The Profile of Multidrug Tuberculosis Regimen and Treatment Outcomes in Pulmonary MDR-TB Patients at the Tertiary Referral Hospital Dr. Soetomo, East Java, Indonesia: A Seven-Year Retrospective Study on Bedaquiline

Muhamad Frendy Setyawan[1], Ni Made Mertaniasih[2,4,5], Soedarsono[3,4,5]*

[1] Doctoral Program of Medical Science, Faculty of Medicine Universitas Airlangga, Surabaya, Indonesia.
[2] Department of Medical Microbiology, Faculty of Medicine Universitas Airlangga, Surabaya, Indonesia.
[3] Divison of Pulmonology, Department of Internal Medicine, Faculty of Medicine Hang Tuah University, Surabaya, Indonesia.
[4] Dr. Soetomo Hospital, Surabaya, Indonesia.
[5] Tuberculosis Laboratory, Institute of Tropical Disease, Universitas Airlangga, Surabaya, Indonesia.

Corresponding Author:
Prof. Ni Made Mertaniasih, MD., PhD. Department of Medical Microbiology, Faculty of Medicine Universitas Airlangga. Jl. Mayjen. Prof. Dr. Moestopo No. 47, Surabaya 60131, Indonesia. Email: ni-made-m@fk.unair.ac.id.

ABSTRACT

Background: *The use of bedaquiline has been reported to minimize the number of lost to follow-up and fewer rejections from the patients. This study is the first to depict the use of bedaquiline. It aims to provide information related to the profile of the MDR-TB drug regimen in the last 7 years with the treatment outcomes of pulmonary MDR-TB patients at a tertiary referral hospital in East Java.* ***Methods:*** *This study was a retrospective, descriptive, and data analysis on 1053 pulmonary MDR-TB patients in tertiary referral hospital Dr Soetomo, East Java, Indonesia, with the SPSS software version 25 and Microsoft Excel 2021.* ***Results:*** *The study analyzed the MDR-TB treatment regimen following the latest guidelines from WHO (2020) at a tertiary referral hospital in East Java. This study shows that a bedaquiline-containing regimen started in January 2015 to July 2022 with the percentage of distribution (1, 3, 11, 4, 18, 13, 29, 21)% consecutively in the regimen. The treatment outcome profile of MDR-TB patients shows the average percentage of cured (15%), died (12%), lost-to-follow-up cases (27%), moved to an individualized regimen or a different health facility (42%), and currently in the evaluation stage (4%). Overall from January 2017 to July 2022, the number of LTFU cases decreased (42, 46, 29, 19, 8, 4)%. However, the cured case fluctuated between 2017-2022 (16, 28, 26, 32)% respectively after Bdq started to be included in the regimen regularly for treating RR/MDR-TB.* ***Conclusion:*** *After seven years of study, we revealed an association between adding bedaquiline to the regimen and the treatment success and decreasing lost-to-follow-up cases.*

Keywords: *MDR-TB treatment regimen, bedaquiline, pulmonary TB, treatment outcomes.*

INTRODUCTION

The WHO consolidated guidelines on drug-resistant (DR) and multi-drug-resistant (MDR) TB treatment in 2020 and recommended two categories of treatment. The shorter and the longer treatment (individualized) consists of a combination of three groups of medicines. The use of Bedaquiline (Bdq) in the MDR-TB drug regimen started in 2015 in Indonesia also in Dr Soetomo Hospital as a tertiary referral hospital, after being recommended by WHO. All MDR-TB drug regimens are used with patient consent.

The treatment dose is adjusted to the guidelines from the WHO in 2020 based on the patient's body weight.[1–6] Despite the availability of treatment guidelines from WHO, it has never been reported the data regarding a combination of drugs in the patient's regimen.[3,7–9] This study is important to provide actual data on drugs prescribed in the regimen and the very first to show the use of Bdq in 7 years of study. This study shows more data on the clinical use of Bdq and patients' outcomes to descriptively evaluate the safety and effectiveness of the drug in MDR-TB patients. The study also shows that Bdq could be safely given to patients with a disease comorbid.

Bedaquiline has been known to cause a prolonged QT interval in previous reports, however, the composition of the regimen and the metabolic differences could also determine the occurrence of this Adverse event in MDR-TB patients. In other studies, it is reported if Bdq is safe to be administered in MDR-TB patients with HIV comorbid.[10,11] Bedaquiline-containing regimens help to decrease the treatment period, faster culture conversion rate, and reduce mortality among HIV/AIDS patients infected with MDR-TB. The major adverse events have been reported in previous studies and thus create alarm of fear in the increase of loss to follow-up (LTFU) cases, this article has a clinical significance in reporting the update on the association between receiving a bedaquiline regimen with treatment success and LTFU case and the AE events in MDR-TB patients. Moreover, the inappropriate composition of the drug regimen will subsequently affect a patient's treatment outcome. Patients with a history of treatment or relapse and new drug-resistant TB patients are receiving bedaquiline-containing regimens.

The use of Bdq has been reported to minimize the number of lost to follow-up patients and less rejection from the patients, lower risk of resistance, faster bacterial culture conversion, and fewer side effects.[12,13] It is important to measure the level of efficacy of the updated regimen, especially in Dr Soetomo, the tertiary referral hospital in East Java, a leading medical center for treating drug-resistant tuberculosis. Medical reports such as patient cured, dead, and lost to follow-up status are important in monitoring regimen composition efficacy.

METHODS

This study is an observational retrospective. This study used data sources for MDR-TB treatment regimens at a tertiary referral hospital, Dr Soetomo, East Java, Indonesia. Data were collected from January 2015 to July 2022, and a number of 1053 MDR-TB patients' data were analyzed. The data was obtained from the medical record. This research has undergone ethical approval with certificate No. 0456/KEPK/VIII/2022 from the Ethical Committee of Dr Soetomo Hospital.

Data Processing and Analysis

Analysis was performed using SPSS software version 25 and Microsoft Excel 2021. The study is descriptive quantitative by analyzing patient demographics in the form of frequency and percentage of variables. Any incomplete data is removed from the analysis. Furthermore, the data is represented in Figures and Tables.

RESULTS

Demographic Characteristics

This research aimed to study the MDR-TB treatment regimen profile and the administration of Bedaquiline in the WHO-recommended treatment regimen in a tertiary referral hospital in East Java, Indonesia. A total of 1053 data of pulmonary MDR-TB adult patients were evaluated, and it was observed that men dominated multidrug-resistant pulmonary TB patients. From 2015 to 2022, the number of new and relapsed MDR-TB patients fluctuated, with 2017 recording the highest number of cases. The MDR polyclinic began categorizing new and relapsed pulmonary TB patients in 2018, with the most relapsed patients in 2019. The incidence of relapse was observed to be higher in women. From 2015 to 2020, the number of MDR-TB patients grew as new cases rose. The most significant recurrence prevalence was recorded in the group weighing 33-50 Kg. **Table 1** shows the data on the MDR-TB patient's characteristics registered between 2015 and 2022.

Table 1. Characteristics of a total of 1053 Patients with MDR-TB in the tertiary referral Hospital Dr Soetomo, East Java, Indonesia, January 2015 to July 2022

Characteristics	Number	Frequency (%)
Sex		
Male	608	57.7
Female	445	42.3
Age (years)		
≤ 50	628	59.6
≥ 50	425	40.4
Body weight		
<33 Kg	41	3.9
33-50 Kg	529	50.2
>50 – 70 Kg	382	36.3
>70 Kg	53	5.0
NR	48	4.6
Case		
Relapse	368	34.9
New	684	65.0
NR	1	0.1
Type of regimens		
Shorter	641	60.9
Individualized	409	38.8
NR	3	0.3
Comorbid		
Extrapulmonary and others	12	11.9
Chronic Renal Disease	2	2.0
HIV	5	5.0
Type II DM	82	81.2

Clinical Characteristics

The analysis of comorbid from the pulmonary MDR-TB patients acquired data on up to 101 patients with type II DM higher among other types including HIV, renal diseases, extrapulmonary, and others. Based on a statistical evaluation of the profile of the treatment regimen offered to patients from 2015 to July 2022, it was revealed that 15 different anti-TB drugs for MDR-TB patients were utilized and available at the East Java tertiary referral hospital, as shown in **Figure 1** shows an increase in the use of bedaquiline containing regimen was started to be regularly added to the regimen in 2017-2022. Based on the 2020 WHO recommendation, which proposes a treatment combination for MDR-TB that does not comprise Km and Cm, such medications will no longer be prescribed to MDR-TB patients beginning in 2021.[14–16] Patients with comorbid such as chronic renal disease, HIV, and diabetes type II were treated with Bdq-containing regimens.

Profile of Drug Regimen in Multidrug Tuberculosis Patients

The latest WHO recommendations in 2020 stated kanamycin and capreomycin are no longer included in long-term or individualized regimens. There has been a change in the shorter drug regimen guidelines from the 2016 WHO

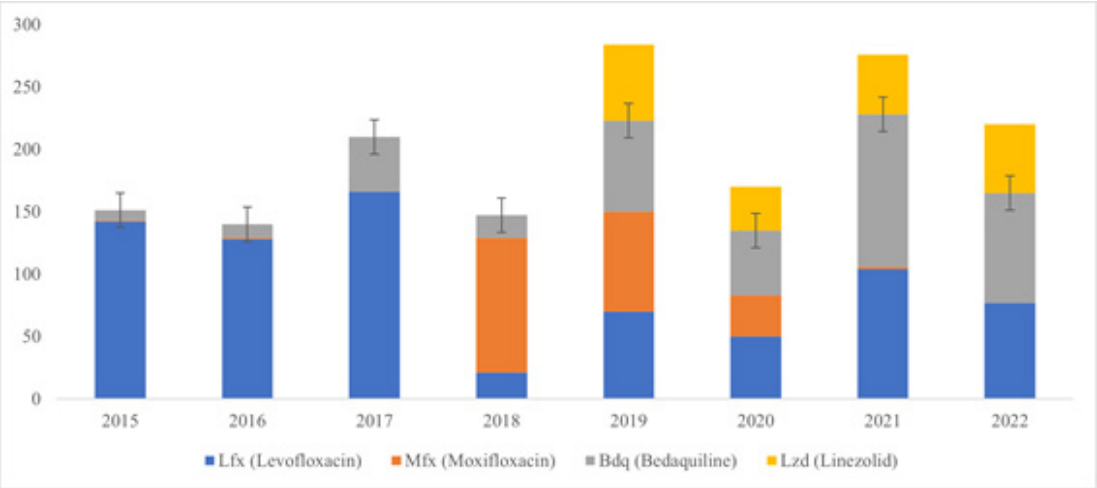

Figure 1. The profile of main Group A anti-TB drugs prescribed to pulmonary MDR-TB patients in the tertiary referral hospital Dr. Soetomo from January 2017- July 2022.

guideline.[3,14,17] The shorter regimen is given in two stages, namely the initial stage and the advanced stage, with high doses of isoniazid, the duration of the initial stage ranging from 4-6 months, and a follow-up stage of 5 months. Analysis of the type of treatment regimen in **Table 2** shows that standardized shorter treatment regimens have a greater frequency of being given to patients. However, if conditions such as drug allergies and side effects cannot be tolerated, then treatment is continued with a long-term regimen, individualized with a duration of 18-20 months, with the length of therapy after conversion being 15 months.[18,19] The previously reported outcomes of treatment with a Bdq-containing regimen in MDR-TB patients across nations are summarized in **Table 3**.

Profile of Multidrug-Resistant Tuberculosis Treatment Outcomes

The treatment outcome profile of MDR-TB patients can be seen in **Figure 2** categorized into cured, died, Lost To Follow-up (LTFU), moved to an individualized regimen or a different health facility, and currently in the evaluation stage. Newly enrolled patients in this study were categorized in the evaluation stage of administering a regimen tailored to the patient's condition. The number of patients who recovered and died both fluctuated, before Bedaquiline was used, the number of patients who died increased from 2015-2020, and after Bedaquiline was endorsed by WHO, it seems patients who died decreased in 2021-2022, and the lowest occurred in 2022 after Bedaquiline started to be prescribed regularly to treat RR/MDR-TB cases.

Table 2. Profile of drugs administered in patients with MDR-TB.

Regimen	Drugs name	Number (%)	
		Short/Standardized Regimen (n=641)	Individualized Regimen (n=410)
Category A	Levofloxacin (Lfx)	562 (86)	197 (48)
	Moxifloxacin (Mfx)	52 (8)	173 (42)
	Bedaquiline (Bdq)	191 (30)	225 (55)
	Linezolid (Lzd)	74 (12)	125 (30)
Category B	Clofazimine (Cfz)	217 (34)	367 (90)
	Cycloserine (Cs)	526 (82)	93 (23)
	Terizidone (Trd)	-	-
Category C	Ethambutol (E)	567 (88)	287 (70)
	Delamanid (Dlm)	5 (1)	12 (3)
	Pyrazinamide (Z)	560 (87)	314 (77)
	Imipenem-cilastatin (Ipm-Cln)	-	-
	Meropenem (Mpm)	-	-
	Amikacin (Am)	-	-
	Streptomycin (S)	-	-
	Ethionamide (Eto)	552 (86)	256 (62)
	Prothionamide (Pto)	-	-
	p-aminosalicylic acid (PAS)	37 (6)	-
Other drugs in the WHO-endorsed regimen (2020-2022)	High dose Isoniazid (H)	124 (19)	237 (58)
	Kanamycin (Km)	263 (41)	99 (24)
	Capreomycin (Cm)	245 (38)	21 (3)

Table 3. Previous studies on the clinical significance of Bedaquiline-containing regimen in the treatment of MDR-TB.

Study Location	Study period	Total number of patients	Regimen	Treatment duration	Outcome	Clinical significance	Reference
South Africa	2015-2017	5981 MDR-TB	A bedaquiline-containing or non-bedaquiline-containing regimen	< 6 months	Success rate - Bedaquiline-treated patients (66.9%) - Non-bedaquiline-treated patients (49.4%) Death rate - Bedaquiline treated patient (15.4%) - Non-bedaquiline treated patient (25.6%)	Bedaquiline-containing regimen was associated with higher survival and effectiveness benefit. Few patients reported bedaquiline-related adverse events (1.8%), and discontinuations (1.4%); QTcF prolongation >500 ms (2.5%) was observed during treatment.	(20)
East China	2016-2020	Patients with refractory RR/MDR/XDR-TB; Total of 202 patients; BDQ group, n = 102) and BDQ-free regimens (non-BDQ group, n = 100).	A bedaquiline-containing or non-bedaquiline-containing regimen.	18-20 months.	Culture conversion rates in the BDQ group at month 3, month 6, month 9, and month 12 (94.1% vs 65.0%) were all significantly higher than those in a non-BDQ group ($p < 0.001$).	- BDQ-containing regimen has a better clinical outcome and similar safety compared to the regular non-bedaquiline-treated patients - Adverse Effects (AEs) were similarly reported in 26.5% of patients in the BDQ group and 19.0% in the non-BDQ group ($p = 0.2$).	(21)
India	2019-2021	A total of 165 patients with pre-XDR-TB; 158 had MDR-TBFQ+.	Bedaquiline, Delamanid, Linezolid, and Clofazimine	6-9 months	139 (91%) patients had a successful treatment; 14 (9%) patients had unfavorable outcomes: 4 deaths, 7 treatment changes, 2 bacteriological failures, and 1 withdrawal.	Bedaquiline-containing regimen has a minimum cardiotoxicity and myelosuppression.	(22)

Table 3. Previous studies on the clinical significance of Bedaquiline-containing regimen in the treatment of MDR-TB.

Study Location	Study period	Total number of patients	Regimen	Treatment duration	Outcome	Clinical significance	Reference
Multicenter (16 countries)	2015-2018	A total of 2296 patients of MDR-TB.	Regimens Containing Bedaquiline and	16.5 months	Treatment success was not reported	- Clinically relevant QT interval prolongation was reported in a small proportion of patients (3%) 2.6 times per 1000 patient-months of bedaquiline, even when 96% of them received at least 1 QT-prolonging anti-TB drug (Mfx, Lfx, or Cfz).	(23)
			Delamanid; injectable; linezolid.			- Arrhythmia possibly related to QT prolongation is a potential cause in the Bedaquiline-containing regimen group.	
South Korea	2014-2020	Of 1998 patients; 315 (15.8%) and 292 (14.6%) received bedaquiline and delamanid respectively.	Regimens containing bedaquiline and regimens containing delamanid.	Approx. 24 months	Bedaquiline and delamanid did not increase the risk of all-cause death at 24 months (HR 0.73 and 0.89).	Bedaquiline-containing regimen increased the risk of acute liver injury (1.76[Ci:1.31-2.36]).	(24)
						Safety concerns associated with hepatic-related AEs for bedaquiline received little attention.	

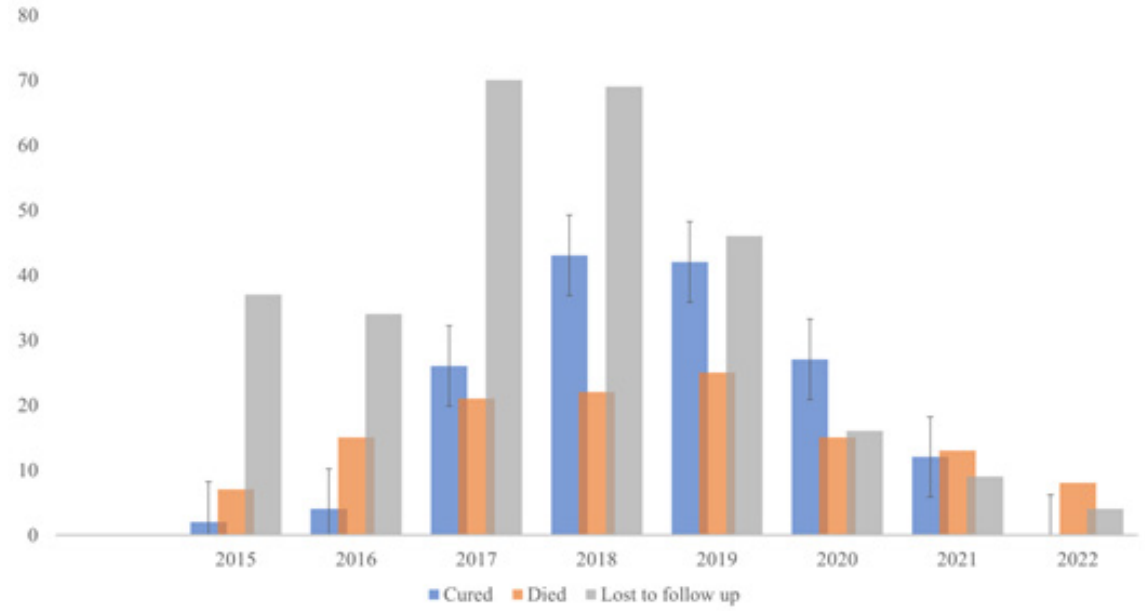

Figure 2. Distribution of the treatment outcomes of pulmonary MDR-TB patients in the tertiary referral hospital Dr Soetomo from January 2015 to July 2022.

DISCUSSION

In this study, the use of bedaquiline increases the chance of a cure and reduces the risk of death in MDR-TB patients.[7,25–27] The use of Bdq takes 12 months and requires evaluation; hence individuals who have side effects should be re-evaluated.[18,28] The statistical use of Bedaquiline in shorter and long-term regimens supports therapeutic success in treating MDR-TB, Bedaquiline combined with other drugs has the potential to significantly increase therapeutic efficacy, especially with Levofloxacin, Clofazimine, and Linezolid. No significant drug interaction was found between Bedaquiline and Moxifloxacin. The use of Moxifloxacin has reduced significantly in 2021 at hospitals, thus can be due to distribution issues, and the efficacy of the drugs based on clinical evaluation such as higher rejection and more side effects.[29] In the study, we found a small number of patients who reported a prolonged QT interval and some patients reported minor AEs such as skin itchy, and numbness have been reported but did not discontinue the treatment. Patients with a history of treatment or relapse and new DR-TB patients received a Bdq-containing regimen. Previously relapse patients received non-Bdq-containing regimens which reported to have many side effects and a higher risk of resulting in LTFU cases.

The clinical outcomes of pulmonary MDR-TB patients are lower in the lost-to-follow-up cases; the inclusion of Bedaquiline in the regimen seems an increase the number of cured and decrease the number of patients who died and lost to follow-up. In 2019, a similar study was performed by Borisov using the same research design in Italy, the data collected between January 2007 and March 2015 found that Bdq in surgery cases can be safely and effectively combined with appropriate drugs and result in a higher percentage of treatment success, and only a few had unfavorable outcomes including LTFU cases with fewer side effects such as complication.[30] Another study conducted by Korala in 2015 worldwide, unfortunately, Indonesia is not one of them, discovered a great potency of Bedaquiline-containing regimen for treating MDR-TB cases showed by higher percentage (75%) of treatment success and a lower chance of treatment failure (25%).[31] From our study, however, we revealed additional information based on our findings showed more patients are in either individually based regimens or moved to other health care facilities due to mild syndrome, and demographic reasons are higher than in previous years when Bdq is not yet started in the regimen. This report

is supported by evidence of the potential of Bdq as a therapeutic agent in MDR-TB patients has been widely reported to have faster culture conversion times, less toxicity, high efficacy and cure rates, and low mortality rates. Bdq kills active and dormant bacteria by binding to ATPase and blocking the energy production of bacteria, the affinity of this drug is 20.000 times more in Mycobacteria than in humans became the main reason for the safety and specificity of the drug's pharmacokinetics.[30–33] Bdq is given in a dose of 400 mg during the initial 1-2 weeks, followed by lower 200 mg doses in weeks 3-24. In the clinical setting, it has a steady killing activity after 7 days with a steady-state plasm concentration of 600 ng/mL. Furthermore, Bedaquiline can penetrate the alveoli tissue in mild-severe cases of MDR-TB. However, Bedaquiline has also been reported to cause prolonged QT intervals to >500 ms.[30,32]

The action of Bdq affects several pathophysiologies of patients including oxidative metabolism through the CYP3A4 pathway, with the formation of N-mono-desmethyl metabolite (M2), and the use of this drug should not be co-administered with the CYP3A4 inducer such as Rifampicin which could cause liver toxicity. The regimen for MDR-TB is made from the combination of groups A, B, and C of drug categories within WHO consolidated guidelines, without the use of rifampicin. Co-administration with Rifampicin decreased the effectiveness of Bdq, therefore, these two drugs should not be prescribed together.[32] However previous study reported that Bdq is safe to use in patients with diabetes mellitus, HIV, renal complications, and extra-pulmonary TB with strict evaluation from clinicians. This study finds no adverse effects in the patients such as previously reported peripheral neuropathy, hyperuricemia, nausea, arthralgia, liver injury, and prolonged QT. However, this study reveals the treatment also depends on the host metabolism capability to compensate for the action of Bdq. Some patients have mild reactions that do not lead to discontinuance. Treatment regimens including Linezolid, Clofazimine, and Moxifloxacin have also been reported to help the compensation mechanism of these drugs to achieve fewer side effects and faster culture conversion.[34–37] Further study needs to evaluate the efficacy and safety of Bedaquiline when combined with Pretonamid, Linezolid, and Delamanid in the treatment of DR-TB.

The clinical benefit from this research is showing evidence based on the treatment outcomes from different regiments to treat drug-resistant tuberculosis which includes the efficacy of Bedaquiline-containing regimen yields in all-oral, better treatment success rate, fewer rejections, LTFU cases, and lower risk of resistance when combined with appropriate drugs. This research is the first to investigate the profile of a drug-resistant treatment regimen and the efficacy of the Bedaquiline-containing regimen after seven years of use, hence giving a new perspective in a clinical care setting. Furthermore, in a clinical care setting other factors might contribute to the patient's treatment outcomes such as nutrition and immunity, demographic characteristics, diagnosis, drugs and logistics, patient support, integrated record system, management system, also financial support.[38] Patients with comorbid have been reported to be safely treated with a Bdq-containing regimen and have a similar success rate with those with no comorbids. The use of a Bdq-containing regimen seems to have no antagonist action against the antiretroviral treatment and blood glucose-lowering drugs for diabetes.

Finally, from this study, we believe that future multicentre studies need to be performed to broadly define the efficacy of Bedaquiline in MDR-TB drug regimen for MDR-TB patients and advance discovering more effective, fewer drug compositions and side effects, and also a faster conversion rate treatment including Bedaquiline-containing regimen.

CONCLUSION

Our study revealed a relation between adding Bedaquiline to the regimen and the decrease in lost-to-follow-up cases. Although the treatment success of the patient fluctuated, the drug Bedaquiline has a positive response to patient health improvement, fewer rejections due to tolerable side effects, fewer cases of resistance, and a faster smear and bacterial culture conversion after seven years of evaluation.

REFERENCES

1. Oliveira O, Gaio R, Correia-Neves M, Rito T, Duarte R. Evaluation of drug-resistant tuberculosis treatment outcome in Portugal, 2000–2016. PLoS One. 2021;16(4 April).
2. Khan I, Ahmad N, Khan S, et al. Evaluation of treatment outcomes and factors associated with unsuccessful outcomes in multidrug resistant tuberculosis patients in Baluchistan province of Pakistan. J Infect Public Health. 2019;12(6):809–15.
3. Secretary of Jan Swasthya Sahyog, Laux TS, Patil S. Predictors of tuberculosis treatment outcomes among a retrospective cohort in rural, Central India. J Clin Tuberc Other Mycobact Dis. 2018;12:41–7.
4. El-Shabrawy M, El-Shafei DA. Evaluation of treatment failure outcome and its predictors among pulmonary tuberculosis patients in Sharkia Governorate, 2013–2014. Egyptian Journal of Chest Diseases and Tuberculosis. 2017;66(1):145–52.
5. Guglielmetti L, Hewison C, Avaliani Z, et al. Examples of bedaquiline introduction for the management of multidrug-resistant tuberculosis in five countries. International Journal of Tuberculosis and Lung Disease. 2017;21(2):167–74.
6. Hatami H, Sotgiu G, Bostanghadiri N, et al. Bedaquiline-containing regimens and multidrug-resistant tuberculosis: a systematic review and meta-analysis. J Bras Pneumol. 2022;48(2):e20210384.
7. Gao JT, Shu W, Zhang LJ, et al. Prolonged use of bedaquiline in two patients with pulmonary extensively drug-resistant tuberculosis: Two case reports. World J Clin Cases. 2021;9(10):2326–33.
8. Gao M, Gao J, Xie L, et al. Early outcome and safety of bedaquiline-containing regimens for treatment of MDR- and XDR-TB in China: a multicentre study. Clinical Microbiology and Infection. 2021;27(4):597–602.
9. Nahid P, Mase SR, Migliori GB, et al. Treatment of drug-resistant tuberculosis an official ATS/CDC/ERS/IDSA clinical practice guideline. Am J Respir Crit Care Med. 2019;200(10):E93–142.
10. O MR, Padayatchi N, Wolf A, et al. Bedaquiline Adherence Measured by Electronic Dose Monitoring Predicts Clinical Outcomes in the Treatment of Patients With Multidrug-Resistant Tuberculosis and HIV/ AIDS [Internet]. Vol. 90, J Acquir Immune Defic Syndr. 2022. Available from: www.jaids.com|325
11. Koirala S, Borisov S, Danila E, et al. Outcome of treatment of MDR-TB or drug-resistant patients treated with bedaquiline and delamanid: Results from a large global cohort. Pulmonology. 2021;27(5):403–12.
12. Fekadu G, Yao J, You JHS. Bedaquiline-based treatment for extensively drug-resistant tuberculosis in South Africa: A cost-effectiveness analysis. PLoS One. 2022;17(8 August).
13. Khoshnood S, Goudarzi M, Taki E, et al. Bedaquiline: Current status and future perspectives. Journal of Global Antimicrobial Resistance. Elsevier Ltd; 2021;25:48–59.
14. Mirzayev F, Viney K, Linh NN, et al. World health organization recommendations on the treatment of drug-resistant tuberculosis, 2020 update. European Respiratory Journal. 2021;57.
15. Putra ON, Damayanti A, Wijayanti N, Nurrahman D, Devi T, Aluf W. Evaluation of category I of anti-tuberculosis therapy in intensive phase pulmonary TB by conversion of acid-fast Bacilli sputum. Original Article Pharmaceutical Sciences and Research (PSR). 2019;6(3):183–8.
16. Pontali E, Raviglione MC, Migliori GB, et al. Regimens to treat multidrug-resistant tuberculosis: Past, present and future perspectives. European Respiratory Review. 2019;28.
17. WHO. Rapid communication: Key changes to the treatment of drug-resistant tuberculosis [Internet]. 2022. Available from: https://www.who.int/about/licensing.
18. Indarti HT, Kristin E, Soedarsono S, Endarti D. Treatment outcomes of multidrug-resistant Tuberculosis patients in East Java, Indonesia: A retrospective cohort analysis. Int J Mycobacteriol. 2022;11(3):261–7.
19. Giri VP, Giri OP, Pandey PT, et al. The Characteristics and patterns of Drug-Resistant Pulmonary Tuberculosis in Eastern India. Trop Med Infect Dis. 2022;7(9).
20. Pai H, Ndjeka N, Mbuagbaw L, et al. Bedaquiline safety, efficacy, utilization and emergence of resistance following treatment of multidrug-resistant tuberculosis patients in South Africa: a retrospective cohort analysis. BMC Infect Dis. 2022;22(1).
21. Zhang SJ, Yang Y, Sun WW, et al. Effectiveness and safety of bedaquiline-containing regimens for treatment on patients with refractory RR/MDR/XDR-tuberculosis: a retrospective cohort study in East China. BMC Infect Dis. 2022;22(1).
22. Padmapriyadarsini C, Vohra V, Bhatnagar A, et al. Bedaquiline, Delamanid, Linezolid, and Clofazimine for treatment of pre-extensively drug-resistant Tuberculosis. Clinical Infectious Diseases. 2023;76(3):E938–46.
23. Hewison C, Khan U, Bastard M, et al. Safety of treatment regimens containing Bedaquiline and Delamanid in the end TB cohort. Clinical Infectious Diseases. 2022;75(6):1006–13.
24. Kim JH, Lee H, Oh IS, et al. Comparative safety of bedaquiline and delamanid in patients with multidrug resistant tuberculosis: A nationwide retrospective cohort study. Journal of Microbiology, Immunology and Infection. 2023;56(4):842–52.
25. Zhang SJ, Yang Y, Sun WW, et al. Effectiveness and safety of bedaquiline-containing regimens for treatment on patients with refractory RR/MDR/XDR-tuberculosis: a retrospective cohort study in East China. BMC Infect Dis. 2022;22(1).

26. Traoré AN, Rikhotso MC, Banda NT, et al. Effectiveness of the novel anti-TB Bedaquiline against drug-resistant TB in Africa: A systematic review of the literature. Pathogens. MDP. 2022;11.
27. Fu L, Weng T, Sun F, et al. Insignificant difference in culture conversion between bedaquiline-containing and bedaquiline-free all-oral short regimens for multidrug-resistant tuberculosis. International Journal of Infectious Diseases. 2021;111:138–47.
28. World Health Organization. WHO consolidated guidelines on tuberculosis. Module 4, Treatment: drug-resistant tuberculosis treatment. [Internet]. 2020 [cited 2022 Oct 22]. 98 p. Available from: https://apps.who.int/iris/rest/bitstreams/1280998/retrieve
29. Nunn AJ, Rusen ID, van Deun A, et al. Evaluation of a standardized treatment regimen of anti-tuberculosis drugs for patients with multi-drug-resistant tuberculosis (STREAM): Study protocol for a randomized controlled trial. Trials. 2014;15(1).
30. Borisov SE, D'Ambrosio L, Centis R, et al. Outcomes of patients with drug-resistant-tuberculosis treated with bedaquiline-containing regimens and undergoing adjunctive surgery. Journal of Infection. 2019;78(1):35–9.
31. Koirala S, Borisov S, Danila E, et al. Outcome of treatment of MDR-TB or drug-resistant patients treated with bedaquiline and delamanid: Results from a large global cohort. Pulmonology. 2021;27(5):403–12.
32. Deshkar AT, Shirure PA. Bedaquiline: A novel diarylquinoline for multidrug-resistant pulmonary Tuberculosis. Cureus. 2022.
33. Belachew T, Yaheya S, Tilahun N, et al. Multidrug-resistant Tuberculosis treatment outcome and associated factors at the University of Gondar comprehensive specialized hospital: A ten-year retrospective study. Infect Drug Resist. 2022;15:2891–9.
34. Borisov SE, Dheda K, Enwerem M, et al. Effectiveness and safety of bedaquilinecontaining regimens in the treatment of MDR- and XDR-TB: A multicentre study. European Respiratory Journal. 2017;49(5).
35. Wang MG, Wu SQ, He JQ. Efficacy of bedaquiline in the treatment of drug-resistant tuberculosis: a systematic review and meta-analysis. BMC Infect Dis. 2021;21(1).
36. Mase S, Chorba T, Parks S, et al. Bedaquiline for the treatment of multidrug-resistant tuberculosis in the United States. Clinical Infectious Diseases. 2020;71(4):1010–6.
37. Lee T, Lee SJ, Jeon D, et al. Additional drug resistance in patients with multidrug-resistant Tuberculosis in Korea: a multicenter study from 2010 to 2019. J Korean Med Sci. 2021;36(26):1–11.
38. Ministry of Health and Family Welfare India. Guideline for programmatic multidrug resistant TB in India 2021. Ministry of Health and Family Welfare India [Internet]. 2021 [cited 2022 Dec 16]; Available from: https://tbcindia.gov.in/showfile.php?lid=3590