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Association between baseline factors and linezolid dose reduction in a non-linezolid randomized sample from the endTB clinical trial

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BMI	Body mass index
BPaLM	Bedaquiline + petromanid + linezolid + moxifloxacin
BPaL	Bedaquiline + petromanid + linezolid
Cmin	Minimum blood plasma concentration
CRF	Case Report Form
endTB	Evaluating Newly approved Drugs for multidrug-resistant TB
DST	Drugs Susceptibility Testing
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
HR	Hazard Ratio
ICF	Informed Consent Forms
IQR	Interquartile Range
IRB	Institutional Review Board
IRD	Interactive Research and Development
Lzd	Linezolid
MSF	Médecins Sans Frontières
mITT	Modified Intent-to-treat
MDR-TB	Mult-drug resistant tuberculosis
PIH	Partners in Health
PS	Performance Status
RR	Relative Risk
aRR	Adjusted Relative Risk
RCT	Randomized Controlled Clinical Trials
TB	Tuberculosis
XDR-TB	Extensively drug-resistant tuberculosis
	*In the NixTB clinical trial the definition of XDR-TB was: MDR-TB plus resistance to any fluoroquinolone and any second-line injectable
WHO	World Health Organization

Abstract

Background: Tuberculosis is the second leading cause of death in infectious diseases. Treatment has become a priority in the fight against the disease, particularly MDR-TB. Linezolid was approved for use as part of MDR-TB treatment, but its dosing is still under investigation to balance efficacy and toxicity.

Methods: This cross-sectional study used a sample of non-linezolid randomized MDR-TB participants from the linezolid-containing arms of the endTB clinical trial (NCT02754765). All participants received initially 600 mg of linezolid daily and were subsequently reduced to either 300 mg daily or 600 mg thrice weekly by the clinician's decision. The aim of this study was to assess the association between participant's baseline characteristics and linezolid dose reduction strategy.

Results: From 193 non-linezolid-randomized participants, 85 were assigned to 300 mg daily and 108 to 600 mg thrice weekly. Investigators from trials countries such as Georgia, Lesotho, Peru, and South Africa allocated most or all the participants in one single linezolid dose reduction strategy. However, using a multivariable relative risk regression, sex, smoking, HIV status and performance status were found significantly associated with the linezolid dose reduction strategy. Males (aRR = 1.31, 95% CI = 1.01, 1.69) and participants with reduced performance status (aRR=1.44, 95% CI= 1.07, 1.92) had higher risk to being assigned to 600 mg thrice weekly. While people living with HIV (aRR= 0.17, 95% CI= 0.06, 0.50) and smokers (aRR=0.74, 95% CI = 0.57, 0.97) had a lower risk to being assigned to 600 mg thrice weekly.

Conclusions: Country was found to explain most of the variability associated with linezolid dose reduction strategies (300 mg daily and 600 mg thrice weekly). Other baseline variables were found to be associated, although it is difficult to establish their precise role.

Key words: Linezolid, Multi-drug resistance, Tuberculosis, Clinical trial

1.Introduction

In 2022, 10.6 million people were estimated to fall ill with tuberculosis (TB), the second leading cause of death among infectious diseases with 1.30 million attributed deaths. This was not in line with World Health Organization (WHO) objective of achieving a mortality reduction of 75% in 2025 (1). The incidence rate was estimated to be 133 per 100,000 population in 2022, far from the WHO milestones.

India, just ahead of Indonesia, China, and Philippines, Pakistan, Nigeria, Bangladesh and the Democratic Republic of Congo had two-thirds of the global TB burden (1). The estimated highest mortality rate has been concentrated in Africa during 2021 (2).

In addition, sociodemographic and economic factors that increase an individual's risk of contracting the disease might contribute to the higher incidence rates reported in certain groups. Socioeconomic status can increase a person's susceptibility to diseases such as TB through factors such as lower income, congested living conditions, undernutrition, and lack of education. TB burden according to sex was reported as 5.8 million cases among men (aged ≥15 years) and 3.5 million cases among women (aged ≥15 years) in 2022 (1). Thus, TB affects more men than women, and that might be explained by gaps in case detection and reporting among men (1,3–5). This is likely to be associated with social roles and social networks established in society (6,7). Therefore, social determinants of health might affect a person's ability to receive high-quality medical care and increase their risk of TB infection (8).

The availability of medical care and diagnosis differs relevantly depending on the setting. While overall 61% of people living with TB received diagnosis and treatment when required in 2021, this proportion was highly heterogeneous among different settings. For instance, Brazil, India, Uganda and Zambia, countries with high TB burden, had a high TB treatment coverage (≥80%) (1). Central African Republic, Lesotho, Liberia, Mongolia, and Myanmar, countries with an equally high TB burden, had low levels of TB treatment coverage (<50%) (1).

1.1 Multidrug-resistant tuberculosis (MDR-TB)

In 2022, an estimated 410 000 people were diagnosed with multidrug-resistant tuberculosis (MDR-TB) and rifampicin resistant TB (RR-TB), defined by resistance to isoniazid and rifampicin, two key first-line drugs for the treatment of TB (1). India, the Philippines and the Russian Federation represent 42% of people diagnosed with MDR/RR TB (1). Certain populations are at

risk of developing TB, such as people living with HIV, who are 42% more likely to develop MDR-TB (OR=1.42 95% CI=1.17-1.71) (9).

Since 2022, WHO guidelines recommend the use of three regimens to treat MDR-TB. The first is a 6-month regimen, referred to as BPaLM, which includes the following drugs: bedaquiline, pretomanid, linezolid, and moxifloxacin. The second regimen, also referred to as the 9-month regimen, is a combination of seven drugs given for a duration of 9 to 11 months. The last regimen is individualized, typically including 4 to 6 oral drugs, and has a duration of 18-20 months (1,10).

1.2 Linezolid

Seeking new therapeutic options to fight antibiotic resistance, linezolid, belonging to the oxazolidinones family, was approved in 2000 by U.S. Food and Drug Administration (FDA) to face infections caused by gram-positive bacteria (11,12), such as pneumonia, skin infections, and diabetic foot infections. At the time, the FDA report recommended a dose of 600 mg twice daily for adults and children. In the last decade, linezolid has been repurposed for MDR-TB treatment and is now considered one of the most effective MDR-TB drugs, although burdened by substantial toxicity.

1.3 Linezolid-related toxicity

Studies conducted in vitro and in vivo have evaluated the effectiveness of linezolid against M. tuberculosis and its drug-resistant strains (13,14). Despite its efficacy, studies have described important side effects including peripheral and optic neuropathy, myelosuppression, serotonin syndrome, and lactic acidosis. A few of these were discussed in the FDA's toxicology and clinical analysis, with special attention to the effects on animals and humans (3–5,12).

Early case studies identified peripheral and optic neuropathy (15), as a possible side effect of linezolid-containing treatments (16). Optic neuropathy affects color perception and causes blurred vision in patients (15) while peripheral neuropathy presents symptoms such as paresthesia and numbness in the extremities, in particular the lower limbs (17). Both types of neuropathic adverse events have been linked to linezolid and the duration of linezolid exposure while receiving MDR/XDR-TB treatment. A systematic review/ meta-analysis of 22 studies reported a pooled proportion of 29.92% for neuropathy events (18). While another meta-analysis reported a similar pooled proportion of 30.9% for peripheral neuropathy and 8.0% for optic neuritis (18–20).

Myelosuppression is known as bone narrow suppression, and leads to anemia, neutropenia and thrombocytopenia (21,22). A meta-analysis by Agyeman and Ofori-Asenso, the pooled proportion of myelosuppression, reported as anemia or neutropenia, in 23 studies 32.93% (18). A lower incidence of myelosuppression was related to lower linezolid doses (18). Cytopenia events, defined as leukopenia, anemia, and thrombocytopenia, have been reported when monitoring MDR-TB patients receiving a linezolid-containing treatment. Notably, this study revealed that patients exposed to a value >2 mg/L linezolid-Cmin concentrations had a higher likelihood of developing cytopenia's compared with those exposed to lower Cmin values (OR= 4.40, 95% CI = 0.79 -24.4) (23).

For many years, linezolid has been used as part of long, individualized treatment MDR-TB regimens. In 2019, however, linezolid use was approved to treat extensively drug-resistant TB (XDR-TB) as part of a standardized regimen along with pretomanid and bedaquiline (24). This approval was supported by the Nix-TB trial results. A single-group, open-label trial without an internal control arm, Nix-TB showed that the BPaL regimen (bedaquiline, pretomanid, linezolid) was effective in 82% of XDR-TB patients and 92% of MDR-TB participants. However, 81% of participants reported at least mild or moderate peripheral neuropathy symptoms. Myelosuppression was another frequent adverse event affecting 52 (48%) individuals. These results were considered related to the high dose of linezolid used (600 mg twice daily) in that study (5).

Throughout the years, recommended linezolid doses have changed, and dosing reductions were proposed to avoid toxicity. A systematic review highlighted two dosing strategies: 600 mg twice daily and 600 mg once daily (25). The 600 mg was identified as potentially the best balance of effectiveness and toxicity for short and long treatment (25). Although, toxicity was still identified as a concern for both doses. The variability of doses proposed by clinicians and researchers in studies underscores the lack of clear guidance on the optimal administration of linezolid (21,26).

Some studies suggested that a dose reduction to 300 mg daily might mitigate side effects (27–29). Supporting this assumption, Lee, and colleagues (2012) found that, after adding linezolid to their regimen, participants who received a 600 mg daily dose of linezolid were 2.7 times more likely (95% CI= 1.1, 6.5) to have an adverse event than those who receive a 300 mg daily dose (3). A study by Mase and colleagues (5,30) revealed similar results in 2022. In a follow-up study, linezolid doses (1200 mg and 600 mg daily) were compared as part of the BPaL regimen,

suggesting the use of 600 mg daily to reduce adverse events (5). Non-clinical and clinical studies support the adjustments of linezolid doses and schedule, highlighting the effect of an intermittent dose by maintaining a daily dose and reducing the lowest concentration of the drug in blood (Cmin) to mitigate toxicity effects (31). Chang and colleagues (2013) study publication linezolid was dosed to 800 mg daily and, after consecutive negative cultures, the dose was reduced to 1200 mg thrice weekly (32). When side effects were observed while using the intermittent doses, linezolid was dosed to 600 mg thrice weekly (32). This study has shown that after reducing the linezolid dose to 600 mg thrice weekly, a small sample of patients with peripheral neuropathy gradually improved (32).

The previous studies suggested the efficacy of linezolid as a treatment for MDR-TB, while also highlighting the side effects. Yet, a systematic review conducted for The Cochrane Library revealed that, due to a high risk of bias and differences in methodologies used across these studies, it was not feasible to compile and compare the existing studies. This research highlights that most available evidence on safety, duration and optimal dosing of linezolid remained imprecise, particularly because of the limitations of methodologies employed in research (26).

1.4 Characteristics related to TB

Certain well-described factors play a pivotal role in explaining disease severity and may influence progression and ultimately tuberculosis treatment outcomes. These may include, among others, performance status (PS), sputum smear results, the presence of lung cavitation, body mass index (BMI). PS, a critical factor guiding treatment decisions, assesses a patient's ability to perform daily activities comfortably. PS has been linked to mortality rates in pulmonary tuberculosis patients, indicating that individuals with a grade 3 or 4 PS, reflecting higher levels of physical limitation, face an increased risk of death (33). This factor is not only employed in tuberculosis studies but also in oncology research, where evaluating a patient's performance is crucial for determining appropriate drug administration (34).

The severity of tuberculosis, as indicated by factors such as the presence of lung cavitation and positive sputum smear results, can vary depending on the timing of diagnosis. Researchers conducted a pooled analysis of randomized controlled clinical trials (RCTs) that combined these indicators to create distinct phenotypes: easy-to-treat (a low smear grade or absence of cavitation) and hard–to–treat (smear 3+ and presence of cavitation) (35). These phenotypes aimed to characterize the level of disease severity and guide appropriate treatment approaches. The hard-to-treat phenotype (smear 3+ and presence of cavitation) or extensive disease was

associated with slower culture conversion during MDR-TB treatment (20). This approach might allow the clinicians to closely monitor and tailor treatment for patients.

As mentioned previously, undernutrition is related to TB as one of the social determinants of health. Nutritional status has been described as an important prognostic factor due to its possible interaction with low serum levels of TB treatment drugs (36).A study has shown that a decrease in body mass index (BMI) of 5 kg/m^2 was associated (HR= 1.4; 95% CI= 1.0–1.7) with unfavorable outcomes for drug-susceptible pulmonary tuberculosis (35). Similarly, a study on BMI trajectories revealed that MDR-TB patients who achieved cure had an increase in BMI (37). However, BMI values decreased for patients who die, and variables such as HIV-positive, poor treatment adherence and depression symptoms were found as main characteristics for this subgroup (37). These findings suggest that BMI could be a useful factor for treatment monitoring and to assess the achievement of favorable outcomes for MDR-TB treatment studies. However, adjustments by different variables should be considered as BMI may depend on other variables such us income and access to healthcare.

The variables discussed, which explain the severity of the disease and its association with tuberculosis treatment-related outcomes could potentially be involved in the decision-making process to reduce linezolid doses. As previously explained, determining the optimal dose requires a balance between treatment effectiveness while mitigating safety concerns and toxicity effects.

1.5 endTB clinical trial

Table 1: Description of endTB regimens

Abbreviature	Regimens	Description
endTB1	9BLMZ	Bedaquiline + **linezolid** + moxifloxacin + pyrazinamide for 9 months
endTB2	9BCLLfxZ	Bedaquiline+ clofazimine+ **linezolid**+ levofloxacin + pyrazinamide for 9 months
endTB3	9BDLLfxZ	Bedaquiline+ delamanid +**linezolid**+ levofloxacin+ pyrazinamide for 9 months
endTB4	9DCLLfxZ	Delamanid+ clofazimine+ **linezolid**+ levofloxacin+ pyrazinamide for 9 months
endTB5	9DCMZ	Delamanid+ clofazimine+ moxifloxacin+ pyrazinamide for 9 months
endTB control	18-24 months of standard care according to WHO guidelines in each country	

The endTB trial is a phase III randomized, controlled, open-label, non-inferiority clinical trial designed and implemented by Médecins Sans Frontières (MSF), Partners in Health (PIH), and Interactive Research and Development (IRD) to find a new short and well-tolerated regimen for

MDR-TB. The primary results of the endTB trial have been recently shared showing that three different 9-month regimens, 9BLMZ, 9BCLLfxZ, and 9BDLLfxZ, are non-inferior compared to the standard treatment (control arm) when assessing favorable outcome rates at Week 73 (38).

A secondary goal of endTB trial was to assess the optimal linezolid dose reduction. All study participants included in linezolid-containing experimental arms (9BLMZ, 9BCLLfxZ, 9BDLLfxZ, and 9 DCLLfxZ) received 600 mg daily linezolid dose initially: this dose was reduced after 16 weeks of treatment, or earlier in case of adverse events, to either 300 mg daily or 600 mg thrice weekly. The decision between the two possible dose reduction strategies was initially made for each individual participant by site investigators. After two years of enrollment, a protocol amendment introduced a secondary randomization to select the dose reduction strategy.

This study aims to assess baseline factors that influenced the choice of linezolid dose reduction strategy – 300 mg daily or 600 mg thrice weekly – during the first phase of enrollment, when the decision was taken by site investigators and no secondary randomization was performed. To achieve that, the study sample will comprise participants who were randomized to a linezolid-containing experimental arm (9BLMZ, 9BCLLfxZ, 9BDLLfxZ, and 9DCLLfxZ) and later were assigned to a linezolid dose-reduction strategy by site investigators.

Assessing linezolid dose adjustment aims to highlight variations in the decisions made by clinicians according to baseline clinical, social, and demographic data gathered at the beginning of endTB trial. When discussing health care decision-making, it is important to acknowledge significant factors involved in this process to elucidate the variance of decisions taken.

This study was undertaken as part of an internship project at Médecins Sans Frontières under the direction of the endTB team, wherein the thesis preparation and statistical analysis were carried out. This work will help to elucidate the characteristics of one specific subgroup of the clinical trial and to better understand the association of linezolid dose reduction and baseline variables.

2. Objective

The main objective is to assess the association between baseline factors and linezolid dose reduction (300 mg daily or 600 mg thrice weekly) in MDR-TB participants who were randomized to one of the four endTB arms containing linezolid (9BLMZ, 9BCLLfxZ, 9BDLLfxZ, and 9 DCLLfxZ) and were not linezolid-randomized.

3. Methodology

3.1 Study design and population

The study follows a cross-sectional design based on a selected sample of participants from the endTB clinical trial. endTB is a multicountry, phase III, randomized, controlled, non-inferiority clinical trial (NCT02754765) which took place across sites in 7 countries and evaluated five new 9-month treatment regimens against one control arm based on WHO guidelines in participants with rifampicin-resistant and fluoroquinolone susceptible TB. Participants were randomized at inclusion to one of the six treatments arms (Figure 1). Participants who were assigned to a linezolid-containing treatment received a linezolid dose of 600 mg daily; however, this was modified at Week 16, or earlier, in case of linezolid-related toxicity, to one of two reduced linezolid doses (300 mg daily or 600 mg thrice weekly). The study protocol and primary results have been published elsewhere (38,39).

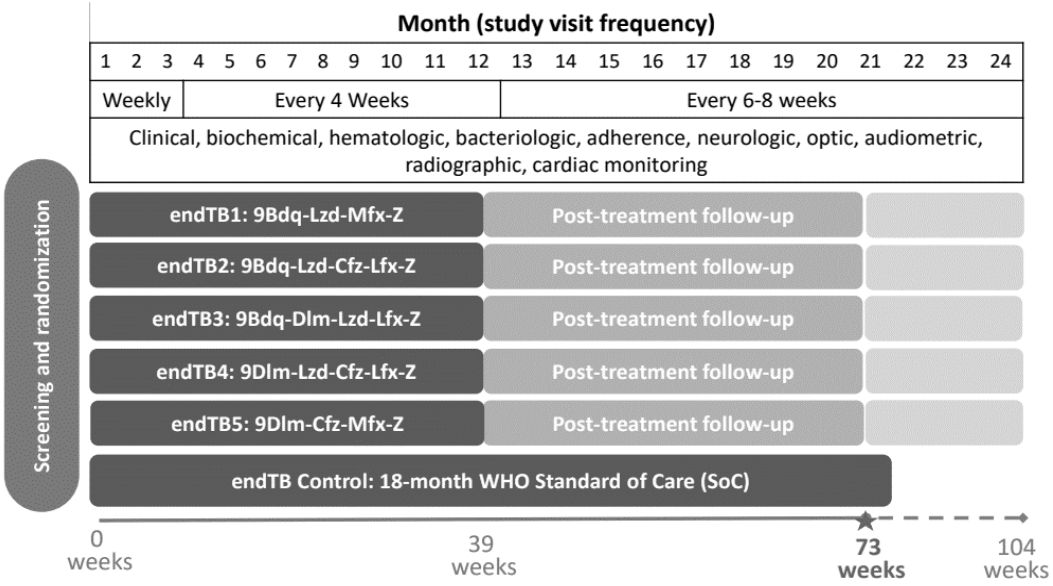

Figure 1. endTB trial design, including experimental and control arms and time periods (40).

At the beginning of trial inclusion (2017-2018), the decision of linezolid reduction dose was left to the site investigators. However, after a protocol revision, a secondary randomization was introduced to assign linezolid dose reduction strategies. This process was introduced on September 12, 2019.

This study is focused on endTB participants randomized to the four linezolid-containing endTB arms (9BLMZ, 9BCLLfxZ, 9BDLLfxZ, and 9DCLLfxZ) who received a linezolid dose reduction and for whom linezolid dose reduction was not determined by secondary randomization.

3.2 Data source

Data used for this study was selected from the endTB clinical trial. Data was collected from 2017 to 2023 (Figure 2). Data was collected by professionals and gathered on OpenClinica (http: endtb.epicentre-msf.org).

Figure 2: endTB Timeline inclusion of sites, primary randomization, and closure of database (40).

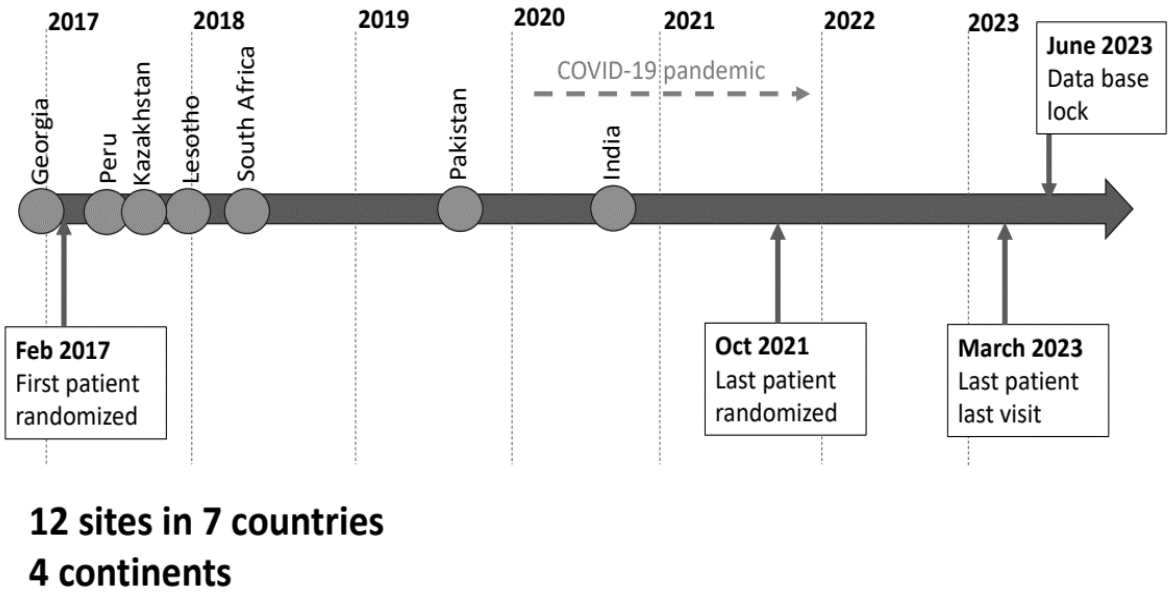

Figure 2: endTB Timeline inclusion of sites, primary randomization, and closure of database (40).

Study analysis populations were defined in the endTB clinical trial, according to each objective. For this study, we included participants belonging to the modified Intention-To-Treat population (mITT). The mITT population includes participants who were randomized to an experimental or control arm, had a positive culture result, and obtained rifampicin-resistant and fluroquinolone-susceptible result from a molecular test (41). However, they were excluded from this population if:

- Never started treatment in the trial,
- They were randomized by error,
- They did not obtain a positive culture result before primary/treatment randomization,
- They had resistance to fluroquinolone, bedaquiline, delamanid, linezolid or clofazimine.

According to these criteria, data was filtered to retain the sample that was not secondary randomized to assign linezolid dose reductions. After this process, baseline or screening variables and the outcomes were included in the database.

3.3 Settings

This study includes participants from seven countries: Georgia, India, Kazakhstan, Lesotho, Pakistan, Peru, South Africa. Twelve sites started their activities between 2017 and 2021. Countries were initially included in the endTB trial based on MDR-TB burden and other characteristics (41).

3.4 Main outcome of interest

The main outcome is the linezolid-dose reduction strategy (300 mg daily and 600 thrice weekly), defined as the first reduction assigned by clinicians to each patient, who were not linezolid randomized, along the care pathway. Both strategies proved to be effective, therefore none of them was chosen as a reference (300 mg).

3.5 Factors

I. Sociodemographic variables were collected using a form.
    a. Sex (Female, Male)
    b. Age (< 65 years,>= 65 years)
    c. BMI (< 25 kg/m^2, >= 25 kg/m^2)
    d. Country (7 countries)

II. Comorbidities

a. Diabetes (yes/ no) results were obtained from a medical history report and a glucose test.
b. HIV status (positive/ negative) variable was defined using information provided in medical history, and screening assessment.

III. Risk factors reported in a form at screening/baseline evaluation.
a. Alcohol use (Yes/No)
b. Smoking (Yes/No)

IV. TB disease severity
a. The extent of disease was established as a combination of two variables: sputum smear result and presence of any lung cavity, both assessed at screening/baseline. The smear result was categorized as scanty, 1+, 2+ and 3+. The presence of lung cavity was established using the participant's chest X-ray, describing the laterality (unilateral and bilateral). However, it was categorized as a binary (absent/present) with the purpose of combining both results. The following table explains how the extent of TB disease was established (42):

Table 2: Description of extent of disease (TB)

Lung cavity	Smear negative (Scanty)	Smear 1+	Smear 2+	Smear 3+
Lung cavity absent	Limited	Limited	Extensive	Extensive
Lung cavity present	Limited	Extensive	Extensive	Extensive

V. Other variables
a. Prior exposure to TB treatment (First-line treatment and other)
b. Visual acuity test is an ophthalmological assessment of participants ability to identify elements at 3, 5 and 6 meters of distance from the chart (Snellen or Tumbling E). The examination ranged from 0 to 4 on a grade scale. This variable was categorized as binary (normal or grade 1-2/ grade 3-4) for this analysis.
c. Brief Peripheral Neuropathy Screen (BPNS) is a screening tool designed to assess clinical and subjective symptoms of peripheral neuropathy. Clinical staff (non-neurologist) conducted the assessment. Grades from 0 to 4 explain the presence of symptoms, where zero is normal, and grades 1-4 are labelled as mild discomfort, moderate discomfort, severe discomfort, and life threatening.

d. Laboratory test results were graded according to *MSF Severity Grading Scale* (43). All of them were defined as two levels: normal (grade 0) and abnormal (grades 1-4). The following grades are considered as abnormal for each variable.
    i. Hemoglobin: grade 1(10.5-9.5g/dl), grade 2 (9.4-8.0 g/dl), grade 3 (7.9-6.5 g/dl), and grade 4 (<6.5g/dl).
    ii. Neutrophils: grade 1 (99.9- 75.0 x 10^9/L), grade 2 (74.9 -50.0 x 10^9/L), grade 3 (49/9 – 20.0 x 10^9/L), and grade 4 (<20.0 x 10^9/L).
    iii. Platelets: grade 1 (99.9- 75.0 x 10^9/L), grade 2 (74.9 -50.0 x 10^9/L), grade 3 (49/9 – 20.0 x 10^9/L) and grade 4 (<20.0 x 10^9/L).
e. Performance status (PS) was assessed using the Eastern Cooperative Oncology Group (ECOG) assessment (44). This scale developed to evaluate the quality of life, measure the patient's well-being and capability to perform self-care activities. Grades are defined from 0 (fully active and capable of performing activities without restriction) to 5 (dead).

3.4 Statistical analysis

The database was examined to describe the group of participants who received each linezolid reduced dose. Baseline variables were summarized using median and interquartile range (IQR) for continuous variables. Categorical variables were described using frequencies and percentages.

Because of the similar prevalence in each linezolid dose reduction strategy and considering that the outcome is not a rare event, a relative risk regression was used. Baseline variables related to linezolid dose reduction strategy (600 mg thrice per week versus 300 mg daily) were identified by using a univariable relative risk regression model, where 300mg was the reference. Variables associated with linezolid dose reduction strategy in the univariable model ($p<0.10$) were considered for inclusion in a log binomial relative risk multivariable regression model. Using backward elimination, only significant and independent variables with $p<0.05$ were retained in the final model. To conduct the statistical analysis, R version 4.3.2 and the package "logbin" were used (45).

3.5 Ethical consideration

The endTB clinical trial procedures adheres to the Declaration of Helsinki and the Harmonization Good Clinical Practice regulations and guidelines as well as local standard. The protocol and informed consent forms (ICFs) were submitted to IRBs, and the last version was approved in March 2019. Each site submitted their protocol to local committees for further review and approval. The ICFs described the endTB clinical trial screening, risks and interventions patients received. This information and patients' questions have been solved by a designated person taking the ICF. All ICFs were written in local language and English. In case of having minor (15 to 17 years old) or an illiterate person as prospective participant, all information in the assent form was explained orally. A similar process was conducted when a caregiver or parent had to provide their approval. (41)

Confidentiality was assured when harmonizing the database and assigning an identifier number to each patient. Collected information was protected in locked cabinets and virtual records were protected by passwords (41). Access to records has been restricted to team members and information shared to be a subject of analysis has been protected using MSF outlook password. In this study, databases are provided to be used in the professional assigned computer, assuring the use of outlook password to access them.

4. Results

Overall, 754 participants were randomized to the six arms of the endTB clinical trial (5 experimental arms and a control arm). From them, 504 (66.84%) participants were randomized to one of the linezolid-containing arms and 250 (33.16%) were assigned to the fifth endTB arm or the control arm. In addition, 31 participants randomized to a linezolid-containing arm were excluded because they did not meet mITT criteria. As a result, 473 participants were included in the mITT population. Linezolid-dose reduction randomization was conducted among 247 (54.33%) participants randomized to one of the linezolid-dose strategies, leaving 226 (47.78%) participants not randomly assigned to a linezolid-dose reduction strategy.

Figure 3. Flowchart illustrating the sample selection process used for retaining non-randomized linezolid participants.

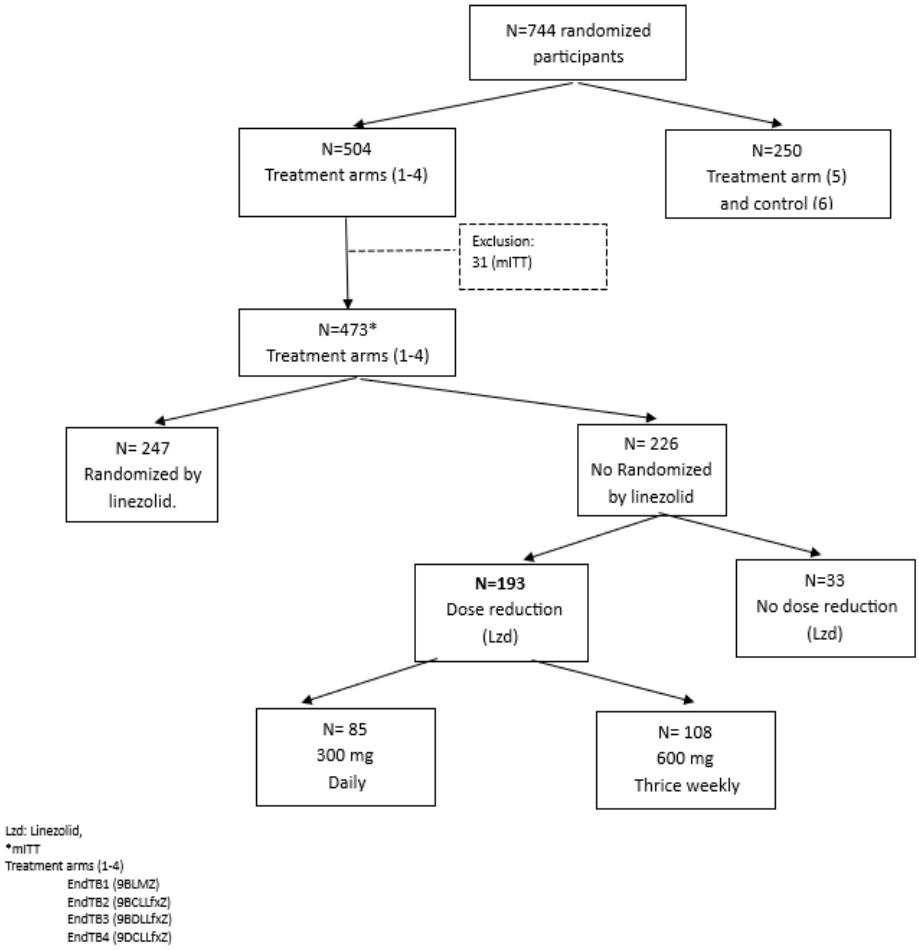

Figure 3. Flowchart illustrating the sample selection process used for retaining non-randomized linezolid participants.

Of the 226 participants in this latter group, 193 (85.40%) received a reduced linezolid dose. This was the group that was ultimately included in this analysis. From this group, 85 (44.04%) received a linezolid dose reduction of 300 mg daily and 108 (55.96%) received 600 mg thrice weekly.

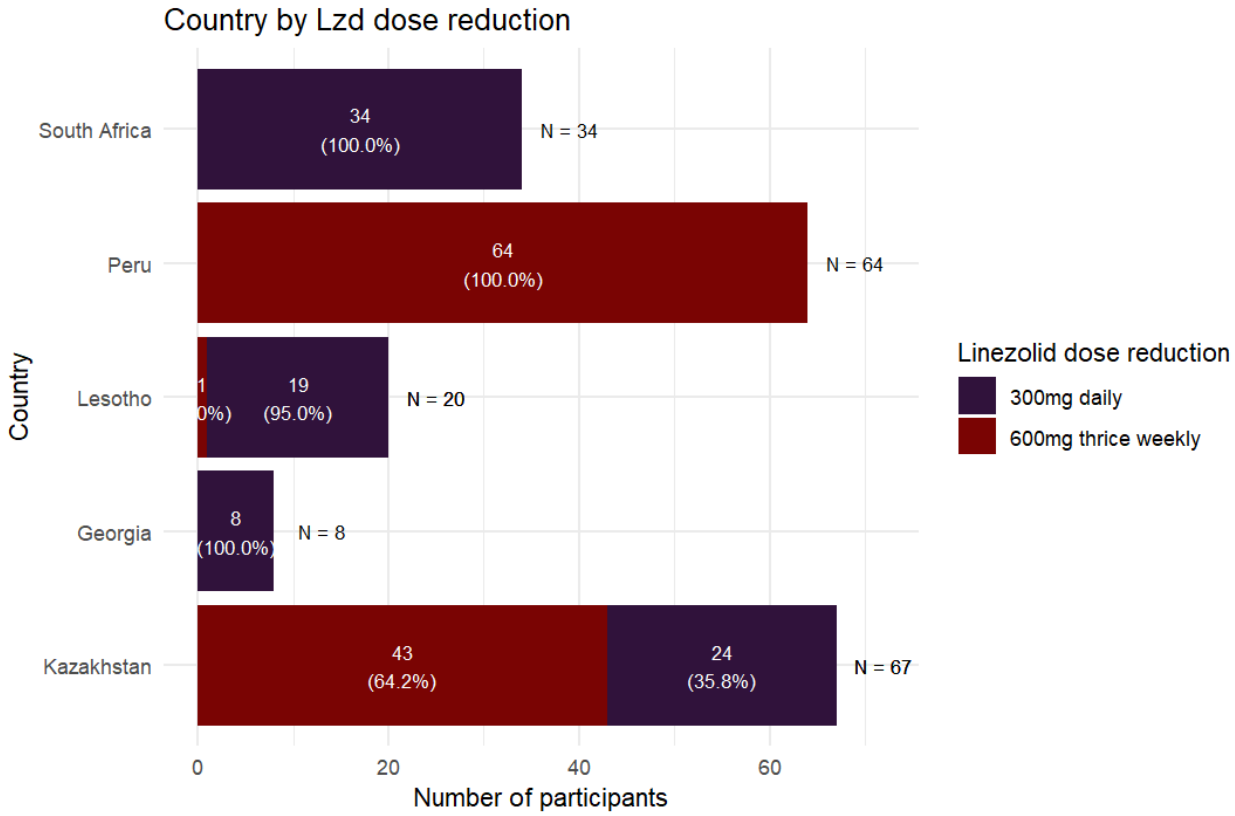

Figure 4: Linezolid dose reduction by country (N=193).

*Lesotho: 1(5%) 600mg thrice weekly; 19 (95%) 300 daily

Some endTB trial countries, such as India and Pakistan do not have any participants in this analysis as they started enrollment after the implementation of secondary linezolid randomization (Appendix (1) and Figure 4). Investigators in most countries, such as Georgia, Lesotho, Peru, and South Africa, allocated most (or all) of their participants to one of the linezolid dose reduction strategies. Conversely, Kazakhstan participants were assigned to both dose reduction strategies. Therefore, the country variable was not included in the univariable or multivariable regression analyses, due to zero or small counts of participants in each cell when distributed by linezolid dose reduction strategies.

Based on the univariable regression (Appendix 2), sex, diabetes, HIV, smoking, visual acuity, hemoglobin, and performance status (ECOG) were found to be associated ($p < 0.10$) with the outcome of linezolid dose reduction strategy (600 mg thrice weekly versus 300 mg daily). These variables were adjusted in a multivariable regression. Assumptions to run a binary regression analysis were met: the outcome is binary, all observations are independent, and the independent

variables were not correlated to each other. Variance influence factor (VIF) was evaluated, resulting in values ranging from 1.03 to 1.10.

After a backward selection of covariates, four variables (sex, smoking, HIV, performance status) were identified as statistically significant ($p<0.05$) and remained in the final multivariable model. These variables were not correlated to each other: sex (VIF= 1.04), smoking (VIF=1.04), HIV (VIF=1.02), and performance status (VIF= 1.03). The Hosmer-Lemeshow test provided a p-value of 0.76, proving there is no evidence of poor fit.

After adjusting for the other statistically significant covariates, we observed the following:

- males had a 31 % (aRR = 1.31, 95% CI = 1.01, 1.69) higher risk of being assigned to the 600 mg thrice weekly dose reduction compared with females;
- people living with HIV had an 83% (aRR= 0.17, 95% CI= 0.06, 0.50) lower risk of receiving 600 mg thrice weekly as a first reduction of linezolid dose, when comparing with people who tested negative for HIV;
- participants who reported to smoke tobacco had a 26% (aRR=0.74, 95% CI = 0.57, 0.97) lower risk of receiving the lowest dose of linezolid (600 mg thrice weekly) than participants who did not smoke;
- Finally, people with a reduced performance status had a 44% (aRR=1.44, 95% CI= 1.07, 1.92) higher risk of being assigned to 600 mg thrice weekly compared to those with a normal performance status.

5. Discussion

The previous analysis revealed that the likelihood of receiving a reduced dose of linezolid was associated with the allocation made in the clinical trials countries. Using relative risk regression, we identified sex, HIV status, smoking, and performance status as associated variables.

The decision to reduce the linezolid dose appears to be mainly driven by the country where the clinical trial was conducted, as evidenced by the allocation of participants to different linezolid dose reduction strategies shown in Figure 4. This variability comes from differences in clinical practices in terms of the choice of linezolid dose reduction between these options, as previously reported (19, 24). The decision to reduce the dose in the endTB trial fell under the responsibility of healthcare professionals and in particular of the principal investigator of each trial site.

In our study, we did not find a clear preference in terms of a single dose reduction strategy across all sites. We therefore hypothesize that different factors might influence this decision. The main factor, as discussed above, appears to be the country (and the site) where the trial was conducted. This is linked to individual knowledge of existing evidence and published literature, but also concordance with local guidelines and clinical practices which may be influenced by the opinion of known local stakeholders. While all these elements concur to define the “a priori” inclination of each investigator to choose a dose reduction strategy, we tried to investigate which other “individual” participant factors were considered by the investigator.

To do so, a univariable regression analysis was conducted to explore the association between various variables and linezolid dose reduction strategies. While many variables were included in the analysis, only seven variables were found to be significantly related to this outcome. Most of the significant variables were previously described as risk factors and side effects associated with linezolid (18–20) . Surprisingly, peripheral neuropathy and myelosuppression did not demonstrate a statistically significant association (Appendix 2). However, sex, HIV status, smoking, and performance status were found to be statistically significant predictors of linezolid dose reduction strategies when adjusting for these variables in a multivariable regression analysis.

The analysis revealed that men had an increased risk of being assigned to an intermittent linezolid dose reduction strategy compared to women (aRR = 1.31, 95% CI = 1.01-1.69). Typically, men experiences challenges with treatment adherence and have higher exposure to certain diseases

such as TB (1,46,47). One potential explanation for this finding is that clinicians may have anticipated poorer adherence or higher risk of linezolid-related adverse events among male patients, leading them to assign intermittent linezolid doses, such as 600 mg three times weekly, to mitigate the risk of toxicity from prolonged high-dose exposure. The analysis did not explicitly explore whether this assignment to men was primarily driven by anticipated adherence issues or the occurrence of adverse events during treatment.

While smoking is a well-established risk factor for the development of TB and for poor TB treatment outcome (48), the findings of this study suggest that smokers were less likely to receive a linezolid dose of 600 mg thrice weekly compared to non-smokers. A plausible explanation for this finding is that clinicians may have considered participant who smoked at higher risk of unfavorable treatment outcome and would have therefore preferred a daily linezolid dosing.

Having a reduced performance status graded from 1 to 3 was associated with being assigned 600 mg thrice weekly of linezolid. These grades encompass restrictions to perform physical strenuous activities from a mild level to being confined to bed or spending more than 50% of the time in a chair (31, 32). As literature has shown, performance status is a factor to monitor while providing care for MDR-TB patients (33,34). This finding suggests that clinicians likely relied on the evaluation of the performance status as a global marker of participant's wellbeing to guide their decision regarding linezolid dose reduction strategies.

The assessment of global performance status testing results in the trial suggest that clinicians use it based on their observations, and clinical experience to classify patients into five grades of physical restriction. Moreover, social desirability, sex, age and socioeconomic factors have been recognized as a potential factor influencing decision-making when assessing PS for oncology services (49). These findings might elucidate the complexity of accounting PS as a possible risk factor when decision-making depends on the variability of clinician's assessments.

While HIV-positive individuals are known to have a higher risk of developing MDR-TB (39) and overall worse treatment outcome (51), the current study had a relatively small number of HIV-positive participants (N=33) across the different linezolid dose reduction strategies. Despite the low sample size, HIV status was included in the analysis due to its clinical relevance, as a previous study have reported adverse events associated with linezolid treatment in HIV-positive patients with MDR/XDR-TB, although without statistically significant findings (52). Interestingly,

the multivariable regression results indicated that participants living with HIV had a decreased risk of being assigned to the higher linezolid dose of 600 mg three times weekly compared to HIV-negative individuals. We could infer that investigators may have been comfortable with a daily treatment strategy in this group of participants, in light of the additional risk of poor outcome.

Finally, it may be interesting to compare the results of this study with the one performed on the linezolid-randomized sample of the endTB trial (N=247) (Figure 3). The linezolid-randomized subset demonstrated a balanced distribution of participants across countries and the four linezolid-regimens containing regimens (40). No difference was found between the two dose reduction strategies in terms of safety, measured as the rate of grade 3 or higher adverse events such as peripheral and optic neuropathy, anemia, thrombocytopenia and leukopenia, and of efficacy (Appendix 5 and 6) (40).

The large difference between the results observed in the linezolid-randomized (N=247) and non-randomized (N=193) samples underlines the importance of mitigating bias when comparing two experimental groups. These findings support, in particular, the use of randomization to prevent bias linked to the assignment of treatment. Indeed, leaving the decision of the linezolid reduction strategy to clinicians would have made it difficult to draw reliable conclusion on the comparison between the two linezolid doses.

5.1 Strengths

The data was collected prospectively, with rigorous monitoring and quality control measures in place. To maintain high standards of data quality and consistency, regular reconciliation and review data procedures were carried out. This process involved the collaborative efforts of data managers, central study coordinators, and site personnel. Their diligent work ensured the quality and coherence of all collected data.

Therefore, there are not many missing observations for the explanatory variables, and no missing observations for the outcome variable.

5.2 Limitations

One of the limitations of this study is the low sample size. However, the sample size was higher than seventy, for seven variables included in the multivariable regression model. Therefore, the recommendation of ten observations per independent variable was accomplished.

Some variables (e.g. peripheral neuropathy) had to be recategorized due to the lack of observations at higher grades. Maintaining variables as binary categories may limit the interpretation of findings, as it does not allow testing clinically important categories (e.g. grade 3 or higher vs. normal).

Usually, randomized clinical trials compile a sample according to strict eligibility criteria, which may limit the external validity and generalization of these findings.

5.3 Public Health Implications

Tuberculosis remains a disease of major concern because of its impact on vulnerable populations, the emergence of resistance strains and the impact of some adverse events related to drugs on patients' wellbeing. Therefore, it remains important to develop new treatments that are tolerable and facilitate patient adherence. By identifying the variables associated with the decision to reduce the dose to one of the linezolid strategies (300 mg daily and 600 mg thrice weekly), we can explain or describe how or on what variables clinicians make this decision. Ultimately, if one of the doses is considered more effective and less associated with adverse events, the variables described in this study could be considered involved.

In addition, the adverse effects of any linezolid dose reduction strategy will affect patients' daily lives, particularly mobility and ability to carry out daily activities. This is important because it could make the experience of receiving MDR-TB treatment difficult and make people less likely to adhere to treatment.

5.4 Future research

Future research involves analyzing the association of linezolid dose reduction strategy with the primary efficacy and safety outcome. Due to the inherent bias of this comparison in a non-randomized sample, this analysis will require advanced causal inference methods and adjustment on both baseline and time-varying variables. This analysis will provide clarification when comparing results with previous analysis made by endTB team using the linezolid-randomized sample. In addition to the quantitative analysis conducted in this study, interviewing clinicians who were involved in making decisions could provide valuable insights into their decision-making processes and rationales. This qualitative approach could support a deeper understanding of the factors and participants characteristics that clinicians consider when determining the appropriate dose reduction strategy.

5.5 Conclusion

The exploratory analysis made as part of this study reveals that most of the variability explaining the outcome is linked to the trial country. Additionally, four factors potentially related to the outcome have been identified. However, it is important to acknowledge the inherent difficulty in establishing the precise role of these variables in the clinicians' decision processes regarding linezolid dose reduction strategies.

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7. List of appendices

Appendix 1. Description of participants according to variables of interest and the outcome: linezolid dose reduction

Characteristic	Linezolid 300 mg daily N= (85)	Linezolid 600 mg thrice weekly N= (108)	Total N=193
Sex			
Male	47(55.29%)	78(72.22%)	125(64.77%)
Female	38(44.71%)	30(27.78%)	68(35.23%)
Age median, (IQR)	31(25-40)	31(22.75-45.0)	31(23-41)
(< 65)	83(97.65%)	104(96.30%)	187(96.86%)
(>=65)	2(2.35%)	4(3.70%)	6(3.11%)
BMI (median, IQR)	20.04(18.69-22.09)	21(19.12-23.38)	20.62(18.82-21.31)
(< 25)	73(85.88%)	87(80.56%)	160(82.9%)
(> = 25)	12(14.12%)	21(19.44%)	33(17.1%)
Country			
KZ	24 (28.24%)	43 (39.81%)	67(34.72%)
PE	0	64(59.26%)	64 (33.16%)
GE	8(9.41%)	0	8(4.15%)
LS	19 (22.35%)	1 (0.93%)	20(10.36%)
ZA	34(40.00%)	0	34(17.62%)
IN	0	0	0
PK	0	0	0
Sites			
KZ-1	1(1.18%)	37(34.26%)	38(19.69%)
KZ-2	23(27.06%)	6(5.56%)	29(15.03%)
PE-1	0	28(25.93%)	28(14.51%)
PE-2	0	25(23.15%)	25(12.95%)
PE-3	0	11(10.19%)	11(5.70%)
GE-1	8(9.41%)	0	8(4.15%)
LS-1	19(22.35%)	1(0.93%)	20(10.36%)
ZA-1	34(40.00%)	0	34(17.62%)
Diabetes			
No	79 (91.76%)	91(84.26%)	169(87.56%)
Yes	7(8.24%)	17(15.74%)	24(87.56%)
HIV			
Negative	54(63.53%)	105(97.22%)	159(82.38%)
Positive	31(36.47%)	3(2.78%)	34(17.62%)

Alcohol			
No	64(75.29%)	85(78.70%)	149(77.2%)
Yes	21(24.71%)	23(21.30%)	44 (22.8%)
Smoking			
No	50(58.82%)	81(75.00%)	131(67.88%)
Yes	35(41.18%)	27(25.00%)	62(32.12%)
Extent of disease *NA (N= 6)*			
Limited	36(42.35%)	40(37.04%)	76(39.38%)
Extensive	48(56.47%)	63(58.33%)	111(57.51%)
Prior exposure to TB treatment			
First line (+None)	71(83.53%)	82(75.93%)	153(76.27%)
Other	14(16.47%)	26 (24.07%)	40(20.73%)
Peripheral Neuropathy (BPNS grade)			
Normal	71(83.53%)	84 (77.78%)	155(80.31%)
Grade1- 3	14 (16.47%)	24(22.22%)	38(19.69%)
Visual acuity			
Normal	72(84.71%)	79(73.15%)	151(78.24%)
Grade3-4	13(15.29%)	29(26.85%)	42(21.76%)
Laboratory test			
Hemoglobin (g/dL) (median, IQR)	12.20(10.80-13.55)	13.45(11.20-14.50)	12.80(11.55-17.90)
Normal	64(75.29%)	99(91.67%)	163(84.46%)
Abnormal	21(24.71%)	9(8.33%)	30(15.54%)
Neutrophils (10^9/L) (median, IQR)	3.28(3.10-3.47)	5.99(4.70-7.99)	5.74(4.39-7.89)
Normal	69 (81.18%)	84(77.78%)	153(79.27%)
Abnormal	16 (18.82%)	24 (22.22%)	40(20.73%)
Platelet Count (10^9/L) (median, IQR)	385(277.5-470)	316(258.8- 437.5)	346(260-446)
Normal	69 (81.18%)	79(73.15%)	148(76.68%)
Abnormal	16(18.82%)	29(26.85%)	45(23.32%)
Performance Status (ECOG)			
Normal	44(51.76%)	26 (24.07%)	70(36.27%)
1-3 grades	41(48.24%)	82(75.93%)	123(63.73%)

Appendix 2: Univariable regression analysis and multivariable relative risk regression (N=193).

Characteristic	Linezolid dose reduction		Univariable regression			Multivariable Regression		
	300 mg daily N= (85) (Ref)	**600 mg thrice weekly** N= (108)	**RR**	**95%CI**	**P value**	**aRR**	**95%CI**	**P value**
Sex								
Female	38 (44.71%)	30 (27.78%)	1	-	-	1		
Male	47 (55.29%)	78 (72.22%)	1.41	1.05, 1.91	**0.02**	1.31	1.01, 1.69	0.04
Age								
(< 65)	83 (97.65%)	104 (96.30%)	1	-	-			
(>=65)	2 (2.35%)	4 (3.70%)	1.20	0.67, 2.14	0.50			
BMI								
(< 25)	73 (85.8 %)	87 (80.56%)	1	-	-			
(>= 25)	12 (14.12%)	21 (19.44%)	1.17	0.87, 1.57	0.30			
Diabetes								
No	79 (91.76%)	91 (84.26%)	1	-	-			
Yes	7 (8.24%)	17 (15.74%)	1.32	0.98, 1.76	**0.07**			
HIV								
Negative	54 (63.53%)	105 (97.22%)	1	-	-	1	-	-
Positive	31 (36.47%)	3 (2.78%)	0.13	0.05, 0.40	**<0.01**	0.17	0.06, 0.50	0.00
Alcohol								
No	64 (75.29%)	85 (78.70%)	1	-	-			
Yes	21 (24.71%)	23 (21.30%)	0.92	0.67, 1.26	0.60			
Smoking								
No	50 (58.82%)	81 (75.00%)	1	-	-	1		
Yes	35 (41.18%)	27 (25.00%)	0.70	0.51, 0.96	**0.03**	0.74	0.57, 0.97	0.03
Extent of disease *NA (N= 6)*								
Limited	36 (42.35%)	40 (37.04%)	1	-	-			
Extensive	48 (56.47%)	63 (58.33%)	1.08	0.82, 1.41	0.60			
Prior exposure to TB treatment								
First line (+None)	71 (83.53%)	82 (75.93%)	1	-	-			

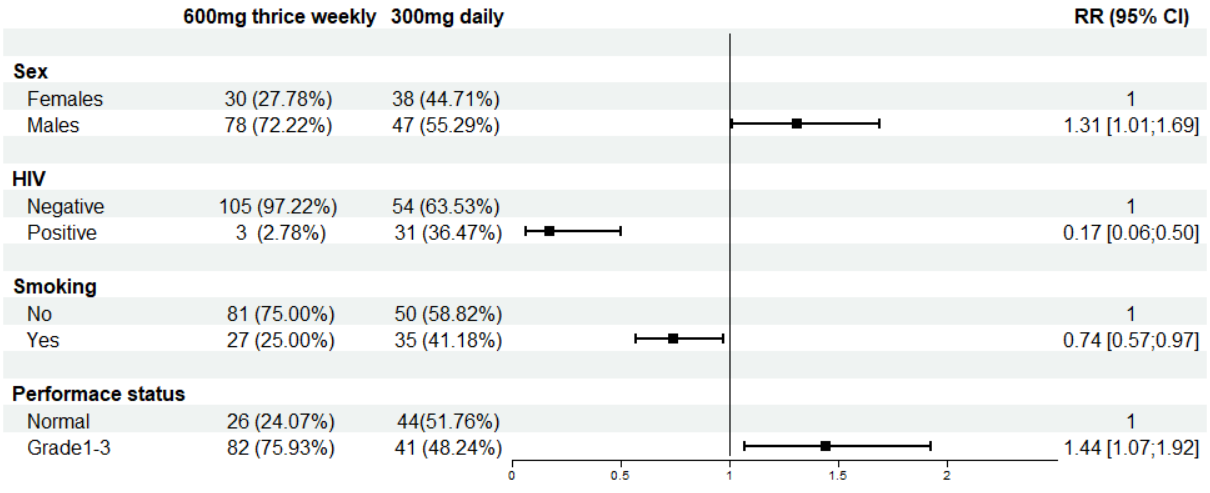
Other	14 (16.47%)	26 (24.07%)	1.21	0.92, 1.59	0.20			
Neuropathy (BPNS grade)								
Normal	71 (83.53%)	84 (77.78%)	1	-	-			
Grade1- 3	14 (16.47%)	24 (22.22%)	1.17	0.88, 1.55	0.30			
Visual acuity								
Normal	72 (84.71%)	79 (73.15%)	1	-	-			
Grade3-4	13 (15.29%)	29 (26.85%)	1.32	1.02, 1.70	**0.03**			
Hemoglobin (g/dL)								
Normal	64 (75.29%)	99 (91.67%)	1	-	-			
Abnormal	21 (24.71%)	9 (8.33%)	0.49	0.28, 0.87	**0.01**			
Neutrophils (10^9/L)								
Normal	69 (81.18%)	84 (77.78%)	1	-	-			
Abnormal	16 (18.82)	24 (22.22)	1.09	0.82, 1.46	0.50			
Platelet Count (10^9/L)								
Normal	69 (81.18%)	79 (73.15%)	1	-	-			
Abnormal	16 (18.82%)	29 (26.85%)	1.21	0.93, 1.57	0.20			
Performance Status (ECOG)								
Normal	44 (51.76%)	26 (24.07%)	1	-	-			
Grade1-3	41 (48.24%)	82 (75.93%)	1.79	1.29, 2.50	**<0.01**	1.44	1.07, 1.92	0.02

Appendix 3: Table of baseline variables described by country (N=193)

Characteristic	**Georgia** N = 8[1]	**Kazakhstan** N = 67[1]	**Lesotho** N = 20[1]	**Peru** N = 64[1]	**South Africa** N = 34[1]
Sex					
Females	1.00 (12.50%)	24.00 (35.82%)	11.00 (55.00%)	17.00 (26.56%)	15.00 (44.12%)
Males	7.00 (87.50%)	43.00 (64.18%)	9.00 (45.00%)	47.00 (73.44%)	19.00 (55.88%)
Age					
(<65)	8.00 (100.00%)	64.00 (95.52%)	19.00 (95.00%)	62.00 (96.88%)	34.00 (100.00%)
(>=65)	0.00 (0.00%)	3.00 (4.48%)	1.00 (5.00%)	2.00 (3.13%)	0.00 (0.00%)
BMI					
< 25	7.00 (87.50%)	56.00 (83.58%)	19.00 (95.00%)	52.00 (81.25%)	26.00 (76.47%)
>=25	1.00 (12.50%)	11.00 (16.42%)	1.00 (5.00%)	12.00 (18.75%)	8.00 (23.53%)
Diabetes					
No	7.00 (87.50%)	54.00 (80.60%)	18.00 (90.00%)	57.00 (89.06%)	33.00 (97.06%)
Yes	1.00 (12.50%)	13.00 (19.40%)	2.00 (10.00%)	7.00 (10.94%)	1.00 (2.94%)
Alcohol Use					
No	8.00 (100.00%)	61.00 (91.04%)	15.00 (75.00%)	45.00 (70.31%)	20.00 (58.82%)
Yes	0.00 (0.00%)	6.00 (8.96%)	5.00 (25.00%)	19.00 (29.69%)	14.00 (41.18%)
Smoking					
No	6.00 (75.00%)	39.00 (58.21%)	13.00 (65.00%)	56.00 (87.50%)	17.00 (50.00%)
Yes	2.00 (25.00%)	28.00 (41.79%)	7.00 (35.00%)	8.00 (12.50%)	17.00 (50.00%)
Extent of TB					
Limited	3.00 (37.50%)	35.00 (57.38%)	6.00 (30.00%)	17.00 (26.56%)	15.00 (44.12%)
Extended	5.00 (62.50%)	26.00 (42.62%)	14.00 (70.00%)	47.00 (73.44%)	19.00 (55.88%)
Unknown	0	6	0	0	0
Prior TB Treatment					
First line (+None)	8.00 (100.00%)	44.00 (65.67%)	20.00 (100.00%)	53.00 (82.81%)	28.00 (82.35%)
Other	0.00 (0.00%)	23.00 (34.33%)	0.00 (0.00%)	11.00 (17.19%)	6.00 (17.65%)
Peripheral Neuropathy Grade					
Normal	8.00 (100.00%)	58.00 (86.57%)	15.00 (75.00%)	45.00 (70.31%)	29.00 (85.29%)
Grade1- 3	0.00 (0.00%)	9.00 (13.43%)	5.00 (25.00%)	19.00 (29.69%)	5.00 (14.71%)
Visual Acuity Grade					
Normal	8.00 (100.00%)	40.00 (59.70%)	19.00 (95.00%)	54.00 (84.38%)	30.00 (88.24%)

Grade 3-4	0.00 (0.00%)	27.00 (40.30%)	1.00 (5.00%)	10.00 (15.63%)	4.00 (11.76%)
Performance Status (ECOG)					
Normal	5.00 (62.50%)	24.00 (35.82%)	7.00 (35.00%)	5.00 (7.81%)	29.00 (85.29%)
Grace 1-3	3.00 (37.50%)	43.00 (64.18%)	13.00 (65.00%)	59.00 (92.19%)	5.00 (14.71%)
Neutrophil Grade					
Normal	6.00 (75.00%)	35.00 (52.24%)	19.00 (95.00%)	61.00 (95.31%)	32.00 (94.12%)
Abnormal	2.00 (25.00%)	32.00 (47.76%)	1.00 (5.00%)	3.00 (4.69%)	2.00 (5.88%)
Platelet Grade					
Normal	8.00 (100.00%)	40.00 (59.70%)	20.00 (100.00%)	58.00 (90.63%)	22.00 (64.71%)
Abnormal	0.00 (0.00%)	27.00 (40.30%)	0.00 (0.00%)	6.00 (9.38%)	12.00 (35.29%)
Hemoglobin Grade					
Normal	8.00 (100.00%)	58.00 (86.57%)	13.00 (65.00%)	61.00 (95.31%)	23.00 (67.65%)
Abnormal	0.00 (0.00%)	9.00 (13.43%)	7.00 (35.00%)	3.00 (4.69%)	11.00 (32.35%)
HIV Result					
Negative	8.00 (100.00%)	66.00 (98.51%)	8.00 (40.00%)	63.00 (98.44%)	14.00 (41.18%)
Positive	0.00 (0.00%)	1.00 (1.49%)	12.00 (60.00%)	1.00 (1.56%)	20.00 (58.82%)
[1]n (%)					

Appendix 4: Forest plot describing the estimates from a final multivariable regression model (N=193)



Appendix 5: Severe Linezolid-Associated Toxicity from a linezolid-randomized sample (N=247) (40)

Population/Outcome	Total	300 mg daily	600 mg thrice weekly	Risk difference and HR [95% CI]	P-value
Total in safety population	260 (100%)	128 (100%)	132 (100%)		
Severe linezolid-related toxicity	46 (17.7%)	21 (16.4%)	25 (18.9%)	2.5% [-6.8%; 11.8%]	0.592
Time to severe linezolid-related toxicity, months, median (IQR)	3.0 (1.3; 5.9)	4.6 (2.6; 6.2)	2.5 (0.9; 3.6)	0.85 [0.47; 1.51]	0.570

Appendix 6: Treatment Outcomes at W73 and W104 from a linezolid-randomized sample (N=247)(40)

Population/Outcome	Total	300 mg daily	600 mg thrice weekly	Risk difference [95% CI]	P-value
Total in mITT population	247 (100%)	123 (100%)	124 (100%)		
Favorable outcome (W73)	224 (90.7%)	111 (90.2%)	113 (91.1%)	0.9% [-6.4%; 8.1%]	0.811
Favorable outcome (W104)	217 (87.9%)	107 (87.0%)	110 (88.7%)	1.7% [-6.4%; 9.9%]	0.679

8. Résumé (Abstract in French)

Contexte : La tuberculose est la deuxième cause de décès parmi les maladies infectieuses. Le traitement est devenu une priorité dans la lutte contre la maladie, en particulier contre la tuberculose multirésistante. L'utilisation du linézolide a été approuvée dans le cadre du traitement de la tuberculose multirésistante, mais son dosage fait toujours l'objet d'études afin d'équilibrer l'efficacité et la toxicité.

Méthodes : Cette étude a suivi un plan transversal en utilisant un échantillon de participants à l'essai clinique endTB (NCT02754765) sur la tuberculose MR non randomisée par le linézolide. Cet échantillon a été assigné aux groupes contenant du linézolide. Tous les participants ont reçu 600 mg par jour et ont ensuite été réduits à 300 mg par jour ou 600 mg trois fois par semaine sur décision du clinicien. L'objectif était d'évaluer l'association entre les caractéristiques de base et les stratégies de réduction de la dose de linézolide.

Résultats : Sur les 193 participants non randomisés pour le linézolide, 85 ont été assignés à une dose de 300 mg par jour et 108 à une dose de 600 mg trois fois par semaine. Les chercheurs des pays où se sont déroulés les essais, tels que la Géorgie, le Lesotho, le Pérou et l'Afrique du Sud, ont affecté la plupart ou la totalité des participants à une seule stratégie de réduction de la dose de linézolide. Cependant, lors d'une régression à rebours du risque relatif des covariables, le sexe, le smoking, le statut VIH et le niveau de performance se sont révélés significatifs dans le modèle final. Les hommes (aRR = 1,31, IC 95 % = 1,01, 1,69) et les participants aux performances réduites (aRR = 1,44, IC 95 % = 1,07, 1,92) présentaient un risque plus élevé d'être assignés à une dose de 600 mg trois fois par semaine. Les personnes vivant avec le VIH (aRR= 0,17, 95% CI= 0,06, 0,50) et les fumeurs (aRR=0,74, 95% CI = 0,57, 0,97) avaient un risque plus faible d'être assignés à 600 mg trois fois par semaine.

Conclusions : Le pays s'est avéré être la variable la plus importante expliquant la variabilité associée aux stratégies de réduction de la dose de linézolide (300 mg par jour et 600 mg trois fois par semaine). D'autres variables ont été associées, bien qu'il soit difficile d'établir leur rôle précis.

Mots clés : Linézolide, multirésistance, tuberculose, essai clinique

Association entre les facteurs de base et la réduction de la dose de linézolide dans un échantillon randomisé non linézolide de l'essai clinique endTB