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Improving diagnosis and treatment of HIV-associated Tuberculous meningitis

Submission date
09/03/2018

Recruitment status
No longer recruiting

Registration date
24/04/2018

Overall study status
Completed

Last Edited
07/05/2025

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
Tuberculous meningitis (TBM), the most severe form of Tuberculosis, is caused by bacteria and affects the brain and spine. Over 100,000 children and adults suffer from TBM yearly, of which up to half die and a quarter are left disabled. These appalling outcomes are driven by:
I. Delay in diagnosis - there is no reliable test;
II. Substandard antibiotic treatment – rifampicin, the key antibiotic, doesn't reach an effective level in spinal fluid.
This study aims to assess the levels of rifampicin in blood and spinal fluid, and monitor the safety and effects of this on death and disability.

Who can participate?
Adults aged 18 years and over with Tuberculous Meningitis

What does the study involve?
Participants are randomly allocated to one of three groups. Those in the first group receive an antibiotic called rifampicin delivered through their veins for two weeks, and then take it orally for six weeks.
Those in the second group receive a higher than standard dose of oral rifampicin for eight weeks, whilst those in the control take the standard dose of rifampicin for eight weeks.
Participants are treated in hospital for the first two weeks, then as an outpatient. They have blood samples taken, and physical and mental assessments throughout the trial.

What are the possible benefits and risks of participating?
Participants benefit from careful medical follow-up during the 24 week trial period including blood tests, additional diagnostic tests on spinal fluid and brain scans where required. This follow-up is likely to be more detailed than the normal medical care in the public hospitals in Uganda, so potentially complications can be detected and managed earlier if people are in the trial. Additionally, transport costs and expenses are covered by the trial for follow-up appointments.
Other studies using high dose rifampicin have shown that it is as safe as the standard dose, but these studies were in a different patient population. We will carefully monitor trial participants in case there are any safety issues with higher dose rifampicin in this patient population. Trial

participants receive one to two additional lumbar punctures, which is likely to be more than they would have in routine hospital care in Uganda. This may have clinical benefits but lumbar punctures can rarely also cause harm (pain, infection, bleeding). Patients are counselled about these risks and lumbar punctures will be avoided if there are any concerns.

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

When is the study starting and how long is it expected to run for?
September 2017 – October 2020

Who is funding the study?
Wellcome Trust (UK)

Who is the main contact?
Dr Fiona Cresswell (Scientific)
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Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
MHREC: 1260

Study information

Scientific Title
High dose oral and intravenous rifampicin for improved survival of adult Tuberculous meningitis: a phase II open-label randomised controlled trial

Acronym

RifT

Study objectives
The primary hypothesis is that intravenous rifampicin (20mg/kg) and high dose oral rifampicin (35mg/kg) will result in significantly increased plasma exposure and CSF penetration during the critical early days of TB treatment as compared to common control (10mg/kg oral rifampicin). The secondary hypothesis is that this leads to improved early mycobacterial clearance from the CNS, reduced inflammatory response, and thereby will result in a reduction in neurocognitive disability, TBM-IRIS and mortality. It is hypothesised that the two investigational arms (IV 20mg /kg and oral 35mg/kg) will be equivalent to one another.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Mulago Hospital Research Ethics Committee, 01/03/2018, ref: MHREC 1260
2. London School of Hygiene and Tropical Medicine Research Ethics Committee, 11/12/2017, ref: 14388

Primary study design
Interventional

Study design
Parallel group open-label phase II randomized study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Tuberculosis of nervous system

Interventions
Participants are randomised (stratified by site and MRC severity grade) into one of three arms:
1. Intravenous 20mg/kg/day rifampicin for 2 weeks (followed by oral rifampicin 35mg/kg/day for 6-weeks)
2. Oral 35mg/kg/day rifampicin for 8 weeks
3. Standard of care oral rifampicin (~10mg/kg/day) for 8-weeks
Other standard anti-TB drugs and steroids are given to all participants, as recommended by the World Health Organisation. Participants are treated in hospital for the first 14 days then followed up every 4 weeks as an outpatient, until 24 weeks.

Intervention Type
Drug

Phase
Phase II

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

Primary outcome(s)

1. Individual pharmacokinetic parameters (plasma and CSF AUC0-24h, Cmax) are measured using intensive PK sampling of blood at 0, 2, 4 and 8 hours and a single CSF sample on day 2 and by sparse PK sampling on day 12.
2. Safety composite endpoint is assessed during the intervention period by measuring:
2.1. Adverse Events, Clinical Grade 3-5 as classified by Division of AIDS Toxicity Scale, or
2.2. All serious adverse events, or
2.3. Drug-induced liver injury, grade 3-5, (ALT >5x ULN; or Bilirubin >2.6x ULN) or
2.4. Discontinuation of rifampicin for >5 days in the first 8 weeks for any cause

Key secondary outcome(s)
1. Survival time is measured at 8 and 24 weeks after randomisation
2. Time to normalization of mental status is measured using the Glasgow Coma Scale score (GCS) of 15 which is maintained for >2 days
3. Degree of disability/dependence is measured using the Modified Rankin Scale score at 8 and 24 weeks
4. Neurocognitive performance is measured using detailed quantitative neurocognitive performance Z-score (QNPZ-8) at 8 and 24 weeks
5. Paradoxical TB-related immune reconstitution inflammatory syndrome (TB-IRIS) is assessed using published case definition at 4 weekly follow up.

Completion date
01/10/2020

Eligibility

Key inclusion criteria
1. Age ≥ 18 years
2. Provision of written informed consent by participant or surrogate
3. Clinical diagnosis of TBM: meningitis symptoms, clinical signs of meningism and antituberculous chemotherapy planned by the attending physician
AND
4. Bedside CSF glucose to plasma ratio <50%, or absolute CSF glucose <40mg/dl or 2.2 mmol/L
OR
5. Positive CSF AFB smear or Xpert MTB/ Rif or Ultra

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Total final enrolment
61

Key exclusion criteria
1. Presence of jaundice or known liver cirrhosis (Due to emergent need to begin TBM therapy to reduce mortality, enrolment will not be delayed and participants will be replaced a posteriori if baseline ALT>3x ULN)
2. Greater than 3 doses of TB treatment received within the previous 3 days (induction of cytochrome P450 enzymes occurs after 3-5 days of rifampicin therapy which would affect PK data)
3. Discontinued TB treatment in the prior 14 days (induction of cytochrome P450 enzymes persists for up to 2-weeks after cessation of R and would make interpretation of the PK data challenging)
4. Known allergy to Rifamycins, H, Z, E or study drug excipients
5. Known current/previous rifampicin drug-resistant M. tuberculosis infection
6. Current cryptococcal meningitis: India ink stain positive or culture positive or cryptococcal antigen positive in the absence of prior effective treatment and prophylaxis.
7. Use of any drug that has a clinically relevant interaction with rifampicin or other first-line TB drugs, including ritonavir, atazanavir or darunavir (see appendix 2 for further detail)
8. Cannot or unlikely to attend regular clinic visits
9. Pregnancy / Breastfeeding. Women of childbearing potential must agree to use barrier contraception or abstinence for 8 weeks. Hormonal contraception is unacceptable as rifampicin induces metabolism.
10. Lack of consent from participant or family member
11. Known porphyria
12. Known chronic renal failure with eGFR <10 ml/min

Date of first enrolment
01/06/2018

Date of final enrolment
01/12/2019

Locations

Countries of recruitment
Uganda

Study participating centre
Infectious Diseases Institute
Kampala
Uganda
PO Box 22418

Sponsor information

Organisation
London School of Hygiene and Tropical Medicine

ROR
https://ror.org/00a0jsq62

Funder(s)

Funder type
Research organisation

Funder Name
Wellcome Trust

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be anonymised and stored in the LSHTM data compass repository.

IPD sharing plan summary
Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		07/09/2021	08/11/2021	Yes	No
Protocol article	protocol	10/07/2018	06/01/2021	Yes	No
Other publications	Fujifilm SILVAMP TB LAM Assay on Cerebrospinal Fluid for the Detection of Tuberculous Meningitis in Adults With Human Immunodeficiency Virus	01/11/2021	07/05/2025	Yes	No
Participant information	version V1	26/03	01/04	No	Yes

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