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A study comparing two WHO recommended all oral shorter treatment regimens for pre-extensively drug resistant tuberculosis: evaluating their effectiveness, cost-effectiveness, and implementation outcomes in Pakistan setting

Submission date
28/07/2025

Recruitment status
No longer recruiting

Registration date
11/08/2025

Overall study status
Ongoing

Last Edited
08/08/2025

Condition category
Infections and Infestations

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

Plain English summary of protocol

Background and study aims
Pakistan has one of the highest rates of drug-resistant tuberculosis (TB) in the world. Many patients with this form of TB, especially in Punjab, have a type called pre-XDR TB, which is harder to treat. In the past, treatment involved long and difficult regimens with injections that could last up to 20 months. Newer treatments are shorter, safer, and taken by mouth. One such treatment, called BPaL, is already being used in Pakistan. Another newer option, called BDLC, has been recommended by the World Health Organization but hasn't yet been tested in real-world settings in Pakistan. This study aims to compare the BPaL and BDLC treatments to see which one works better, is safer, and is more cost-effective. The results will help health officials decide whether to adopt the BDLC regimen more widely.

Who can participate?
People aged 14 years or older who have pre-XDR TB (a form of TB resistant to certain key drugs) can take part. They must be able to give informed consent and not have allergies to the study drugs. Pregnant or breastfeeding women and people with serious health problems like heart rhythm issues or severe liver or kidney disease cannot join the study.

What does the study involve?
Participants will be randomly assigned to receive either the BPaL or BDLC treatment. Both are taken by mouth and last 6 to 9 months, depending on how the patient responds. Participants will visit their local TB clinic every month for check-ups, provide sputum and blood samples, and be monitored for side effects. They may also be followed for up to a year after treatment to check if the TB comes back. All treatment and support will be provided free of charge through Pakistan's National TB Program.

What are the possible benefits and risks of participating?
Benefits include free, high-quality treatment and close medical monitoring. The study may also help improve TB care for future patients. Risks include possible side effects from the medications, such as nausea, tiredness, nerve pain, vision problems, or changes in liver or heart function. These risks will be managed through regular check-ups and adjustments to treatment if needed.

Where is the study run from?
The study is led by the Association for Social Development (ASD) in partnership with the National TB Control Program. It will take place at 12 drug-resistant TB clinics across Punjab province (Pakistan)

When is the study starting and how long is it expected to run for?
April 2025 to December 2027

Who is funding the study?
The study is funded by the National TB Control Program of Pakistan, with technical and implementation support from ASD.

Who is the main contact?
Dr Muhammad Amir Khan, ccp@asd.com.pk

Contact information

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Additional identifiers

Protocol serial number
ASD-EAG-25-003

Study information

Scientific Title
A randomized controlled non-inferiority trial comparing the effectiveness of BPaL (bedaquiline, pretomanid, linezolid) versus BDLC (bedaquiline, delamanid, linezolid, clofazimine) regimens for the treatment of pre-extensively drug resistant (DR) tuberculosis at 12 DR TB sites in Punjab, Pakistan

Acronym
BDLC-BPaL trial

Study objectives
1. The BDLC regimen (bedaquiline, delamanid, linezolid, clofazimine) is non-inferior to the BPaL regimen (bedaquiline, pretomanid, linezolid) in achieving treatment success at end of treatment among patients with pre-extensively drug resistant tuberculosis.
2. There is no significant difference in the occurrence of serious adverse events between the BDLC and BPaL regimens.
3. The BDLC regimen has a comparable safety and tolerability profile to the BPaL regimen over the treatment period.
4. The total cost of treatment per patient using the BDLC regimen is comparable to the cost of the BPaL regimen from a healthcare system perspective.

Ethics approval required
Ethics approval required

Ethics approval(s)

Approved 22/07/2025, Association for Social Development, Pakistan IRB (House: 12, Street: 48, Sector: F-7/4, Islamabad, 44000, Pakistan; +92 51 2611530; irb@asd.com.pk), ref: ASD-EAG-25-003

Primary study design
Interventional

Study design
Randomized controlled non-inferiority trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Pre-extensively drug resistant tuberculosis (pre-XDR TB)

Interventions
Intervention arm regimen: BDLC
Participants in the intervention arm will receive the BDLC regimen, which includes:
• Bedaquiline: 400 mg once daily for 2 weeks, then 200 mg three times per week for the remaining treatment duration
• Delamanid: 100 mg twice daily for the complete treatment duration
• Linezolid: 600 mg once daily for the complete treatment duration
• Clofazimine: 100 mg once daily for the complete treatment duration
Comparator arm regimen: BPaL
Participants in the comparator arm will receive the BPaL regimen, which includes:
• Bedaquiline: 400 mg once daily for 2 weeks, then 200 mg three times per week for the remaining treatment duration
• Pretomanid: 200 mg once daily for the complete treatment duration
• Linezolid: 600 mg once daily for the complete treatment duration

In both trial arms:
• Treatment will last for 6 to 9 months, depending on individual patient response and tolerance.
• All drugs will be administered orally.
• During treatment, all patients will be followed-up (at their respective DR-TB sites), every month, for clinical assessment and drug dispensing.
• A 12-months post-treatment clinical assessment will be conducted for relapse/recurrence.

Randomisation Process:
Participants who meet the inclusion criteria and provide informed consent will be randomly assigned to one of the two treatment arms using a central randomisation system.

Intervention Type
Drug

Phase
Phase II/III

Drug/device/biological/vaccine name(s)
Bedaquiline, delamanid, linezolid, clofizamine, pretomanid

Primary outcome(s)
Proportion of pre-extensively drug resistant tuberculosis (pre-XDR TB) patients with a successful treatment outcome, defined as “cured” or “treatment completed” at the end of treatment (6 to 9 months), based on National TB Program definitions measured using patient records

Key secondary outcome(s)
1. Mortality during treatment is measured using programmatic records and death certificates at any time during the treatment period
2. Loss to follow-up is measured using treatment records and defined as treatment interruption for 2 consecutive months or more at any time during the treatment period
3. Treatment failure is measured using bacteriological and clinical criteria defined in the study protocol, including sputum culture results and clinical assessments, at 4 months and end of treatment
4. Adherence to treatment is measured using treatment cards and adherence records as the proportion of prescribed doses taken, assessed monthly throughout the treatment period
5. Adverse events of special interest are measured using clinical assessments and laboratory tests recorded in the DR-TB 01 form at baseline and monthly during treatment
6. Health-Related Quality of Life (HRQoL) is measured using the EQ-5D-5L questionnaire at baseline and at the end of treatment
7. Time to sputum culture conversion is measured using monthly sputum cultures until two consecutive negative cultures at least 30 days apart are obtained
8. Post-treatment recurrence is measured using clinical and bacteriological assessments during optional follow-up visits at ...
9. Incremental cost of delivering BDLC compared to BPaL is measured using cost data on drugs, diagnostics, personnel, adverse event management, and hospitalization from provider records at the end of the treatment period

Completion date
30/12/2027

Eligibility

Key inclusion criteria
1. Aged 14 years or older at the time of diagnosis. Patients younger than 14 will be excluded and managed according to national guidelines.
2. Provides informed consent to participate in the study and attend follow-up visits. If the patient is illiterate, consent must be obtained through a witnessed process (signed or thumb-printed).
3. Has bacteriologically or molecularly confirmed tuberculosis (TB) with documented resistance to at least rifampicin and a fluoroquinolone, as identified through rapid molecular testing and/or conventional culture-based drug susceptibility testing (DST).
4. Has no known contraindication to the use of drugs in the study regimens (BPaL or BDLC), and is medically fit to receive second-line anti-TB treatment.
5. Is able to take oral medications and adhere to the treatment and follow-up schedule under programmatic management of drug-resistant TB (PMDT) conditions.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
14 Years

Sex
All

Key exclusion criteria
1. Drug susceptibility testing (DST) shows fluoroquinolone sensitivity, or DST results are not yet available at baseline.
2. Inability to take oral medication due to clinical or functional limitations (e.g., severe gastrointestinal conditions, swallowing difficulty).
3. Known hypersensitivity or allergy to one or more drugs in the study regimens (BPaL: bedaquiline, pretomanid, linezolid; BDLC: bedaquiline, delamanid, linezolid, clofazimine).
4. Baseline QTcF interval ≥500 milliseconds, which is not correctable with medical management, as confirmed by ECG.
5. Concurrent use of medications that are contraindicated with any drugs included in the study regimens, and which cannot be safely discontinued or substituted.
6. Pregnant or breastfeeding at the time of enrolment, due to insufficient safety data for study drugs during pregnancy and lactation.
7. Severe baseline organ dysfunction, including:
7.1. Liver dysfunction: ALT or AST > 5 times the upper normal limit.
7.2. Renal impairment: Serum creatinine > 2 times the upper normal limit, or creatinine clearance < 50 mL/min.

Date of first enrolment
11/08/2025

Date of final enrolment
30/08/2026

Locations

Countries of recruitment
Pakistan

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Sponsor information

Organisation
Association for Social Development

Funder(s)

Funder type
Research organisation

Funder Name
Association for Social Development

Funder Name
National TB Control Program

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).

IPD sharing plan summary
Available on request