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# Salvage Therapy for MDR-TB Combining Bedaquiline and Delamanid: A Systematic Review for an Effective Treatment for Tuberculosis

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**ABSTRACT**

Multidrug-resistant tuberculosis continuing its drug emergence among the population, the sensitivity to anti-TB drugs thus remains crucial. When existing therapy fails, a new approach is mandatory to control the spread of infection. The introduction of Bedaquiline (Bdq) and Delamanid (Dlm) alone has proven its effect in MDR-TB patients. Thus, the combination of these two efficacy proven drugs can be a milestone in controlling the emergence of MDR-TB. Even though WHO has not recommended a combined use of Bdq and Dlm unless mandatory, few studies that were carried out, shows a promising turning point to curb the MDR-TB. So, the study was aimed to identify, review, and understand the outcome of MDR-TB using Bdq and Dlm combination through a systematic review.

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## INTRODUCTION

MDR-TB has become one of the most urgent and difficult challenges worldwide. As per the WHO Indian TB report, the number of MDR-TB cases was 10822, and XDR-TB cases were 3794 [(1)]. The drug susceptibility test is a definitive diagnosis requirement for MDR-TB or XDR-TB. Various risk factors that contribute to MDR-TB are failure to category 1 or 2 of DOTS regimen, relapse or treatment after default from the first-line regimen, exposure to MDR-TB cases, or institution such as prison or hospital and the presence of HIV as a co-infection.

The reason for this growing number of MDR-TB cases is the continuing evolution of resistance to anti-TB drugs. The patients showing resistance to isoniazid and rifampicin are referred to as MDR-TB patients, whereas the XDR-TB represents resistance to fluoroquinolones and at least one SLIDs (capreomycin, kanamycin, and amikacin), in addition to MDR-TB [(2)]. Treating MDR-TB is a difficult task because second-line TB drugs require a longer duration of treatment with high toxicity. Each MDR-TB regimen is designed for the patient based on their DST. Due to the limited options of sensitive drugs in MDR-TB patients, the emergence of a newer drug regimen with Bedaquiline (Bdq) and Delamanid (Dlm) is quite promising.

Bdq was initially approved by the FDA in 2012 whereas Dlm was approved later in the year 2014. Both the drug should be added to a conventional MDR-TB or XDR-TB regimen designed specifically for the individuals.

This review aimed to identify, review, and understand the outcome of MDR-TB using Bedaquiline (Bdq) and Delamanid (Dlm) combination.

### Bedaquiline

A di-aryl quinolone (Bdq) has potent bactericidal activity with a specific mechanism to inhibit mycobacterial ATP synthase**.** When compared to its monotherapy, there was a significant increase in early bactericidal activity when combined with other bactericidal drugs (FQs, Z) [(3)]. The elimination half-life of Bdq is 5-6 months [(4)].

**Delamanid**

It is a mycolic acid biosynthesis inhibitor that has been approved by a European medicine agency but not by the FDA. Due to the weakness and paucity of existing evidence on Dlm, its effectiveness and kinetics are yet to be known**.** The elimination half-life of Dlm is 38 hours [(5)].

**Combined use of Bedaquiline and delamanid**

The WHO has not yet recommended their combined use even-though it can be used for 24 weeks in combination for patients with no other therapeutic option [(6)]. There are no prospective studies published yet in this area. Although many retrospective and observational studies have shown promising results. In 2016, a case report [(7, 8)] and case series published on the combination of these two drugs as salvage therapy for individuals were there where limited treatment option was recommended. Thereafter, various reports stated that the drugs can bring in QTc prolongation, which is still a major concern for this therapy thus, close electrocardiography remains mandatory while on these drugs.

**MATERIALS AND METHODS**

This work was done by searching various peer reviews and scientific evidence to assess the safety, tolerability, and efficacy of Delamanid and Bedaquiline combination regimen in MDR and XDR-TB patients.

Relevant manuscripts published in PubMed and Embase were used for systematic review using the keywords TB, Bedaquiline, Delamanid and their combination.

Conferences abstract, correspondence, reviews, and editorials studies on animal models with TB were excluded. Only original manuscripts written in the English language were included.

The articles which met inclusion criteria were selected by the authors independently after performing rigorous search and evaluation, followed by a critical cross-analysis of each paper that was performed to conclude salvage therapy.

## RESULTS AND DISCUSSION

**Maryandyshev et al. (2017),** this retrospective observational research enrolled patient's ≥ 15 years of age. Out of 428 patients treated with Bdq (400 mg for 14 days followed by 200 mg for 3weeks) and Dlm (200 mg/day), it was given in combination 5 patients (4 females and 1 male). The median age of patients was found to be 30 years. The median duration for drug exposure was 168 days. Among 5 patients, 1 patient was cured, 3 patients achieved culture conversion with 2 continuing treatment, and 1 changing therapy because Bdq and Dlm were already administered. Remaining 1 patient died from respiratory insufficiency. Only 2 patients experienced QTcF (Fridericia's corrected QT interval) prolongation where QT interval at 500 ms is the threshold. The patient who reached 520 ms at week 16 were advised for dosage adjustment and initiated verapamil, another patient with 509 ms required closer clinical observation with frequent ECG monitoring. Both patients' QTcF Interval were normalized. QT-prolonging drugs in addition to Bdq and Dlm like moxifloxacin (Mfx) and clofazimine need to be avoided if possible.

The authors concluded the study by stating, that the use of combination therapy of Bdq and Dlm is justifiable only in case of non-availability of other regimens for patients [(9)].

**Kim et al. (2018)**, enrolled a total of 61 patients (49 males and 12 females) with pulmonary MDR-TB retrospectively using cohort study. The median age of the patients was 53 years. Among 11 patients treated with both Bdq and Dlm, 10 were administered dose sequentially and 1 patient was given both the drug as co-administration. Sequentially 9 patients received Bdq followed by Dlm with a median interval of 71 days and 1 patient received Dlm followed by Bdq with a one-day interval. The duration of treatment in Bdq and Dlm was longer when compared treating with these drugs alone. The median duration of treatment with both drugs was 168 days among which Linezolid receiving 33 patients had a median duration of 673 days. Out of 55 patients who have completed 6 months of treatment, 11 patients were on both Dlm and Bdq, among which 7 achieved culture conversion, followed by 2 patients experienced QTcF prolongation resulting in discontinuation of the therapy, one was treated sequentially (Dlm and Bdq) and another receiving co-administration. These patients also received other QTcF prolonging drugs like Clofazimine (Cfz), Clarithromycin augmenting their potential harm, thus these drugs must be either avoided or administered with regular cardiac monitoring.

The study concluded that treating MDR-TB patients with both drugs simultaneously or sequentially needs careful monitoring of QTcF prolongation. Both the drugs were found to be effective and safe in treating MDR-TB, sequential administration of these drugs can be considered as a treatment strategy [10].

**Guglielmetti et al. (2018**), established a multi-centric case series of MDR-TB patients exposed to Bdq and Dlm combination for more than 30 days. 10 patients were included in the study among which all were male. The median age was 32 years with 171 days of exposure to the combination of both the drugs. Adverse events were reported in 7 patients, while 2 patients experienced QT prolongation due to additional drugs like Mfx and Cfz. Dlm was discontinued due to adrenal insufficiency and Bdq discontinued in a patient who was experiencing oligoarthritis and osteonecrosis. Among 10 patients, after 3 months of treatment, 8 of them achieved sputum culture conversion. After 8 months of treatment 9 patients were cured and one was lost to follow.

This study, in conclusion, stated that the tolerance of both drugs in combination was high among the population and the treatment option where there is a limited therapeutic alternative can be considered in resistance cases [11].

**Ferlazzo et al. (2018),** carried out a retrospective cohort study, which included 28 patients (17 males and 11 females) from January 2016 – August 2016. The median age was found to be 32.5 years and the median duration of treatment was 171 days. None of the patients showed a QTcF value greater than 500ms. Mild QT prolongation occurred in 4 patients, none of them were symptomatic or lead to discontinuation of Bdq or Dlm. They were receiving other QTc prolonging drugs like Cfz and Mfx. The study specified that 23 patients out of 28 were initially culture-positive and got converted to culture-negative in 2 months of treatment in the case of 8 patients, whereas for 17 patients it took 6 months of treatment with the drug to become culture negative. One patient passed away in the sixth week of treatment, due to HIV infection-induced severe immunosuppression.

In conclusion, the results of the study represented that the simultaneous use of both drugs in a patient is beneficial when there is no other treatment option left. The study also states the importance of regular assessment and monitoring for the safe use of the drug [12].

**Hyun et al. (2019),** the treatment duration of Bdq and Dlm were approved for 18 - 24 weeks. Here, a 45-year-old female patient with the previous history XDR-TB left untreated for 9 years due to non-availability of MDR sensitive drug and was later administered with Bdq and Dlm. Thus, a prolonged treatment duration involving Dlm (100mg BD) and Bdq (400mg OD for 2 weeks followed by 200mg for 3 weeks) for 48 weeks were administered in this patient. In this case, no serious ADRs were reported, even clinically significant QT prolongation was not observed. Culture conversion occurred after one month of treatment. Treatment was completed after 48 weeks with clinical improvement in chest radiography.

While concluding a prolonged and concomitant treatment with Bdq and Dlm under strict surveillance is a treatment option in intractable MDR-TB patients without serious ADRs [(13)].

**Holland et al. (2020),** Conducted a retrospective study with adolescents (10-19 years) initiating injectable free regimen containing Bdq (400mg followed by 200 mg for 3 weeks) and/or Dlm (100 mg BD, 10 years of age [50mgBD]). A total of 22 patients were enrolled in the study with a median age at 17 years among which 10 received Bdq, 8 received Dlm and the remaining 4 received both drugs. Several ADR's were experienced by patients. From 4 patients on combination therapy 2 patients were successfully treated, one failed treatment, and one passed away which was not drug-induced. Percentage of culture conversion from positive to negative with months of Bdq and/or Dlm treatment increased with time.

From the results, the study concluded that adolescents achieved excellent outcomes and were able to well-tolerated the injectable free RR-TB treatment regimen containing Bdq and Dlm [(14)].

The summary of all the studies selected for systematic review are tabulated in **Table No: 1.**

**Table No. 1: Summary of observed studies**

| First author, Year of publication | Patients(n) | MDR-TB Cases | XDR-TB | Sequential (Seq.)/ Concomitant (con.) | Additional QTc prolonging drugs | Median duration of treatment | ADR/discontinuation | Sputum conversion | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| Maryandyshev et al. (2017)[9] | 5 | 0 | 5 | Seq.-0 Con-5 | Cfz (3), Mfx (1), Mfx + Cfz (1) | 168 | QTc prolongation and no discontinuation(2) | 3 | Cured-1, Culture converted-3, Death - 1(respiratory failure) |
| Kim et al. (2018)[10] | 11 | 7 | 4 | Seq.-10 Con.-1 | Cfz, Clarithromycin | 168 | QTc prolongation due to Dlm, Bdq and discontinued(2) | 7 | culture conversion-7 |
| Guglielmetti et al. (2018)[11] | 10 | 4 | 6 | Seq.-4 Con-4 | Cfz (3), Mfx (1), Mfx + Cfz (4) | 171 | QTc prolongation and discontinued(Cfz, Mfx)(2) | 8 | Cured-9,LFTU-1 |
| Ferlazzo et al. (2018)[12] | 28 | 14 | 14 | Seq-0 Con-28 | Cfz(17),Mfx(4) ,Mfx+ Cfz(2) | 171 | Mild QT prolongation due to concomitant drugs(4) but not discontinued | 17 | Culture conversion-22, Culture positive-2,LFTU-1, Death – 1(HIV),Unclassified-1,Unable to produce sputum-1 |
| Hyun et al. (2019)[13] | 1 | 1 | 0 | Seq-0 Con-1 | Cfz | 336 | Cfz stopped(skin hyperpigmentation) | 1 | Cured |
| Holland et al. (2020)[14] | 3 | 1 | 0 | Seq-0 Con-4 | Cfz(4) | 171 | No | 2 | Cured-2, Failure1,Death-1 (Non-drug induced) |
| **TOTAL** | **58** | **27** | **29** | **Seq-14 Con-43** | - | **168-171** | **2/58** | **38** | **Cured-13/19** |

Bdq- Bedaquiline, Dlm - Delamanid, Cfx - Clofazine, Mfx- Moxifloxacin, MDR-TB- Multidrug resistance tuberculosis, XDR-TB- extensive drug-resistant tuberculosis, LFTU- Lost to follow up, Seq- Sequential, Con- Concomitant.

The data collection for the review involved 6 studies from the year 2017–2020 from various countries, with a total of 58 cases been treated with salvage regimen of Delamanid and Bedaquiline. Among the patients being treated, there were 27 cases of MDR-TB and 29XDR-TB cases.

Treating the patients with Bedaquiline and Delamanid was done sequentially in 14 patients and concomitantly in 29 patients. Sequential therapy was mostly done by Bedaquiline followed by Delamanid involving 13 patients and Delamanid followed by Bedaquiline in 1 patient.

In all the studies along with the Bedaquiline and Delamanid, there was a preferred background regimen. The usage of QTc prolonging drugs (Clofazimine, Moxifloxacin, and Clarithromycin) along with Bdq and Dlm increased potential harm which needs to be avoided if possible or monitored.

The duration of therapy varied from 168–171days in 5 studies, except for one study in which prolonged treatment effects were studied for 48 weeks.

QTc prolongation being the major concern with Bdq and Dlm its effect was monitored in the study. However, only 2 patients experienced QT prolongation leading to discontinuation of drugs (Bdq, Dlm). Various other adverse events have been reported due to concomitant drugs therapy which was insignificant.

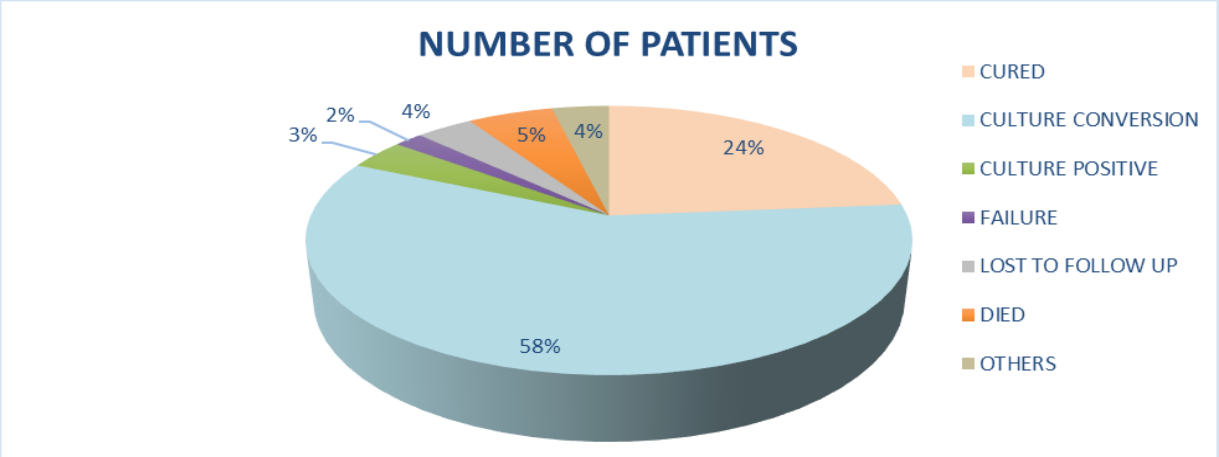


**Figure No. 1: Outcome**

The outcome of combination therapy (**Figure No: 1**) was estimated using sputum culture conversion, seen in 38 patients out of 58 patients. Whereas 13 out of 19 (24%) patients were cured due to the treatment involving the salvage regimen.

## CONCLUSION

Salvage regimen therapy combining Bedaquiline and Delamanid have shown promising and reliable efficacy in treating MDR-TB patients with very few other treatment regimen availabilities. The QT prolongation was not frequently observed due to synergism or additive effect from Bedaquiline and Delamanid.

The available studies were retrospective and limited, which were the major challenge in the study to completely understand the efficacy and safety of these drugs.

## ACKNOWLEDGMENT

Not applicable

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