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Randomised trial to evaluate the effectiveness and safety of varying doses of linezolid with bedaquiline and pretomanid in adults with pre-extensively drug-resistant or treatment intolerant/non-responsive multidrug-resistant pulmonary tuberculosis: study protocol

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ABSTRACT

Introduction Drug-resistant tuberculosis (DR-TB) is a global public health problem. Patients suffer for months if undiagnosed or treated inadequately, transmitting DR-TB in the community before succumbing to the disease. Early diagnosis, prompt treatment initiation and completion play a significant role in treatment success. However, extended regimens with injectable result in poor treatment adherence and outcomes. Our objective is to evaluate the effectiveness, safety and tolerability of various doses and duration of linezolid (LZD) in combination with bedaquiline (BDQ) and pretomanid (Pa) after 26 weeks of treatment in adults with pre-extensively drug-resistant or treatment intolerant/non-responsive multidrug-resistant pulmonary TB.

Methods and analysis A multicentric, randomised pragmatic clinical trial in India will enrol participants in one of the three arms—control arm (arm 1): BDQ, Pa and LZD 600 mg daily for 26 weeks or intervention arms (arm 2): BDQ, Pa and LZD 600 mg for 9 weeks followed by 300 mg for 17 weeks or arm 3: BDQ, Pa and LZD 600 mg for 13 weeks followed by 300 mg for 13 weeks. The primary endpoint is the proportion of patients with favourable outcomes as sustained cure and treatment completion. The secondary endpoint is unfavourable outcomes, including deaths, treatment failure, toxicity/adverse events and lost to follow-up till 48 weeks post-treatment.

Ethics and dissemination The study has been approved by the ethics committees of participating institutes and the National Institute for Research in TB. The trial results will help establish evidence towards a safe and effective dose of LZD that can be used in a fully, all-oral short course regimen for highly DR-TB patients. The results of this study will be shared with the National TB Elimination Programme of the country and the WHO guidelines development group through publications and dissemination meetings.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Pragmatic randomised trial design will add considerable value to the study as it will consider a real-world population under field conditions in a clinical trial, thus decreasing bias and minimising unequal distribution.
⇒ The trial includes an active control arm (appropriate comparison arm) instead of a placebo arm and has relevant outcomes for optimal healthcare decisions at the end of the study.
⇒ The trial lacks stratification based on disease severity. This may result in the possibility of more severe cases in one group of treatment. We hope randomisation will be able to cover this.
⇒ As there is no blinding in this trial, the treating physician may be biased to assign the causality of all adverse events to the drug concerned.
⇒ Data heterogeneity may be present as it is a planned multicentric study.

Trial registration number NCT05040126.

INTRODUCTION

The WHO estimates that globally in 2020, 132 222 cases of multidrug resistant (MDR)/rifampicin-resistant tuberculosis (RR-TB) and 25 681 cases of pre-extensively drug-resistant (pre-XDR-TB) or XDR-TB, totalling 157 903 cases, were detected. However, testing for fluoroquinolone (FQ) resistance remains much lower; at just over 50% worldwide in 2020.[1] Of these, 150 359 people with MDR/RR-TB were enrolled in treatment in 2020,

fewer than in the previous years. The treatment success rate of the 2018 MDR/RR-TB cohort was 59%; though improved from earlier cohorts, the treatment failure, lost to follow-up and death remain high.[1] Also, this was not uniform across the globe–the treatment success rate was below 50% in countries like India and Indonesia due to increased death and lost to follow up. Globally, the treatment success rate of highly drug-resistant TB (DR-TB) remains unacceptably low.

With the availability of newer drugs and patient-friendly approaches, it is now possible to design newer regimens that are less toxic, safer and of shorter duration. The WHO consolidated treatment guidelines for DR-TB recommend longer and shorter treatment regimens for MDR/RR-TB treatment.[2] A South African study using a combination of bedaquiline (BDQ), pretomanid (Pa) and linezolid (LZD) to treat highly DR-TB showed a favourable outcome of 90% at the end of 6 months of treatment.[3] However, the high dose of LZD used in this study led to more than 70% of patients having adverse events (AEs) to LZD, often leading to either treatment interruption or dose reduction of LZD between 2 and 3 months of treatment. Though LZD is efficacious for DR-TB, AEs and treatment discontinuation are also to be expected.[4]

The multicountry ZeNIX study with consistent dosing of BDQ and Pa reported a 93% success rate with LZD 1200 mg for 6 months and 91% with LZD 600 mg for 6 months. Among those receiving 1200 mg LZD for 6 months, AEs reported were 38%, while in those receiving 600 mg of LZD for 6 months, it was 24%.[5] Though there seemed to be a modestly greater early bactericidal effect over 14 days at the highest dose of 1200 mg/day (NC-003 study), this dose appeared to be associated with a greater incidence of neuropathic and myelosuppressive effects than the 600 mg/day dose in the ZeNIX and NixTB trials. While a full 6 months of LZD therapy in the regimen may give higher culture conversion and avoid relapse, the mouse model found that more than 2 months of LZD, combined with BDQ and Pa, does not increase relapse-free cure.[6] The study also found that LZD increases the sterilising activity of the BDQ-Pa combination; no MTB could be cultured from the lungs of mice 3 months after cessation of 3 months of treatment with this combination.

Given the above evidence, both in terms of safety and toxicity of higher doses and longer duration of LZD and the ability of LZD to act synergistically with the combination of BDQ and Pa, this study is planned with the primary objective of determining the effectiveness of various doses and duration of LZD in combination with BDQ and Pa given for 26 weeks in adults with either Pre-XDR or non-responsive/treatment intolerant multidrug-resistant ($MDR_{NR/TI}$) pulmonary TB. Secondary objectives include

1. To determine the safety and tolerability of various doses and duration of LZD with Pa and BDQ following 26 weeks of therapy among adults with either Pre-XDR or $MDR_{TI/NR}$ pulmonary TB.
2. To determine the baseline resistance to the newer and repurposed drugs.
3. To determine the M.tb strain mutation by whole genome sequencing in participants with treatment failure while on treatment or recurrence of TB during the follow-up period.

METHODS AND ANALYSIS

Study design and oversight

Modified BPaL (mBPaL) study is a multicentre, pragmatic randomised clinical trial under field conditions. The study will enrol 400 adults, pre-XDR or $MDR_{TI/NR}$ pulmonary TB patients meeting all study eligibility criteria after the screening procedure. The enrolled patients will be randomised to receive any of the three regimens using block randomisation. The study is supported by the US Agency for International Development, under the iDEFEAT TB Project with the Union, Cooperative Agreement No. 72038620CA00007, and implemented by the ICMR-National Institute of Research in Tuberculosis (NIRT) in collaboration with the National TB Elimination Programme through its tertiary care DR-TB centres and WHO Country Office for India. The institutional ethics committee of NIRT (ID: 2021004, 12 July 2021), and the participating sites approved the study and began enrolment on 20 October 2021.

Study setting

Eight sites in India will implement the mBPaL trial. The study sites were selected based on the 2019 census of XDR and MDR_{FQ} TB patients attending the DR-TB centres in the country and their capacity for conducting clinical trials, including trained personnel, reporting to regulators, expertise in managing DR-TB patients and severe AEs, and a previous record of conducting drug trials. The study sites include DR-TB centres at Sarvodaya Charitable Trust Hospital and Shatabdi Centenary Hospital, Mumbai; King George's Medical College and University, Lucknow; SN Medical College, Agra; Govt. Medical College, Surat and Bhavnagar, Gujarat, National Institute for Tuberculosis and Respiratory Diseases, New Delhi; Rajan Babu Institute of Pulmonary Medicine and Tuberculosis, New Delhi and Govt. Rajaji Medical College and Hospital, Madurai, Tamilnadu.

Study patients and eligibility

Adults between the ages of 18 and 65 years diagnosed with pre-XDR-TB or $MDR_{TI/NR}$ accessing TB care services in selected DR TB centres across the country are eligible for the study.

Table 1 provides the detailed eligibility criteria based on which patients visiting the study sites will be screened for participation in the study.

Recruitment process

Potential trial participants who visit the DR-TB centres in the selected trial sites will be approached by the study staff and explained in detail about the study in their native

Table 1 Study eligibility criteria

Inclusion criteria	Exclusion criteria
Adults aged between 18 and 65 years	A patient who has received more than 2 weeks of BDQ or LZD before the first dose of the mBPaL regimen OR If the result of DST for FQ or LZD is not available and h/o more than 2 weeks of consumption of drugs used in the study regimen
Pulmonary pre-XDR-TB patients or MDR-TBTI/NR patients	
Bodyweight of ≥30 kg (in light clothing)	Intolerance or risk of toxicity or allergic any of the drugs in the treatment regimens should not be enrolled in the study
Provide informed written consent before all study-related procedures, including HIV testing	All forms of extra pulmonary TB (except lymph node TB or pleural effusion associated with pulmonary DR-TB)
Alanine aminotransferase or aspartate aminotransferase <2.5 × ULN; total bilirubin lesser than ULN	Platelet count <10x10^5/mm^3 or Haemoglobin level of <9.0 g/L
QTc(f) less than or equal to 450 ms at baseline	QTc (f) >450 msec at baseline & normal electrolytes, ECG to be repeated after 6 hours, and if both ECGs show QTc (f) >450 msec, then the patient should not be challenged with cardiotoxic drugs. Having risk factors for Torsade de Pointes, for example, hypokalaemia, heart failure, history of long QT syndrome among family members Currently having an uncontrolled cardiac arrhythmia that requires medication
Female patients should not be pregnant or should be using a birth control method	Pregnant or lactating
	HIV-infected patient with a CD4+ count of ≤50 cells
	Grade III or IV peripheral neuropathy Major psychiatric illness
	Very seriously ill patients (Karnofsky scores <50 within last 30 days)

BDQ, bedaquiline; DR-TB, drug-resistant tuberculosis; DST, drug susceptibility test; FQ, fluoroquinolone; LZD, linezolid; MDRTI/NR, treatment intolerant/non-responsive multidrug-resistant; Pre-XDR-TB, pre-extensively drug-resistant-tuberculosis; ULN, Upper limit of normal.

language. Patients willing to participate in the trial will be given a patient information sheet and a consent form explaining all study-related procedures. After obtaining written informed consent, a detailed medical, surgical, medication and alcohol history will be collected to assess the eligibility for trial participation along with investigations as outlined in table 2. The diagnosis of pre-XDR TB will be made by *Mycobacterium tuberculosis* positivity in the culture of sputum specimen collected within 3 months and with documented resistance to rifamycins with or without isoniazid resistance and, additionally resistant to at least one FQ[7] while MDR-TB$_{TI/NR}$ was all of the above AND with documented intolerance or non-response to the current treatment regimen for 6 months or more when the participant was adherent to the treatment regimen. Eligible participants will be enrolled within the next 14 days.

Study regimen and drug dosing

The study participant will be randomised in the ratio of 1:1:1 to receive one of the mentioned treatment regimens:

Arm 1: 26 weeks. BDQ+Pa + LZD (600 mg).

Arm 2: 9 weeks. BDQ+Pa + LZD (600 mg) followed by 17 weeks. BDQ+Pa+ LZD (300 mg).

Arm 3: 13 weeks. BDQ+Pa + LZD (600 mg) followed by 13 weeks. BDQ+Pa+ LZD (300 mg).

Four 100 mg tablets (400 mg) of BDQ will be administered by mouth once a day for 2 weeks, followed by 200 mg (two 100 mg tablets) orally thrice a week for 24 weeks. Pa will be administered as one 200 mg tablet daily for 26 weeks. In arm 2, the LZD dose will be reduced from 600 mg to 300 mg after 9 weeks and 13 weeks in arm 3, irrespective of the smear and culture results. At the time of randomisation, dosing of LZD and other drugs is not weight-based and is pre-fixed in the protocol. LZD is given the ability to interrupt or reduce the dose if needed based on Grade three toxicity. The continuation of the regimen beyond 26 weeks and up to 39 weeks will be based on the culture results of week 16.

Randomisation procedures

A computer-generated list of random numbers using REDCap software will be used for randomisation centrally. The site physician using these computer-generated randomisations will be able to randomise the study participants to any one of the three arms in a ratio of 1:1:1. Block randomisation will be used to randomise participants in the trial. The NIRT statistician will assign the unique study identification number after confirming all the study-related eligibility criteria. There is no blinding in the trial.

Treatment allocation

The study participants will be randomised to receive one of the three treatment regimens in a 1:1:1 ratio using block randomsation. A computer-generated list of random numbers using REDCap software will be used for randomisation centrally. NIRT centre will generate the allocation codes at the time of the study. At the time of patient's admission to the study, the site physician will be able to randomise them at the site on REDCap software based on predefined factors.

Treatment delivery, compliance and retention

The study participants will be hospitalised for 2 weeks wherever feasible, and study drugs will be administered under supervision. Ambulatory care can also be offered if hospitalisation is not needed. After discharge, medications will be supplied—weekly for the first month, then fortnightly till the third month, and then monthly till the end of treatment. A healthcare provider or a family member will be assigned and trained to supervise the drug intake and monitor adherence to treatment. During the treatment phase, the patient will be reviewed every week for 16 weeks, then monthly until the end of the treatment phase (26/39 weeks). During these visits, a detailed

Table 2 Schedule of enrolment, interventions and assessments of a participant in the mBPaL trial

Completed weeks	–2	0	1	2	3	4	5	6	7	8	9*	10	11	12	13†	14	16	20	26‡	30	38	50	62	74
Informed consent	X																							
Inclusion/exclusion criteria	X																							
Demography	X																							
Medical history	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination and vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fundus examination/colour vision	X										X				X				X					
12 lead ECG§	X			X		X		X			X		X		X	X	X	X	X	Monthly once for 6 months				
Chest X-ray	X																X		X					
Sputum smear (one early monring/1 spot)¶	X					X					X				X		X	X	X		X	X	X	X
Sputum culture (LJ/MGIT) and DST for first and second line drugs including linezolid	X					X					X				X		X	X	X		X	X	X	X
Whole-genome sequencing (NIRT site)	X																							
Line probe assay and first-line and second-line DST (at sites)**	X																							
MGIT DST (bedaquiline/ pretomanid) at NIRT††	X																							
Complete blood count	X			X		X		X			X		X		X	X	X	X	X	X	X	X		X
Liver function test	X			X		X		X			X		X		X	X	X	X	X	X	X	X		X
Renal function test	X					X					X								X		X			X
Blood glucose	X					X					X								X		X			X
HbA1C	X														X				X					
Sr.amylase and lipase	X					X									X				X		X			X
S.Electrolytes (Na, K, Cl) and calcium, magnesium	X					X									X				X		X			X
Urine Gravindex test	X					X					X				X		X	X	X	X	X			
HBsAg, HCV and HIV	X																							
HRQoL	X																		X					X
Adverse events‡‡		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

±DST performed at baseline (with strain stored at –20°C), 16th week in case of positive culture and if any culture is found positive during the 48 weeks following the end of the treatment (with strain of the recurrent episode stored for genotyping analysis).
*Week 9—linezolid dose will be modified at week 9 in arm 2.
†Week 13—linezolid dose will be modified at week 13 in arm 3.
‡End of treatment for patients whose 12th-week cultures are negative and if 16th week cultures are not available then no clinical or radiological evidence of TB.
§Baseline ECG should be obtained and additional ECGs conducted daily for the first 2 weeks after starting treatment (if hospitalised) ECG should be repeated as necessary in case of clinical suspicion of heart rhythm and conduction disturbances.
¶Patients will give 2EM and 1Spot sputum sample at baseline.
**LPA is performed only if sputum results are positive.
††Sputum isolates at baseline, at time of treatment failure and relapse will be sent to NIRT for MGIT DST to Bdq, and pretomanid for whole-genome sequencing. Isolates will also be saved at the regional labs until subculture results are available for any further DST required for patient management.
‡‡Adverse event monitoring over the phone weekly from the 17th week onwards till the end of treatment (except during the days of the scheduled visit).
DST, drug susceptibility test; HbA1C, glycosylated heamoglobin; HBsAG, Hepatitis B Antigen; HCV, hepatitis C virus; HRQoL, health-related quality of life; LJ, Lowenstein-Jensen; LPA, Line probe assay; MGIT, Mycobacterial Growth Inhibitor Tube; NIRT, National Institute of Research in Tuberculosis; TB, tuberculosis.

medical history will be collected; adverse drug reactions and tolerability to study drugs will be monitored. The site medical officer does the management of AEs and the causality assessment with the grading of AEs as per Division of AIDS (DAIDS) criteria.[8] Treatment adherence will be assessed by reviewing treatment cards, empty pill covers, on-time drug refills and hospital attendance. Offering enhancers such as nutrition supplements, reimbursing nominal costs for loss of wage, or transportation will improve the treatment compliance. Post-treatment follow-up visits will be done for 48 weeks.

Concomitant medication while in the trial

A detailed medical history will be collected during every study visit. Any medications consumed while in the trial will be entered on the concomitant medications page of the case record form. Medication entries shall be specific to the generic name, dose, unit, frequency, route of administration, start, stop date and reason for use. Drugs prohibited from being used during the study include aspirin or ibuprofen or medicines that can cause gastrointestinal bleeding; any antibiotics until clinically warranted, and efavirenz-based antiretroviral therapy.

Criteria for study participants discontinuation/withdrawal

The trial regimen may be discontinued in some patients in situations such as resistance to study drugs, intolerable or severe toxicity, or treatment failure. A patient may be withdrawn from the study if he or she is unwilling to participate due to any reason, including pregnancy, drug-drug interaction, non-compliance and non-availability, drug resistance or recommendation by the data safety and monitoring board (DSMB).

Study outcome

The primary outcome of the trial is the proportion of patients with favourable treatment outcomes, defined as sustained treatment success at 12 months post successful TB treatment, being alive and free of TB. Indicators of successful TB treatment include Cure (patient who has completed 26 or 39 weeks of treatment without evidence of failure and with at least two consecutive negative sputum cultures taken at least 7 days apart) and treatment completed (patient who has completed 26 or 39 weeks of treatment whose outcome does not meet the definition of cure or treatment failure) as defined by WHO.[9] The secondary outcome includes the proportion of patients with (1) serious AEs or adverse drug reactions, including tolerability of the study drugs during the treatment and follow-up period and (2) unfavourable outcomes, comprising death, bacteriological or clinical failure and lost to follow-up.

Participant timeline

Each participant involved in the trial will have a screening period of 2 weeks, followed by a treatment period of 26 weeks to 39 weeks based on sputum culture results at week 16, and a post-treatment follow-up of 12 months. Table 2 shows the entire schedule of enrolment of a patient, the interventions to be given, and the assessments to be done for a participant in the trial.

Patient and public involvement

Since the scientific problem is still not proven, patients were not involved in the research question development or the design of this study. However, learning from the difficulties faced by patients on the higher dose of LZD, there is an urgent need to find the correct dose of LZD with lower toxicity, better tolerability, and, at the same time, not compromise the efficacy of the regimen to prevent recurrence of TB. The study proposal is discussed among the members of the Institutional Scientific Advisory Committee, the Institutional Ethics Committee, the Drug Controller General of India, and the Community Advisory Board. Meetings, conference presentations, and publications will be used to disseminate study findings.

Sample size assumption mBPaL trial will evaluate the effectiveness of various doses and duration of LZD with BDQ and Pa after 26 weeks of treatment in adults with pre-XDR or MDR (TI/NR) pulmonary TB patients. The efficacy of BDQ with Pa and LZD (600 mg) for 26 weeks is reported to be about 91%.[5] Assuming that the effectiveness of treatment arms of BDQ+Pa with either LZD 600 mg for 9 weeks followed by 300 mg for 17 weeks or LZD 600 mg for 13 weeks followed by 300 mg for 13 weeks would be about the same based on the recently released interim outcomes of ZeNIX trial results, we hypothesise that these treatment arms with planned reduction of LZD would be non-inferior to the LZD 600 mg for 26 weeks arm with a non-inferiority margin of about 10% ineffectiveness. To demonstrate this, with a power of 80% and an alpha error of 5%, we require about 111 patients in each arm. Factoring in a loss of 20% (due to default or migration), we need 133 patients in each arm, or a total of 399 patients (approx. 400) to achieve our study objective.

Data collection, management and interim analysis

Clinical and demographic information and laboratory reports will be collected from the individual participants in the paper case report forms (CRFs) and entered in REDCap software at all the participating sites. AEs will be monitored during weekly and monthly visits through physical examination, history-taking and laboratory investigations as specified in the study schedule.

Solicited and unsolicited AEs will be recorded and managed per DAIDS criteria. The data will be verified for accuracy and completeness. Data access would be restricted to the study statisticians at NIRT and Central TB Division. Third-party access to data is restricted and will be made available only on request to NIRT. Data analysis will be done using SPSS software by statisticians at NIRT. An interim analysis is planned when at least 33% (approximately 120) of the study participants complete 26 weeks of treatment and the results of sputum smear and MGIT culture are available.

Study outcome analysis

The primary effectiveness analysis will be conducted using the culture results from MGIT culture. A modified intention-to-treat (mITT) analysis will be carried out to evaluate the effectiveness of the newer regimens. We will evaluate the hypothesis that the investigational regimens are non-inferior to the standard of care regimen for the treatment of Pre-XDR-TB, $MDR_{/TI/NR}$ in terms of favourable outcomes (including sustained cure and treatment completed) and unfavourable outcomes (including death, treatment failure and lost to follow-up) in the field settings. Time to culture conversion and AEs at the end of 9 weeks and 26/39 weeks will be estimated using survival analysis methods. Deaths and study withdrawals within the first 7 days of treatment and baseline study drug resistance will be considered initial exclusions. They will not be included in the final mITT analysis. Kaplan-Meier survival curves will be constructed, and time to culture conversion and AEs will be calculated at the end of 9 and 26/39 weeks and compared among regimens using the log-rank test. To identify the important covariates with culture conversion, a Cox regression model will be used. Count regression models will be employed to compare the number of AEs experienced across treatment regimens adjusting for other covariates. The health-related quality of life (HRQOL) between the regimens will be compared using analysis of variance or the non-parametric alternative. Ordinarily least square regression will be used to compare the quality of life across regimens after adjusting for other variables. Per protocol analysis will be done for those patients who comply with the treatment regimen they were assigned. All participants who have consumed >80% of the drugs will be included in this analysis. Safety analysis will include data from all who received at least one dose of the study regimen.

Data and safety monitoring board

The DSMB comprises a statistician, clinical trial experts, a pharmacologist and a pulmonologist. They will be notified about the safety data after every ten patients are enrolled in the trial and complete 9 weeks of treatment in each of the three arms. This review will mainly be by circulation to members. An in-person review will be conducted when at least 33% (approximately 120) of the enrolled patients have completed 26 weeks of treatment and sputum smear, and MGIT culture results are available. They will review the progress of the trial and safety issues for the trial participants in the early stages focusing majorly on grade three or four AEs and serious AEs. DSMB may ask for ad hoc analysis and can recommend continuing or discontinuing or making modifications in the protocol based on any of these criteria: Grade 3 or grade 4 AE >10%; deaths due to any cause>15%; non-cardiac notifiable events >15% and QTc(F) >500 ms in more than 10% of enrolled patients.

Study site monitoring and quality assurance

A study monitoring committee formed by the sponsor and other stakeholders will monitor the study data quality per trial standard operating procedures. The monitoring plan will be followed to perform field visits and audits at various stages. The CRFs, patient records, and all source documents of the study participants in this study will be made available to be reviewed by the study monitors. Regular virtual meetings with the investigators of each study site will be conducted to discuss the study's progress. Any critical protocol changes made during the research will be communicated to the Institutional Ethics Committee, CTRI and the trial participants. At any time during or after completion of the study, the sponsor, through independent non-study staff, may conduct a quality assurance assessment of the site records, and the regulatory agencies may conduct a regulatory inspection.

Confidentially of trial data

All study-related CRFs and documents related to the trial will remain in the custody of the site principal investigator under lock and key until transferred to archives. The records identifying the patient will be kept confidential and will not be made publicly available. All electronic data will be saved securely in password-protected systems. The final data from the study will be accessible only to the statisticians in NIRT and the Central TB division. When trial results are published, the patient's identity will remain confidential. The confidentiality of the patients included in this trial will be maintained during the conduct of the study period following the Indian-Good Clinical Practice (GCP) and the relevant regulations by the laws of India.

Ethics and dissemination

The study has been approved by the ethics committees of participating institutes and the ICMR-National Institute for Research in TB. The current ICH GCP and the ICMR ethical guidelines for biomedical research in human participants will be followed in the current trial. This will ensure public assurance that the well-being, safety and rights of the participants are considered, which is consistent with the principles originating from the Declaration of Helsinki and will maintain the credibility of the clinical trial data. The personal data necessary to analyse the safety, tolerability and antibacterial activity of the investigational product will be used. Manuscript preparation, result dissemination and publication materials are the principal investigator's responsibility. After the completion of the trial, the investigators anticipate publishing the study results in peer-reviewed scientific journals, presenting the findings in meetings and sharing the results widely with the programme managers and policy-makers.

DISCUSSION

WHO has released the Global list of High Burden Countries for MDR/RR-TB for 2021–2025. The list contains the top 20 countries with an estimated absolute number of incident cases and the top 10 countries with a severe burden of incident rate totaling thirty countries. Compared with 2016–2020, few countries like Ethiopia

have transitioned out, while countries like Nepal have been added to the list.[1] Average success rate of conventional XDR-TB patients put on treatment (without BDQ) from 2016 to 2018 is 29%. This has increased to 48% in 2018.[10] Managing MDR-TB and XDR-TB remain a significant challenge in eliminating TB. DR-TB patients treated with short regimens with newer oral drugs are expected to have a better quality of life than patients on standard (either short or long) DR-TB regimens for multiple reasons. Patients' adherence improves with injectable-free treatment and facilitates the implementation of community programmes. This would reduce the costs incurred for the patients on travel to health facilities for injections, loss of wages, or hospitalisation expenses during the intensive phase of treatment of standard regimens. Hence, it is reasonable to assume that injectable-free treatment regimens that potentially reduce adverse reactions would likely improve patients' overall HRQOL. Second, BDQ-containing regimens reduce the costs per treatment success by 18%–20% in short course regimens and 49%–50% in long course regimens. Approximately 61 000 more patients are estimated to be treated successfully over 5 years with BDQ-containing regimens.[11] The success rate of DR TB patients treated under the BDQ conditional access programme is 71%.[10]

Studies have compared the outcomes of an extended oral regimen containing BDQ with the shorter oral regimen. A shorter all-oral BDQ-containing regimen showed more beneficial effects than an injectable-free longer regimen containing BDQ. The favourable OR of 3.9 (1.7–9.1) was observed for success vs failure/recurrence, 1.6 (1.2–2.2) for success versus all unfavourable outcomes, and 0.5 (0.4–0.8) for lost to follow-up, thereby supporting the use of all-oral shorter regimen.[12] Also, studies have evaluated the safety of the newer drugs in shorter oral regimens. The NIXTB study reported LZD toxicity such as peripheral neuropathy and myelosuppression among 81% and 48% of the study population. AEs leading to death and serious AEs were 9% and 30%, respectively, in the 600 mg two times per day LZD group and 3% and 9% in the 1200 mg once daily LZD group.[3] In the ZeNIX trial, peripheral neuropathy was reported in 38% of those receiving 1200 mg of LZD for 6 months; 24% of those receiving 1200 mg of LZD for 2 months; 24% of those receiving 600 mg of LZD for 6 months and 13% of those receiving 600 mg of LZD for 2 months. Similarly, anaemia, secondary to LZD exposure, was noticed in 22% of those receiving 1200 mg of LZD for 6 months; 17% of those receiving 1200 mg of LZD for 2 months; 2% of those receiving 600 mg of LZD for 6 months and 7% in those receiving 600 mg of LZD for 2 months.[5] The mBPaL study will determine the effectiveness in managing DR-TB patients by comparing the varying dose of LZD with BDQ and Pa regimens. Safety assessment in the mBPaL study is one of the significant components in measuring the outcome of the regimens.

We are proposing to conduct a pragmatic clinical trial (mBPaL study) with varying doses of LZD along with BDQ and Pa as a planned reduction of LZD for the treatment of pre-XDR and $MDR_{TI/NR}$ pulmonary TB patients for 26–39 weeks. Given the poor tolerability and increased frequency of dose interruption in regimens containing LZD, this trial will help us decide on the effective dosing of LZD to be given with BDQ and Pa for an entirely oral short-course regimen to treat highly DR-TB in the field setting. The main drivers of the acceptability of the BPaL regimen were the short duration of treatment, fully oral regimen without injectable, reduced pill burden, anticipated higher treatment success, the lower financial burden for patients and the programme, reduced load on the health system, using existing diagnostic processes and lesser burden to TB laboratories for monitoring of bacteriological treatment. This study will create a new standard of care for Pre-XDR and $MDR_{TI/NR}$-pulmonary TB patients that will not only have better and earlier culture conversion but also reduce the proportion of patients who do not adhere to the entire course of therapy.

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