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MORALITY BEFORE KNOWLEDGE

Effectiveness of the 6-month BPaLM regimen in a patient with rifampicin-monoresistant tuberculosis

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ABSTRACT

Background: Tuberculosis (TB) is an infectious disease caused by the bacterium *Mycobacterium tuberculosis* and remains a global health problem, including in Indonesia. Rifampicin-resistant tuberculosis (TB) (RR-TB) is a form of anti-tuberculosis drug resistance in which *Mycobacterium tuberculosis* only shows resistance to rifampicin, without resistance to isoniazid or other first-line drugs. The combination of Drug Resistant Tuberculosis (TB RO) treatment regimens greatly influences the effectiveness of TB RO patient treatment management. The purpose of this study was to see the effectiveness of the 6-month BPaLM regimen in a patient with rifampicin-monoresistant tuberculosis in Sabu Raijua Regional Hospital, Sabu Raijua Regency, East Nusa Tenggara. **Methods**: This type of research is a quantitative study with a cross-sectional approach to see the effectiveness of the 6-month BPaLM regimen in a patient with rifampicin-monoresistant tuberculosis at Sabu Raijua Regional Hospital in 1 case treated from the beginning of treatment (baseline), monthly follow-up and until the end of treatment. **Findings:** The study results show that the BPaLM regimen is highly effective in eradicating RR-TB in patients in areas with limited facilities, such as the 3T (*terpencil, terluar, dan tertinggal*/ disadvantaged, frontier, and outermost) areas. Multidisciplinary clinical, laboratory, and radiological monitoring are key to successful therapy, including early detection of side effects and ensuring adherence. Therefore, this 6-month BPaLM regimen is highly effective in assisting in the management of RR-TB treatment. **Conclusion**: In conclusion, the 6-month BPaLM regimen demonstrates high effectiveness in treating rifampicin-monoresistant tuberculosis (RR-TB), even in limited-resource settings such as disadvantaged, frontier, and outermost areas. Comprehensive multidisciplinary monitoring is essential to ensure treatment success and patient adherence. **Novelty/Originality of this article:** This study provides new evidence of the successful implementation of the 6-month BPaLM regimen for rifampicin-monoresistant tuberculosis (RR-TB) in a remote, limited-resource setting (disadvantaged, frontier, and outermost area), demonstrating its practicality and effectiveness beyond controlled or urban healthcare environments.

KEYWORDS: BPaLM; rifampicin resistance; tuberculosis.

1. Introduction

Tuberculosis (TB) is an infectious disease caused by the bacterium *Mycobacterium tuberculosis* and remains a global health problem, including in Indonesia. According to the 2023 Global TB Report, Indonesia has the second-highest estimated TB burden after India, with an incidence rate of 1,060,000 cases, or 385 per 100,000 population, and a mortality rate of 141,000, or 51 per 100,000 population.

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Tuberculosis (TB) remains one of the most challenging infectious diseases globally, not only due to its high incidence rate but also due to the complexity of its prevention, diagnosis, and treatment. Despite various control strategies, including increased access to early detection and effective therapy, TB morbidity and mortality remain high. This is primarily influenced by the emergence of resistance to key drugs, particularly rifampin, which heralds the development of drug-resistant TB (DR-TB) with a worse prognosis. This resistance further complicates targeted TB elimination efforts by the WHO and national programs in various countries, including Indonesia (Dheda et al., 2017; World Health Organization, 2023c).

Indonesia, as the country with the second-highest TB burden in the world, faces serious challenges in its efforts to eliminate this disease. The high burden of rifampicin-resistant TB (RR-TB) cases not only impacts individual health but also poses a major obstacle to achieving the 2030 TB elimination target. The fact that the majority of RR-TB cases in Indonesia are dominated by RR-TB demands an effective, efficient, and widely applicable treatment strategy, particularly in areas with limited resources.

Data on TB case detection coverage in Indonesia in 2024 showed 856,420 cases (78%) of the target of 1,092,000 cases, with 788,766 cases treated (92%). As of the update up to July 2025, the coverage of TB case detection in Indonesia had reached 448,109 cases (41%) of the target of 1,090,000 cases with 389,464 cases (87%) treated by SITB in 2025. Based on Tuberculosis Information System (SITB) data, the TB case detection rate in East Nusa Tenggara Province in 2024 was 10,495 (58%) cases out of a target of 17,961 cases, with 9,232 cases treated (88%). In 2025, as of the July update, the case detection rate was 5,387 (31%) out of a target of 17,928 cases, with 4,701 cases treated (89%). Meanwhile, the TB case detection rate in Sabu Raijua Regency in 2024 was 454 cases (38%) out of a target of 1,209 cases, with 432 cases treated (95%).

Rifampicin-resistant tuberculosis (TB) (RR-TB) is a form of anti-tuberculosis drug resistance in which *Mycobacterium tuberculosis* exhibits resistance only to rifampicin, without resistance to isoniazid or other first-line drugs. Rifampicin is a key component of standard TB therapy, so resistance to it has a significant impact on treatment success.

Globally, there will be more than 450,000 cases of rifampicin-resistant/multidrug-resistant TB by 2024, with a death toll of approximately 191,000. In Indonesia, the number of cases of DR-TB is considered quite high, with a total of 5,795 cases detected by July 2025.

Treatment for TB-RR with conventional regimens was previously known to be very lengthy, complex, and often accompanied by significant side effects. Treatment durations, which can reach 18–20 months, place a significant burden on patients, healthcare workers, and the healthcare system. Patient compliance is often a major obstacle, due to the long duration and the large number of medications required, which often cause serious side effects, such as hepatotoxicity, hematological disorders, neuropathy, hearing loss, and psychiatric disorders. The socioeconomic impact is also significant, as the majority of TB-RR patients are from the productive age group and from lower-middle economic backgrounds (Migliori et al., 2021; Ahmad et al., 2018).

This situation has prompted an urgent need for new, shorter, more effective, and safer treatment regimens. In 2022, the WHO recommended the BPaL/BPaLM regimen, consisting of bedaquiline, pretomanid, linezolid, and moxifloxacin, as first-line treatment for RR-TB. This regimen is designed to reduce treatment duration to just 6 months, significantly shorter than previous regimens. The introduction of the BPaLM regimen is expected to increase therapy success rates, reduce discontinuation rates, and lower the risk of death from RR-TB (Conradie et al., 2020).

Beyond clinical effectiveness, the implementation of the BPaLM regimen also has important public health implications. A shorter, more patient-tolerated regimen allows for increased medication adherence, thereby reducing the risk of additional resistance emerging (Esmail et al., 2022). This aligns with the principles of the Directly Observed Treatment, Short-course (DOTS) program, which emphasizes the importance of patient adherence to treatment. Increased adherence can suppress the chain of TB-RR transmission

in the community, which in turn reduces the incidence of new cases (Guglielmetti et al., 2022a).

In Indonesia, the implementation of the BPaLM regimen is still in its early stages, making case reports and observational studies from various regions crucial to provide field evidence regarding its effectiveness and safety. This is particularly relevant for 3T (*terpencil, terluar, dan tertinggal*/disadvantaged, frontier, and outermost) areas such as Sabu Raijua Regency in East Nusa Tenggara Province, which face limited health infrastructure, human resources, and access to advanced diagnostic and treatment facilities. Case reports documenting the journey of TB-RR patients on the BPaLM regimen in disadvantaged, frontier, and outermost areas are valuable contributions to policy development and implementation of the national TB elimination program.

Furthermore, the background of patients with RR-TB often involves complex risk factors, such as poor adherence to previous TB treatment, low socioeconomic status, high-density living environments, and risky lifestyles such as smoking or alcohol consumption. This combination of factors not only impacts treatment success but also increases the likelihood of community transmission. Therefore, shorter and more effective regimens benefit not only patients but also have broader implications for communities and health systems.

Epidemiologically, RR-TB also presents unique challenges because untreated patients have the potential to transmit resistant strains to others (Dheda et al., 2017). This differs from drug-sensitive TB, where standard treatment is usually sufficient to break the chain of transmission (Ahmad et al., 2018). The transmission of resistant strains can create a double burden for health programs, requiring specialized regimens that are more expensive and last longer (Migliori et al., 2021). With the BPaLM regimen, the opportunity to reduce the risk of resistant strain transmission is greater because the time to negative sputum can be achieved more quickly (Esmail et al., 2022).

Globally, the WHO has emphasized that the availability of the BPaLM regimen is a critical milestone in the "End TB" strategy (World Health Organization, 2022c; World Health Organization, 2023c). Several large clinical trials, such as TB-PRACTECAL (Conradie et al., 2020; Conradie et al., 2022) and a multi-country cohort study (Guglielmetti et al., 2022a), have consistently demonstrated the safety and effectiveness of this regimen. However, implementation requires adaptation to local contexts, including health worker preparedness, monitoring systems, and patient support (Johnson et al., 2024a; Simanjuntak et al., 2023).

In Indonesia, the implementation of the BPaLM regimen requires a holistic approach, given the significant variation in conditions between regions (Ministry of Health of the Republic of Indonesia, 2024b). Urban areas with comprehensive healthcare facilities may not face significant challenges, but remote areas face additional challenges such as limited logistics, patient transportation, and adverse event monitoring systems (Migliori et al., 2021). Therefore, case studies from areas like Sabu Raijua are crucial to demonstrate how this regimen can be adapted to challenging conditions (Simanjuntak et al., 2023).

As of July 2025, Nusa Tenggara Province had identified 51 cases of drug-resistant tuberculosis, and Sabu Raijua Regency had identified two cases of DR-TB receiving treatment at Sabu Raijua Regional Hospital. One case has completed treatment and the other is still undergoing treatment. The National TB Control and Management Program has established a TB Policy and TB Elimination Map as outlined in the 2020–2024 National Strategy through several indicators, namely the implementation of Minimum Service Standards (SPM) for Health, TB case detection and TB treatment initiation through tiered monitoring of TB indicator achievements, acceleration of TB examinations, early detection of TB disease and strengthening cross-sector coordination and involving all stakeholders in TB control in their regions.

One of them is the implementation of a 6-month treatment combination for RO TB, namely the BPaLM and/or BPaL Regimen through WHO recommendations in 2022 with a combination of Bedaquiline, Pretomanid, Linezolid and Moxifloxacin as First Line therapy through diagnosis using the Molecular Rapid Test (TCM/Xpert MTB-RIF) which can detect

the presence of *Mycobacterium tuberculosis* and rpoB gene mutations associated with rifampicin resistance. Based on the experience of treating 1 RO TB patient at Sabu Raijua Regional Hospital who has completed treatment, the use of this regimen has proven to be more effective, safe and shorter than the previous regimen which can last from 9–11 months to 18–20 months. The study of the effectiveness of the use of BPaLM in RO TB patients, researchers reported through case reports from the start of treatment (baseline), monthly follow-ups until the completion of treatment.

Furthermore, the success of the BPaLM regimen is determined not only by pharmacological factors but also by a multidisciplinary support system (Guglielmetti et al., 2022b). Clinical, laboratory, and radiological monitoring must go hand in hand with psychosocial support for patients. Factors such as social stigma, discrimination, and economic pressure must also be addressed to ensure patients undergo therapy effectively (Migliori et al., 2021). Therefore, the background to the discussion of the BPaLM regimen encompasses not only medical aspects but also social, economic, and health policy aspects (Dheda et al., 2017).

In summary, the background of this research and this case report emphasize that drug-resistant TB (TB-RR) is a significant challenge in Indonesia's TB elimination program. The BPaLM regimen appears to be a promising innovation, as it is more effective, shorter, and safer than the previous regimen (Conradie et al., 2020; Conradie et al., 2022). However, evidence of implementation in the field, particularly in resource-limited areas, is urgently needed to ensure that this therapy can truly become a national and global solution for tackling drug-resistant TB (World Health Organization, 2022a; Ministry of Health of the Republic of Indonesia, 2024a).

2. Methods

2.1 Study design, setting, and subject

The aim of this study was to examine the effectiveness of the 6-month BPaLM regimen in a patient with rifampicin-monoresistant tuberculosis: a case report from Sabu Raijua Regional Hospital, Sabu Raijua Regency, East Nusa Tenggara. This type of research is a quantitative study with a cross-sectional approach to see the effectiveness of the 6-month BPaLM regimen in a patient with rifampicin-monoresistant tuberculosis at Sabu Raijua Regional Hospital in 1 case treated from the beginning of treatment (baseline), monthly follow-up and until the end of treatment.

The patient was followed longitudinally from baseline (prior to treatment initiation) through monthly follow-up visits until completion of the 6-month BPaLM regimen. Data were collected retrospectively from medical records and prospectively during routine clinical monitoring. The subject was a 24-year-old male diagnosed with pulmonary rifampicin-monoresistant tuberculosis, confirmed by two molecular rapid tests (Xpert MTB/RIF) showing rifampicin resistance. The patient met eligibility criteria for the BPaLM regimen based on WHO 2022 recommendations, including documented susceptibility to fluoroquinolones and linezolid.

2.2 Diagnostic procedures and treatment regimen

Baseline diagnostic evaluation included clinical assessment, sputum microscopy, molecular testing (Xpert MTB/RIF), sputum culture, drug susceptibility testing (DST), chest radiography, laboratory investigations (hematology, liver and renal function tests, electrolytes), and electrocardiography. Microbiological monitoring using sputum microscopy and culture was performed periodically to assess bacteriological conversion. Furthermore, the patient received the standard 6-month BPaLM regimen consisting of bedaquiline, pretomanid, linezolid, and moxifloxacin, administered according to WHO and Indonesian Ministry of Health guidelines. Drug dosing was adjusted according to body

weight and tolerance. Treatment was delivered under a directly observed treatment (DOT) strategy.

In addition for clinical, laboratory, and radiological evaluations were conducted monthly to monitor treatment response, drug safety, and adherence. Treatment effectiveness was assessed based on clinical improvement, sputum smear and culture conversion, radiological resolution, and absence of severe adverse drug reactions. Cure was defined according to WHO and national TB program criteria. This case report was conducted in accordance with ethical principles. Patient confidentiality was maintained, and all identifying information was anonymized.

3. Results and Discussion

3.1 Research Results

This case report discusses a 24-year-old male patient at Sabu Raijua Regional Hospital, Sabu Raijua Regency, East Nusa Tenggara Province, who successfully completed 6 months of BPaLM therapy without serious side effects. This case demonstrates the effectiveness of BPaLM treatment even in the disadvantaged, frontier, and outermost areas with limited facilities and resources. Mr. DDD, a 24-year-old male farmer residing in Raemude, presented for clinical examination on July 6, 2024. The patient's chief complaint was a productive cough with sputum that has persisted for approximately two years.

The patient presented with a cough with phlegm that had been present for two years. The cough was sometimes accompanied by blood spots. The cough caused shortness of breath when coughing vigorously. The patient also complained of increasing weight loss, especially in the last six months. Initially, the patient weighed 65 kg, but now it is down to 48 kg. At night, the patient often sweats and feels weak throughout his body. His appetite is decreased. The patient also complains of fatigue during activities. He denied lymph node enlargement. The patient was initially confirmed to have drug-resistant TB at the Seba Community Health Center. Two TCM tests, on June 26, 2024, showed resistance to rifampicin, and another on July 4, 2024, showed the same resistance to rifampicin. The patient was subsequently referred to the TB DOTS Clinic at Sabu Raijua Regional Hospital on July 6, 2024.

The patient, Mr. DDD, was diagnosed with drug-sensitive TB on August 22, 2022, but did not regularly take anti-tuberculosis medication. A chest X-ray at the time indicated pulmonary TB. The patient only took the medication for the first two months, after which he stopped taking it regularly in the continuation phase. Furthemore, no other family members have similar complaints. The patient lives with his older sibling, his sister-in-law, and one nephew. His father, mother, and other siblings live in Kupang City. The patient works as a farmer, helping to cultivate the family's rice fields. He occasionally travels to Kupang for odd jobs. The patient is a frequent smoker, consuming one to two packs of cigarettes per day. He denies any history of alcohol consumption. Four neighbors in the patient's neighborhood have also been confirmed to have drug-sensitive pulmonary TB and are currently undergoing treatment. The patient frequently gathered, ate, and drank with his neighbors before becoming ill. The neighbors also worked with him in the rice fields.

3.1.1 Physical examination

At the initial visit on July 6, 2024, the patient arrived in a moderately ill general condition, with a compos mentis level of consciousness (GCS 456). Vital signs revealed a blood pressure of 110/60 mmHg, a pulse rate of 110 beats per minute, a body temperature of 36.6°C, a respiratory rate of 24 breaths per minute, and an oxygen saturation (SpO_2) of 96%. Her weight was recorded as 48 kg with a height of 165 cm, resulting in a Body Mass Index (BMI) of 17.63 kg/m^2, which is categorized as underweight underweight according to WHO classification.

A general physical examination revealed no signs of anemia or jaundice, and no enlarged lymph nodes in the head or neck. A cardiovascular examination revealed single, regular S1 and S2 heart sounds, without murmurs or gallops, but tachycardia was present. A respiratory examination revealed vesicular breath sounds with fine, moist rhonchi and minimal wheezing confined to the right lung apex, while the left lung was normal. This was consistent with the radiological findings of the infiltrate at the right lung apex. An abdominal examination revealed normal bowel sounds and epigastric tenderness. The extremities were warm, dry, and rosy, with no edema. These physical findings support the patient's clinical presentation as chronic pulmonary infection and active tuberculosis, with evidence of decreased nutritional status and a systemic response to the infection.

3.1.2 Supporting Examination

Table 1 summarizes the patient's laboratory examination results obtained on July 16, 2024, including hematological parameters, biochemical profiles, electrolyte levels, thyroid function, blood gas analysis, and electrocardiographic findings, which provide an overview of the patient's baseline clinical condition prior to further management.

Table 1. Laboratory (16 July 2024)

Check	Result	Check	Result
WBC	9,600/µL	Ureum	15.10 mg/dL
Hb	10.8 g/dL	Kreatinin	0.6 mg/dL
HCT	32.3%	SGOT	28.87 U/L
PLT	382,000/µL	SGPT	73.47 U/L
RBC	4.22 million /µL	TSH	2.4 µIU/mL
LED	75 mm/jam	EKG	*Sinus tachycardia*, FC: 103 bpm
Golongan Darah	A+	Na	144 mmol/L
Asam Urat	5.20 mg/Dl	K	4.18 mmol/L
iCa	1.56 mmol/L	Cl	114 mmol/L
GDS	156 mg/Dl	pH	7.49

Table 2 presents the chronological results of sputum examinations conducted between June and October 2024 at different health facilities, including RSUD Sabu Raijua and Central Public Health Laboratory/*Balai Besar Laboratorium Kesehatan* (BBLK) Surabaya. The examinations comprised molecular testing using TCM MTB/RIF (Xpert), microscopic examination, culture, and drug susceptibility testing (DST), which collectively illustrate the progression of microbiological findings and drug sensitivity patterns over the course of diagnosis and treatment monitoring.

Table 2. Sputum Examination on June 26, 2024, July 4, 2024, August 30, 2024, September 11, 2024, and October 1, 2024

	June 26, 2024 (RSUD Sabu Raijua)	July 4, 2024 (RSUD Sabu Raijua)	August 30, 2024 (BBLK Surabaya)	September 11, 2024 (BBLK Surabaya)	October 1, 2024 (BBLK Surabaya)
Check	Result	Result	Result	Result	Result
TCM MTB RIF (Xpert)	Resisten Rifampisin	Resisten Rifampisin	-	-	-
Microscopic Examination	-	-	Positive +3		-
Culture				Positive	
Drug Susceptibility Test (DST)	-	-	-	-	High-dose H,, H, Lfx, Mfx, Bdq, Lzd, Cfz: Sensitive

The first chest x-ray was performed on July 6, 2024, before the patient began treatment. The x-ray revealed an active infiltrate in the right lung apex, with minimal infiltrate in the left lung. These findings are consistent with active pulmonary tuberculosis infection, which generally shows a predilection for the upper lung fields, particularly the apex. Infiltrates on the chest x-ray indicate inflammation, consolidation, or granulomas due to an immune response to *Mycobacterium tuberculosis*. The bilateral distribution (right dominant) also supports the suspicion of an active and infectious process, in line with the laboratory results of a positive microscopic +3 and positive cultures.

After 6 months of treatment with the BPaLM regimen, a repeat chest X-ray was performed on January 25, 2025, as a final evaluation of treatment. Results showed resolution of the infiltrate in the left lung and minimal remaining infiltrate in the right lung apex. This indicates significant radiological improvement, reflecting the success of the therapy in eliminating the active infection process. The minimal remaining infiltrate in the right apex may represent residual lesions or scarring (post-infectious fibrosis), which commonly found in pulmonary TB patients after treatment, especially if there was a previous high bacterial load or delayed treatment.

a b

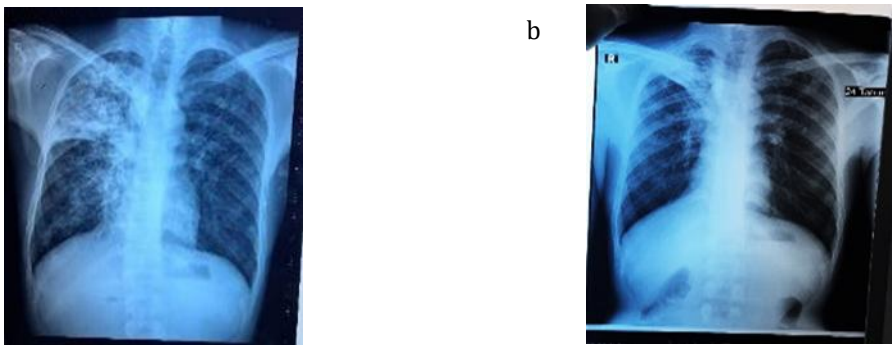

Fig. 1. (a) Thorax photo before treatment; (b) Thorax photo after treatment

3.1.3 Patient follow up

During treatment with the BPaLM regimen, the patient underwent routine clinical and laboratory monitoring every month. At the first monthly evaluation, on September 9, 2024, the patient still complained of a productive cough and weakness, but there were early signs of improvement, such as an increased appetite and reduced fatigue. The patient's general condition remained moderately ill, with relatively stable vital signs. Physical examination revealed minimal rhonchi and wheezing in the right lung apex, accompanied by mild epigastric tenderness. Body weight increased from 48 kg to 49.5 kg, and hemoglobin levels also increased, reflecting an improvement in hematologic status. Albumin remained low but had increased compared to baseline. Sputum microscopy was negative, but cultures remained positive, indicating the presence of active bacteria despite a decreasing bacterial load.

Entering the second month of treatment, on October 21, 2024, the patient's condition continued to improve. Coughing and weakness had significantly reduced, appetite had increased, and he felt more energetic. His general condition had improved to mild illness, with vital signs also improving. A physical examination revealed no further lung abnormalities, and abdominal tenderness had disappeared. His weight had increased to 50 kg, albumin levels had returned to normal, and other laboratory results, including liver and kidney function, and electrolytes, were also within the normal range. Microscopic examinations remained negative, and culture results reported a month later showed a negative conversion, indicating that the therapy was beginning to be effective in eradicating the TB bacteria.

By the third month, on November 20, 2024, the patient had no more cough, had a good appetite, and was not easily fatigued. His general condition remained mild, but his

functional condition was approaching normal. His weight had increased to 51 kg, and his hematologic and nutritional parameters had improved. Microscopic and culture results remained negative, supporting evidence that the active infection had been successfully controlled. No abnormalities were found on physical examination, and vital organ function remained within normal limits.

On December 21, 2024, the patient was in good general condition after the fourth month of treatment. He had an occasional cough, and no longer complained of weakness or fatigue. His weight reached 52 kg, with laboratory results indicating metabolic and nutritional stability. A physical examination revealed no abnormalities in the heart, lungs, abdomen, or extremities. All sputum examinations were negative, both microscopically and by culture, indicating consistent eradication of the bacteria.

At the final follow-up, the fifth month of treatment or final evaluation on January 25, 2025, the patient was in excellent condition. There were no complaints of coughing, weakness, or disruption of daily activities. Body weight reached 54 kg, indicating optimal recovery of nutritional status. Blood tests and organ function results remained stable and good, with hemoglobin reaching 13.7 g/dl and albumin within normal limits. An ECG showed normal sinus rhythm with a heart rate that had decreased to 72 bpm. Microscopic examination was negative, and the final culture results released on February 15, 2025, were also negative, which served as the basis for declaring the patient cured of rifampin-resistant TB based on clinical and laboratory criteria.

3.2 TB Resisten rifampisin (TB RR/RO)

Rifampin-monoresistant tuberculosis (RR-TB) is a form of tuberculosis caused by *Mycobacterium tuberculosis* that is resistant only to rifampin, without resistance to isoniazid or other first-line drugs. Because rifampin is a key component of the standard TB treatment regimen, resistance to this drug has a significant impact on treatment success. According to the WHO Global TB Report 2024, of the approximately 410,000 drug-resistant TB cases worldwide in 2023, a significant proportion will be RR-TB. The WHO classifies RR-TB and MDR-TB as a single epidemiological entity. In Indonesia, approximately 5–7% of new TB cases are diagnosed as RR-TB, most of which are non-isoniazid resistant.

Risk factors for RR-TB include a history of inadequate TB treatment, poor adherence to therapy, close contact with patients with RR-TB, limited access to quality healthcare, HIV co-infection, and immunocompromised conditions including malnutrition.

Pathophysiologically, rifampin resistance in *Mycobacterium tuberculosis* is primarily caused by mutations in the rpoB gene, which encodes the beta subunit of RNA polymerase, a key enzyme in bacterial DNA transcription. Rifampin works by binding to RNA polymerase and inhibiting transcription, thus preventing the synthesis of proteins vital for bacterial survival. Mutations in the "Rifampicin Resistance-Determining Region" (RRDR) of the rpoB gene cause conformational changes in the enzyme's target, preventing rifampin from binding effectively. Approximately 95% of rifampin resistance cases are caused by mutations in this region. As a result of this resistance, even when rifampin is administered, transcription inhibition is not achieved and the bacteria continue to actively replicate, leading to therapy failure.

Furthermore, a high infectious burden, a hypoxic lung environment, and the presence of granulomas further challenge drug penetration. TB granulomas consist of a necrotic core surrounded by macrophages, lymphocytes, and fibrotic tissue. Drugs like rifampin have limited penetration into these tissues, especially if resistance is present. This combination of changes in the target molecule's structure and pharmacological distribution barriers underlies the failure of first-line treatment for RR-TB.

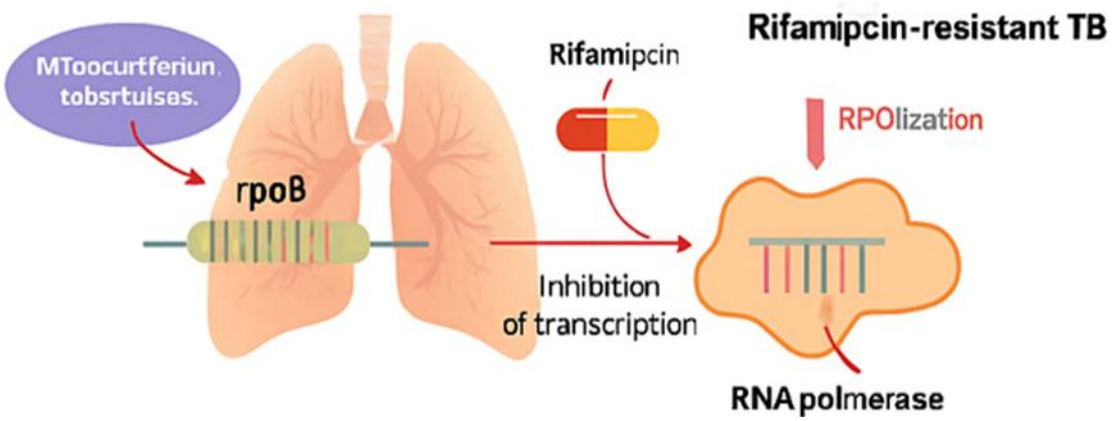

Fig. 2. Pathophysiological process diagram

3.3 Pathogenesis of rifampicin resistance

Clinically, RR-TB does not have any distinctive manifestations that distinguish it from sensitive TB. Symptoms include persistent cough, weight loss, fever, night sweats, and sometimes hemoptysis. However, if not properly managed, RR-TB can show more rapid progression and a higher rate of treatment failure[3]. Radiological examinations such as chest X-rays are an important initial modality and generally show infiltrates in the upper lung fields or cavities. CT scans provide better detail, such as bronchiectasis and satellite nodules. MRI is used primarily for extrapulmonary TB (Dheda et al., 2017).

In addition to molecular mechanisms, environmental factors also play a role (Dheda et al., 2017). TB granulomas, with their hypoxic environment and caseous necrosis, can inhibit drug penetration to the site of infection. This creates a microniche that supports *Mycobacterium tuberculosis* survival despite therapy. This explains why rifampin monoresistance can rapidly progress to multiple resistance if treatment is inadequate (Migliori et al., 2021).

3.4 Risk factors and social determinants

Risk factors for RR-TB include both biological and social aspects. From a biological perspective, patients with a history of incomplete or irregular TB treatment are at highest risk (Ahmad et al., 2018). From a social perspective, factors such as poverty, overcrowding, malnutrition, and smoking play a significant role in worsening the disease's course. In the context of disadvantaged, frontier, and outermost areas, limited access to healthcare facilities makes patients vulnerable to stopping therapy early, increasing the risk of resistance (Dheda et al., 2017). HIV co-infection is another important determinant, as HIV patients have a weakened immune response and are more susceptible to therapy failure (Migliori et al., 2021). The combination of RR-TB and HIV significantly increases the risk of mortality, making new regimens such as shorter and more effective BPaLM regimens strategically valuable in this group (Conradie et al., 2020).

3.5 Clinical manifestations

Clinically, RR-TB does not have any distinctive manifestations that distinguish it from sensitive TB. Symptoms include persistent cough, weight loss, fever, night sweats, and sometimes hemoptysis. However, if not properly managed, RR-TB can show more rapid progression and a higher rate of treatment failure[3]. Radiological examinations such as chest X-rays are an important initial modality and generally show infiltrates in the upper lung fields or cavities. CT scans provide better detail, such as bronchiectasis and satellite nodules. MRI is used primarily for extrapulmonary TB.

The clinical manifestations in the patient in this report also show typical features of active pulmonary TB, including chronic productive cough, weight loss, fever, and weakness. On initial examination, the patient had an active infiltrate in the right lung apex, supported by a positive microscopic result of +3, indicating a high bacterial load. Systemic signs such as tachycardia (pulse 110 beats/minute) and a markedly elevated ESR (75 mm/hour) further support the picture of active infection. These findings are consistent with severe clinical manifestations of RR-TB before therapy was initiated and gradually improved with the administration of the BPaLM regimen.

3.6 Diagnosis

A definitive diagnosis of RR-TB is established through bacteriological detection. Rapid molecular tests such as TCM/CBNAAT detect the presence of MTB and the rpoB gene mutation, which is a marker of rifampin resistance. Microscopic examination and sputum culture remain essential, with culture serving as the gold standard for identification and drug susceptibility testing. Histopathology showing caseous granulomas supports the diagnosis but is insufficient to determine resistance, so molecular testing and culture remain the mainstay.

The image below is a simplified TB-RR diagnostic pathway adapted from an observational study published in the journal Antibiotics in 2025. The diagnosis of RR-TB begins with sputum microscopic examination, followed by rapid molecular testing (Xpert MTB/RIF or Xpert MTB/XDR) for rpoB gene detection, and is confirmed through liquid culture (MGIT 960) and drug susceptibility testing (DST), with the addition of Whole Genome Sequencing (WGS) in some complex cases.

In the patient in this report, the diagnosis of RR-TB was confirmed through two TCM examinations, which revealed MTB with rifampin resistance. Microscopic results showed AFB smear positive (+3), and cultures were also positive. Second-line drug susceptibility testing revealed sensitivity to levofloxacin, moxifloxacine, bedaquiline, linezolid, and clofazimine, making the patient eligible for the BPaLM regimen according to the WHO 2022 guidelines.

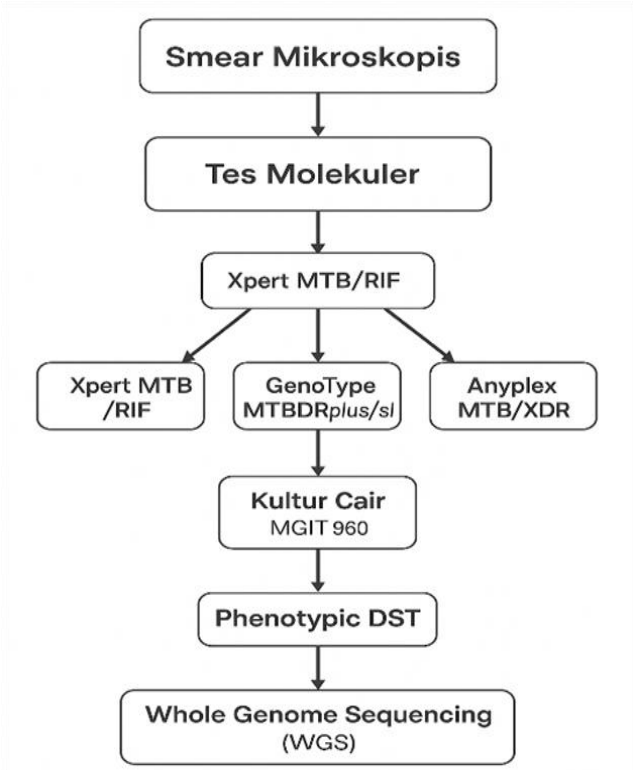

Fig. 3. Flowchart of laboratory diagnosis of rifampicin-resistant TB

3.7 TB-RR therapy paradigm

For decades, TB-RR therapy has relied on long-term regimens (up to 20 months) with a combination of various second-line drugs, including injectable aminoglycosides. In addition to the long duration, these regimens are often accompanied by serious side effects such as ototoxicity, nephrotoxicity, and peripheral neuropathy (Ahmad et al., 2018). Treatment success rates with older regimens ranged from only 55–60%, highlighting the need for a new approach (Migliori et al., 2021).

The emergence of the BPaL/BPaLM regimens represents a major paradigm shift in tuberculosis treatment. These regimens are entirely oral (without injections) and consist of a combination of drugs that act through complementary mechanisms. Bedaquiline (Bdq) inhibits the proton pump in bacterial ATP synthase, thereby halting energy production (Guglielmetti et al., 2022b). Pretomanid (Pa) works by activating nitroimidazoles, which generate free radicals and inhibit cell wall synthesis, remaining effective under both aerobic and anaerobic conditions (Simanjuntak et al., 2023). Linezolid (Lzd) inhibits protein synthesis by binding to the 50S ribosomal subunit and is active against dormant and slow-replicating bacteria (Johnson et al., 2017). Moxifloxacin (Mfx), a fluoroquinolone antibiotic, inhibits DNA gyrase and has excellent tissue penetration (Conradie et al., 2022). This combination is specifically designed to target various phases of bacterial metabolism, including dormant bacteria that are typically difficult to eradicate with conventional regimens.

The strong treatment response observed in this patient can be explained by the complementary pharmacodynamic properties of the BPaLM regimen. Bedaquiline inhibits mycobacterial ATP synthase, targeting both replicating and dormant bacilli; pretomanid is active in hypoxic and anaerobic environments; linezolid inhibits protein synthesis in slow-growing organisms; and moxifloxacin provides potent intracellular and pulmonary tissue penetration (Esmail et al., 2022; Johnson et al., 2024b). This multi-targeted mechanism enables effective bacterial clearance across different metabolic states, which is critical in rifampicin-resistant TB.

Systematic reviews have confirmed that pretomanid-containing regimens are associated with faster bacteriological clearance and improved treatment outcomes compared to older MDR-TB regimens (Simanjuntak et al., 2023; Silva et al., 2025a). The early culture conversion and sustained microbiological negativity in this patient are therefore consistent with current pharmacological evidence.

3.8 Management medication therapy

Treatment of tuberculous osteomyelitis involves first-line medication therapy, tailored to the bacterial sensitivity to anti-TB drugs. The WHO and several studies recommend a minimum of 6 to 12 months of treatment, depending on the location and response to therapy. For cases of drug-resistant TB, such as RR-TB involving the bone, a shorter regimen such as BPaLM can be used if sensitivity to second-line drugs is confirmed (Silva et al., 2025b). Drug penetration into bone tissue is an important consideration. Linezolid demonstrates excellent penetration into bone tissue and synovial fluid, while moxifloxacin also has widespread distribution and high concentrations in musculoskeletal tissue (Ministry of Health of the Republic of Indonesia, 2024a). Bedaquiline, although primarily targeting the lungs, also exhibits activity against dormant bacteria in necrotic lesions. Pretomanid has demonstrated effectiveness in anaerobic conditions, as is often seen in chronic tuberculous osteomyelitis (World Health Organization, 2022b).

In this patient, although the initial focus of infection was the lungs, there were no clinical or radiological manifestations of tuberculous osteomyelitis. However, understanding the tissue distribution of OAT remains crucial because patients exhibit poor nutritional status and active systemic inflammation, potentially exacerbating hematogenous spread to bone. Administration of the BPaLM regimen, which has broad tissue distribution, provides good

systemic protection against the possibility of clinically undetected extrapulmonary dissemination. The BPaLM regimen consists of four oral drugs recommended by the WHO for the treatment of rifampicin-resistant TB (MDR-TB) for 6 months: Bedaquiline (Bdq), Pretomanid (Pa), Linezolid (Lzd), and Moxifloxacin (Mfx). According to the TB RO Operational Handbook (Ministry of Health of the Republic of Indonesia, 2024b), doses are given according to age group and body weight as follows in Table 3 (World Health Organization, 2017).

Table 3. Dosage of anti-tuberculosis drugs in the BPaLM regimen

Type of Drug (Formulation)	Anti-TB Drug Dosage (OAT)
Bedaquiline / Bdq (100 mg tablet)	400 mg once daily for the first 2 weeks, followed by 200 mg three times per week
Pretomanid / Pa (200 mg tablet)	200 mg once daily
Linezolid / Lzd (600 mg tablet)	600 mg once daily
Moxifloxacin / Mfx (400 mg tablet)	400 mg once daily

The dosage can be adjusted based on the patient's weight and tolerance. This medication is administered directly (DOT), with close monitoring of side effects performed monthly. Linezolid is known to carry a high risk of anemia and optic neuropathy, therefore, blood and optic nerve function must be monitored regularly. In this patient, all four components of the regimen were administered as recommended, and regular monitoring revealed no serious side effects requiring discontinuation of therapy. Final evaluation showed weight gain, improved vital signs, increased albumin, negative culture and microscopy results, and improved radiological findings, supporting the success of therapy using the standard BPaLM dose for 6 months.

3.9 Clinical effectiveness of the BpaLM regimen

Several large clinical trials have demonstrated the effectiveness of the BPaLM regimen. The TB-PRACTECAL study, published by the WHO in 2023, reported a treatment success rate of over 80%, significantly higher than that of conventional regimens. The most frequently reported side effects were anemia (due to linezolid) and gastrointestinal disturbances, but these were largely manageable with regular monitoring and dose adjustments (Conradie et al., 2020; Esmail et al., 2022).

In Indonesia, early reports also show encouraging results. Patients tend to be more compliant due to the shorter duration and fewer medications. Sputum smear conversion to negative generally occurs from the second month on, meaning the risk of transmission decreases more quickly than with the traditional regimen (Ministry of Health of the Republic of Indonesia, 2024b).

The favorable clinical course observed in this patient characterized by rapid symptom resolution, progressive weight gain, early sputum smear and culture conversion, and radiological improvement supports the effectiveness of the 6-month BPaLM regimen for rifampicin-resistant tuberculosis. These findings are consistent with outcomes reported in recent high-quality clinical trials and real-world studies published within the last five years.

The TB-PRACTECAL randomized controlled trial demonstrated significantly higher treatment success rates for BPaL/BPaLM regimens compared to conventional longer regimens, with success rates exceeding 80% and a substantially reduced treatment duration (Conradie et al., 2020; Conradie et al., 2022). Importantly, rapid microbiological conversion was commonly observed within the first two months of therapy, which parallels the early sputum conversion documented in this case.

Similar results have been reported in real-world cohort studies. A prospective cohort study evaluating BPaL-based regimens outside controlled trial settings showed sustained culture conversion and favorable safety profiles, confirming the external validity of trial

findings (Sinha et al., 2023). This is particularly relevant to the present case, which was managed in a resource-limited hospital setting rather than a specialized referral center.

3.10 Therapy evaluation

Therapy evaluation of TB-RR patients undergoing the BPaLM regimen includes three main components: clinical evaluation, laboratory evaluation, and radiological evaluation. Clinically, patients are assessed for symptom improvement such as cough relief, weight gain, decreased body temperature, and increased exercise tolerance. Laboratory parameters include microscopy results and periodic sputum cultures to assess negative conversion. Routine blood tests, including ESR, hemoglobin, albumin, and liver and kidney function tests, are also indicators of recovery. Radiological evaluation is performed through serial chest x-rays to assess the resolution of lung infiltrates or cavities.

Based on the guidelines from the World Health Organization (WHO) and the Indonesian Ministry of Health, a patient can be considered cured of tuberculosis (TB) if several criteria are met. Firstly, the patient's last culture test must be negative, indicating the absence of active *Mycobacterium tuberculosis*. Secondly, there should be no clinical symptoms suggestive of active TB, such as persistent cough, fever, night sweats, or weight loss. Thirdly, the patient must have completed the full prescribed treatment regimen without significant interruptions, ensuring adequate exposure to anti-TB medications. Finally, radiological evaluation should demonstrate significant improvement or complete resolution of previously identified active lesions, confirming the healing process (Pontali et al., 2018). Meeting all these criteria provides a comprehensive assessment of the patient's recovery and supports the declaration of cure.

In the patient in this report, evaluation showed complete improvement: cough and systemic symptoms disappeared, weight increased from 48 kg to 54 kg, ESR decreased from 75 mm/hour to normal, and albumin increased from 2.3 to 4.3 g/dL. Microscopic examination and sputum culture results showed negative conversion from the second month of treatment, and a chest X-ray showed improvement in the infiltrate at the apex of the right lung. All criteria for cure were met, so the patient was declared cured based on national guidelines and WHO recommendations (World Health Organization, 2017; World Health Organization, 2023a; Pontali et al., 2022a).

No serious adverse drug reactions were observed during the 6-month treatment period in this case. This aligns with recent studies reporting improved tolerability of BPaLM regimens compared to injectable-based MDR-TB regimens, which are associated with ototoxicity, nephrotoxicity, and poor adherence (Pontali et al., 2022b; Migliori et al., 2021). Although linezolid-associated hematological toxicity remains a concern, recent WHO operational guidelines emphasize that routine laboratory monitoring allows early detection and prevention of severe complications (World Health Organization, 2023a; World Health Organization, 2024). The absence of significant toxicity in this patient highlights the feasibility of safe BPaLM administration with appropriate monitoring, even in peripheral hospitals.

3.11 Implementation challenges

Despite its promise, implementing the BPaLM regimen is not without challenges. First, the availability of new drugs like pretomanid remains limited and requires a robust distribution system. Second, monitoring linezolid side effects requires adequate laboratory facilities, which not all underdeveloped areas have. Third, treatment costs are relatively higher than those of older regimens, necessitating ongoing funding from the government and global partners (Guglielmetti et al., 2022a).

Furthermore, patient adherence remains a key factor. Even with shorter regimens, without a robust monitoring system, patients are still at risk of discontinuing treatment. Therefore, a multidisciplinary approach involving doctors, nurses, community health

workers, and the patient's family remains crucial to ensuring successful therapy (Migliori et al., 2021; Johnson et al., 2024a).

The successful completion of BPaLM therapy in this case demonstrates the practical applicability of WHO-recommended regimens in disadvantaged, frontier, and outermost (3T) areas. The fully oral regimen, shorter duration, and reduced pill burden directly address key barriers to adherence commonly encountered in remote settings (World Health Organization, 2022a; World Health Organization, 2022b). Studies assessing early implementation of BPaLM in low-resource countries have shown improved adherence, reduced loss to follow-up, and faster return to daily activities among patients (Guglielmetti et al., 2022b; Simanjuntak et al., 2023). These findings are consistent with the improved functional status and nutritional recovery observed in this patient.

3.12 Socio-economic impact

The use of the BPaLM regimen also has significant socioeconomic implications. With a shorter treatment duration, patients can return to work more quickly, reducing the economic burden on their families. This is particularly important in areas where the majority of people work in the informal sector, such as agriculture, where months of lost productivity can have a significant impact on income (Ahmad et al., 2018).

Furthermore, healthcare system costs can be reduced due to reduced outpatient length of stay, shorter monitoring requirements, and lower treatment failure rates. Health economic studies estimate that, despite higher drug prices, the BPaLM regimen remains more cost-effective than the traditional regimen due to lower total costs per successfully cured patient (Simanjuntak et al., 2023).

3.13 TB Elimination policy and program perspectives

In the context of the national TB elimination program, the BPaLM regimen aligns with the WHO's “End TB Strategy”, which targets a 90% reduction in TB incidence by 2035. This regimen offers new hope for accelerating the achievement of this target, particularly by reducing the burden of RR-TB, which remains the greatest obstacle (World Health Organization, 2022c; World Health Organization, 2023c).

The Indonesian Ministry of Health, through the Operational Handbook for Treatment of RR-TB (2024), has recommended the use of the BPaL/BPaLM regimen as the new standard. However, full implementation requires training of healthcare workers, strengthening of the logistics system, and regular monitoring of effectiveness and safety. Case studies from various regions, including Sabu Raijua Regional Hospital, can provide empirical input for policy improvements at the national level.

Rapid sputum conversion has important public health implications, as it reduces the period of infectiousness and potential community transmission of resistant strains. Modeling and cohort studies suggest that widespread use of short, effective regimens such as BPaLM could significantly reduce RR-TB transmission at the population level (Guglielmetti et al., 2022a; World Health Organization, 2024). In Indonesia, early programmatic data indicate that BPaLM implementation aligns with national TB elimination strategies by improving treatment outcomes while optimizing healthcare resource utilization (Ministry of Health of the Republic of Indonesia, 2024a). The present case provides real-world evidence supporting the scalability of this regimen beyond tertiary referral centers.

3.14 Relevance of cases in disadvantaged, frontier, and outermost regions

The successful treatment of TB-RR cases with the BPaLM regimen at Sabu Raijua Regional Hospital in Sabu Raijua Regency demonstrates the regimen's feasibility, even in areas with limited facilities. This success demonstrates that with proper multidisciplinary

monitoring, treatment can be effective. This reinforces the argument that the BPaLM regimen is not only superior in large referral centers but can also be adapted in remote areas (Simanjuntak et al., 2023). From the perspective of innovation diffusion theory, the implementation of the BPaLM regimen in the disadvantaged, frontier, and outermost areas can be seen as a form of "early adoption" crucial for accelerating expansion to other areas. Early success will boost the trust of healthcare workers and patients, thereby minimizing resistance to regimen changes.

Taken together, the clinical, microbiological, and radiological outcomes in this case strongly support current international evidence that the 6-month BPaLM regimen is an effective, safe, and feasible treatment for rifampicin-resistant tuberculosis. Importantly, this case adds valuable real-world evidence from a remote 3T region, reinforcing global and national recommendations for broader implementation of BPaLM-based therapy (Conradie et al., 2022; World Health Organization, 2023b).

3.15 Future prospects

Going forward, further research is needed to evaluate the effectiveness of the BPaLM regimen in special populations such as children, patients with extrapulmonary TB, and patients with severe comorbidities. Furthermore, the possibility of combining this regimen with other interventions, such as immunomodulatory therapy or new TB vaccines, should be explored to improve outcomes (Johnson et al., 2017). The development of new drugs such as delamanid, sutezolid, or combinations of bedaquiline with other agents is also being explored to complement or replace the current regimen. However, to date, BPaLM remains the current gold standard in the treatment of RR-TB (Conradie et al., 2022).

4. Conclusions

A case report of a 24-year-old man diagnosed with rifampin-monoresistant pulmonary tuberculosis (TB) based on two TCM results showing MTB with rifampin resistance. Initial symptoms included chronic productive cough, weakness, weight loss, fever, and an active infiltrate in the right lung apex on chest X-ray. Microscopic examination revealed a positive AFB smear (AFB), an ESR of 75 mm/hour, and an initial albumin of 2.3 g/dL. Culture results were positive, but drug susceptibility testing revealed sensitivity to levofloxacin, moxifloxacine, bedaquiline, linezolid, and clofazimine.

The patient then received a 6-month BPaLM regimen with standard doses: bedaquiline 400 mg for the first 14 days, followed by 200 mg three times weekly; pretomanid 200 mg/day; linezolid 600 mg/day; and moxifloxacin 400 mg/day. No serious side effects were observed during treatment, and no dose adjustments were required. Monthly evaluations showed marked clinical improvement: cough disappeared, body weight increased from 48 kg to 54 kg, albumin increased to 4.3 g/dL, and pulse rate decreased from 110 bpm to 72 bpm. Sputum microscopy and culture results became negative starting in the second month of treatment. A recent chest X-ray showed resolution of the infiltrate.

This case highlights all stages of scientific and clinical evidence demonstrating the efficacy of the BPaLM regimen. The patient presented with typical symptoms of RR-TB at diagnosis, supported by molecular and microscopic examinations. After six months of full treatment, progressive clinical improvement occurred: the cough and systemic complaints disappeared, weight significantly increased, ESR and nutritional parameters improved, and final culture results showed negative conversion. These findings confirm that the use of the BPaLM regimen is not only theoretically effective but also proven successful in clinical practice, particularly in RR-TB patients with mild comorbidities and a good therapeutic response in the 3T (*terpencil, terluar, dan tertinggal*/disadvantaged, frontier, and outermost) area.

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During the preparation of this work, the authors used Grammarly to assist in improving grammar, clarity, and academic tone of the manuscript. After using this tool, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

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