Journal of Tuberculosis Research, 2025, 13(2), 61-68
https://www.scirp.org/journal/jtr
ISSN Online: 2329-8448
ISSN Print: 2329-843X

Efficacy of Bedaquiline in the Management of Multidrug-Resistant Tuberculosis in the Central African Republic

Boris Jolly Lokoti[1,2*], Alain Farra[1,2], Alexandre Manirakiza[1,2], Herve Gando[3,4], Doriane Ouanibilo[2], Wilfrid Sylvain Nambei[1,4]

[1]Faculty of Health Sciences, Doctoral School of Human and Veterinary Health Sciences, University of Bangui, Bangui, Central African Republic
[2]National Reference Laboratory for Tuberculosis Control, Institut Pasteur of Bangui, Bangui, Central African Republic
[3]National Tuberculosis Control Program, Ministry of Public Health and Population, Bangui, Central African Republic
[4]National AIDS Council, Ministry of Public Health and Population, Bangui, Central African Republic
Email: *borisjolly@yahoo.fr

How to cite this paper: Lokoti, B.J., Farra, A., Manirakiza, A., Gando, H., Ouanibilo, D. and Nambei, W.S. (2025) Efficacy of Bedaquiline in the Management of Multidrug-Resistant Tuberculosis in the Central African Republic. *Journal of Tuberculosis Research*, **13**, 61-68.
https://doi.org/10.4236/jtr.2025.132006

Received: May 10, 2025
Accepted: June 21, 2025
Published: June 24, 2025

Abstract

Multidrug-resistant tuberculosis (MDR-TB) poses a major challenge in the Central African Republic (CAR), as the high incidence of tuberculosis and resistance rates to anti-tuberculosis drugs compromise efforts to manage MDR/RR-TB patients. This study evaluates the efficacy of bedaquiline, integrated into the short BPaLM regimen (Bedaquiline-Pretomanid-Linezolid-Moxifloxacin), in 68 patients with MDR-TB or pre-extensively drug-resistant (pre-XDR) TB. Strains from the National Reference Laboratory of Bangui underwent whole-genome sequencing and in silico resistance analysis. Among the participants (mean age: 32 years; 60.29% male), 82.35% had MDR-TB and 4.42% had pre-XDR TB. All strains were sensitive to bedaquiline, with no mutation detected in the atpC gene. Of the 59 patients treated, 57 (96.6%) successfully completed the 9-month protocol, confirmed by a negative culture at month 21. Two deaths, occurring before the start of treatment (due to a drug stockout), were not attributable to the treatment regimen. These results demonstrate exceptional efficacy of bedaquiline in a real-world setting, with a 100% therapeutic success rate among patients who received the treatment. The study underscores the importance of continuous access to medications and supports adopting the BPaLM regimen in CAR to improve MDR/RR-TB management. These findings support the integration of bedaquiline into national strategies, aligned with WHO objectives for tuberculosis elimination.

Keywords

Multidrug-Resistant Tuberculosis, Bedaquiline, Central African Republic,

Genomic Sequencing, BPaLM Regimen

1. Introduction

Discovered in 1882 by Robert Koch, the tubercle bacillus is the cause of human tuberculosis. Very common in African and Asian countries, this disease presents several clinical manifestations, primarily affecting the respiratory tract, and can develop into extrapulmonary forms. For several decades, antituberculosis drugs have been used, with the standard treatment consisting of a four-drug regimen (isoniazid, rifampicin, pyrazinamide, ethambutol) [1] during the initiation phase and a two-drug regimen (isoniazid, rifampicin) during the continuation phase, provided complete sensitivity has been demonstrated [2]. However, over time, strains resistant to one or more drugs have been identified. Drug-resistant tuberculosis remains a major public health problem worldwide [3]. Indeed, strains resistant to antituberculosis medications are more challenging to treat than sensitive strains, posing a significant challenge not only for National Tuberculosis Control Programs but also for the WHO's "End TB 2030" strategy. The progressive increase in MDR-TB cases globally threatens the progress made and the targets set by the World Health Organization's (WHO) Strategy to End Tuberculosis [3]. The Central African Republic (CAR) is among the world's 30 high TB burden countries, with an estimated incidence of 540 cases per 100,000 population in 2022 [4]. The estimated proportion of TB cases with MDR/RR-TB was 9.1% for new cases and 46.6% for previously treated cases, with an overall incidence estimated at 8.9 cases per 100,000 population. In 2022, the country reported 122 MDR-TB cases (or 24% of expected cases), among which 108 (89%) were started on treatment. The treatment success rate for MDR/RR-TB patients who started second-line treatment in 2020 was 80%. Given the significant emergence of resistance to first-line antituberculosis drugs, low treatment success rates, and numerous adverse effects, the introduction of new antibiotics and treatment regimens is essential for controlling MDR-TB. Bedaquiline (SIRTURO®) is a diarylquinoline antimycobacterial agent with a novel mechanism of action that inhibits ATP synthase, offering bactericidal and sterilizing properties [5]. Several studies have demonstrated the efficacy of bedaquiline-based regimens in treating multidrug-resistant tuberculosis, showing better treatment outcomes, reduced mortality, and the potential to shorten treatment duration [6]. It is in this context that the CAR recommended in 2022 the use of the 9-month regimen combining Bedaquiline-Pretomanid-Linezolid-Moxifloxacin (BPaLM) for patients with MDR/RR-TB [7]. The objective of this study was to evaluate the efficacy of bedaquiline in patients with multidrug-resistant tuberculosis in the Central African Republic.

2. Materials and Methods

2.1. Patients and Compliance with Ethical Guidelines

This is a cross-sectional study conducted at the National Reference Laboratory for

Tuberculosis (NRL-TB) at the Pasteur Institute of Bangui, in collaboration with the treatment center for multidrug-resistant tuberculosis patients at the National University Hospital Center of Bangui (CNHUB) and the University Hospital Institute of Marseille in France. Patients with at least one GeneXpert test (Cepheid, USA) detecting a rifampicin-resistant M. tuberculosis complex and sequencing results confirming rifampicin resistance were included. This study project was submitted to the committee responsible for validating study protocols and results in the CAR and received approval from the ethics committee on November 26, 2023 (registration number 45/UB/FACSS/IPB/CES/023). A predefined questionnaire was used to collect sociodemographic data, including age, sex, address, and HIV serological status (**Table 2**). All data were analyzed anonymously to protect patient privacy.

2.2. Treatment of Clinical Samples and Quality Control

Rifampicin-resistant M. tuberculosis strains were cultured in the BSL-2+ laboratory of the NRL-TB at the Pasteur Institute of Bangui. Under a Type II microbiological safety cabinet (BSC II), sputum samples were decontaminated using 4% NaOH according to Petroff's method [8] and then inoculated onto two Löwenstein-Jensen medium tubes. These cultures were incubated at 37˚C and monitored weekly for eight weeks. For internal quality control, growth and sterility tests were conducted on each new batch of cultures. For external quality control, evaluations were carried out by the Supranational Tuberculosis Reference Laboratory in Cotonou, Benin, which achieved a performance score of 100%. Growing colonies from the sloped Löwenstein-Jensen tubes were incubated with 180 µL of ATL buffer (QIAGEN GmbH, Hilden, Germany) and 20 µL of proteinase K in a final volume of 200 µL for one hour at 56˚C. These inactivated strains were then sent to the University Hospital Institute of Marseille, France, for sequencing.

2.3. Whole Genome Sequencing

DNA was extracted using a manual tissue extraction kit (EZNA, R Tissue DNA; QIAGEN GmbH, Hilden, Germany) in the BSL-3 laboratory at the University Hospital Institute of Marseille, France, according to the supplier's recommendations. Library preparation and sequencing were conducted using Illumina-Nextra Novaseq Technology (ILLUMINA, USA).

2.4. Genome Typing and Cluster Identification

After storing the reads for delayed analysis, Kaiju was used with default parameters to detect contamination levels. This was accomplished using the NCBI BLAST non-redundant protein database, which includes bacteria, archaea, and viruses. The overall quality of the sequencing reads, before and after trimming, was assessed using FastQC [9]. Subsequently, the tool Trimmomatic was used to remove residual Illumina adapters and specific sequences. Species, lineages, and sub-lineages were identified directly from the output iSeq reads using Tb-profiler (TB_v0.1.3) (https://tbdr.lshtm.ac.uk/) and MTBseq [10], both with default parameters by

mapping specifically to the M. tuberculosis H37Rv reference (NC_000962.3). MTBseq was specifically used to retrieve statistical mapping data of the output sequencing reads using M. tuberculosis H37Rv (NC_000962.3) as the reference genome. A phylogenetic tree was constructed using PhyML V-3.0 (https://ngphylogeny.fr/tools/) with the WAG model and 100 bootstrap replicates. The raw sequencing data has been deposited in GenBank under accession numbers PRJNA1152264 [11].

2.5. Drug Sensitivity and Resistance Profile

The Tb-profiler (https://tbdr.lshtm.ac.uk/) was used to retrieve in silico sensitivity-resistance profiles for isoniazid, ethambutol, pyrazinamide, streptomycin, fluoroquinolones in general, amikacin, capreomycin, kanamycin, cycloserine, ethionamide, clofazimine, para-aminosalicylic acid, delamanid, bedaquiline, and linezolid. Each detected mutation was confirmed by mapping the output sequencing reads to the reference resistance genes of M. tuberculosis H37Rv [12].

2.6. Initiation of Patient Treatment

MDR-TB patients were referred to the treatment center for MDR-TB patients for their treatments. Before starting treatment, paraclinical assessments were carried out (Table 1).

Table 1. Follow-up assessment for short treatment.

	M0	M1	M2	M3	M4	M5	M6	M7	M8	M9	(M10)	(M11)	M15	M21
Clinical Evaluation (and Weight)	X	X	X	X	X	X	X	X	X	X	(X)	(X)	X	X
Sputum Smear	X	X	X	X	XX	X(X)	X(X)	X	X	XX	(XX)	(XX)	X	X
Xpert	X													
LPA-FL & SL	X													
Sputum Culture	X	X	X	X	X	X	X	X	X	X	(X)	(X)	X	X
Chest X-ray	X									(X)	(X)	(X)		
ECG (Day 0, Day 7)	XX	X	X	X	X	X	X							
Blood Count (Hb, CBC, etc.)	X													
Serum Creatinine	X	X	X	X	X	(X)	(X)							
SGOT, SGTP	X		X		X	(X)	(X)							
K+	X	X	X	X	X	(X)	(X)							
TSH	X													
Blood Glucose	X													
Pregnancy Test	X													
HIV Test	X													

The patients were put on a 9-month treatment as recommended by the WHO.

This 9-month oral short regimen includes an intensive phase of 4 months followed by a fixed-duration continuation phase of 5 months, which includes 2 months of continued Bedaquiline that will be combined with the Mfx-Cfz-E-Z drugs and 3 months with only the four drugs Mfx-Cfz-E-Z: **4Bdq-Mfx-Pto-Cfz-E-Z-Hh/2Bdq-Mfx-Cfz-E-Z/3Mfx-Cfz-E-Z.**

3. Results

Patients. A total of 68 patients were included in the study, with ages ranging from 8 to 62 years and an average age of 32 years. The majority of the study population consisted of men (41 men and 27 women), corresponding to a male-to-female ratio of 1.5. The HIV status was known to be positive for 6 out of the 68 patients (Table 2).

Table 2. Sociodemographic characteristics.

	Number	Percentage (%)
Sex		
Female	27	39.71
Male	41	60.29
Age Range		
8 - 18 years	3	4.41
19 - 29 years	19	27.94
30 - 40 years	36	52.94
41 - 51 years	9	13.24
≥52 years	1	1.47
HIV Status		
Negative	62	91.18
Positive	6	8.82

In the study of 68 strains, the antibiotic resistance profile showed that 9 out of 68 (13.2%) Mycobacterium tuberculosis isolates were sensitive to all the antituberculosis drugs tested. Meanwhile, 56 out of 68 (86.7%) were MDR strains, resistant to Rifampicin and Isoniazid. Three isolates were Pre-XDR strains 3 out of 68 (4.41%), resistant to rifampicin and Isoniazid in addition to fluoroquinolones such as Moxifloxacin, Ofloxacin, Levofloxacin, and Ciprofloxacin (Table 3).

Table 3. Antituberculosis drug resistance profile.

	No.	Percentage %
Sensitive	9	13.23
MDR	56	82.35
Pre XDR	3	4.42
TOTAL	68	100

A total of 59 patients were put on treatment, including 56 MDR-TB patients and three Pre-XDR patients. We observed two deaths among the MDR-TB patients at the beginning of the treatment.

Regarding the follow-up of the treatment, 57 patients successfully completed their treatment with a negative culture result at the 21st month (M21).

Concerning sensitivity to bedaquiline, no mutations were found in the atpC genes (Table 4).

Table 4. Treatment outcomes with bedaquiline for MDR-TB patients in CAR.

	MDR/Bedaquiline	Pre XDR/Bedaquiline
Cured	54 (96%)	3 (100%)
Treatment completed	54 (100%)	3 (100%)
Deceased	02 (3.7%)	0
Lost to follow-up	0	0
Treatment success	54 (100%)	3 (100%)

4. Discussion

The objective of this study was to describe the progression, bacteriological profile, and outcomes of patients with multidrug-resistant tuberculosis (MDR-TB) treated under a therapeutic protocol including bedaquiline in 2024.

The MDR-TB patients were mainly men (61.01%, 36/59) and young (aged 30 - 40 years). This predominance among men and the young may be related to their socio-professional situation, which increases their exposure to tuberculosis in general and probably to multidrug-resistant tuberculosis. These results are similar to a study conducted in the Central African Republic by (Farra *et al.*), where men with MDR-TB represented 66.3% [4] [13].

Simultaneous resistance to rifampicin and isoniazid, which defines multidrug-resistant tuberculosis, was found in 82.35% of cases. These results are similar to a study conducted by Dje.bi *et al.* in 2023 in Bouake, which found a prevalence of 62.9% of MDR-TB and 4.42% of Pre-XDR patients [13]-[16]. We note that the proportion of MDR-TB cases has almost increased in CAR. These results are contrary to the efforts made by the WHO to reduce the emergence of resistant forms of tuberculosis, which represent a significant public health problem.

Regarding the outcomes of patients under treatment, 100% of patients on treatment had a favorable outcome (treatment completed, success of treatment, and declared cured) by the end of the short treatment established for 9 months with follow-up examinations (microscopy and culture on Löwenstein-Jensen medium) at months 10, 11, 15, and 21. These data are higher than those of Jayadeep *et al.*, with a success rate of 88.9%. We regret two cases of death, which were unrelated to the treatment; these patients were diagnosed with MDR-TB but had not yet been started on treatment when they died, as the country had experienced a two-month medication shortage.

5. Conclusion to Review

Here, we must highlight the key findings of the results and consider future perspectives.

Given the unmet needs of patients with multidrug-resistant tuberculosis (MDR-TB) and the significant side effects, the introduction of bedaquiline is necessary. The primary goal is to eliminate tuberculosis. According to the data from our study and other similar studies, improving the culture conversion rate and achieving favorable outcomes after the introduction of bedaquiline could offer new perspectives for effective therapeutic management of MDR-TB patients in the Central African Republic.

This study on the efficacy of bedaquiline in patients with multidrug-resistant tuberculosis treated at the MDR-TB patient care center at CNHUB, with patient follow-up through sputum culture at the NRL/TB at the Pasteur Institute of Bangui and strain sequencing, showed a success rate of 100%. Bedaquiline has proven to be a major advancement in the treatment of multidrug-resistant tuberculosis, offering a more effective therapeutic option. Inadequate use could encourage the development of resistance, highlighting the need for rigorous monitoring of patients under treatment and strengthening the genomic platform at the NRL/TB for proper follow-up and effective therapeutic management of MDR-TB patients in the Central African Republic.

Acknowledgements

We thank the staff of the diagnostic and treatment centers who referred suspected multidrug-resistant tuberculosis patients to the National Reference Laboratory for Tuberculosis at the Pasteur Institute of Bangui for diagnosis. We also thank the Global Fund to Fight AIDS, Tuberculosis, and Malaria for its support to the NRL-TB, which provided the necessary reagents free of charge for conducting the Xpert MTB/RIF test, culturing samples, and monitoring patients under treatment. Additionally, we thank the French Embassy in the Central African Republic for awarding a grant that enabled me to sequence the strains at the IHU Marseille.

Conflicts of Interest

The authors declare no conflicts of interest.

References

[1] Nicolet, G., Rochat, T. and Zellweger, J. (2003) Traitement de la tuberculose. *Forum Médical Suisse-Swiss Medical Forum*, 506-516.

[2] Sabeel, S.M.A., Salih, M.A., Ali, M., EL-Zaki, S., Abuzeid, N., Elgadi, Z.A.M., *et al.* (2017) Phenotypic and Genotypic Analysis of Multidrug-Resistant *Mycobacterium tuberculosis* Isolates from Sudanese Patients. *Tuberculosis Research and Treatment*, **2017**, Article 8340746. https://doi.org/10.1155/2017/8340746

[3] Bagcchi, S. (2023) WHO'S Global Tuberculosis Report 2022. *The Lancet Microbe*, **4**, E20. https://doi.org/10.1016/s2666-5247(22)00359-7

[4] Farra, A., Danebera, L.V., Ngaya, G., Yambiyo, B.M., Manirakiza, A. and Mossoro-

Kpinde, C.D. (2023) The Contribution of the Xpert® MTB/RIF Assay to the Surveillance of Drug-Resistant Tuberculosis in the Central African Republic. *Journal of Tuberculosis Research*, **11**, 23-32. https://doi.org/10.4236/jtr.2023.111003

[5] Li, Y., Sun, F. and Zhang, W. (2018) Bedaquiline and Delamanid in the Treatment of Multidrug-Resistant Tuberculosis: Promising but Challenging. *Drug Development Research*, **80**, 98-105. https://doi.org/10.1002/ddr.21498

[6] Migliori, G., Pontali, E., Sotgiu, G., Centis, R., D'Ambrosio, L., Tiberi, S., *et al.* (2017) Combined Use of Delamanid and Bedaquiline to Treat Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis: A Systematic Review. *International Journal of Molecular Sciences*, **18**, Article 341. https://doi.org/10.3390/ijms18020341

[7] Diacon, A.H., Pym, A., Grobusch, M.P., de los Rios, J.M., Gotuzzo, E., Vasilyeva, I., *et al.* (2014) Multidrug-Resistant Tuberculosis and Culture Conversion with Bedaquiline. *New England Journal of Medicine*, **371**, 723-732. https://doi.org/10.1056/nejmoa1313865

[8] Zingué, D., Hien, H., Kaboré, A., Kanyala, E., Sanou, A. and Méda, N. (2012) Avantages et limites des méthodes de décontamination des expectorations. *Revue d'Épidémiologie et de Santé Publique*, **60**, S126. https://doi.org/10.1016/j.respe.2012.06.309

[9] Verboven, L., Phelan, J., Heupink, T.H. and Van Rie, A. (2022) TBProfiler for Automated Calling of the Association with Drug Resistance of Variants in *Mycobacterium tuberculosis*. *PLOS ONE*, **17**, e0279644. https://doi.org/10.1371/journal.pone.0279644

[10] Kohl, T.A., Utpatel, C., Schleusener, V., De Filippo, M.R., Beckert, P., Cirillo, D.M., *et al.* (2018) MTBseq: A Comprehensive Pipeline for Whole Genome Sequence Analysis of *Mycobacterium tuberculosis* Complex Isolates. *Peer J*, **6**, e5895. https://doi.org/10.7717/peerj.5895

[11] Pichat, C., Couvin, D., Carret, G., Frédénucci, I., Jacomo, V., Carricajo, A., *et al.* (2016) Combined Genotypic, Phylogenetic, and Epidemiologic Analyses of *Mycobacterium tuberculosis* Genetic Diversity in the Rhône Alpes Region, France. *PLOS ONE*, **11**, e0153580. https://doi.org/10.1371/journal.pone.0153580

[12] Tiberi, S., Pontali, E., Tadolini, M., D'Ambrosio, L. and Migliori, G.B. (2019) Challenging MDR-TB Clinical Problems—The Case for a New Global TB Consilium Supporting the Compassionate Use of New Anti-TB Drugs. *International Journal of Infectious Diseases*, **80**, S68-S72. https://doi.org/10.1016/j.ijid.2019.01.040

[13] Farra, A., Manirakiza, A., Yambiyo, B.M., Zandanga, G., Lokoti, B., Berlioz-Arthaud, A., *et al.* (2019) Surveillance of Rifampicin Resistance with Genexpert MTB/RIF in the National Reference Laboratory for Tuberculosis at the Institut Pasteur in Bangui, 2015-2017. *Open Forum Infectious Diseases*, **6**, ofz075. https://doi.org/10.1093/ofid/ofz075

[14] Dje Bi, I. and Al, E. (2025) Profil épidémiologique, bactériologique et évolutif de la tuberculose résistante à Bouaké de 2017 à 2023. *Revue Malienne D'Infectiologie et de Microbiologie*, **19**, 25-31. https://doi.org/10.53597/remim.v19i4.2949

[15] Mounguengui, D., Ondounda, M., Mandji Lawson, J.M., Fabre, M., Gaudong, L., Mangouka, L., *et al.* (2012) Tuberculose multirésistante à l'hôpital d'instruction des armées de Libreville (Gabon) à propos de 16 cas. *Bulletin de la Société de Pathologie Exotique*, **105**, 1-4. https://doi.org/10.1007/s13149-011-0195-8

[16] Patra, J., Irving, H., Maini, P., Liang, J., Patra, A., Paradkar, M., *et al.* (2025) Treatment Outcomes among Children and Adolescents with Extensively Drug-Resistant (XDR) and Pre-XDR Tuberculosis: Systematic Review and Meta-Analysis. *PLOS Global Public Health*, **5**, e0003754. https://doi.org/10.1371/journal.pgph.0003754