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Integrated care to improve outcomes for adults with advanced HIV disease

Submission date
02/11/2021

Recruitment status
No longer recruiting

Registration date
05/11/2021

Overall study status
Completed

Last Edited
10/02/2026

Condition category
Infections and Infestations

[X] Prospectively registered

[X] Protocol

[_] Statistical analysis plan

[X] Results

[_] Individual participant data

Plain English summary of protocol

Background and study aims
Tuberculosis (TB) remains the most common cause of death in people living with HIV. One-quarter of the world's population are estimated to have TB infection which without tuberculosis preventative treatment may progress to cause TB disease. There is strong evidence that TB preventative treatment – as recommended for all people living with HIV by the World Health Organisation (WHO) – prevents TB infection from progressing to TB disease. This study aims to investigate the best strategy for providing tuberculosis preventative treatment for the prevention of TB disease for people living with HIV and cryptococcal meningitis.

Who can participate?
Patients aged over 18 years who have both HIV infection and cryptococcal meningitis

What does the study involve?
Participants will all be given a short course of tuberculosis preventative treatment consisting of 1 month of isoniazid and rifapentine. They will be randomly allocated to start treatment either as an inpatient or as an outpatient. Participants will be followed up until week 18 to determine treatment completion, safety and effectiveness.

What are the possible benefits and risks of participating?
By taking tuberculosis preventative treatment it is anticipated that participants will have a reduced chance of developing TB disease or dying from TB. Participants will be cared for by the specialist meningitis research team. There is the possibility of side effects from the anti-tuberculous drugs used in the study. Rifapentine and isoniazid are both usually safe and well-tolerated but side effects have been reported. Most patients taking rifapentine will notice that their urine, tears, sweat and sputum turns red. This is temporary side effect and the colour will return to normal once a participant stops taking the rifapentine. Some patients report feeling generally unwell when taking rifapentine with flu-like symptoms or nausea, loss of appetite but these symptoms are again temporary and not generally harmful. Serious complications associated can occur and include liver problems, kidney problems, hypersensitivity reactions, or abnormalities with blood cells. These complications are rare. Participants will be given ample education about possible reactions. Participants will be reviewed regularly by the specialist research team and will have regular safety monitoring blood tests.

Where is the study run from?
1. London School of Hygiene & Tropical Medicine (LSHTM) (UK)
2. Infectious Diseases Institute (Uganda)

When is the study starting and how long is it expected to run for?
June 2021 to November 2024

Who is funding the study?
Wellcome Trust as part of the Wellcome Global Health Research Clinical PhD Fellowship programme (LSHTM) (UK)

Who is the main contact?
Dr Jayne Ellis
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Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

Protocol serial number
V2.5, 222938/Z/21/Z

Study information

Scientific Title
Integrated management of cryptococcal and opportunistic infections to improve outcomes in advanced HIV disease: a strategy trial

Acronym
IMPROVE

Study objectives

Research question: What is the preferred strategy (safety and feasibility) for delivery of 1HP (1 month of isoniazid and rifapentine) TB preventive therapy (TPT) for adults with HIV-associated cryptococcal meningitis?

Study hypothesis: Early (inpatient initiation) 1HP TPT will be non-inferior to standard (outpatient initiation) 1HP TPT with respect to TB-disease free 1HP treatment completion in individuals in whom active TB has been excluded, and 1HP TPT is feasible (adherence and tolerability) and safe (adverse events) in patients with HIV-associated cryptococcal meningitis.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 05/08/2021, Mulago Research and Ethics Committee (PO Box 7051, Kampala, Uganda; +256 (0) 41554008/1; mulagohospitalrec@gmail.com), ref: MHREC 2021-25
2. Approved 07/06/2021, London School of Hygiene & Tropical Medicine Observational / Interventions Research Ethics Committee (Room LG36, Keppel Street, London, WC1E 7HT, UK; +44 (0)20 7927 2221; ethics@lshtm.ac.uk), ref: 24059

Primary study design
Interventional

Study design
Nested randomized strategy trial

Study type(s)
Prevention

Health condition(s) or problem(s) studied
HIV-associated cryptococcal meningitis

Interventions
A nested randomised strategy trial to evaluate the safety and feasibility of two strategies for the delivery of TB preventive therapy (TPT) in HIV-associated cryptococcal meningitis: inpatient initiation (early, week 2) or outpatient initiation (standard, week 6) delivery of 1HP (1 month of isoniazid and rifapentine) TPT.

Participants will be randomised individually, using random block size, using a computer-generated programme. Randomisation will be stratified by study sites only. Participants will be randomised to receive either a 1-month course of rifapentine 600 mg daily plus isoniazid 300 mg daily (1HP) to be initiated as an inpatient or as an outpatient. Amongst participants in the inpatient initiation arm, 1HP TPT will be started in hospital during the second week after cryptococcal meningitis diagnosis. Amongst participants in the outpatient initiation arm, 1HP TPT will be started in the outpatient clinic during the sixth week after cryptococcal meningitis diagnosis.

Intervention Type
Drug

Phase
Phase II/III

Drug/device/biological/vaccine name(s)
Rifapentine, isoniazid

Primary outcome(s)
TB-disease free 1HP treatment completion at 18 weeks (after cryptococcal meningitis diagnosis and commencement of anti-fungal therapy). Treatment completion is defined as participant-reported adherence to >90% of the study medications for the duration of the trial. TB disease-free at 18 weeks is defined as (1) not receiving a diagnosis of active TB disease for the duration of the trial and (2) a negative WHO TB symptom screen at trial completion.

Key secondary outcome(s)
1. 1HP treatment completion (defined as participant-reported adherence to >90% of the study medications) at 18 weeks
2. 1HP discontinuation of the study drugs for ≥5 consecutive days for any reason, measured using participant interviews and pill counts at 18 weeks
3. Incidence of grade 3-4 adverse events and serious adverse events (SAEs), measured using clinical and laboratory review at 18 weeks
4. Incidence of drug-induced liver injury defined as elevation of blood transaminase (ALT) alone ≥5x ULN (or ALT ≥3x ULN if bilirubin abnormal) or alkaline phosphatase (ALP) alone ≥2x ULN, measured at 18 weeks
5. Incident active TB (defined as clinician diagnosed TB based upon clinical syndrome and/or radiological evidence and/or mycobacteriological evidence), measured at 18 weeks
6. Survival measured using clinical review at 18 weeks
7. Fluconazole, rifapentine and dolutegravir concentrations measured using liquid chromatography-tandem mass spectrometry on days 5 and 14 of 1HP (for n=20 participants)

Completion date
25/11/2024

Eligibility

Key inclusion criteria
HIV-positive adults (aged ≥18 years) with HIV-associated cryptococcal meningitis (CSF CrAg positive)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
120 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Active TB disease (as evidenced by any positive TB screening test or taking TB therapy at time of screening)
2. Jaundice
3. Abnormal liver function tests (bilirubin >3.5 mg/dl or ALT >200 IU/L)
4. Active hepatitis B infection (defined as hepatitis B surface antigen positive)
5. Known chronic liver disease
6. A clinical syndrome which in the opinion of the attending clinician, puts the patient at significant risk if he/she were to participate in the 1HP trial
7. Pregnant
8. Breastfeeding
9. Hypersensitivity to rifamycins or isoniazid
10. Contraindicated medication(s) (e.g. protease inhibitor)

Date of first enrolment
25/11/2021

Date of final enrolment
25/11/2023

Locations

Countries of recruitment
Uganda

Study participating centre
Kiruddu National Referral Hospital
Kampala
Uganda
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Sponsor information

Organisation
London School of Hygiene & Tropical Medicine

ROR
https://ror.org/00a0jsq62

Funder(s)

Funder type
Research organisation

Funder Name
Wellcome Trust

Alternative Name(s)
Wellcome, WT

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The anonymised database will be shared with the journal, if required, upon request from Dr Jayne Ellis (jayne.ellis1@lshtm.ac.uk).

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		06/02/2026	10/02/2026	Yes	No
Protocol article		05/06/2024	16/07/2024	Yes	No
Participant information sheet	version 5	23/07/2021	05/11/2021	No	Yes
Participant information sheet	Luganda version 5	23/07/2021	05/11/2021	No	Yes
Protocol file	version 2.5	19/10/2021	05/11/2021	No	No