placebo-controlled trial). Each participant will be followed up for up to 4 years. At the end of the study and at yearly intervals during the study, we will test the blood sugar levels in the participants. We will use the oral glucose tolerance test to do this. This is the gold standard for testing for diabetes. The primary objective of the trial is to determine the number of participants who develop diabetes in the two groups over the follow-up period. All participants in the trial will receive basic advice on diet and lifestyle to prevent diabetes.

What are the possible benefits and risks of participating?
The benefits of participating are that the study will provide information on a possible prevention

strategy for those that are at risk of developing diabetes. There are risks associated with taking metformin. A proportion of people who take this drug experience side effects, particularly of the gastro-intestinal system like nausea, abdominal pain, vomiting and diarrhoea, although these symptoms should decrease with time. There are also more serious side effects like the development of a condition calls lactic acidosis, but is very rare and unlikely to occur. We will be monitoring all participants in the study closely.

Where is the study run from?
This study has been run from the UK and the Republic of Tanzania in East Africa. In Tanzania we will recruit patients for this study from 5 sites in Dar es Salaam. These are Amana Regional Referral hospital, Temeke Regional Referral Hospital, Mwanyanamala Hospital, Mnazi Moja Hospital, and the Shree Hindu Mandal Hospital.

When is the study starting and how long is it expected to run for?
Preparation for this study began in April 2020. Testing of patients to see who would be able to join the study began in October 2021, and the follow up of the all participants will be complete by the start of 2026.

Who is funding the study?
This study is funded by grants from the European & Developing Countries Clinical Trial Partnership (EDCTP), including an initial grant from EDCTP2 and further funding from EDCTP3.

Who is the main contact?
Prof Shabbar Jaffar, s.jaffar@ucl.ac.uk

Study website
https://www.inteafrica.org/related-projects/meta-trial/

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
Nil known

Study information

Scientific Title
Preventing and delaying the development of diabetes in Africa: a randomised placebo-controlled double-blind phase III trial of metformin in people living with HIV-infection and pre-diabetes.

Acronym
META

Study objectives
Can treatment with Metformin prevent or delay the development of diabetes among HIV-infected persons on antiretroviral therapy in Africa?

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 21/10/2021, Research Ethics Committee of the Liverpool School of Tropical Medicine (Pembroke Place, Liverpool, L3 5QA, UK; +44(0)151 705 3100; lstmrec@lstmed.ac.uk); Ref 20-089
2. Approved 06/02/2021, Medical Research Coordinating Committee of the National Institute of Medical Research of Tanzania (National Institute for Medical Research, 3 Barack Obama Drive, P. O.Box 9653, Dar es Salaam; +255 22 21211400; nimrethics@gmail.com), ref NIMR/HQ/R.8a/Vol.IX /3613

Study design
Randomized placebo-controlled double-blind phase III trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)

Prevention

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet.

Health condition(s) or problem(s) studied
Prediabetes, HIV-infection

Interventions
Metformin extended release at a dose of 2000mg per day and matching placebo. The follow up period will be three years. Eligible patients will be randomised using permuted blocks in a 1:1 ratio, stratified by health facility and sex.
All participants in the trial will receive basic advice on diet and lifestyle to prevent diabetes.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Metformin extended release

Primary outcome measure
Current primary outcome measure as of 17/01/2025:

Incidence of diabetes, measured over up to a 48-month follow-up period. The diagnosis of diabetes will be made using an oral glucose tolerance test, which will be conducted annually

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Previous primary outcome measure:

Incidence of diabetes, measured over a 36-month follow-up period. The diagnosis of diabetes will be made using an oral glucose tolerance test, which will be conducted annually

Secondary outcome measures
1. Prevalence and incidence of glycaemia related complications, measured at the start and end of the study, and at any point during follow up where clinically indicated. The study will assess for the following diabetes related complications:
1.1. Retinopathy using retinal photography
1.2. Neuropathy using the Neuropathy Disability Score and the Diabetic Neuropathy Symptom Score
1.3. Nephropathy using serial assessment of eGFR
2. Time to diabetes-free survival, measured at the end of study follow up
3. Cost consequences. Costs associated with lost productivity, and health services and social care resource use will be collected, during and at the end of the study
4. Health-related quality-of-life, measured using EuroQol EQ-5D and 12-item Short Form-12
5. Cost-effectiveness, measured at the end of study follow up. Information on costs will be collected using economic patient questionnaires to measure patients related costs (out-of-

pocket expenses, costs associated with lost productivity) as well as costs of all resources used by patients (health service and social care resource use costs). The collected costs and health outcomes will be used to estimate possible cost savings and/or cost-effectiveness of metformin (i.e., cost changes per patient, cost per diabetes case prevented, and QALYs gained).

Overall study start date
01/04/2020

Completion date
28/02/2026

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 12/12/2022:
1. Adult HIV-positive persons on antiretroviral therapy (ART) for at least 6 months and considered stable on treatment (i.e. in regular attendance for care). Considered by the clinical team to be in routine care with a plasma viral load of less than 1000 copies per ml taken within the last 12 months.
2. Either impaired fasting glucose (≥6.1 to ≤6.9 mmol/L) and/or impaired glucose tolerance at 2 hours (≥7.8 to <11.10 mmol/L)
3. Planning to remain in the area for > 12 months
4. Written informed consent

Previous participant inclusion criteria:
1. HIV-positive and stable on the same antiretroviral therapy for at least 6-months
2. Attending the HIV clinic regularly for at least 6 months
3. Impaired fasting glucose of between 6.1 to 6.9 mmol/L and/or impaired glucose tolerance at 2 hours of 7.8 to 11.10 mmol/L
4. Planning to remain in the area for > 1 year
5. Willing to provide written informed consent

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
2100

Total final enrolment
1691

Key exclusion criteria
Current participant exclusion criteria as of 12/12/2022:
1. Pregnant women
2. Patients who were participants of the META Phase II study
3. Renal disease or renal dysfunction (eGFR<45)
4. Signs and symptoms of any form of acute metabolic acidosis including lactic acidosis and diabetic ketoacidosis
5. Other acute conditions with:
5.1. The potential to alter renal function including dehydration, severe infection or shock
5.2. The potential to cause tissue hypoxia including decompensated heart failure, respiratory failure, recent myocardial infarction, shock
6. Congestive heart failure requiring pharmacological treatment
7. Clinical evidence of liver disease
8. Evidence of alcoholism or acute alcohol intoxication
9. Known hypersensitivity to metformin or any excipients associated with the preparation (in this case: Magnesium stearate, sodium carboxymethylcellulose, hypromellose)
10. Other acute conditions requiring hospital admission or emergency clinical intervention, including blood pressure >180/110 mmHg, haemoglobin<6.5g/dL for women or haemoglobin <7. 0g/dL for men (grade 3); white cell count <1.5 x 109 cells/mm3(grade 3) and any baseline liver function derangements at grade 4 according to DAIDS criteria.

Previous participant exclusion criteria:
1. Pregnant women
2. Renal disease or renal dysfunction (eGFR < 45)
3. Signs and symptoms of any form of acute metabolic acidosis including lactic acidosis and diabetic ketoacidosis
4. Other acute conditions with:
4.1. The potential to alter renal function including: dehydration, severe infection or shock
4.2. The potential to cause tissue hypoxia including decompensated heart failure, respiratory failure, recent myocardial infarction, shock
5. Congestive heart failure requiring pharmacological treatment
6. Clinical evidence of liver disease
7. Evidence of alcoholism or acute alcohol intoxication
8. Known hypersensitivity to metformin or any excipients associated with the preparation (in this case: Magnesium stearate, sodium carboxymethylcellulose, hypromellose)
9. Other acute conditions requiring hospital admission

Date of first enrolment
26/10/2021

Date of final enrolment
31/03/2024

Locations

Countries of recruitment
Tanzania

Study participating centre

Amana Hospital
Uhuru Street
Dar es Salaam
Tanzania
-

Study participating centre
Hindu Mandal Hospital
Chusi Street
Dar es Salaam
Tanzania
-

Study participating centre
Mwananyamala Hospital
61665 Kinondoni
Dar es Salaam
Tanzania
-

Study participating centre
Temeke Regional Referral Hospital
Temeke Street
Temeke District
Dar es Salaam
Tanzania
-

Study participating centre
Mnazi Moja Hospital
Bibi Titi Mohamed Road
Dar es Salaam
Tanzania
-

Sponsor information

Organisation
University College London

Sponsor details
Faculty of Population Health Sciences, Gower Street
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Sponsor type
University/education

Website
https://www.ucl.ac.uk/population-health-sciences

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Charity

Funder Name
European and Developing Countries Clinical Trials Partnership

Alternative Name(s)
Le partenariat Europe-Pays en développement pour les essais cliniques, A Parceria entre a Europa e os Países em Desenvolvimento para a Realização de Ensaios Clínicos, The European & Developing Countries Clinical Trials Partnership, European and Developing Countries Clinical Trials, EDCTP

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
Netherlands

Results and Publications

Publication and dissemination plan

A publication policy is in preparation. It is intended that study findings will be published in a high-impact peer-reviewed journal. Research papers will be Open Access. Research data will also be made open access in accordance with EDCTP guidelines on data sharing.
Dissemination will be done through academic channels (peer-reviewed journal publications, conference abstracts/proceedings), the project website, public and professional seminars, factsheets, social media and press activities.

Intention to publish date
31/12/2026

Individual participant data (IPD) sharing plan
The current data sharing plans for this study are unknown and will be available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date