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HARVEST trial - improving outcomes from TB meningitis with high-dose oral rifampicin

Submission date
23/05/2019

Recruitment status
No longer recruiting

Registration date
17/06/2019

Overall study status
Completed

Last Edited
09/05/2025

Condition category
Infections and Infestations

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Tuberculous meningitis accounts for 1-5 % of all TB infections and carries a high case-fatality (up to 50%) and many survivors are left with long-term disabilities. Rifampicin is the most important anti-TB drug but at the currently recommended dose (10 mg/kg) it fails to penetrate into the brain and spinal fluid adequately. This trial is testing whether giving a much higher dose of rifampicin by mouth, in addition to the normal anti-TB drugs, can reduce death and disability caused by TB meningitis.

Who can participate?
Patients aged 18 and over with first episode tuberculous meningitis suspected by attending physician and anti-TB treatment planned

What does the study involve?
Participants are allocated by chance to receive either four rifampicin 300 mg capsules in addition to standard fixed dose combination TB treatment, or standard fixed dose combination TB treatment. Participants are followed up in hospital until discharge and then as an outpatient for 12 months.

What are the possible benefits and risks of participating?
The high dose rifampicin may be more effective at treating the infection so the participants' chance of dying or being left with a disability may be reduced (though this won't be known until the end of the trial). More intensive monitoring of blood tests and clinical status may allow complications to be picked up and treated earlier than in they would in the normal care environment. Transport and costs of follow-up are covered by the study which may reduce financial burden on the participant. Possible risks of participation include: side effects or toxicity from the high-dose rifampicin; more frequent blood tests and an additional lumbar puncture; and the high dose rifampicin may not have an impact on clinical outcomes.

Where is the study run from?
1. Infectious Diseases Institute (Uganda)

2. University of KwaZulu Natal (South Africa)
3. Eijkman-Oxford Clinical Research Unit (Indonesia)
4. Universitas Padjadjaran (Indonesia)

When is the study starting and how long is it expected to run for?
November 2019 to June 2025

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
Dr Fiona Cresswell
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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
MHREC 1554

Study information

Scientific Title

High-dose oral rifampicin to improve survival from adult tuberculous meningitis: a double-blinded randomised placebo-controlled Phase III trial

Acronym
HARVEST

Study objectives
High dose oral rifampicin (35 mg/kg) alongside other regular first-line antituberculous drugs will improve survival and neurological outcomes from Tuberculous meningitis compared to standard of care TB treatment.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approvals have been received from 8 regulatory authorities across the 3 participating countries:
UGANDA
Approved 17/06/2020, Mulago National Referral Hospital IRB (Mulago National Referral Hospital, P.O. Box 7051, Kampala, Uganda; +256 414 53 25591; admin@mulago.or.ug), ref: MHREC 1554.
National Drug Authority; ref: CTA0118
Uganda National Council of Science and Technology; ref: HS428ES

SOUTH AFRICA
Approved 20/04/2021, University of KwaZulu-Natal Biomedical Research Ethics Committee (Research Ethics Office, Westville Campus, Govan Mbeki Building; Private Bag X54001, Durban 4000; BREC@ukzn.ac.za); ref: BFC003/19
South Africa Health Product Regulatory Authority; ref: 20200331

INDONESIA
Approved 22/07/2020, Universitas Indonesta Fakultas Kidokteran (Gedung Fakultas Kedokteran Ul, Jl. Salemba Raya No.6, Jakarta 10430, PO.Box 1358); +62.21.3912477, 3193037 1, 31 930373, 3922977, 3927360, 31 53236; E. humas @fk.ui.ac.id, office @fk.ui.ac.id); ref: 19-03-0238
Universitas Padjadjaran Research Ethics Committee (Jl. Prof Eyckman No. 38 Bandung 40161; 022-2038697; etik.unpad@gmail.com); ref: 0719070991
National Agency of Drug and Food Control (Badan Pengawas Obat dan Makanan); ref: BPOM-B-RG.01.06.32.321.08.20.513

Study design
Double-blinded parallel group randomised placebo-controlled Phase III trial

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital

Study type(s)
Treatment

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

Health condition(s) or problem(s) studied
Tuberculous meningitis

Interventions
Participants are allocated by chance to receive either:
1. Four oral rifampicin 300-mg capsules in addition to standard fixed-dose combination TB treatment
2. Standard fixed-dose combination TB treatment
Participants are followed up in hospital until the time of discharge and then as an outpatient for 12 months.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Rifampicin

Primary outcome measure
6-month survival

Secondary outcome measures
1. 12-month survival
2. Functional and neurocognitive outcomes measured using the following instruments:
2.1. Normalization of mental status with Glasgow coma scale score (GCS) of 15 and maintained for >2 days (among those with GCS <15 at study entry). A substantial proportion of TBM patients (~50%) present with altered mental status and depressed consciousness. In these participants, early response to treatment is assessed by determining the days from randomization until observation of a GCS of 15 which is achieved for >2 consecutive days
2.2. Functional outcomes assessed by Liverpool Outcome Score at month 6 (Appendix C)
2.3. Quantitative neurocognitive performance Z-scores (QNPZ-8) at 2 and 12 months (Uganda only). QNPZ-8 is derived from a test battery, which includes:
2.3.1. Grooved Pegboard test
2.3.2. Colour Trails 1 and 2 tests
2.3.3. WAIS-III Digit Symbol test
2.3.4. Finger Tapping test
2.3.5. WHO-UCLA Auditory Verbal Learning Test
2.3.6. Semantic Verbal Fluency test (category fluency)
3. Safety and tolerability endpoints:
3.1. Clinical AEs, grade 3-5 as classified by Division of AIDS (DAIDS) Toxicity Scale
3.2. Laboratory AEs, grade 3-5 as classified by DAIDS Toxicity Scale
3.3. All Serious AEs (SAEs)

3.4. Drug-induced liver injury (grade 3-5)
§ Alanine transaminase (ALT) or aspartate transaminase (AST) >5x upper limit of normal (ULN)
3.5. Discontinuation of TB treatment for >5 days in the first 8 weeks for any cause
4. Cumulative days of hospitalization (and re-hospitalization)
5. Incidence of re-hospitalization for neurologic deterioration
6. Incidence and management of drug-induced liver injury

Overall study start date
01/11/2019

Completion date
01/06/2025

Eligibility

Key inclusion criteria
1. First episode TBM suspected by attending physician (>3 days of meningitis symptoms and CSF abnormalities) and anti-TB treatment planned
2. Age ≥18 years
3. Provision of written informed consent by participant or surrogate

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
500

Key exclusion criteria
1. Presence of jaundice, known liver cirrhosis, or known elevated ALT >5x ULN
2. More than 5 doses of any TB treatment received within the previous 7 days
3. Known allergy to: isoniazid, rifampicin, ethambutol, or pyrazinamide
4. Known current/previous rifampicin-resistant M.tb infection
5. Additional active and confirmed CNS infection
6. Corticosteroids contraindicated
7. Cannot or unlikely to attend regular clinic visits
8. Pregnancy or breastfeeding
9. Known renal failure with eGFR <30 ml/min by Modification of Diet in Renal Disease (MDRD) Study equation
10. HIV Protease Inhibitor ongoing use

Date of first enrolment

01/01/2020

Date of final enrolment
01/06/2024

Locations

Countries of recruitment
Indonesia

South Africa

Uganda

Study participating centre
Infectious Diseases Institute
Kampala
Uganda
PO Box 22418

Study participating centre
University of KwaZulu Natal
719 Umbilo Road
Durban
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4001

Study participating centre
Eijkman-Oxford Clinical Research Unit
University of Oxford; Faculty of Medicine Universitas Indonesia
Jl Diponegoro 69
Jakarta
Indonesia
10430

Study participating centre
Universitas Padjadjaran
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Sponsor information

Organisation
Makerere College of Health Sciences

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Sponsor type
University/education

Website
https://www.idi-makerere.com

ROR
https://ror.org/03dmz0111

Funder(s)

Funder type
Government

Funder Name
Medical Research Council

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

Results and Publications

Publication and dissemination plan

The researchers plan to publish the protocol in Wellcome Open Research once they have ethical approval.
The main trial paper will be published open access within 6 months of the last participant completing follow up.
Additional sub-studies will be published open access at the appropriate intervals.
The Meningitis Research Foundation is the researchers' communications partner to maximise the impact of the results. The researchers will engage other stakeholders in trial countries.

Intention to publish date

01/08/2025

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are/will be available upon request from Dr Fiona Cresswell, IDI/LSHTM (fiona.cresswell@lshtm.ac.uk).

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	25/08/2020	23/10/2020	Yes	No