JOURNAL OF PHARMACEUTICAL AND SCIENCES
Electronic ISSN: 2656-3088
Homepage: https://www.journal-jps.com

REVIEW ARTICEL

JPS |Volume 6 | No. 3 | JULI-SEP | 2023 |pp.923-934

# Factors Associated with Unsuccessful Treatment of Bedaquiline and or Delamanid Based Regimens in Multidrug-Resistant Tuberculosis: A Review

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**ABSTRACT**

**Background**: Multidrug-resistant tuberculosis (MDR-TB) is a serious health concern that is difficult to treat, requiring long and complex treatment with highly effective drugs. An all-oral regimen, bedaquiline and or delamanid have already shown low unsuccessful treatment in patients with MDR-TB. **Method**: We comprehensively reviewed factors associated with unsuccessful treatment (death, treatment failure, and loss to follow-up) related to all oral regimen containing bedaquiline and or delamanid in patients with MDR-TB. We conducted a scoping review under the PRISMA guideline for scoping review. **Results**: We included seven observational studies that met the inclusion criteria. Four studies reported the concomitant use of bedaquiline and delamanid. Unsuccessful treatment ranged from 7.8% to 36.6% in regimens containing bedaquiline, delamanid, or both at six months or after treatment completion. Low rates of treatment failure and loss to follow-up were reported in the included studies. Elderly, being underweight (BMI < 18.5 kg/m$^2$), and hepatitis C coinfection among MDR-TB patients were associated with unsuccessful treatment in most studies. None studies reported pre-XDR and XDR-TB as risk factors for unsuccessful treatment. **Conclusion**: In MDR-TB patients receiving regimens containing bedaquiline and delamanid, age, BMI, and hepatitis C coinfection were associated with unsuccessful treatment.

***Keywords***: *Drug-resistant; Risk Factors; Unfavorable; Bedaquiline; Delamanid.*

## INTRODUCTION

Tuberculosis (TB) is a highly infectious disease with high mortality rate worldwide. Drug-resistant tuberculosis (DR-TB) is characterized by resistant to rifampicin and isoniazid with or without resistance to second line antitubercular drugs. The estimated DR-TB cases in Indonesia are 2.4% of all new TB patients and 13% of those previously treated, with a total case of 24.000 or 8.8 per 100.000 population (World Health Organization., 2020). Those who previously treated with antitubercular drugs is an independent risk factor for DR-TB. The administration of second line injectable drugs (SLID), such as amikacin, kanamycin, and capreomycin for the treatment of DR-TB was associated with poor clinical outcome, severe adverse effect, and low cure rate (Soeroto *et al*., 2022a) Therefore, treatment with high efficacy with good safety profiles is urgently required. WHO recommended a full oral regimen containing bedaquiline to treat DR-TB patients (WHO, 2020).

According to WHO, duration of DR-TB treatment was divided into shorter treatment regimen (STR) for 9-11 months and individualized treatment regimen (ITR) for 18-24 months with all oral regimen (WHO, 2020). Replacing second-line

injectable drug with bedaquiline together with optimized background regimen has proven to increase the effectiveness and safety of DR-TB treatment. Bedaquiline and delamanid, two novel antituberculosis drugs, offer favorable outcomes including a high proportion of treatment success and cure rate in DR-TB patients (Nasiri *et al*., 2022; Pontali *et al.,* 2018). Delamanid is included as class C, together with ethambutol and pyrazinamide. The Indonesia National Tuberculosis Program included bedaquiline and delamanid into programmatic use in individualized treatment regimen (ITR) (Ministry of Health of RI, 2020). Van Deun *et al*., proposed bedaquiline as core drug since its highly bactericidal and sterilizing activity and no evidence of cross-resistance to other drugs. Delamanid, a companion drug, has high early bactericidal and sterilization activity to reduce the bacillary load (van Deun *et al*., 2018). In addition, it has an immunomodulatory activity by modulating $Th_1$ and $Th_2$ cytokines, thus enhances the bactericidal activity of macrophages (Lyu *et al.,* 2021). Delamanid is active against both replicating and dormant TB bacteria. They become dormant through decreased metabolism in hypoxic conditions, one of the factors for resistance. An in-vitro study by Chen *et al*., reported that delamanid killed TB bacilli within hypoxic lesions of the lung (Chen et al., 2017).

Data related to favorable or unsuccessful treatment of bedaquiline and delamanid in Indonesia still needs to be available. However, some previous studies have reported that regimens containing bedaquiline, delamanid, or both are relatively safe and no cases of death due to arrhythmia or TdP (Hewison *et al*., 2022; Li *et al*., 2021). Given that delamanid has a beneficial role to treat DR-TB patients, if there is no contraindication, it should be possible to be used in clinical practice. Previous studies have shown high favorable outcomes including sputum culture conversion, treatment completion, and cured with regimens containing bedaquiline and or delamanid in DR-TB patients and some of them reported unfavorable outcomes, such as death, treatment failure, and loss to follow-up (LTFU) (Katrak *et al*., 2021; Olayanju *et al*., 2020). Some studies have reported consistent results that HIV, lung cavity, low BMI, and CKD are risk factors for unfavorable outcomes related to SLID in DR-TB patients. Furthermore, patients with pre-XDR and XDR-TB had a high treatment failure related to SLID (Soeroto *et al*., 2021, 2022a). However, studies related to risk factors for unsuccessful treatment associated with bedaquiline and or delamanid showed conflicting results since they have heterogenous sample size, difference in method and study design, comorbid disease, and resistance profile.

Although regimens containing bedaquiline and or delamanid demonstrate low treatment failure, a good understanding factors associated with unsuccessful treatment can be used as a preventive action or policy-making to reduce the negative impact during treatment. The aim of the present scoping review is to evaluate factors associated with unsuccessful treatment of regimens containing bedaquiline and or delamanid to treat MDR-TB patients.

## METHODS

### Search strategy and study selection

This was a scoping review using the PRISMA extension for scoping review guidelines (Tricco *et al*., 2018) We used secondary data from articles published from 2017 up to December 2022 in Pubmed and Science Direct databases reporting on the risk factors for unfavorable outcome of regimens containing bedaquiline and or delamanid in patients with drug resistant tuberculosis. The search terms were: “drug-resistant tuberculosis” (DR-TB), “pre-XDR-TB”, “XDR-TB”, “MDR-TB”, “bedaquiline”, “delamanid”, efficacy, effectiveness, and “unfavorable outcome”. Boolean operators with “OR”, “AND”, and “NOT” were used to combine these terms in databases.

The inclusion criteria in our review were (a) full text articles written in English; (b) articles as original articles with randomized controlled trial (RCT), cohort, cross-sectional, or case-control study designs; (c) patients treated with regimens containing bedaquiline and or delamanid; (d) reporting risk factors for unfavorable outcome in regimens containing bedaquiline and or delamanid at least at the end of six months or treatment completion, and (e) aged ≥ 18 years old. Risk factors were assessed by multivariate analysis or binary logistic regression for the included studies as described in method section. The exclusion as following: article was written as a review or opinion, case report or series, animal studies, and abstract proceeding or conferences.

## Data extraction

Each study fulfilled the inclusion criteria will be collected, extracted, and summarized including the author's name, year of publication, study design, sample size, comorbid disease, type of DR-TB, and summary of research findings. The results of the scoping review are presented as a descriptive or narrative synthesis due to the relatively heterogeneous study.

## Outcome

Unfavorable outcomes were defined by sputum culture positive for at least at the of six months or after treatment completion, death, and loss to follow-up (LTFU) during treatment. The regimen was considered bedaquiline and or delamanid-containing based on what appeared in the method of the selected studies.

# RESULTS

## Study selection

In a total of 120 articles were identified using combined keywords. From this, 15 articles with duplicate records were removed. Of 105 articles remained, 75 of them were excluded due to irrelevant title and abstract, review/opinion/editorial, and case report or case series. Furthermore, from 30 articles that eligible to be assessed, 23 articles were excluded since they did not report factors associated with unsuccessful treatment in regimens containing bedaquiline and or delamanid to treat MDR-TB patients. Finally, only 7 articles were included for scoping review according to the PRISMA flowchart. PRISMA flowchart for article inclusion is shown in **Figure 1**. Finally, only 7 articles were included for scoping review according to the PRISMA flowchart. PRISMA flowchart for article inclusion is shown in **Figure 1**.

## Study characteristics

The characteristic of the included studies is summarized in **Table 1**. All the included studies in this present review were observational and no studies in Indonesia reporting risk factors for unfavorable outcomes in DR-TB patients in regimens containing bedaquiline and or delamanid.

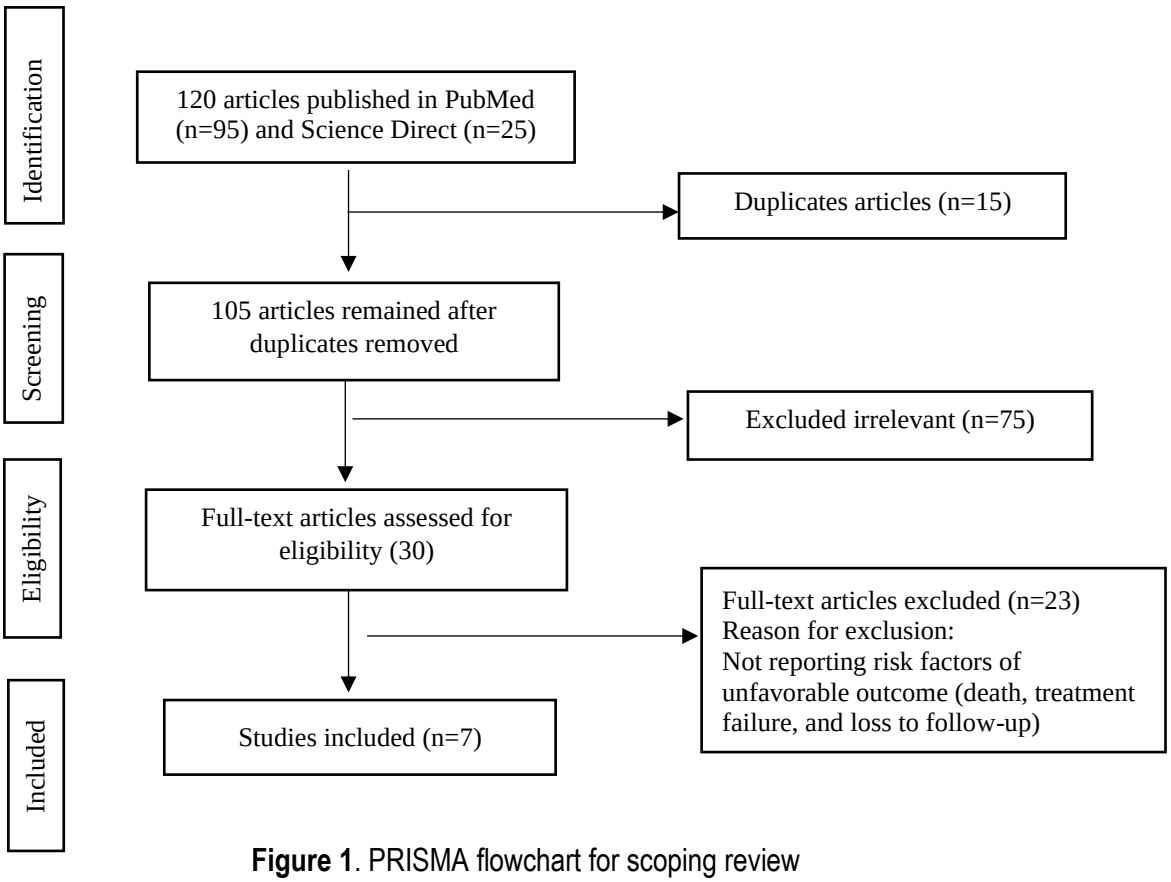


**Figure 1**. PRISMA flowchart for scoping review

**Table 1**. Characteristic of studies included in this scoping review

| No | Author/Year/ Country | Study Design/Method/ Sample Size | Comorbid Disease | DR-TB Profile | Summary of Findings |
|---|---|---|---|---|---|
| 1 | (Olayanju *et al.,* 2020)/2020 / South Africa | Retrospective Cohort<br>122 patients DR-TB with a bad prognosis<br>82 patients in regimens containing DLM<br>40 patients in regimens containing BDQ+DLM | HIV:<br>• BDQ regimens = 42 (51.2%)<br>• BDQ-DLM regimens = 22 (52%) | • BDQ regimens<br>MDR-TB: 5(6.15 %)<br>Pre XDR-TB:10 (12.25)<br>XDR-TB:67 (81.7%)<br>• BDQ-DLM regimens<br>MDR-TB: 6 (15%)<br>Pre XDR-TB:15 (37.5%)<br>XDR-TB: 19 (47.5%) | • 30/82 patients (36.6%) and 13/40 (32.5%) had unfavorable outcomes in BDQ and BDQ-DLM regimens, respectively<br>• Time to culture positivity was significantly associated with unfavorable outcome (HR: 2.681, P-value 0.02) |
| 2 | (Kang *et al.,* 2020)/ 2020 / South Korea | Retrospective cohort<br>282 DR-TB patients<br>• 107 in BDQ regimens<br>• 108 in DLM regimens<br>• 67 in BDQ+DLM regimens | HIV: 3 patients (1.1%) | • MDR-TB: 101 (35.8%)<br>• Pre XDR-TB: 133 (41.5%)<br>• XDR-TB: 48 (17.0%) | • 21/107 patients (19.6%), 13/108 (12.0%), and 9/67 (13.4%) had unfavorable outcomes in BDQ, DLM, and BDQ-DLM regimens, respectively<br>• Age ≥ 60 years and BMI < 18.5 kg/m$^2$ were significantly associated with unfavorable outcome at 12 months |
| 3 | (Auchynka *et al.,* 2021) /2021/ Belarus | Prospective Cohort<br>125 DR-TB patients with 20 in BDQ-DLM regimens. | HIV: 19 patients (15%) | • MDR-TB: 7 (6%)<br>• Pre-XDR-TB:33 (26.4%)<br>• XDR-TB: 85 (68%) | • 15/125 patients (12%) had unfavorable outcomes, including 2% death, 4% treatment failure, and 6% LTFU. |

| No | Author/Year/ Country | Study Design/Method/ Sample Size | Comorbid Disease | DR-TB Profile | Summary of Findings |
|---|---|---|---|---|---|
| | | | | | • DR-TB patients with hepatitis C co-infection was associated with unfavorable outcome after controlling for sex and age (aHR: 3.61, P-value < 0.05) |
| 4 | (Gao *et al.*, 2021)/2021/China | Prospective cohort 177 DR-TB patients in regimens containing BDQ | • HIV: 1 patient<br>• DM: 19 (10.7%) patients | • MDR-TB: 39 (22.0%)<br>• Pre-XDR TB :56 (31.7%)<br>• XDR-TB: 82 (46.3%) | • 26/177 (14.7%) patients had unfavorable outcomes including 3/117 (1.7%) deaths and 23/177 (13.0%) failed after treatment completion.<br>• Patients with underweight (BMI < 18.5 kg/m$^2$) were significantly more likely of experiencing unfavorable outcomes (OR = 7.356; CI 95% = 2.652-20.401) |
| 5 | (Vambe *et al.*, 2020)/2020/Eswatini | Retrospective cohort<br>352 DR-TB patients<br>• BDQ = 292<br>• DLM = 40<br>• BDQ+DLM = 20 | • HIV: 272 patients (77.2%) | • MR TB: 47 (13.3%)<br>• Poly DR-TB:12 (3.4%)<br>• MDR-TB: 196 (55.6%)<br>• Pre-XDR TB :46 (13.0%)<br>• XDR-TB: 44 (12.5%) | • 7.8% and 21.2% patients had unfavorable outcome at 6 and 24 months, respectively.<br>• Patients with age ≥ 60 years and those receiving concomitant use BDQ-DLM were significantly associated with unfavorable outcome, with aHR 4.49 and |

| No | Author/Year/ Country | Study Design/Method/ Sample Size | Comorbid Disease | DR-TB Profile | Summary of Findings |
|---|---|---|---|---|---|
| | | | | | 2.01, respectively (P-value < 0.05) |
| 6 | (Hewison et al., 2022)/2017/ Armenia, Belarus, Georgia, India, Russia, South Africa, Swaziland | Retrospective cohort<br>53 DR-TB patients in regimens containing DLM | • HIV:8 patients | • MDR-TB: 10 (19.6%)<br>• Pre-XDR TB :14 (26.4%)<br>• XDR-TB: 27 (52.9%) | • 14/53 (26.4%) patients had unfavorable outcomes at six months, including death (7/53), remained culture positive (4/53), LTFU (2/53), and treatment failure related to SAE (1/53), respectively<br>• Patients with age > 35 years, hepatitis C infection, sputum smear positive at baseline, and serum albumin < 3.4 g/dl were significantly associated with unfavorable outcomes with OR 5.62; 7.78; 5.21; 7.14, respectively (P-value < 0.05) |
| **7** | (Mbuagbaw *et al.,* 2019)/2019/South Africa, France, Jansen, Armenia, Georgia | Prospective cohort<br>537 DR-TB patients in regimens containing BDQ | • HIV: 135 patients (25.1%) | • MDR-TB:100 (18.6%)<br>• Pre-XDR TB: 202 (37.6%)<br>• XDR-TB: 188 (35.0%) | • 34.2% patients had unfavorable outcomes including death (11.7%), treatment failure (5.1%), and LTFU (14.8%)<br>• Age and lung cavities were significantly associated with death with OR = |

| No | Author/Year/ Country | Study Design/Method/ Sample Size | Comorbid Disease | DR-TB Profile | Summary of Findings |
|---|---|---|---|---|---|
| | | | | | 1.05 and 5.31, respectively (P-value < 0.05) |

DR-TB: drug resistant tuberculosis; MDR-TB: multi-drug resistant tuberculosis; Pre XDR-TB: pre extensively drug resistant tuberculosis; XDR-TB: extensively drug resistant tuberculosis; BDQ: bedaquiline; DLM: delamanid: BMI: body mass index; LTFU: loss to follow-up; SAE: severe adverse effects; OR: odds ratio; aHR: adjusted hazard ratio

## DISCUSSION

This is a first review evaluating risk factors for unfavorable outcomes of all oral regimens containing bedaquiline and or delamanid together with optimized background regimen in DR-TB patients. The administration of bedaquiline and or delamanid as part of an all-oral regimen improve success treatment (culture conversion) and minimize side effects, such as hearing loss, hearing disorders, and renal dysfunction, related to the second line injectable drugs (Yang *et al*., 2017). Several studies have reported that adding bedaquiline and or delamanid to DR-TB regimens effectively increase a culture conversion rate at 6 months or after treatment completion (Kempker *et al*., 2020; Maretbayeva *et al*., 2021) Regimens containing bedaquiline to treat DR-TB is relatively safe with no cases of QTc interval more than 500 ms during six months of treatment as reported by Primadana *et al*.(Primadana *et al*., 2022). On the other hand, beyond its bactericidal activity, delamanid alter the function of host immune cell. The balance between pro-and anti-inflammatory responses is vital in limiting the infection among DR TB patients. Delamanid down-regulated the level of CXCL-10, a proinflammatory cytokine, and reduced inflammation via regulation of JAK2/STAT1 signaling (Qiao *et al*., 2022).

Regimens containing bedaquiline and or delamanid have lower unfavorable outcomes compared to SLID regimens. Studies in Indonesia reported that unfavorable outcomes in MDR-TB patients receiving SLID regimens ranged from 35.4% to 51.8%, with LTFU cases reported at 50% (Soeroto *et al*., 2021, 2022b) Lack of access to health facilities, low education, bad stigma in the community, and severe adverse effects associated with SLID have led to a high rate of LTFU cases (Kamara *et al*., 2022). In our review, four studies reported that age especially elderly was significantly associated with unfavorable outcomes (Hewison *et al*., 2022; Kang *et al*., 2020; Mbuagbaw *et al*., 2019; Vambe *et al.,* 2020) Old age is associated with increased Treg cells, which can interfere with effector T cells suppressing the immune system and making TB infection more difficult to eradicate.

Furthermore, old age is also associated with oxidative stress (ROS) and decreased endogenous antioxidant glutathione (GSH). An antioxidant, N-acetylcysteine, is recommended for elderly TB patients to restore antioxidant levels by reducing ROS and proinflammatory cytokines and increasing macrophage activity against TB bacilli (Yudhawati & Prasanta, 2020). Randomized controlled trials are urgently needed to clarify these findings. In addition, dysregulation of CD8 T cells, overactivation of mTORC1 signaling, and decreased levels of GSH, impair of autophagy and mitophagy processes which impact decreasing M.Tb microbial clearance in elderly.(Bonavida *et al.,* 2022) Interestingly, the absorption of bedaquiline and delamanid was not affected by age, and concomitant use of delamanid with bedaquiline had no impact on the pharmacokinetic profile delamanid and its metabolite, DM-6705 (Tanneau *et al*., 2022).

Two studies in our review reported that low BMI <18.5 kg/m$^2$ as a risk factor for unfavorable outcomes.(Gao *et al*., 2021; Kang *et al*., 2020) Several previous studies reported that low BMI was commonly found in DR-TB patients before treatment initiation (Lee et al., 2020; Seung, Khan, et al., 2020). It can be associated with weight loss for unknown etiology as one of the classical symptoms of TB. A systematic review by Notariza *et al*., reported that low BMI or being underweight

was significantly associated with unsuccessful treatment outcome among MDR-TB, with RR ranged from 1.77 to 4.70 (Notariza *et al*., 2022). TB patients with low BMI cause dysregulation of protective cytokines (IL-10, TGF-β, IL-5, and IL-13) and impact in decreasing M.Tb clearance. In addition, low BMI also impacts high bacillary loads and bilateral lung cavities, which are risk factors for treatment failure (Kornfeld et al., 2020).

Furthermore, low BMI is associated with decreased adipose tissue and low albumin levels. Because bedaquiline is highly bound to plasma albumin by more than 99%, low albumin levels increase the free bedaquiline fraction and accelerate hepatic metabolism to its primary metabolite, M2, with five times lower antimycobacterial activity than the parent drug. Bedaquiline has a cationic amphiphilic group and it is highly bound to intracellular phospholipids, accumulating the drug in tissues with the effect of slow drug release into the blood and maintaining steady-state concentrations. Lower BMI reduces the accumulation of bedaquiline in the tissues, thereby reducing the concentration of free drugs in plasma (Svensson *et al*., 2016). Similar with bedaquiline, delamanid is highly bound to albumin, therefore low albumin level accelerates its clearance. A study by Wang *et al*., reported that clearance of delamanid increased by about 22% and its exposure decreased of about 18% when baseline albumin level < 2.8 g/dl (Wang *et al.,* 2021). However, the relationship between low exposure of delamanid with its mycobacterial activity needs to be explored.

We found no studies reporting HIV status as a risk factor for treatment failure in this present review. Before the inclusion of bedaquiline and delamanid in the DR-TB regimen, SLID (amikacin, kanamycin, capreomycin) were first used to manage DR-TB patients. However, DR-TB patients with HIV are associated with higher treatment failure than those without HIV related to SLID. A recent study by Yuengling *et al*., reported that 58/80 (72.5%) of XDR-TB patients with HIV had unfavorable outcomes compared to those without HIV,14/25 (56.0%) (Yuengling *et al*.,2020). Regimens containing bedaquiline provide high therapeutic efficacy even in patients with HIV infection. HIV status did not alter the pharmacokinetic profile of bedaquiline and delamanid. A study that directly compared the outcome of therapy in HIV patients with the bedaquiline and SLID regimens has been reported by Padayatchi *et al*. The study demonstrated that 95/151 (62.9%) patients who received regimens containing bedaquiline were cured at the end of treatment compared to the SLID regimen, 33/105 (31.4%). Furthermore, patients with HIV who did not receive antiretroviral were significantly associated with death (aOR = 4.37, P-value = 0.004) (Padayatchi *et al*., 2020).

Two studies in our review reported that hepatitis C coinfection was a risk factor for unfavorable outcomes (Auchynka et al., 2021; Hewison et al., 2022). A study by Seung *et al*., reported that the prevalence of hepatitis C infection among DR-TB patients in several countries ranged from 11% to 29% (Seung *et al.,* 2020). Until now, there is not enough strong evidence documenting risk factors related to the prevalence of hepatitis C in TB patients. Nonetheless, a meta-analysis study stated that men have a significantly higher risk than women related to hepatitis C infection. It is associated with consuming alcohol, tattooing, and injecting drug abuse, which is more common in men than women (Behzadifar *et al*., 2019). Hepatitis C infection in TB patients is associated with drug induced liver injury (DILI). However, a study by *(Auchynka et al*., 2021) and (Hewison *et al*., 2022) did not report whether patients with hepatitis C infection were given direct-acting antivirals (DAAs). Interestingly, concomitant use of DAAs with bedaquiline and delamanid provided an excellent therapeutic effect to reduce HCV viral load. A recent study by Melikyan *et al*., demonstrated that concomitant use of DAAs with bedaquiline or delamanid provided 76.7% of treatment success, as indicated by a viral load concentration of less than 121 mIU/L after 12 weeks of treatment without severe adverse effects. Delamanid should be given together with DAAT because hepatic cytochromes minimally metabolize it compared to bedaquiline (Olaru *et al*., 2023).

Patients with CKD are associated with unfavorable outcomes related to SLID. More than 90% of SLID is excreted as an unchanged drug in the urine. Therefore, renal excretion plays an important role in eliminating SLID. Renal clearance of SLID decreased in patients with CKD and causes a prolongation of its elimination half-life and increases its concentration in plasma. Increased plasma concentrations of SLIDs are associated with

adverse effects such as ototoxicity, renal impairment, and electrolyte imbalance. Adverse effects of SLID was reported as a reason why patients discontinued their treatment. A study by Yu *et al*., stated that patients with CKD was less likely to treatment success and were more likely to death (Yu *et al.,* 2018). Although we found no included study reporting CKD among DR-TB patients, however patients with CKD treated with regimens containing bedaquiline experienced treatment success with tolerable adverse effects (Park *et al*., 2018). Bedaquiline is extensively metabolized in the liver and excreted primarily into feces. Bedaquiline and its main metabolite, M2, are only less than 1% excreted in the urine. It indicates that the excretion of bedaquiline is independent of renal function. Furthermore, studies on experimental animal models with renal impairment showed no significant differences in the pharmacokinetic profile of bedaquiline compared to those without renal impairment (Gour *et al*., 2021).

Surprisingly, we found no included studies in our review reporting pre-XDR or XDR-TB as a risk factor for unfavorable outcomes. Conversely, previous studies demonstrated that high DR TB was associated with unfavorable outcomes in regimens containing SLID. Kanamycin and amikacin exhibit poor penetration in cellular and necrotic lung lesions. A study by Lee *et al*., reported patients with pre-XDR and XDR-TB had more lung cavities and bilateral lung disease than those with MDR-TB. The lung cavity facilitates the development of antituberculosis drug resistance due to high TB bacillary load, active bacterial replication, and potentially lower drug concentrations in the lung tissue (Lee *et al*., 2019) A recent study by Maretbayeva *et al.*, stated that among DR-TB patients who did not experience sputum culture conversion after six months, 80% of them were XDR-TB and had lung cavities (Maretbayeva *et al*., 2021).

Of seven studies, only one study reported that concomitant use of bedaquiline and delamanid was associated with unfavorable outcome compared with bedaquiline or delamanid as a single drug *(Vambe et al.*, 2020) It might be overlapped and accumulation of adverse effects of bedaquiline and delamanid with optimized background regimen during the study period. Furthermore, the number of patients receiving bedaquiline and delamanid was small. Therefore, prompt for collection of more data on the combined use of these regimens was required.

The limitation of the present review is the number of the included studies still needs to be more significant. In addition, all studies have reported risk factors associated with unfavorable outcomes generally and have not performed sub-analyses of factors associated with treatment failure, death, and LTFU. Furthermore, observation time regarding the treatment outcome varied between studies. Further study, especially in Indonesia, is urgently needed until treatment completion and is accompanied by a sub-analysis of the factors associated with unfavorable outcomes.

## CONCLUSION

DR-TB patients receiving regimens containing bedaquiline and or delamanid, old age, being underweight, and those with hepatitis C were independent risk factors for unfavorable outcomes at six months or after treatment completion. Among DR-TB patients, those with pre-XDR and XDR-TB had low unfavorable outcomes after initiation regimens containing bedaquiline and or delamanid.

## CONFLICT OF INTEREST

All authors stated that there was conflict of interest during this review.

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