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Efektivitas Terapi dan Kejadian Tidak Dikehendaki Penggunaan Regimen Pengobatan Jangka Pendek pada *MultiDrug-Resistant Tuberculosis: a Scoping Review*

Effectivity Therapy and Adverse Drug Reaction of Short-Regimens for Multidrug-Resistant Tuberculosis: a Scoping Review

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ABSTRAK

Peningkatan kasus Multidrug-Resistant Tuberculosis (TB-MDR) di dunia menjadi masalah mendesak. Durasi terapi, kejadian tidak dikehendaki (KTD), biaya dapat memengaruhi kepatuhan dan keberhasilan pengobatan. Literatur review ini mengulas efektivitas terapi dan KTD pengobatan jangka pendek pada pasien TB-MDR. Dari 13 artikel yang dianalisis, regimen all-oral menjanjikan untuk diimplementasikan. Berdasarkan konversi sputum, angka kesembuhan, dan persentase pasien yang menyelesaikan pengobatan, regimen dengan efektivitas terapi tertinggi adalah 6KmMfxPtoCfzHEZ/5MfxCfzEZ sebesar 92,9%, dan terendah 4KmMfxPtoCfzHEZ/5MfxCfzEZ sebesar 63,6%. Regimen all oral dengan atau tanpa Bedaquilin menunjukkan rata-rata efektivitas terapi yang lebih baik (87.04%) daripada regimen yang mengandung injeksi (78.43%). KTD berat yang muncul adalah meninggal, kardiotoksisitas, hepatotoksisitas, dan ototoksisitas. Pemantauan keamanan regimen diperlukan, dan penelitian perlu diperluas untuk menemukan regimen baru yang lebih efektif terhadap bakteri Mycobacterium tuberculosis yang resisten.

Keywords:

Multidrug-resistant tuberculosis
Short regimens
effectiveness
safety

ABSTRACT

The escalating cases of Multidrug-Resistant Tuberculosis (TB-MDR) worldwide pose an urgent challenge. Treatment duration, adverse events (AEs), and costs can impact treatment adherence and success. This literature review aims to assess the effectiveness of short-course therapies and AEs in short-term treatments for TB-MDR patients. The review encompasses articles retrieved from PubMed, ScienceDirect, and Google Scholar, specifically focusing on English-language research articles published between 2018 and 2022. The search keywords included "multi-drug resistant tuberculosis," "short regimens," or "short-term regimens," "effectiveness," "safety," or "adverse events." Among the 13 articles obtained, all-oral regimens prove promising for implementation in TB-MDR treatment. Based on sputum conversion, cure rates, and the percentage of patients completing treatment, the regimen with the highest therapeutic effectiveness is 6KmMfxPtoCfzHEZ/5MfxCfzEZ at 92.9%, while the lowest is 4KmMfxPtoCfzHEZ/5MfxCfzEZ at 63.6%. All-oral regimens, with or without Bedaquiline, exhibit a higher average therapeutic effectiveness (87.04%) compared to injection-containing regimens (78.43%). Noteworthy severe AEs include mortality, cardiotoxicity, hepatotoxicity, and ototoxicity. Monitoring the safety of regimens is crucial, and further research is needed on larger populations and broader study sites to discover more effective regimens against easily resistant Mycobacterium tuberculosis.

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1. INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by a TB germ called Mycobacterium tuberculosis. TB mostly attacks the lungs but can also affect other body organs. Almost all patients (approximately 90%) who suffer from tuberculosis are adults, with male patients dominating the cases [1]. Some patients develop bacterial infections that are resistant to at least isoniazid and rifampicin, the two most effective TB drugs, known as multidrug-resistant tuberculosis (MDR-TB) [2].

According to data from the WHO Global Tuberculosis Report 2022, the number of MDR-TB patients in the world in 2021 was estimated to increase by 3.1%, from 437,000 people in 2020 to around 450,000 people [3]. The Ministry of Health of the Republic of Indonesia recorded an estimate of 8,268 MDR-TB cases in Indonesia in 2021, with only around 61% beginning the treatment and 46% completing it [4]. In addition, the treatment of MDR-TB in Indonesia has not achieved satisfactory results since the death rate and dropout from treatment remain high while the cost of treatment is still borne by the government [5]. MDR-TB is a public health crisis and a threat to health security. The threat of death from untreated TB is high, reaching approximately 50%. TB becomes the main cause of infection-related deaths and ranks 13th as a cause of death worldwide. The estimate of MDR-TB is around 2.4% of all new TB patients and about 13% of previously treated TB patients [1], [5].

The MDR-TB treatment strategy is employed after a patient is confirmed to have Rifampicin-resistant TB (RR-TB)/MDR based on a molecular examination. In accordance with the 2018 WHO recommendations, the treatment of MDR-TB in Indonesia is administered with all-oral regimens without injections, namely a short-term treatment regimen (9-11 months), consisting of an initial phase with 7 types of drugs for 4-6 months and a continuation phase with 4 types of drugs for 5 months (4-6BdqLfxEtoCfzHEZ/5LfxCfzEZ), and a long-term regimen with modified (individualized) drugs for 18-20 months [5]. Such long duration of treatment has an impact on the emergence of adverse events that influence patient adherence and reduce the success of therapy. A study found that the most frequent incidence of adverse drug reactions from MDR-TB drugs was nausea and vomiting (77.8%) as well as depression (55.6%), which was associated with drug withdrawal [6]. However, evaluation of the therapeutic effectiveness and adverse events of MDR-TB treatment in Indonesia remains limited, especially regarding the use of short-term regimens which has started to be implemented in Indonesia only since 2020.

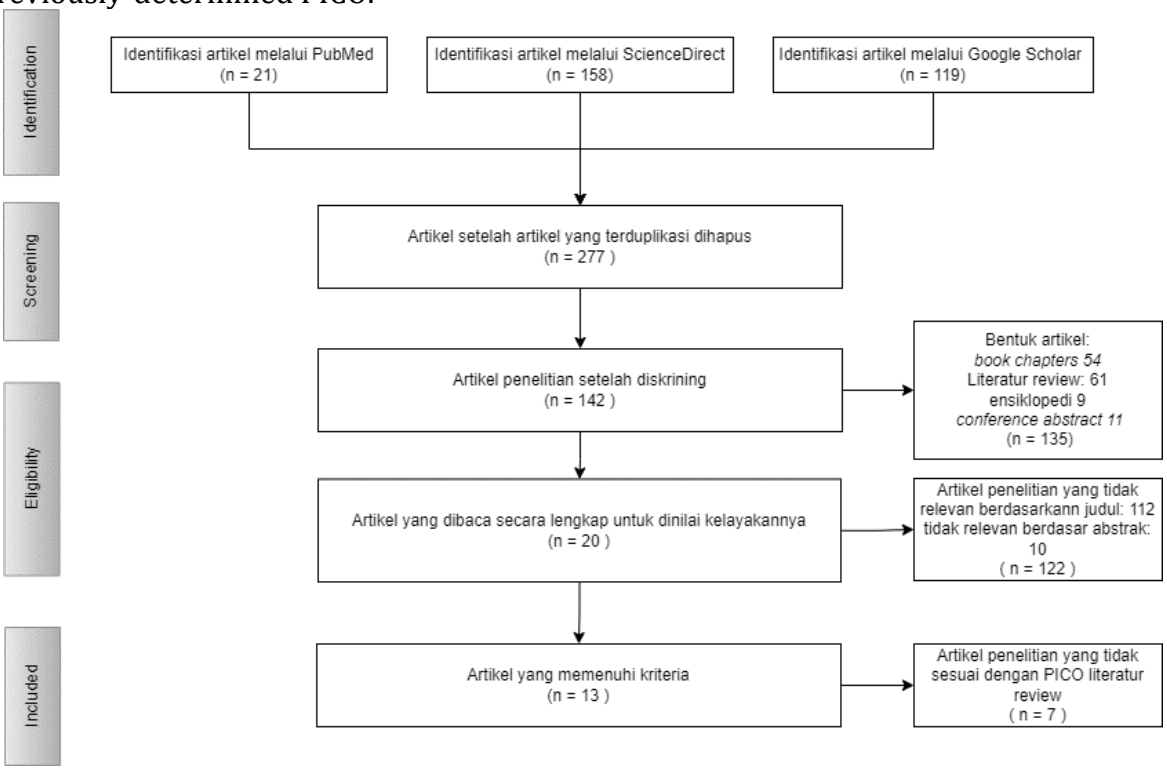
This literature review is conducted to discuss the therapeutic effectiveness and adverse events of short-term treatment regimens in MDR-TB patients. It is expected that this literature review can eventually contribute to more effective and safe treatment of MDR-TB for society in the future.

2. METODE

This literature review was conducted according to the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) principle to evaluate the therapeutic effectiveness and adverse events of short-term treatment regimens in MDR-TB patients. This review reported the findings in some research articles by comparing the population/patient, intervention, control, and outcome (PICO). The population involved was the patients diagnosed with MDR-TB, the intervention made was the use of short-term treatment regimens, the control used was the 2018 WHO guidelines for MDR-TB therapy regimens, and the outcomes observed were the effectiveness of therapy and adverse events in patients.

The data sourced from an in-depth search in PubMed, ScienceDirect, and Google Scholar. The articles retrieved were research articles on MDR-TB therapy from various parts of the world, including Europe, Africa, and Asia. The data searched was research results or articles published from 2018 to 2022 related to MDR-TB therapy with short-term treatment regimens. The keywords used in the article search were "multi-drug resistant tuberculosis", "short regimens" or "short-term regimens", effectiveness, safety" or "adverse events".

The restrictions placed during the search were the type of article, research period, year of publication, and language used. The type of article reviewed was research articles (full articles) in English. Meanwhile, articles in the form of literature review, book chapter, conference abstract, and encyclopedia were excluded. The inclusion criteria for the research articles reviewed were studies involving patients of all ages with MDR-TB, examining the use of short-regimens (9-12 months) for therapy, investigating the effectiveness of therapy and adverse events, and being published between 2018 and 2022. The articles collected were then identified for any duplications. Based on the type of articles, an article screening was done through reading in full and discussion of the findings by some experts in clinical pharmacy and pharmaceutical management. Then, the eligibility was determined based on the inclusion and exclusion criteria by following the PRISMA principle (Figure 1). The articles that fulfilled the criteria were selected based on previously-determined PICO.



Gambar 1. Prisma Diagram

3. HASIL

In the 13 articles examining the therapeutic effectiveness and adverse events of short-term regimens among MDR-TB patients in Asia, Africa, and Europe between 2018 and 2022, the protocol and drug combinations used were relatively diverse. **Table 1** shows that most of the studies used a prospective or retrospective cohort design.

Table 1. Results of article search

No	Authors, year	Research design, location	Population	Regimen	Findings	
					Therapeutic effectiveness	Adverse events
1	U. Ateba-Ngoa, et al., 2019 [7]	Case series, ongoing observational study Location: Republic of Gabon, Africa	11 HIV negative Resistant to min 2 drugs (RH) and max 5 drugs (RHZES)	Intensive phase: 4KmMfxPtoCfzHEZ Continuation phase: 5MfxCfzEZ	64% overall sputum culture conversion rate after 4 months of treatment 7 (63.6%) recovered, 1 (9.1%) failed, 2 (18.2%) died, 1 (9.1%) lost to follow-up	Adverse events: gastrointestinal disorders (nausea-vomiting), 2 (8%) hearing loss, 1 (4%) serious skin allergy, 1 (4%) hemoptysis, 1 (4%) terminal hepatic failure
2	Teona Avalianai, et al., 2021 [8]	Prospective, descriptive study Location: Georgia	25 2 HIV positive 4 DM 3 Hepatitis C	24 patients: 9BdqLzdLfxCfzCs 1 HIV patient: 9BdqDlmLfxCfzCs	88% overall sputum culture conversion rate after 4 months of treatment and 94% after 6 months 22 (88%) recovered, 1 (4%) died, 2 (8%) lost to follow-up	Serious adverse events: cardiotoxicity (8%), hepatotoxicity (8%), mortality (4%) Other adverse events: musculoskeletal disorders (8%), gastrointestinal disorders (4%), myelosuppression, psychiatric disorders (4%), peripheral neuropathy (4%)
3	Liang Fu, et al., 2021 [9]	Prospective non-randomized controlled trial Location: China	103	68 patients: regimen without Bedaquiline (9-12LfxLzdCfzCsZ) 35 patients: regimen with Bedaquiline (9-12LfxLzdBdqCsZ)	83.1% culture conversion rate at 4 months While the article being written: 41 completed treatment, 40 (97.6%) recovered, 1 (2.4%) failed due to adverse events	Adverse events without Bdq: peripheral neuritis (56.31%), myalgia (56.31%), hyperuricemia (48.54%), optic neuritis (46.6%), gastrointestinal disorders (46.6%), weakness, dizziness/headache (42%), rash (30.1%), anxiety, palpitation (26.2%), depression (18.45%), QTc prolongation (17.45%), anemia (9.71 %), liver injury (8.74%), hyperpigmentation (4.85%), thrombocytopenia (1.94%).

						Adverse events with Bdq: peripheral neuritis (37.14%), liver injury (8.57%), optic neuritis (31.43%), thrombocytopenia (2.8%)
4	Vivian S. Lofranco, et al., 2022 [10]	Prospective cohort study Location: Philippines	329	Intensive phase: 4-6Km(Cm)CfzMfx(Lfx)EHZPto Continuation phase: 5CfzMfx(Lfx)EZ	77.8% sputum conversion rate at 6 months 224 (68.0%) recovered, 20 (6.1%) completed treatment, 10 (3.0%) died, 41 (12.5%) lost to follow-up, 33 (10.0%) withdrawn, 1 (0.3%) failed	Most frequent adverse events: vomiting (89.9%), nausea (71.1%), hypokalemia (50.1%), increased SGoT (45.9%), dizziness (45.3%), headache (44.9 %), arthralgia (42.2%), increased SGPT (40.4%), skin discoloration, increased creatinine (37.9%)
5	Ilse Tack, et al., 2021 [11]	Retrospective cohort analysis Location: South Africa	117 80 HIV positive (68.4%)	Intensive phase: high-dose 4-6BdqLfxCfzZE Continuation phase: 3-5LfxCfzZE	.2% therapy success, 12.8% mortality (80% deaths in the first 4 months of treatment)	Adverse events: anemia (27.43%), hepatotoxicity (14.5%), QT prolongation (11.3%), nausea and vomiting (8.1%), renal failure (6.5%), thrombocytopenia (4.8%), visual impairment (3.2%), arthralgia (1.6%), peripheral neuropathy (1.6%), skin disorders (1.6%), central nervous system disorders (1.6%), neutropenia (1.6%)
6	A. Tr´ebucq, et al., 2018 [12]	Prospective observational study Location: 9 African countries	1006	Intensive phase: 4-6KmCfzMfxEHhZPto Continuation phase: 5MfxEZCfz	728 (72.4%) recovered, 93 (9.2%) completed treatment, 59 (5.9%) failed, 78 (7.8%) died, 48 (4.8%) lost to follow-up	Adverse events: gastrointestinal disorders (42.9%), hepatotoxicity (51.2%), neurological disorders (73.1%), osteoarticular (81.8%), renal disorders (84.3%), hearing loss (55.7%)
7	Padmapriyadarsini.C, *et al.*, 2022 [13]	Prospective, open-label, single-group cohort study Location: India	153	BDQ 400 mg once daily (2 weeks), followed by 200 mg 3 times	139 (91.4%) recovered, 7 (4.5%) changed treatment, 3 (1.9%) lost to follow-up, 4 (2.6%) died	Adverse events: breathlessness, fever, gastritis and vomiting, hemoptysis, pneumothorax, acute exacerbation of asthma, anemia grade 3 or 4 (10.3%)

				weekly (22 weeks), DLM 100 mg twice daily, LZD 600 mg once daily, and CFZ 100 mg or 200 mg based on body weight (24 weeks) (8Bdq, Dlm, Lzd, Cfz)		peripheral neuropathy, pancreatic enzyme elevation, liver enzyme elevation (23%), septic shock, urinary tract infection, hyperpigmentation (55%), peripheral neuropathy (42%)
8	Nguyen, *et al.*, 2023 [14]	Prospective cohort study Location: Vietnam	106	Bdq 400 mg daily in the first 2 weeks, followed by maintenance dose of 200 mg three times weekly for 22 weeks, Lfx, Cfz, Lzd, Pza for 9-11 months	88 (83%) recovered, 7 (6.6%) completed treatment, 4 (4%) failed, 6 (5.7%) lost to follow-up, 1 (0.9%) died	12 serious adverse events (29%) and 12 (26.6%) adverse events grade 3 or 4: elevated liver enzymes (28.9%), hypokalemia (11.1%), arthralgia (11.1 %), QT prolongation (8.9%)
9	Ciza, *et al.*, 2020 [15]	Retrospective analysis Location: Republic of Burundi	225	Intensive phase: 6KmMfx PtoCfzZH E Continuation phase: 5MfxCfzZ E	209 (92.9%) recovered, 1 (0.4%) failed, 3 (1.3%) lost to follow-up, 11 (4.9%) died, 1 (0.4%) relapsed six months after being declared cured	9 (4.0%) adverse events grade 3 or 4: hepatotoxicity (30.7%), gastro-intestinal disorders (21.8%), ototoxicity (10.2%)
10	du Cros, *et al.*, 2021 [16]	Prospective observational cohort study Location: Republic of Karakalpakstan, Uzbekistan	128	Intensive phase: 4-6ZEHMfx Cap or KmPtoCfz Continuation phase:	55 (43%) recovered, 37 (28.9%) completed treatment, 2 (1.5%) died, 14 (14%) failed, 12 (9.4%) lost to follow-up	Adverse events: 195 (23.6%) nausea, & vomiting, 87 (10.5%) fatigue & weakness, 87 (10.5%) gastrointestinal disorders, 60 (8.1%) arthralgia, 56 (6 .8%) renal failure, 40 (4.8%) ototoxicity, 28 (3.4%) diarrhea, 24

				5ZEMfxPtoCfz		(2.4%) itching, 21 (2.5%) hepatitis, 20 (2.4%) rash, 15 (1.8%) QTc prolongation, 12 (1.5%) anemia, 11 (1 .3%) depression, 6 (0.7%) neuropathy, 4 (0.5%) visual loss, cramps, gastritis, 4 (0.5%) mental disorders, 3 (0.4%) psychosis, 2 (0.2%) allergic reaction
11	Nunn, *et al.*, 2019 [17]	Randomized, phase 3, non-inferiority study Locations: Ethiopia, Mongolia, South Africa, Vietnam	245	Intensive phase: 4KmHPtoMfxCfzEZ Continuation phase: 6MfxCfzEZ	193 (78.8%) recovered, 24 (8.5%) died	136 (48.2%) serious adverse events, 9.9% cardiac disorders, 1.1% hypokalemia, (8.9%) hepatobiliary disorders, 11% QT prolongation, hearing loss
12	Haroun a, S.H, *et al.*, 2019 [18]	Retrospective cohort study Location: Niger	120 (10 children, 110 adults)	Intensive phase: 4-6KmGfxPthCfzZHE Continuation phase: 5GfxCfzZE	83% success rate in children 88% success rate in adults	Adverse events in children: 3 (30%) nausea & vomiting, 1 (10%) ototoxicity, 1 (10%) hepatotoxicity Adverse events in adults: 44 (40%) vomiting, 20 (18%) ototoxicity, 5 (5%) hepatotoxicity
13	Piubello.A, *et al.*, 2019 [19]	Retrospective observational study Location: Niger	249 9 DM	Intensive phase: 4-6GfxCfzEZKmPtoH Continuation phase: 5-8MfxCfzEZ	207 (83.1%) recovered relapse-free, 8 (3.2%) failed, 23 (9.2%) died, 7 (2.8%) lost to follow-up, 4 (1.6%) relapsed	Adverse events: gastro-intestinal disorders, hepatic disorders, hearing loss, peripheral neuropathy, hyperglycemia (patients treated with Gfx), osteoarticular disorders, dermatological disorders, hypothyroidism

R: Rifampicin; H: Isoniazid; Z: Pyrazinamide; E: Ethambutol; Sm: Streptomycin; Cap: Capreomycin; Km: Kanamisin; Mfx: Moxifloxacin; Pto: Prothionamide; Cfz: Clofazimine; Gfx: Gatifloxacin; Bdq: Bedaquiline; Lzd: Linezolid, Cs: Cycloserine; Dlm: Delamanid

Adverse Events (AEs) occurred to all patients with all the regimens used. Some of the AEs were graded while some others were not. Such grading is apparently useful for determining the severity of the adverse events. Table 2 describes the details of the graded adverse events available in 6 of the 13 articles. Of 2829 patients in 13 studies, 153 patients (5.4%) died.

Table 2. Graded adverse events (AEs) based on the article search

Adverse event	Total subjects	Grade 1	(%)	Grade 2	(%)	Grade 3	(%)	Grade 4	(%)
Gastrointestinal disorders	1745	850	48.71	264	15.13	9	0.52	3	0.17
Nervous system disorders	1745	392	27.39	96	5.50	8	0.46	1	0.06
Cardiovascular disorders	1745	20	1.15	7	0.40	32	1.83	1	0.06
Renal disorders	1745	181	10.37	45	2.58	8	0.46	2	0.11
Hepatic disorders	1745	540	30.95	161	9.23	35	2.01	8	0.46
Dermatological disorders	1745	142	8.14	19	1.09	3	0.17	0	0.00
Hearing loss	1745	391	22.41	98	5.62	52	2.98	31	1.78
Osteoarticular disorders	1745	153	8.77	42	2.41	0	0.00	0	0.00
Psychiatric Disorders	1745	12	0.69	1	0.06	3	0.17	2	0.11
Hyperglycemia	1745	6	0.34	1	0.06	1	0.06	0	0.00
Thyroid disorders	1745	4	0.23	4	0.23	0	0.00	0	0.00
Hematologic disorders	1745	55	3.15	23	1.32	16	0.92	3	0.17
Pancreatic enzyme elevation	1745	18	1.03	5	0.29	1	0.06	0	0.00
Fatigue and weakness	1745	59	3.38	22	1.26	6	0.34	0	0.00
Others	1745	691	39.60	405	23.21	88	5.04	45	2.58

4. DISCUSSION

Composition of the Regimen

The short-term treatment regimen was prepared according to the Bangladesh regimen [20], [21] with Gatifloxacin as the first-line drug. Gatifloxacin belongs to the fourth generation of fluoroquinolone group that is highly effective in killing gram-positive and gram-negative bacteria [22]. Gatifloxacin has proved to be superior to Levofloxacin and Moxifloxacin [23]. The combination of drugs in this short-term regimen is in accordance with the WHO guidelines, in which Fluoroquinolone, Kanamycin, Linezolid, Clofazimine, Pyrazinamide, Isoniazid, and Prothionamide are combined. The intensive phase consists of 5-7 types of drugs for 4-6 months, and the continuation phase comprises 4-5 drugs for 5-8 months [24].

Of the 13 articles, eight articles reported the use of short-term regimens consisting of an intensive phase for 4-6 months with 7 types of drugs and a continuation phase for 5 months with 4-5 types of drugs. The drugs used in the intensive phase are first- and second-line drugs consisting of a combination of Fluoroquinolone, Kanamycin, Pyrazinamide, Clofazimine, Isoniazid, Ethambutol, and Prothionamide. The drugs in the continuation phase include Fluoroquinolone, Clofazimine, Ethambutol, and Pyrazinamide. Pyrazinamide and Clofazimine have a bacteriostatic effect which also helps reduce resistance. Meanwhile, Isoniazid and Ethambutol are important additional drugs to the main drug combination, and the use of high doses is remarkably effective in overcoming drug resistance.

The modification of the short-term regimen studied was indicated by Bedaquiline use in the intensive phase to substitute Kanamycin. The use of Bedaquiline began with a loading dose of 400 mg for 2 weeks followed by a dose of 200 mg 3 times a week for 22 weeks [8], [9], [11], [13], [14].

The study conducted in Georgia used a combination of 5 second-line drugs for 9 months, consisting of Bedaquiline, Linezolid, Levofloxacin, Clofazimine, and Cycloserine [8]. This is an example of injectable-free regimen, where Kanamycin is usually used to reduce the risk of bacterial mutation and prevent resistance because of its strong bactericidal properties but is recommended to be substituted with Bedaquiline due to the potential for severe adverse drug reactions [24]. The subjects tested in Georgia were 2 HIV-positive patients out of a total of 25 subjects. One of the HIV-positive subjects was

given Delamanid (Dlm) instead of Linezolid due to his clinical conditions, but there was no difference in the results between HIV-positive and HIV-negative patients; this is in accordance with Berhan's literature review which found that drug-resistant TB is not associated with HIV-positive infection [25]. Meanwhile, the regimen used in South Africa has also proved to be effective for HIV-infected patients, and although deaths are substantially more frequent among HIV patients, they have no effects on the microbiological effectiveness of the regimen [11], [12].

The non-randomized prospective trial conducted in China combined 4-5 types of drugs for 9-12 months, comprising Pyrazinamide, Linezolid, Levofloxacin, Clofazimine, and Cycloserine. In some subjects, Cycloserine was substituted with Bedaquiline. Of the 39.80% patients completing the treatment, no significant difference was found between the two drug compositions, and there was 94.4% conversion in the fourth month [9].

Of all the articles included in this literature review, only one article reported the use of Gatifloxacin, and at the end of the study period Gatifloxacin was substituted with Moxifloxacin since Gatifloxacin was no longer available in Niger in October 2013 [19].

Therapeutic Effectiveness

The effectiveness of therapy in all the studies conducted used the sputum conversion rate and therapy success rate parameters. The success of therapy is seen from the number of patients who are cured and the number of patients who complete treatment. The therapy success rate was between 63.6-92.9%. This is a fairly large range. The best results were found in the study in Burundi with the regimen of the intensive phase: 6Km, Mfx, Pto, Cfz, Z, Hh, E and the advanced phase: 5Mfx-Cfz-ZE [15]. The lowest therapeutic effectiveness was found in a study in the Republic of Gabon with the intensive phase regimen: 4-6Z, E, H, Mfx, Cm or Km, Pto, Cfz and the continuation phase: 5Z, E, Mfx, Pto and Cfz [7]**.** This low rate of therapeutic effectiveness is likely due to the small number of the subjects involved and the patient's medical history that shows a delay in establishing a diagnosis of MDR-TB, thus causing patients to receive unnecessary and inefficient treatment with first-line drugs [7]**.** The same regimen with different durations can provide different results.

Bedaquiline is a new drug on trial to be included in short-term treatment regimens to replace Kanamycin that has the potential for severe ototoxicity effects. Research using Bedaquiline has been carried out in several countries, including Georgia, China, Africa, and India. The effectiveness of all-oral regimens containing Bedaquiline is apparently higher than those with Kanamycin, reaching 88%-94%. Bedaquiline that is administered orally is preferred to Kanamycin which is used by injection. Therefore, all-oral regimens can improve patient adherence and ultimately increase therapeutic effectiveness. For the first time in decades, new regimens with new TB drugs are being introduced to treat people with MDR-TB, offering many potential benefits. Shorter duration of treatment, replacement of injectable drugs with orally administered drugs, and use of drugs with a better safety profile become the major improvements of this regimen to increase the likelihood of treatment success for people with MDR-TB [8], [11]**.**

Meanwhile, the use of a short-term regimen in MDR-TB pediatric patients showed relatively good therapeutic effectiveness with a therapy success rate of 83% although this was lower than that of adult patients which reached 88% in the same study [18]**.**

Adverse Events

Serious adverse events that occur during the use of short-term regimens include death, hepatotoxicity, cardiotoxicity, and ototoxicity. Death occurs more frequently in HIV-positive than in HIV-negative patients. Some patients also died due to COVID-19 co-

infection [9]. The regimen used in the research in the Republic of Gabon showed the highest mortality, reaching 18.2%. This is likely due to severe health deterioration, extensive lung lesions, and irreversible sequelae such as chronic respiratory failure due to late diagnosis of MDR-TB.

QT prolongation (cardiotoxicity) was also a serious adverse event that occurred mainly among the research participants who used a regimen containing Bedaquiline [8], [9], [11], [13], [14]**.** This is in line with the activity of Bedaquiline that works to inhibit the mycobacterial ATP synthase, an enzyme important for producing energy in Mycobacterium tuberculosis (M.tb). Darmayani stated that the prolongation of QT interval due to the use of Bedaquiline apparently occurs though with relatively low intensity [26], but it tends to increase when combined with Clofazimine (Cfz), Moxifloxacin (Mfx), and Amiodarone. The last serious adverse event was hepatotoxicity experienced by 8-45% of the research participants.

Dermatological and gastrointestinal adverse events (nausea, vomiting, diarrhea, constipation) are the most common adverse events in patients using short-term regimens. This is in line with a study by Dewi in 2020, where gastrointestinal, dermatological, and neurological disorders as well as a combination of the three became the most frequent adverse drug reactions (ADRs) in patients taking antituberculosis drugs [27]**.** Many patients experienced hyperpigmentation or acneiform eruptions during treatment which was thought to be associated with the use of Clofazimine in this regimen.

Neuropathy was also an adverse event commonly experienced by many MDR-TB patients in this study. Linezolid (Lzd) which is suspected of causing neuropathy can be stopped, or the dose can be reduced and reinitiated once the symptoms of neuropathy have subsided. This is quite effective for overcoming such adverse event and improving the success of therapy for MDR-TB patients [13]**.**

Research limitations

This literature review has some limitations, including the diverse composition of the regimens used, the varied duration of treatment, and the unspecified type of patients. In addition, the HIV co-infection was not fully described in all the articles, and not all the adverse events reported were graded. Furthermore, this study only searched for publications in English language, resulting in the likelihood of missed information written in other languages about the therapeutic effectiveness and adverse events of short-term regimens for MDR-TB patients. The various research methods are also a limitation of this literature review.

4. CONCLUSION

All-oral regimens promise better effectiveness, especially with or without Bedaquiline, compared to injection regimens in the treatment of MDR-TB. It is crucial to monitor the safety of regimens and expand research to larger populations and broader research sites.

5. DAFTAR PUSTAKA

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