STUDY PROTOCOL

Linezolid tolerance during the BPaL regimen

with dosage personalization based on Therapeutic

Drug Monitoring (TDM) during

Multidrug-Resistant tuberculosis treatment

February 2025

REPUBLIC OF GUINEA
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WORK – JUSTICE – SOLIDARITY

National Ethics Committee for Health Research (CNERS)

Application form for ethical review of a health research project/protocol

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Section 1 — General information on the health research project/protocol

Title of the health research protocol:

Linezolid tolerance during the BPaL regimen with dosage personalization based on Therapeutic Drug Monitoring (TDM) during Multidrug-Resistant tuberculosis.

Personalized dosage and Linezolid Optimization with TDM in MDR-TB: the PLOT-TB study

Principal investigator:

Name and surname: HASSANE HAROUNA

Profession: Doctor Academic rank: Doctor

Phone: [redacted]

Affiliation institution: Action Damien

Address of the affiliated institution: Action Damien Guinée, Camayenne, Commune of Dixinn

Post Office Box: 1893 City: Conakry Country: Guinea

Research collaborators/team

1. Co-Principal Investigator: Prof. Andrea Gori

Professor Andrea Gori is an expert in infectious diseases, a professor at the University of Milan, and head of the infectious diseases department at Sacco Hospital in Milan. His research focuses on HIV, tuberculosis, and infections in immunocompromised patients. Since 1992, he has led clinical research projects centered on the immunopathogenesis of viral and bacterial infections.

2. Other collaborators

Name	Title	Function in the project	Affiliation	Email	Phone
Dr. Adama Marie Bangoura	Medical Doctor	[redacted]			
Prof. Andrea Gori	Infectious Diseases Professor at Biochemical Sciences Département				
Dr. Aboubacar Sidiki Magassouba	Medical Doctor				
Dr. Alberto Roggi	Medical Doctor				
Dr. Cherif Gba-Foromo	Doctor of medicine, Master's Public health				
Professor Djelo Boubacar Diallo	Professor of pulmonology, responsible for TB-MR				
Dr. Moussa Condé	Dr. Pharmacist-biologist, Head Service				
Dr. Marco Schiuma	Medical Doctor, Infectious Diseases Specialist				

Partner institution(s):

Name	Address	Role in the project	Email	Phone
PNLT	Dixinn, Camayenne/Résidence Micheline ; BP:634.	[redacted]	[redacted]	[redacted]
University from Milan	Department of Biomedical Sciences and "L. Sacco" Clinics Via GB Grassi 74, 20157, Milan, Italy.	[redacted]	[redacted]	[redacted]
Sacco Hospital, Milan	Department of infectious diseases	[redacted]	[redacted]	[redacted]
Action Damien Brussels	263 Boulevard Leopold II, 1081 Koekelberg, Brussels, Belgium.	[redacted]	[redacted]	[redacted]
Ignace Deen University Hospital	Pulmonology Department, Conakry, Guinea.	[redacted]	[redacted]	[redacted]

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LIST OF ABBREVIATIONS

AD	Action Damien
BPaLM	Bedaquiline-Pretomanid-Linezolid-Moxifloxacin
LNRM	National Reference Laboratory for Mycobacteria
Lzd	Linezolid
WHO	World Health Organization
NGO	Non-Governmental Organization
PNLT	National Tuberculosis Control Program
TB	Tuberculosis
TB-MR	Multidrug-resistant tuberculosis
TDM	Therapeutic drug monitoring

1. CONTEXT AND JUSTIFICATION

Multidrug-resistant tuberculosis (MDR-TB) poses a significant challenge to global public health. Globally, the World Health Organization (WHO) estimates the number at 400,000 patients with MDR-TB for 2023. Only 44% were diagnosed and put on treatment, the therapeutic success rate of the 2021 cohort is only 68%[1].

In Guinea, the number of patients with MDR-TB is estimated at 450, and the treatment success rate is 74% for the 2021 cohort, primarily with the 9-months short oral regimen[1].

Since 2022, the WHO has recommended the use of the 6-month short course of BPaL/BPaL-M for national tuberculosis control programs[2] and Guinea began implementing this new regime within the programmatic framework starting in January 2025.

Linezolid, a key component of new therapeutic regimens such as BPaL/BPaL-M, shows high bactericidal activity, although it is associated with serious adverse effects in a high percentage of patients, including myelosuppression, neuropathy and, in some cases, fatal lactic acidosis. In particular, peripheral neuropathy, an adverse event often irreversible that may lead to linezolid and the BPaL/BPaL-M regimen discontinuation, is reported in approximately 24% of patients receiving linezolid at 600 mg[3].

A linezolid blood trough level of above 2 mg/l is associated with side effects, but its pharmacokinetics varies considerably between individuals and over time.

There is little data on the role of therapeutic drug monitoring (TDM) in guiding its administration, some studies showing how the standard dose of 600 mg could exceed the toxicity target and the reduced dose of 300 mg might not achieve the target efficacy[4].

2. OBJECTIVE OF THE STUDY

2.1 General objective

The main objective of this study is to determine the variation in the occurrence of adverse events between patients who undergo a modification of the linezolid dose based on the TDM and patients taking linezolid standard dose

2.2 Specific Objectives

The specific objectives aim to evaluate:

- the role of TDM in the optimization of linezolid dosage in TB-MDR patients treated with the BPaL/BPaL-M regimen

- the treatment outcome in patients who undergo a modification of the linezolid dose based on TDM and patients taking linezolid standard dose

- variations in the distribution of TDM throughout treatment in order to identify potential common trends.

3 METHODOLOGY

3.1 STUDY PLAN AND SITE

This is a prospective, interventional, randomized, controlled clinical trial. It will be conducted at the Tombolia TB-MDR treatment clinic, one of the four sites of the city of Conakry which annually notifies approximately 70 patients out of a national total of approximately 300 MDR-TB cases.
The study will be conducted in collaboration with the University of Milan, the Sacco Hospital of Milan, the the national tuberculosis control program in Guinea and the NGO Action Damien, which works on the operational level and conducts several studies in numerous countries, including Guinea, among patients with MDR-TB. In particular, the University of Milan will supply the entire technical equipment to analize linezolid blood concentrations thanks to the INFACT project.

3.2 POPULATION AND DURATION OF THE STUDY

The study will be conducted on MDR-TB patients receiving linezolid as part of the BPaL/BPaL-M regimen (April 2025 to April 2028).

3.3 INCLUSION CRITERIA

1. Confirmed diagnosis of MDR-TB
2. Linezolid prescribed as part of the BPaL/BPaL-M regimen
3. Age 15 years or older
4. Informed consent obtained from the participant or assent from the parent/legal guardian for participants under 18 years of age.

3.4 EXCLUSION CRITERIA

1. Pregnancy or breastfeeding
2. Severe liver or kidney failure
3. Known hypersensitivity to linezolid
4. Concomitant use of medications with drug interactions potential with linezolid

3.5 SAMPLE SIZE

The sample size was determined based on the reported prevalence in the literature of peripheral neuropathy in patients with MDR-TB[3], given a precision of 7% for the study and a confidence level of 95%[5,6]. The defined sample size includes 150 participants.

3.6 PROCEDURE

The study will include two groups of patients, all of whom will receive linezolid as part of BPaL/BPaL-M, in accordance with current WHO guidelines:

3.6.1 Group A

Linezolid will be administered at the recommended dose of 600 mg. The linezolid level will be measured for each patient once a week during the first month (4 blood samples), then once a month for the following 5 months (5 blood samples) to complete the 6-month regimen (at least 9 blood samples for each patient). One additional sample will be taken if linezolid-related side effects appear. No changes to the linezolid dosage will be made except as directed in accordance with the national guidelines for the management of MDR-TB.

3.6.2 Group B

Linezolid will be administered at the recommended dose of 600 mg. The linezolid level will be measured for each patient once a week during the first month (4 blood samples), then once a month for the following 5 months (5 blood samples) to complete the 6-month regimen (at least 9 blood samples for each patient). Additional samples will be taken if linezolid-related side effects appear or if the trough linezolid concentration in the blood does not reach the reference range of 0.6-2 mg/l. The dosage of linezolid will be modified according to the TDM, in accordance with the figure 1.

The blood sample will be collected in a single 4 mL serum tube at the Tombolia care site by the responsible nurse, then all samples transported to the National Reference Laboratory for Mycobacteria (LNRM) by the MDR-TB recovery agent. At the LNRM, the samples will be centrifuged and stored up to one week at 2 to 8 °C before being processed.

If the analysis is delayed by more than a week, the samples must be kept frozen (-20 °C) for up to four weeks before being submitted for analysis.

The “CDX90” device produced by “Furuno” and supplied by “TEMA Ricerche” will be used to measure the plasma concentration of linezolid by using "ARK™ Linezolid” kit from “ARK Diagnostics Inc. (Fremont, CA)”, supplied by "TEMA Ricerche".

The reference concentration of linezolid will be between 0.6 and 2 mg/l.

Note: The total concentration of linezolid (24 hours after the last dose of the medication) will be obtained for each patient, as it allows the AUC[7] value to be estimated.

3.7 LINEZOLIDE TOXICITY

The toxicity of linezolid will be defined as follows:

- Onset or worsening of peripheral or optic neuropathy
- Drop in hemoglobin below 8 g/dl
- Platelet count below 50,000/mcl
- Neutrophil count below 750/mcl
- Lactate acidosis (Lactate > 3, clinical signs or symptoms consistent with lactate acidosis).

3.8 DATA COLLECTION AND ANALYSIS

The data will be collected through individual forms containing the demographic and clinical characteristics of each patient, later uploaded on REDCap softwere.

Statistical methods, including descriptive statistics and regression analysis will be used to analyze the relationship between plasma concentrations of linezolid and treatment outcomes. Subgroup analyses may be performed based on factors such as age, sex and comorbidities.

3.9 ETHICAL CONSIDERATIONS

1. The study will be conducted in accordance with the principles of the Declaration of Helsinki and the good clinical practices.

2. An information form (Appendix 1) will be read/explained to the participants, as well as an informed consent/assent form (Appendix 2) will be offered to all participants and/or their guarantors for signature before the start of treatment.

3. The confidentiality of participant information will be maintained.

3.10 DISSEMINATION OF RESULTS

The results of the study will be published in journals and at conferences.

Participants will be informed of the overall results of the study.

4 CHRONOLOGY

The study should be conducted over a period of 3 years (3 months for preparation, 24 months For patient recruitment, 6 months to complete treatment, 3 months for analysis of data).

5 BUDGET

CATEGORY		2025	2026	2027	UNIMI BUDGET	Total PLOT-TB	Cost in GNF
[redacted]							

6 BIBLIOGRAPHY

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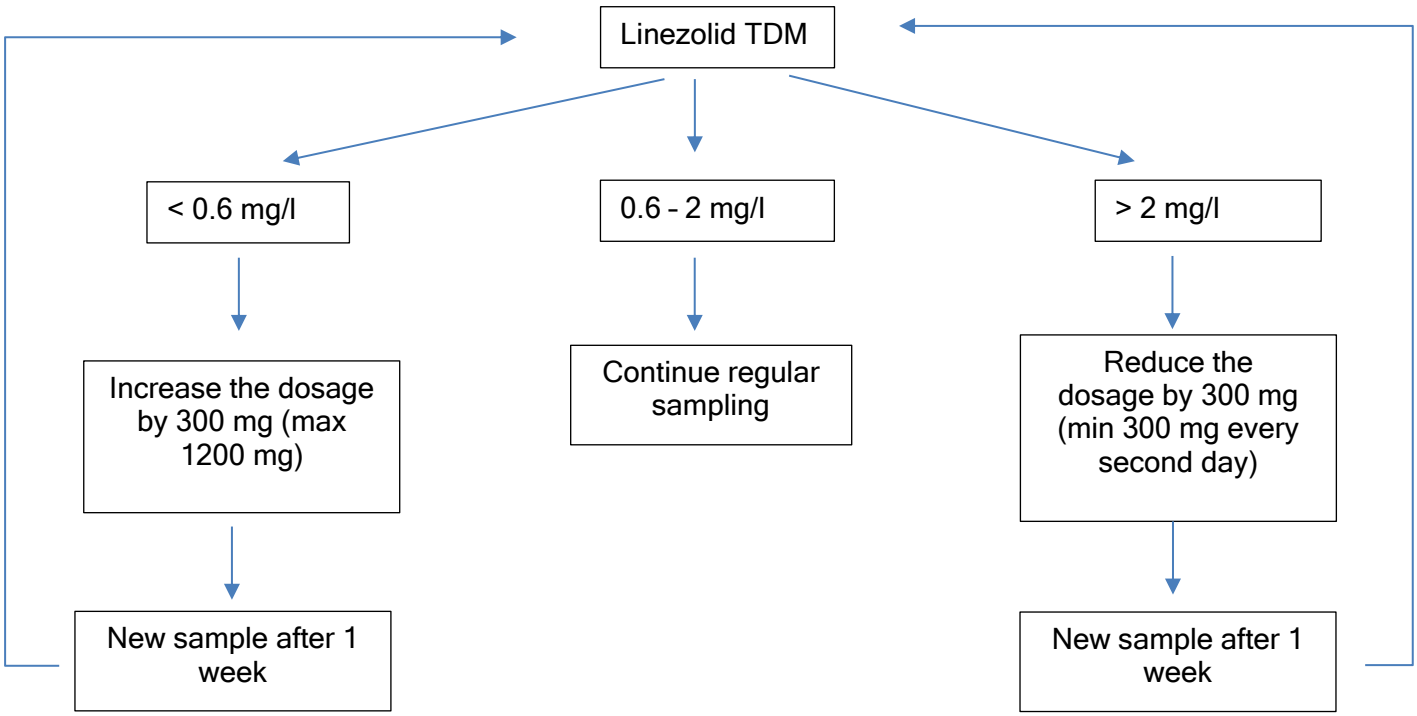
Figure 1


Linezolid TDM
< 0.6 mg/l
0.6 - 2 mg/l
> 2 mg/l
Increase the dosage by 300 mg (max 1200 mg)
Continue regular sampling
Reduce the dosage by 300 mg (min 300 mg every second day)
New sample after 1 week
New sample after 1 week