IJTID. Volume 13 No 2 May-August 2025
Sinta 2 (Decree No: 105/E/KPT/2022)
e-ISSN: 2356-0991; p-ISSN:2085-1103
Available online at https://e-journal.unair.ac.id/IJTID

Article Review

IJTID
(INDONESIAN JOURNAL OF TROPICAL AND INFECTIOUS DISEASE)
Scientific Journal of Tropical and Infectious Disease

Update on The Current Management of Drug-Resistant Tuberculosis (DR-TB)

Rohani Lasmaria Simbolon[1], Elvando Tunggul Mauliate Simatupang[1*], Indra Yovi[1], Zarfiardy Aksa Fauzi[1]

[1]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Riau University, Arifin Achmad General Hospital, Pekanbaru, Riau, Indonesia

OPEN ACCESS

ARTICLE INFO

Received: June 15, 2024
Accepted: March 20, 2025
Published: August 31, 2025
Available online: August 31, 2025

*) Corresponding author:
E-mail: elvando56@gmail.com

Keywords:
Tuberculosis
DR-TB
BPaLM
BpaL

Abstract

Drug-Resistant tuberculosis (DR-TB) is a global public health threat that requires a comprehensive response from all parties. DR-TB cases are often overlooked and tend to increase every year. Efforts to overcome DR-TB cases began in 2009 with the use of a molecular test, Xpert MTB/Rif, as a diagnostic tool. This has now been developed with the procurement of a molecular test with Xpert MTB/XDR. This diagnostic update also formed the basis of the latest DR-TB classification terminology by not categorizing polyresistance into the DR-TB group. This step is still not in accordance with the low success rate of DR-TB treatment in Indonesia, ranging from 45-50%. The latest DR-TB management recommendations by WHO in 2022 have implemented a 6-month treatment regimen to minimize the occurrence of treatment dropout or patient treatment non-compliance. The BPaLM/BPaL regimen is a shorter-duration oral regimen that is expected to help achieve the End TB 2015-2030 targets. Previously used short-term regimens have now been modified with Ethionamide and Linezolid variants as alternatives for DR-TB management if the BPaLM/BPaL regimen does not meet the criteria for use.

Cite this as: Simbolon, R.L., Simatupang, E.T.M., Yovi, I., and Fauzi, Z.A. (2025). Update on The Current Management of Drug-Resistant Tuberculosis (DR-TB). *Indonesian Journal of Tropical and Infectious Disease*, 13(2) : 98–110. https://doi.org/10.20473/ijtid.v13i2.59075

INTRODUCTION

Mycobacterium tuberculosis Complex infection is the causative agent of Pulmonary Tuberculosis (PTB), an infectious lung disease. After COVID-19, PTB cases ranked as the second most common cause of infection-related mortality globally. In 2022, PTB cases will result in twice as many deaths as cases of HIV/AIDS combined with other viruses. PTB continues to be a significant global concern, with an annual rise in cases.[1,2] To eliminate PTB cases by 2030, the World Health Organization (WHO) and United Nations (UN) prefer to improve the incidence rate to 65/100.000 people and the mortality rate to 6/100.000 people.[2,3]

As per the 2023 Global Tuberculosis Report, Indonesia currently maintains the second place globally in terms of PTB cases, with an estimated total of 1.060.000 cases, after India. The amount of mortality of PTB is also strongly associated with an increase in new cases, which exceeded 134.000 cases.[1] Data from the Indonesian Ministry of Health also explains that there was an 809.644 case increase in PTB cases in 2023, above the previous year.[1,4] Indonesia has noticed an increase in PTB cases, mainly because of the unsuccessful outcome of treatment. The amount of Drug Resistant Tuberculosis (DR-TB) cases in Indonesia has also increased in alongside this condition.[5,6]

Globally, by 2022, resistance testing will be conducted on 73% of new PTB cases, with 4,4% having developed DR-TB.[1,6] Incidence of DR-TB is estimated to be 10/100.000 in 2021, with a mortality rate of 52/100.000 people.[7,8] Compared to 7.876 cases in 2021, the incidence of patients with confirmed Multi Drug Resistant (MDR)/Rifampicin Resistant (RR) Tuberculosis until the beginning of 2024 was 12.531 cases.[4,8] Indonesia is one of the nations with the highest incidence of DR-TB cases globally, accounting for 28.000 cases since 2021. In that time, 45–50% of cases continue to end successfully. Along with mortality rates of 15-20% of cases, this condition is caused by a high rate of dropping out of 20-30% of cases.[1,9]

WHO recommended an oral treatment regimen in 2020 with the aim of decreasing the duration of treatment to 9-11 months for cases of MDR-TB. Through the use of injectable Anti Tuberculosis Drugs (ATD), the previous regimen failed to be as assist of prompt treatment accomplishment for each patient as it had been for others.[10,11] The use of medication is affected by reports of patients who, mainly as an outcome of drug side effects, are unable to complete treatment on time.[11] There are additional reasons to search for advanced DR-TB regimens with a shorter duration and fewer side effects, including the logistical challenges of DR-TB regimens, the high expense of current drugs, and an increasing number of treatment failures.[12,13]

The strategy for DR-TB diagnosis requirements, which experienced several changes in accordance with WHO guidelines in 2022, is closely related to tasks that aim at increasing the treatment's success rate. The development of Molecular Rapid Test exams, which can currently detect Isoniazide (INH) and Fluoroquinolone (FQ) resistance in the same test, shows changes in the procedure for the diagnosis of DR-TB. Furthermore, beginning in 2022, clinical trials into the use of ATD without injection and a shorter duration of treatment would be carried out, as the WHO.[14,15]

The Global Tuberculosis Programme of the World Health Organization (GTB-WHO) has incorporated all the latest clinical trial recommendations into one set of integrated guidelines for the global

management of DR-TB cases.[16] The newest regimens recommended by WHO are Bedaquiline, Pretomanid, Linezolid, Moxifloxacin (BPaLM), and Bedaquiline, Pretomanid, Linezolid (BPaL). Already in 2022, 40 nations began using the 6-month BPaL/M regimen for RR/MDR-TB and Pre-Extensively Drug Resistant (Pre-XDR)-TB patients. [16,17]

The National Tuberculosis Programme in Indonesia has started providing INH Monoresistance regimens and BPaLM/BPaL regimens by 2023. This effort is to close the gap between DR-TB case finding and patients who have received DR-TB regimens previously.[16,18] The WHO's decision to implement its most current DR-TB regimen in 2022 indicates a significant advancement in the revision of the Technical Guidelines for DR-TB Management in Indonesia. The success of End Tuberculosis 2030 is expected to be improved by the introduction of the BPaLM/BPaL regimen.[16,18]

DEFINITION

The common term for Tuberculosis is an infectious disease caused by bacilli of *Mycobacterium tuberculosis*. Bacilli of *Mycobacterium tuberculosis* are intracellular pathogens that can reproduce a mycolic acid layer, are immobile, and are capable of cell division every 18-24 hours.[19] The WHO 2022 summary of multiple investigations has led to an upgrade in the nomenclature used to describe the cause of PTB. The Genus of Mycobacterium, which includes *M. tuberculosis*, *M. bovis*, *M. caprae*, *M. africanum*, *M. microti*, *M. canneti*, *M. orygis*, and *M. pinnipedii*, is the source of PTB. This group of species is known as the *Mycobacterium tuberculosis* Complex.[20]

CLASSIFICATION

According to the WHO's 2022 recommended terminology, PTB can be classified according to anatomical location, previous PTB treatment history, HIV status, and drug test sensitivity.[16,19] Drug-sensitive TB (DS-TB) and DR-TB are the two categories of PTB that are based on drug sensitivity tests. The most recent DR-TB treatment is directly related to the updated DR-TB classification approach that takes *Mycobacterium tuberculosis* microbe resistance patterns into view. As shown in Figure 1, there are five groups in the DR-TB classification.[19,21]

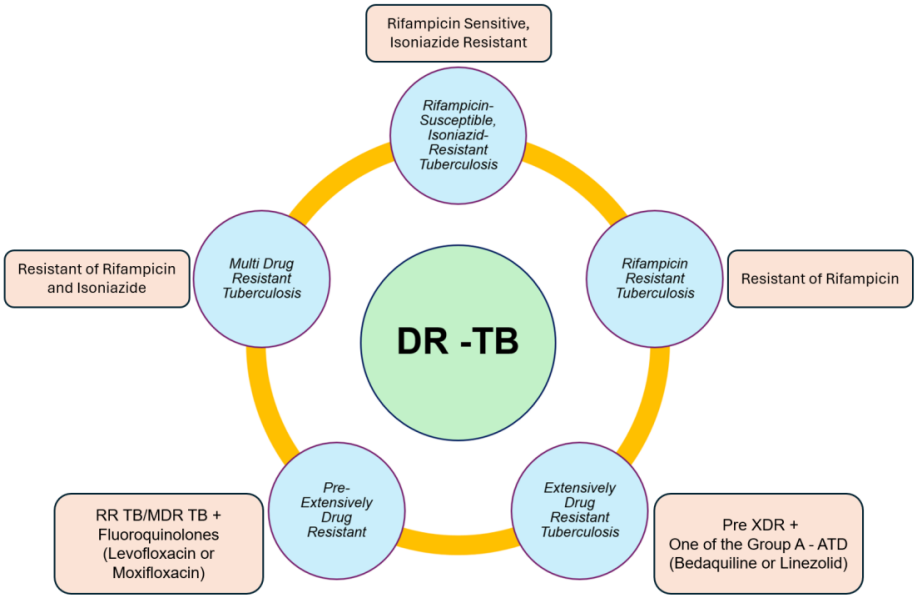


Figure 1. Classification of DR-TB[19]

CRITERIA OF DR-TB SUSPECTED

Suspected DR-TB was reduced to two criteria in accordance with WHO recommendations in 2022. For paediatric or adult DS-TB patients with or without HIV that worsened clinical (symptomatic or radiological) or bacteriological improvement by the end of the 2nd month, one month before the end of treatment, and the end of treatment, despite receiving an appropriate mix and dose and following ATD, the initial criterion is to be used. The second criteria is relevant to patients that belong to paediatric or adult with symptoms of PTB and had one of the following histories: (1) history of close contact with DR-TB patients; (2) a history of close contact with DS-TB patients that died about PTB, failed treatment, and were not committed during treatment; and (3) had history of DS-TB or DR-TB treatment.[16,18,22]

DIAGNOSIS APPROACH

The Molecular Rapid Test examination is the first approach used to diagnose PTB, employing Xpert MTB/Rif cartridges. The Molecular Rapid Test examination has been able that detect the *Mycobacterium tuberculosis* complex and measure resistance to Rifampicin, Isoniazide, and Fluoroquinolones since 2006, as evidenced by the Xpert MTB/XDR cartridge.[23] Xpert MTB/XDR was created to improve the rate of finding cases for DS-TB and DR-TB, which will decrease morbidity and mortality. The development of this Molecular Rapid Test examination also improves the diagnosis of patients who meet the criteria for suspected DR-TB. The MRT Xpert MTB/XDR examination serves as a substitute for first and second-line Probe Assay (LPA) and culture examinations, showing quicker test results.[16,23]

The algorithm for identifying PTB was also altered to prioritise the results of the Molecular Rapid Test of Xpert MTB/XDR test (Figure 2).[24] The new algorithm also enables a more targeted approach to the diagnosis of DR-TB, which in then accelerates the treatment process. The interpretation of Molecular Rapid Test examination results assists in the detection of XDR-TB, RR-TB/MDR-TB, Pre-XDR-TB, and Monoresistance TB.[24,25]

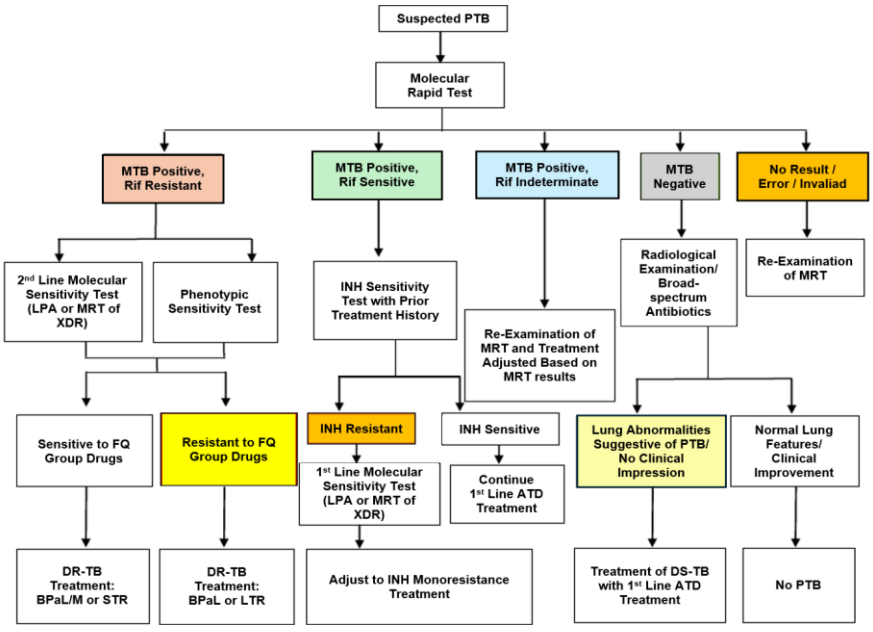


Figure 2. Update of the Diagnosis Algorithm of PTB in Indonesia with a Treatment Approach in Cases of INH Monoresistance and DR-TB based on Current Molecular Rapid Test Interpretation[18,24]

ALGORITHM OF CURRENT MANAGEMENT FOR DR-TB

So as to achieve the goal End TB 2030, WHO demonstrates that each of the bacteriologically confirmed PTB patients experiences early diagnosis of PTB and increased sensitivity tests. People who show classic symptoms of PTB, have a history of contact with PTB patients, and have comorbid or co-infected with HIV are prioritized for molecular tests. The sensitivity test is also implemented to evaluate the patient's resistance to Second Line ATD through genotypic and phenotypic analysis.[16,26]

Based on Figure 3, the WHO published the current management strategy for DR-TB in 2022. The most recent update on the management of DR-TB suggests that the BPaLM/BPaL regimen be administered and that the Short Term Regimen (STR), which variant of the Ethionamide and Linezolid options, get revised.[16,22,27]

There are three general treatment regimens that are currently used to manage DR-TB (Figure 3). The first treatment regimen consists of BPaLM, BPaL, and Monoresistance (Hr-TB) regimens and will be given for six months.[16,18,25] The second regimen, which was previously identified as the STR, refers to the nine-month treatment regimen. The STR treatment is updated in accordance with the criteria of DR-TB patients and is divided into Ethionamid and Linezolid variants. The Long Term Regimen (LTR) is the last regimen, extending for 18-24 months.[16,26,27]

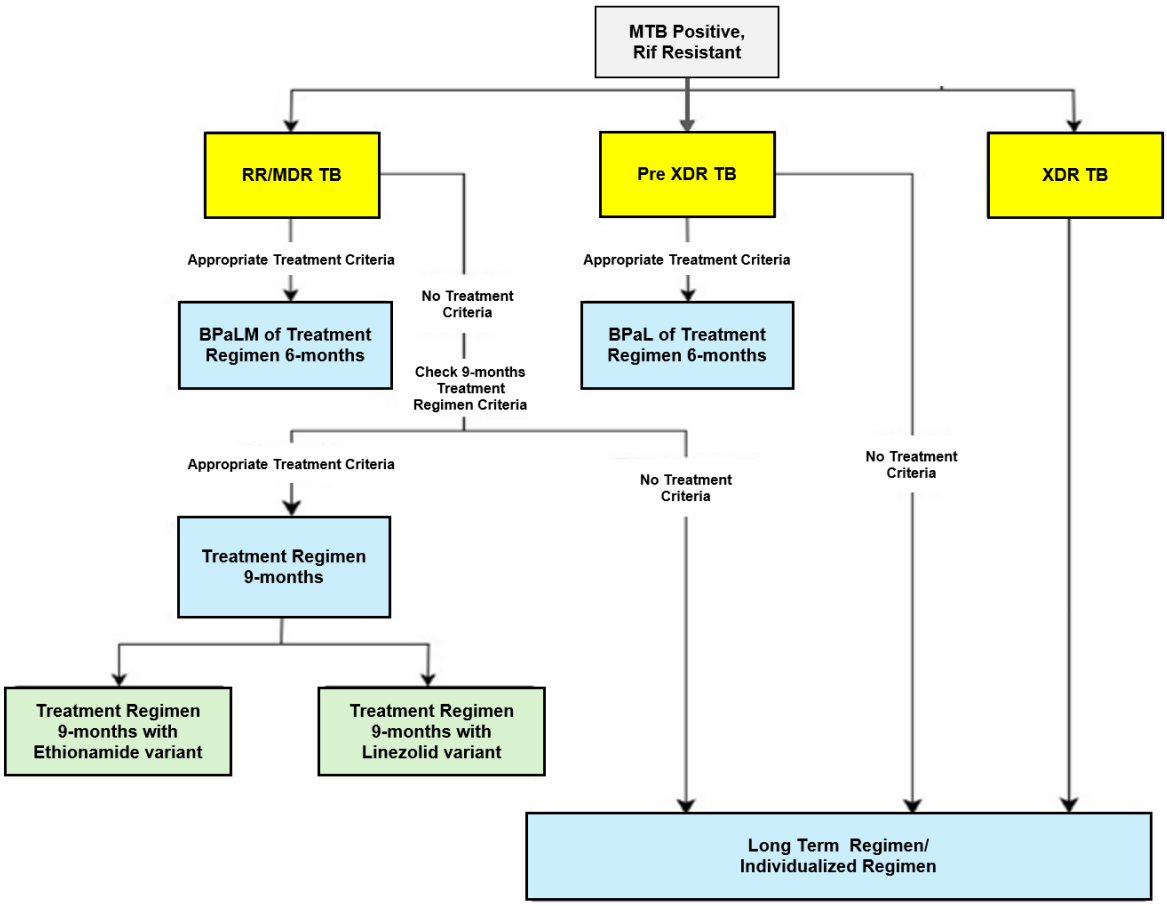


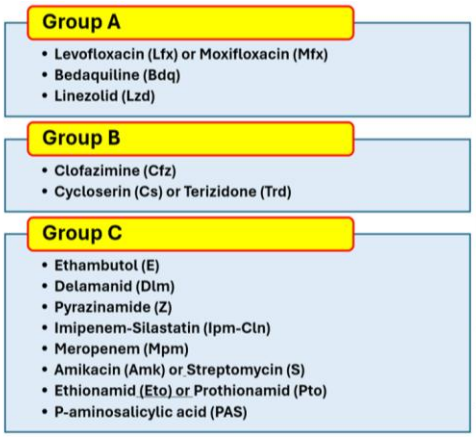
Figure 3. Current Management of DR-TB with BPaL/M Regimen as the Main Priority for DR-TB Treatment with a Shorter Duration of Treatment[18]

REGIMEN of BPaL/M

Criteria for Administration of BPaL/M Regimen

The criteria for using BPaLM or BPaL regimens differ based on the indications for diagnosis and the results of resistance tests of the components of the BPaL/M regimen. There are similarities in the criteria for giving the BPaL/M regimen, including: (1) Adult or adolescent patients >14 years, no matter the presence of HIV; (2) Patients with confirmed PTB or Extra Pulmonary Tuberculosis (EPTB), with the exception of TB that involve the Central Nervous System (CNS), Osteoarticular, and Disseminated/Millary; (3) Have not used Bedaquiline, Pretomanid, Linezolid, or Delamanid for a period more than one month; and (4) Cannot be administered in pregnancy and lactation. Although the two criteria differ by the criteria is BPaLM regimen is recommended for patients diagnosed with RR-TB/MDR-TB, and the BPaL regimen is recommended for patients diagnosed with Pre XDR-TB. Furthermore, the BPaL regimen must be administered in an approach that ensures the drug components are not resistant. It displays the difference between the two regimens.[16,18]

The administration of Moxifloxacin was the only difference between the composition and dosage of OAT in the BPaL/M regimen, as shown in Figure 4.[16-18] BPaLM and BPaL regimens also differ by the duration of treatment. The BPaLM regimen is given at the same time daily for a maximum of 6 months or 26 weeks. Compared to the BPaLM regimen, the duration of the BPaL regimen can be prolonged by 3 months at the time of clinical progress, even if the sputum culture results have not converted by the end of the 6 months of treatment. The BPaL regimen's extended treatment duration aims to achieve a total treatment duration of 9 months or 39 weeks.[16,18,22]



Type of ATD	Dose of Administration
Bedaquiline / Bdq (Dosage: 100 mg tablet)	400 mg once/day for the first 2 weeks daily Followed by 200 mg 3 times/week
Pretomanid / Pa (Dosage: 200 mg tablet)	200 mg once/day daily
Linezolid /Lzd (Dosage: 600 mg tablet)	600 mg once/day daily
Moxifloxacin / Mfx (Dosage: 400 mg tablet)	400 mg once/day daily

Figure 4. Type and Dose of ATD in BPaL/M Regimen[16-18]

Modification of BPaL/M Regimen

The BPaL/M regimen may be modified both before and after treatment. The BPaL/M regimen modification principles are comprised of 4 aspects, especially: (1) Dosage adjustments are just available with Linezolid; (2) Not recommended to change the use of Moxifloxacin to Levofloxacin; (3) The administration of a BPaL regimen is advised in the event that Moxifloxacin has contraindicated; and (4) The administration of Pretomanid and Bedaquiline cannot be permanently discontinued during treatment.[16,18,28] The modified BPaL/M regimen contains 3 primary principles for the administration of Linezolid, that are: (1) The only permitted stoppage of Linezolid is not

recommended within the initial 9 weeks; (2) Linezolid should not be stopped for a duration above 14 days; and (3) Discontinuation of Linezolid for a duration over 14 days within the initial 9 weeks was described as Treatment Failure.[16,28]

The administration of BPaL/M regimen is very important to be considered in detail in Linezolid dose adjustment.[16,28] Linezolid dose adjustment is considered in 3 ways, namely: (1) Can be permanently stopped; (2) Temporarily suspended; and (3) Linezolid administration dose reduction. Indications for permanent discontinuation of Linezolid include a finding of significant toxicity effects in the first 9 weeks of administration of 600mg/day. Where conditions such as optic neuritis, grade 3-4 peripheral neuropathy, recurrent anemia, and severe thrombocytopenia are present, toxicity effects are considered significant. If the remaining treatment time is less than 8 weeks and culture conversion has occurred, there are additional conditions that may result in a permanent end of Linezolid administration.[28,29]

The administration of Linezolid 600 mg/day within the first 9 weeks of treatment may be just stopped if the duration of Linezolid discontinuation is less than 14 days. Any condition that fails to satisfy these criteria will be classified as treatment failure. Linezolid can be reduced to 300 mg/day if it has been administered within the first 9 weeks and there are low toxicity effects, such as grade 1 or 2 peripheral neuropathy and myelosuppression, that have improved after transfusion.[16,30]

Criteria for Treatment Failure of BPaL/M Regimen

The eligibility criteria for each patient are modified prior to the administration of the BPaL/M regimen. Patients who fail to meet the criteria for BPaLM regimens may be considered for BPaL regimens if there is resistance to fluoroquinolones. The subsequent option is STR treatment that is customized to the criteria of Ethionamide or Linezolid variants, as the administration of the BPaLM regimen is contraindicated.[16,18]

The LTR treatment is recommended for patients who fail to meet the criteria for BPaL/M or STR treatment. If there was no sputum conversion at the conclusion of the 6th month of treatment with the BPaLM regimen or the 9th month of treatment with the BPaL regimen, patients were classified as treatment failures.[16] Additionally, treatment failure will be characterized as permanent discontinuation of Bedaquiline or Pretomanid, or the development of resistance to Bedaquiline, Pretomanid, and Linezolid during the treatment period.[28,29] In the event of BPaL/M modification, the criteria for treatment failure also apply if there is substantial toxicity following Linezolid administration and adverse events involving discontinuation of Linezolid for more than 14 days within the first 9 weeks. The patient's treatment is maintained with the LTR treatment following the failure in the BPaL/M regimen.[16,30]

SHORT-TERM REGIMEN (STR)

Generally, the criteria for STR are still unaltered and continue to be applied in accordance with the previously established criteria. The main treatment option for DR-TB management is no longer STR due to recent advances in BPaLM/BPaL regimens (Figure 3).[16] Criteria that are inappropriate for BPaLM/BPaL will be matched with criteria that are acceptable for STR. Patients with RR-TB/MDR-TB may be advised to get STR with the most recent

two variants. If the STR criteria fail to be satisfied, patients will continue to receive LTR treatment.[16,18]

Treatment criteria for STR should be customised for Ethionamide and Linezolid variants according to the most recent WHO recommendations for 2022.[16] In patients with severe peripheral neuropathy, visual impairment, or very low haemoglobin/neutrophils/thrombocytes, STR with Ethionamide variants may be recommended. Pregnancy and breastfeeding are not recommended contraindications to STR with the Ethionamide variant. The STR with the Linezolid variant is considered more effective than Ethionamide in terms of treatment compliance. Comprehensive supervision should be maintained during the administration of Linezolid, as it has the potential to cause toxicity effects.[16,31]

However, the duration of STR treatment with Ethionamide or Linezolid variants remains 9-11 months. Additionally, the two variants maintain similarities in the composition and type of ATD, specifically the administration of Bedaquiline for 4-6 months during the initial stage and the use of the same type of ATD during the advanced stage (Figure 5).[16,31] The two categories of STR variants do not exhibit a significant difference in terms of the duration and advanced stage of treatment. The difference between these two variants is in the initial stage of treatment. The Ethionamide variant involves the administration of Ethionamide for 6 months, and the Linezolid variant involves the administration of Linezolid for 2 months.[31]

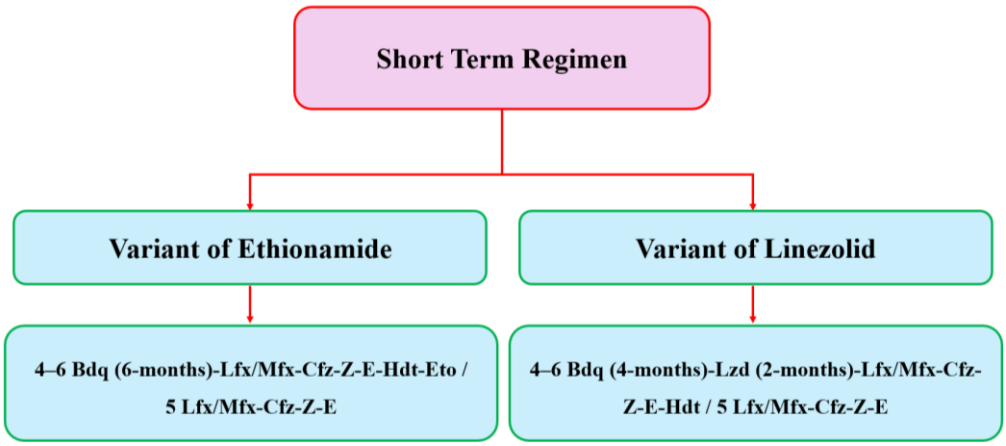


Figure 5. Current Differences of Anti-Tuberculosis Drugs Components in Short-Term Regimens as Alternative Treatment of Contra-Indications in BPaL/M Regimens[16,31]

Treatment with STR is assessed in stages to determine the conversion status of sputum culture. Evaluation of the conversion status to determine the duration of treatment is approximately 9-11 months. The initial phase of treatment is the basis for establishing the parameters used to determine the duration of treatment. Treatment can be administered for 9 months, provided that the sputum culture results at the conclusion of the 4th month have converted, and the following stage continues for 5 months. Patients who have received negative initial AFB or sputum culture results can be administered the initial stage for a period of 4 months. Additionally, for the purpose of ensuring that patients experience proper wellness, clinical and radiological conditions are assessed in stages.[31,32]

Treatment can be administered in 10 or 11 months if no conversion has occurred by the outcome of the 4th month. Therefore, the initial phase of treatment continues to the 5th or 6th month. For confirmation of ATD sensitivity in the treatment regimen

component, it is recommended that second LPA tests and ATD test sensitivity be repeated. Treatment failure is declared if STR treatment is used and LTR treatment is continued after the 5th or 6th month, and there is no sputum culture conversion.[33]

LONG-TERM REGIMEN (LTR)

The initial introduction of DR-TB management started in Indonesia in 2009. The management of DR-TB from 2009-2017 was examined, and it was observed that there was a trend of decreasing treatment success rates, increasing dropout rates, and increasing mortality rates. An oral treatment regimen for the management of DR-TB was issued by the WHO in 2018 in response to these findings. The result is further supported by the 2017 Decree of the Indonesian Minister of Health, which aims to break the link for transmission of DS-TB and DR-TB in the community by conducting DR-TB treatment and expanding the availability of DR-TB health care facilities.[18,34]

Based on the above history, the LTR treatment was initially introduced by the WHO in 2018 as an alternative management option following STR treatment in the treatment of DR-TB. Several studies of clinical trials conducted by the WHO in 2020 to 2022 showed that LTR treatment is still an effective treatment for DR-TB.[1,2,18,34] LTR treatment is the final option in the current management of DR-TB, particularly in patients who have failed treatment after BPaLM, BPaL, and STR treatment, as described in the current management pathway for DR-TB (Figure 3).[33,34]

Individualised regimens are one of the terms used to describe LTR treatment. This is because the ATD components in this regimen can be adjusted in phases depending on the level of the 2nd Line ATD group. The optimal treatment regimen includes 3 Group A drugs and 2 Group B drugs. According to the event that the ideal regimen failed to conform to the criteria for the completion of the 5 drug components in LTR treatment, the use of Group C drugs may be prescribed. The most recommended drug is administered from the highest position of the list. Group C drugs are administered in the following sequence.[16,18,34]

The primary LTR treatment regimen begins with 5 types of ATD that are considered to be effective, and must consist of a minimum of 3 types of ATD after the end of Bedaquiline (Figure 4). The LTR treatment has been customised to the patient's clinical history and treatment, which includes the results of the 2nd Line ATD sensitivity test, a history of disease intolerance, and any comorbidities that may result in ATD interactions with other drugs.[16,33-35] The duration of the LTR treatment regimen was 18-24 months and was modified based on the duration of sputum culture conversion. Individuals who do not achieve culture conversion by the 8th month of treatment are classified as treatment failures and must begin the LTR treatment from the start, with the drug composition adjusted according to the most recent sensitivity test results.[34,35]

STRENGTH AND LIMITATION

The strength of this review article is that it can be used as an updated guide to DR-TB management. This article is expected to provide information to all communities, especially health agencies, in managing DR-TB cases with shorter treatment. The limitations of this review article are subject to change, and the latest scientific developments based on research being developed in the treatment of DR-TB

that is more efficient and effective.

CONCLUSION

The annual increase in cases of DR-TB presents a significant global health burden. The significant prevalence of drug dropout and mortality rates provides a foundation for scientific advancement in enhancing the identification and efficacy of treatment. The MRT examination, using the MTB/XDR cartridge, is an advanced technique for accelerating the identification of PTB cases. It is able to detect the Mtb Complex, which is the main cause of PTB infection. Furthermore, a further benefit is being able to detect both resistance to INH and Fluoroquinolones as a diagnostic approach to monoresistant TB and pre-XDR-TB. This upgrade is anticipated to accelerate the detection of DR-TB in nations with a high prevalence of the disease, such as Indonesia.

Following that, a new strategy for managing DR-TB was implemented, with a shorter treatment period and minimal side effects. The principal treatment for DR-TB has now been superseded by this shift in DR-TB treatment, making STR and LTR useless. According to the WHO Guideline 2022, the BPaL/M regimen has been identified as the primary treatment choice for managing DR-TB. This regimen has been evaluated in multiple clinical trials and is recommended for a treatment period of 6 months. The BPaLM regimen is recommended for cases of RR-TB/MDR-TB, while the BPaL regimen is recommended for cases of Pre XDR TB. The modifications in the BPaL/M regimen specifically apply to the period and dose of Linezolid administration before and after the treatment. Extensive clinical monitoring was conducted to evaluate the adverse effects caused by the administration of Linezolid. The linezolid dose was adjusted during the initial 9 weeks of treatment and was not stopped for more than 14 days.

The administration of STR treatment could be considered for patients who do not meet the criteria of the BPaL/M regimen or who fail treatment with the BPaL/M regimen initially. STR treatment is currently divided into two variants, namely Ethionamide and Linezolid. The administration of both variants is accommodated to the treatment criteria and clinical indications. In the management of DR-TB, LTR treatment is the last option for patients who do not qualify for STR administration or STR treatment failure. It is anticipated that the current approach to the diagnosis and management of DR-TB will be updated in order to enhance the efficacy of DR-TB treatment and decrease the incidence of drug withdrawal, as well as mortality from PTB.

ACKNOWLEDGMENT

We extend our gratitude to all those who supported and contributed to the improvement and enhancement of this study.

FUNDING

This study did not receive any funding.

CONFLICT OF INTEREST

The authors declared there is no conflict of interest.

AUTHOR CONTRIBUTION

Idea and concept: RLS, ETMS, IY, ZAF. Design and manuscript writing: RLS, ETMS. Data collection and processing: ETMS. Control and supervision: RLS, IY,

ZAF. Review and revision: RLS, IY, ZAF. All authors contributed to and approved the final version of the manuscript.

REFERENCES

1. World Health Organization (WHO). Global Tuberculosis Report 2023. WHO. 2023.
2. World Health Organization (WHO). Global Tuberculosis Report 2022. WHO. 2022.
3. Kementerian Kesehatan Republik Indonesia. Tuberculosis Control in Indonesia 2023. Kementerian Kesehatan Republik Indonesia. 2023.
4. Kementerian Kesehatan RI. Laporan Program Penanggulangan Tuberkulosis Tahun 2022. Kementerian Kesehatan RI. Jakarta. 2023.
5. Kaaffah S, Kusuma IY, Renaldi FS, Pratiwi ADE, Bahar MA, Lestari YE. Knowledge, Attitudes, and Perceptions of Tuberculosis in Indonesia: A Multi-Center Cross-Sectional Study. Infect Drug Resist. 2023;16(January):1787–800. DOI:https://doi.org/10.2147/IDR.S404171
6. Lestari T, Fuady A, Yani FF, Putra IWGAE, Pradipta IS, Chaidir L, et al. The development of the national tuberculosis research priority in Indonesia: A comprehensive mixed-method approach. PLoS One. 2023;18(February):1–14.DOI: 10.1371/journal.pone.0281591
7. Noviyani A, Nopsopon T, Pongpirul K. Variation of tuberculosis prevalence across diagnostic approaches and geographical areas of Indonesia. PLoS One. 2021;16(10 October): 1–12. DOI: 10.1371/journal.pone.0258809
8. Tim Kerja Tuberkulosis. Dashboard Data Kondisi TBC di Indonesia Data Diperbarui 02 Januari 2024. Kementerian Kesehatan Republik Indonesia. 2024. Available:https://tbindonesia.or.id/pustaka-tbc/dashboard/
9. Alsayed SSR, Hendra G. Tuberculosis: Pathogenesis, Current Treatment Regimens and New Drug Targets. International Journal of Molecular Sciences. 2023; 24: 5202. DOI: 10.3390/ijms24065202
10. Meeting report of the WHO expert consultation on the definition of extensively drug-resistant tuberculosis, 27-29 October 2020. Geneva: World Health Organization; 2021.
11. Lestari Bony Wiem, et al. Management of drug-resistant tuberculosis in Indonesia: a four-year cascade of care analysis. The Lancet. 2024 March; (22). DOI: 10.1016/j.lansea.2023.100294
12. Fekadu G, Tolossa T, Turi E, et al. Pretomanid development and its clinical roles in treating tuberculosis. J Glob Antimicrob Resist. 2022; 31:175-184. DOI: 10.1016/j.jgar.2022.09.001
13. Simanjuntak AM, Daenansya R, Aflandhanti PM, et al. Efficacy of pretomanid regiment for drug-resistant tuberculosis: A systematic review and meta-analysis of clinical trials. Narra J 2023; 3 (3): e402. DOI:10.52225/narra.v3i3.402

14. Viney K, Linh NN, Gegia M, et al. New definitions of pre-extensively and extensively drug-resistant tuberculosis: update from the World Health Organization. Eur Respir J 2021; 57: 2100361. DOI: 10.1183/13993003.00361-2021
15. Direktorat Jenderal Pencegahan dan Pengendalian Penyakit. Pemberitahuan Penggunaan Kartrid Xpert MTB/Rif Ultra dan Tindak Lanjut Hasil MTB Trace Detected Rif Resistance Indeterminate. Kementerian Kesehatan Republik Indonesia. 2023.
16. WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update. Geneva: World Health Organization; 2022.
17. Knapp RO, Edwards S, Kuchukhidze G, Kröger S, Häcker B, et al. Availability of drugs for the treatment of multidrugresistant/rifampicin-resistant tuberculosis in the World Health Organization European Region, October 2023. Euro Surveill. 2024;29(17):pii=2400211. DOI: https://doi.org/10.2807/1560-7917.ES.2024.29.17.2400211.
18. Kementerian Kesehatan Republik Indonesia. Buku Pegangan Operasional Pengobatan Tuberkulosis Resistan Obat dengan Panduan BPaL/M. Kementerian Kesehatan Republik Indonesia. 2023.
19. Luies L, Preez I. The echo of pulmonary tuberculosis: mechanisms of clinical symptoms and other disease - induced systemic complications. Clin Microbiol Rev. 2020; 33:e00036-20. DOI: https://doi.org/10.1128/CMR.00036-20.
20. Isbaniah F, Burhan E, Sinaga BY, Behtri D, Yanifitri, et al. Tuberkulosis: Pedoman Diagnosis dan Penatalaksanaan di Indonesia. Jakarta: Perhimpunan Dokter Paru Indonesia. Jakarta; 2021.
21. Kherabi Y, Jachym MF, Rioux C, Yazdanpanah Y, Méchaï F, et al. for the MDR-TB Management Group. Revised Definitions of Tuberculosis Resistance and Treatment Outcomes, France, 2006–2019. Emerging Infectious Diseases. Vol. 28, No. 9, September 2022. DOI:https://doi.org/10.3201/eid2809.220458.
22. Lange C, Dheda K, Chesov D, Mandalakas AM, Udwadia Z, et al. Management of drug-resistant tuberculosis. Lancet. 2019 Sep 14;394(10202):953-966. DOI: 10.1016/S0140-6736(19)31882-3.
23. Kay AW, Ness T, Verkuijl SE, Viney K, Brands A, et al. Xpert MTB/RIF Ultra assay for tuberculosis disease and rifampicin resistance in children (Review). Cochrane Database of Systematic Reviews 2022, Issue 9. Art. No.: CD013359. DOI: 10.1002/14651858.CD013359.
24. Günther G, Ruswa N, Keller PM. Drug-resistant tuberculosis: advances in diagnosis and management. Curr Opin Pulm Med. 2022 May 1;28(3):211-217. DOI:10.1097/MCP.0000000000000866.
25. Pillay S, Steingart KR, Davies GR, Chaplin M, Vos MD, et al. Xpert MTB/XDR for detection of pulmonary tuberculosis and resistance to isoniazid,

fluoroquinolones, ethionamide, and amikacin. Cochrane Database Syst Rev. 2022 May 18;5(5):CD014841.
26. Vanino E, Granozzi B, Akkerman OW, Torrico MM, Palmieri F, et al. Update of drug-resistant tuberculosis treatment guidelines: A turning point. Int J Infect Dis. 2023 May:130 Suppl 1:S12-S15. DOI: 10.1016/j.ijid.2023.03.013.
27. Holger DJ, Althubyani A, Morrisette T, Rebold N, Tailor M. Updates in pulmonary drug-resistant tuberculosis pharmacotherapy: A focus on BPaL and BPaLM. Pharmacotherapy. 2024 Mar;44(3):268-282. DOI: 10.1002/phar.2909.
28. Conradie F, Bagdasaryan TR, Borisov S, Howell P, Mikiashvili L, et al. Bedaquiline-Pretomanid-Linezolid Regimens for Drug-Resistant Tuberculosis. N Engl J Med. 2022 Sep 1;387(9):810-823. DOI: 10.1056/NEJMoa2119430.
29. Bo SY, Su AM, Yang F, Yang L. Risk factors for development of hematotoxicity in elderly patients treated with Linezolid. Zhonghua Jie He He Hu Xi Za Zhi. 2022 Jun 12;45(6):533-538. DOI: 10.3760/cma.j.cn11214720220212-00111.
30. Onita T, Ishihara N, Ikebuchi A, Yano T, Nishimura N, et al. Pharmacokinetic and pharmacodynamic simulation for the quantitative risk assessment of linezolid-associated thrombocytopenia. J Clin Pharm Ther. 2022 Dec;47(12):2041-2048. DOI: 10.1111/jcpt.13747.
31. Saluzzo F, Adepoju VA, Duarte R, Lange C, Phillips PPJ. Treatment-shortening regimens for tuberculosis: updates and future priorities. Breathe 2023; 19: 230028. DOI: https://doi.org/10.1183/20734735.0028-2023.
32. Pietersen E, Anderson K, Cox H, Dheda K, Bian A, et al. Variation in missed doses and reasons for discontinuation of anti-tuberculosis drugs during hospital treatment for drug-resistant tuberculosis in South Africa. PLoS ONE 18(2): e0281097. DOI:https://doi.org/10.1371/journal.pone.0281097.
33. Mirzayev F, Viney K, Linh NN, Angulo LG, Gegia M, et al. World Health Organization recommendations on the treatment of drug-resistant tuberculosis, 2020 update. Eur Respir J 2021; 57: 2003300. DOI:https://doi.org/10.1183/13993003.03300-2020.
34. Kementerian Kesehatan Republik Indonesia. Petunjuk Teknis Penatalaksanaan Tuberkulosis Resisten Obat di Indonesia. Kementerian Kesehatan RI. Jakarta. 2020.
35. Maier C, Chesov D, Schaub D, Kalsdorf B, Andres S, et al. Long-term treatment outcomes in patients with multidrug-resistant tuberculosis. Clin Microbiol Infect. 2023 Jun;29(6):751-757. DOI: 10.1016/j.cmi.2023.02.013.