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Anti-TB therapy following drug-induced liver injury (TB-DILI)

Submission date
08/06/2022

Recruitment status
Recruiting

Registration date
25/08/2022

Overall study status
Ongoing

Last Edited
20/01/2025

Condition category
Respiratory

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

Plain English summary of protocol

Background and study aims
The standard 4 drug treatment for active tuberculosis (TB) is very effective if the full 6-month course is completed. However, there can be side effects. An important side effect is drug-induced liver injury (DILI). Around 1 in 14 patients may be affected. For patients experiencing these complications, treatment is usually stopped for a time to allow their liver to recover. Once their liver has recovered treatment will need to be started again - 'reintroduced'.

NICE TB guidelines recommend that all 4 drugs are reintroduced. The American Thoracic Society guidelines differ. These recommend that the drug pyrazinamide (Z) is left out, as it is thought to make DILI more likely. Although this three-drug treatment is still effective, it needs to be taken over nine months. This is more difficult for patients & more costly to the NHS. Currently, clinicians in the UK & globally choose between the two guidelines; some reintroduce Z whilst others do not.

This research will answer which of the 2 treatment options
a) leads to fewer patients experiencing DILI?
b) results in a better quality of life for patients?
c) offers better use of limited NHS resources?

Who can participate?
Adults who experience DILI whilst on standard TB treatment

What does the study involve?
The research will be conducted over 4 years across a number of hospital clinics in the UK. The research will include 350 adults who experience DILI whilst on standard TB treatment, with 90 enrolled for each year of the study. Patients will be selected at random to be in either one of two groups for the study. One group will have 4 drugs reintroduced (i.e. including Z). The other group will have only 3 drugs reintroduced, (i.e. excluding Z). Patients and clinicians will know which treatment they are getting. The trial primary outcome will be a laboratory-based measure of the number of patients that experience the return of DILI.
Patients medical records are checked for DILI recurrence and their quality of life will be measured using the EQ5D.

What are the possible benefits and risks of participating?
Benefits:
Not provided at time of registration
Risks:
The TB-DILI Trial is comparing two standards of care that are already widely in use across the UK, because of this we do not expect there to be any additional risks or disadvantages to taking part in the trial.

Where is the study run from?
Nottingham Clinical Trials Unit (UK)

When is the study starting and how long is it expected to run for?
June 2022 to December 2026

Who is funding the study?
National Institute for Health and Care Research (NIHR) (UK).

Who is the main contact?
Dr Wei Shen Lim, weishen.lim@nhs.net

Study website
http://tb-dili.ac.uk

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2020-004193-21

IRAS number
1005097

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
20RM006, IRAS 1005097

Study information

Scientific Title
Reintroduction of anti-tuberculosis therapy following drug-induced liver injury: a randomised controlled trial (TB-DILI)

Acronym
TB-DILI

Study objectives
The main purpose of the TB-DILI trial is to determine whether restarting TB treatment with only 3 drugs is safer for patients than restarting with 4 drugs. We will determine this by looking at how many patients on each treatment (restarted with 3 or 4 drugs) go on to experience a reoccurrence of DILI.

The trial will also look at which of the treatment options is more cost-effective for the NHS. At the end of this trial, we hope to be able to advise the NHS on the best way that doctors should treat future TB-DILI patients. Patients will be asked to complete quality of life questionnaires to look at the impact quality of life in the different treatment options.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 03/08/2023, Tyne and Wear South REC (HRA Jarrow Room 001 Jarrow Business Centre Rolling Mill Road, Jarrow, NE32 3DT, United Kingdom; +44 207 1048282; tyneandwearsouth.rec@hra.nhs.uk), ref: 22/NE/0111

Study design
Interventional randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
https://tb-dili.ac.uk/information-for-participants/information-for-participants.aspx

Health condition(s) or problem(s) studied
Drug induced liver injury in patients receiving tuberculosis treatment.

Interventions
Eligible patients will be individually randomised on a 1:1 ratio to one of the treatment groups using an online randomisation system developed and maintained by the NCTU.

Intervention
Sequential full-dose reintroduction of a non-Z-containing 3-drug ATT regimen comprising ethambutol, isoniazid and rifampicin (EHR), as recommended by the American Thoracic Society (ATS) TB guideline.
Treatment duration is 9 months, patients are followed up post 12 months randomisation.

Control
Sequential full-dose reintroduction of a Z-containing 4-drug ATT regimen comprising ethambutol, isoniazid, rifampicin and pyrazinamide (EHRZ), as recommended by the National Institute for Health and Care Excellence (NICE) TB guideline.
Treatment duration is 6 months, patients are followed up post 12 months randomisation.
Patients will have a telephone follow-up at 9 months.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Ethambutol, isoniazid, rifampicin, zinamide

Primary outcome measure
DILI recurrence within 12 months following randomisation. DILI recurrence could occur at any timepoint during the treatment period. Sites will perform routine clinical assessments to determine a DILI this data will then be submitted for adjudication.

Secondary outcome measures
1. Severity of DILI recurrence measured using routine clinical assessments at 12 months
2. Physician rated clinical cure at end of treatment (EoT)
3. Clinical cure at 12 months

4. Total number of days on ATT at EoT
5. ATT adherence at EoT
6. Adverse event rate at EoT or at 12 months whichever is sooner
7. Mortality at 12 months
8. Quality of life assessed by EQ-5D-5L and healthcare resource use at 12 months

Overall study start date
01/06/2022

Completion date
31/12/2026

Eligibility

Key inclusion criteria
1. Aged ≥18 years
2. Experienced DILI with standard 4-drug ATT for active pulmonary or extra-pulmonary TB
3. Medically suitable
4. for re-introduction of standard 4-drug ATT

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
350

Key exclusion criteria
1. Requirement for alternative ATT
2. Unable to provide written informed consent

Date of first enrolment
01/08/2022

Date of final enrolment
30/06/2026

Locations

Countries of recruitment
United Kingdom

Study participating centre
-
United Kingdom
-

Sponsor information

Organisation
Nottingham Clinical Trials Unit

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Sponsor type
University/education

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan

Peer reviewed scientific journals
Conference presentation
Publication on website
Other
The dissemination of the proposed research findings will be via a published HTA monograph, research papers for publication in peer reviewed journals, presentation at medical conferences and communication of our findings to groups involved in guideline development.

Results of this trial will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the Chief Investigator and Trial Management Group and authorship will be determined by mutual agreement.

Intention to publish date

31/12/2027

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

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No