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All-oral shorter treatment regimens for multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB): evaluating their effectiveness, safety, feasibility, cost-effectiveness and impact on the quality of life of patients in Pakistan

Submission date
09/09/2020

Recruitment status
No longer recruiting

Registration date
08/02/2021

Overall study status
Completed

Last Edited
08/05/2025

Condition category
Infections and Infestations

[_] 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 aim
Multidrug-resistant tuberculosis (MDR-TB) is a form of tuberculosis (TB) infection caused by bacteria that are resistant to treatment with at least two of the most powerful first-line anti-TB drugs. MDR-TB is a public health crisis and a global health security risk carrying grave consequences for those affected. Globally, 186 772 cases of MDR-TB were detected and notified in 2018, of which 97% were enrolled on treatment. Patients with MDR-TB are treated with a different combination of drugs, which usually has an intensive phase of treatment of 8 months and a total duration of treatment of 20 months. Outcomes with this approach are generally poor, with only 56% of MDR-TB patients reported to have been successfully treated. Globally, multiple studies are being conducted to evaluate the safety and effectiveness of new shorter treatments (less than 12 months) to address the above-mentioned issue. In these new shorter treatments injectable treatments have been replaced with orally administered medicine and drugs with better safety outcomes, so patients are more likely to successfully complete the treatment. A comparison of two selected all oral shorter treatments is being proposed to find out if they are comparable in terms of successful treatment completion rate, safety and feasibility. It is expected that all-oral shorter treatments will improve treatment adherence, mainly by reducing the time duration, increased feasibility, and reduced cost of treatment.

Who can participate?
Patients with rifampicin-resistant TB that is sensitive to fluoroquinolones

What does the study involve?
Participants are randomly allocated to receive either the new all-oral shorter treatment (i.e. bedaquiline + linezolid) or the standard all-oral short treatment (i.e. bedaquiline). The total duration of treatment is 11 months and the duration of follow-up is 12 months after completion of treatment.

What are the possible risks and benefits of participating?
There are no direct benefits to the participants, but it is expected that all-oral shorter treatments will improve treatment adherence, mainly by reducing the costs (direct and opportunity) and the occurrence of adverse reactions. It is therefore likely that the overall health-related quality of life of patients would improve. There are no added risks involved in participating in this study. Whether the patient agrees or not to participate, he/she will have the same tests and treatment.

Where is the study run from?
The study will run from 12 main MDR-TB treating hospitals in Pakistan. Twelve Programmatic Management of Drug-resistant TB (PMDT) sites i.e. ten in Punjab, and one each in Islamabad and Muzafarabad (AJK) districts.

When is the study starting and how long is it expected to run for?
January 2020 to June 2024

Who is funding the study?
World Health Organization (Switzerland)

Who is the main contact?
Dr Muhammad Amir Khan
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Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
ERC0003305

Study information

Scientific Title
Short, all-Oral Regimens for Rifampicin-resistant Tuberculosis (ShORRT)

Acronym
ShORRT

Study objectives
This trial will determine the effectiveness, safety, feasibility, cost-effectiveness and impact on quality of life of an all-oral shorter MDR/RR-TB regimen of 9 to 12 months duration under programmatic conditions.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 21/07/2020, National Bioethics Committee Pakistan (NBC Secretariat, PHRC, Shahrah-e-Jamhuriat, G-5/2, Islamabad, Pakistan; +92 (0)51 9224325, 9207386; nbcpakistan.org@gmail.com), ref: NBC-491, WHO ERC: 0003305

Study design
Stepped-wedge cluster randomized trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Multidrug- and rifampicin-resistant tuberculosis

Interventions
A stepped-wedge design comparing patients receiving the new all-oral shorter MDR/RR-TB regimen (i.e. bedaquiline + linezolid) and patients receiving the standard all-oral MDR/RR-TB short treatment regimen (i.e. bedaquiline) at 12 Programmatic Management of Drug-resistant TB (PMDT) sites in Pakistan.

To minimize the risk of contamination between research participants, the unit of randomization is a PMDT site. PMDT sites are randomized before recruitment of research participants into the intervention or control arm using permuted block randomization method by an independent statistician, on a 1:1 allocation ratio. SAS PROC PLAN is used to generate the randomization code.

Treatment arm: new all-oral treatment regimen:
2 months of linezolid + bedaquiline + levofloxacin* + clofazimine + pyrazinamide + ethambutol + isoniazid (high dose) followed by 4 months of bedaquiline + levofloxacin* + clofazimine + pyrazinamide + ethambutol + isoniazid (high dose) followed by 3 months of levofloxacin* + clofazimine + pyrazinamide + ethambutol

Comparator arm: standard all-oral treatment regimen (currently being implemented in the country):
6 months of bedaquiline + levofloxacin* + clofazimine + ethionamide + pyrazinamide, ethambutol + isoniazid (high dose) followed by 5 months of levofloxacin* + clofazimine + pyrazinamide + ethambutol

*: If levofloxacin resistance found on LPA2 (line probe assay); then substitute with moxifloxacin (if found sensitive)

The total duration of treatment is 11 months and the duration of follow-up is 12 months after completion of treatment.

Intervention Type
Drug

Phase
Phase II/III

Drug/device/biological/vaccine name(s)
Linezolid, bedaquiline, levofloxacin, clofazimine, pyrazinamide, ethambutol, isoniazid, ethionamide, moxifloxacin

Primary outcome(s)
1. Treatment effectiveness: the proportion of MDR-TB patients who have a favorable treatment outcome. This is defined as 'cured' or 'treatment completed' without recurrence during 12 months after successful treatment.
2. Treatment safety: the proportion of MDR-TB patients included in the study with serious adverse events occurring during treatment and up to12 months after the end of the treatment.

Key secondary outcome(s))
1. The proportion of MDR-TB patients who died while on treatment, recorded using DR-TB 01 patient data collection form, during 11 months of treatment
2. The proportion of MDR-TB patients who had a treatment failure, recorded using DR-TB 01 patient data collection form, at 12 months after successful treatment
3. The proportion of MDR-TB patients who had a recurrent episode of MDR-TB, recorded using DR-TB 01 patient data collection form, at 12 months after successful treatment
4. The proportion of MDR-TB patients who are “cured without permanent disability”, recorded using DR-TB 01 patient data collection form, at 12 months after successful treatment
5. The proportion of MDR-TB patients who complete at least 90% of doses (intake adherence, recorded using DR-TB 01 patient data collection form, during 11 months of treatment
6. The average number of adverse events of interest experienced by MDR-TB patients, recorded using DR-TB 01 patient data collection form, during 11 months of treatment
7. The proportion of MDR-TB patients experiencing each adverse event of interest, recorded using DR-TB 01 patient data collection form, during 11 months of treatment
8. The proportion of MDR-TB patients who experience serious adverse drug reactions, recorded using DR-TB 01 patient data collection form, during 11 months of treatment
9. Health-related quality of life measured using EQ-5DL at baseline, at treatment completion, 4 months of treatment intake, at treatment completion and 12 months after treatment completion
10. Feasibility assessed using mixed-method indicators at treatment completion

Completion date
21/06/2024

Eligibility

Key inclusion criteria
The study population includes TB patients with evidence of resistance to at least rifampicin by rapid molecular drug-susceptibility testing (DST).
1. ≥15 years of age; is willing and able to give informed consent to be enrolled in the research project and for follow-up (signed or witnessed consent if the patient is illiterate)
2. Has bacteriologically or molecularly confirmed TB with evidence of resistance to at least rifampicin
3. Has no resistance to fluoroquinolones; no known previous exposure (of > 1 month) or intolerance to one or more second-line drugs in the shorter MDR-TB regimen

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Sex
All

Key exclusion criteria
1. DST showing infection with a strain resistant to fluoroquinolones (or DST results not available)
2. Previous exposure to or intolerance to second-line anti-TB drugs in the intended shorter MDR-TB regimen for more than 1 month
3. Pulmonary TB that is clinically severe, or advanced (i.e. parenchymal lesions) or disseminated
4. Unable to take oral medication, or to attend or comply with treatment or follow-up schedule
5. Taking medication contraindicated with the medicines in the RR/MDRTB regimen
6. Known insufficient function of heart (QTcF >500 ms), liver (ALT/AST >5x UNL), or kidneys (creatinine >2x UNL or creatinine clearance <50 ml/min)

Date of first enrolment
30/07/2020

Date of final enrolment
30/01/2023

Locations

Countries of recruitment
Pakistan

Study participating centre
Association for Social Development
House #12, Street 48, F7/4
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Sponsor information

Organisation
World Health Organization

ROR
https://ror.org/01f80g185

Funder(s)

Funder type
Other

Funder Name
World Health Organization

Alternative Name(s)
, , Всемирная организация здравоохранения, Organisation mondiale de la Santé, Organización Mundial de la Salud, WHO, , ВОЗ, OMS

Funding Body Type
Government organisation

Funding Body Subtype
International organizations

Location
Switzerland

Results and Publications

Individual participant data (IPD) sharing plan
The co-investigator of the study, Ms Nida Khan, can be contacted regarding any information about the study data (nidakhan@asd.com.pk, nidakhaneco@gmail.com).

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		07/05/2025	08/05/2025	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes