

A Study of Sputum Smear Conversion in Drug-Resistant Tuberculosis after Taking Bedaquiline-Based Optimized Background Regimen (OBR) in a Tertiary Health Care Centre of South Gujarat

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Abstract

Background: Bed aquiline and delamanid offer a promising avenue for a more effective and less detrimental approach to treating multidrug-resistant tuberculosis (MDR-TB). Despite the advancements in this treatment, certain patients still confront a significant risk of an unfavorable treatment outcome. Due to a lack of conclusive evidence, the World Health Organization recommends their use under specific conditions in adults. We in the current study aimed to determine the Sputum Smear Conversion in Multi-Drug Resistant Tuberculosis after taking Bed aquiline-based Optimized Background Regimen (OBR).

Methods: The criterion for patients to receive Bed aquiline as approved by the Drug Resistant TB Committee guidelines: Adults aged >18 years having pulmonary DR-TB. Additional requirements: Non-pregnant females or females not on effective hormonal birth control methods are eligible. Patients with controlled stable arrhythmia can be considered after obtaining cardiac consultation. Bed aquiline is indicated in adult Multi-Drug Resistant TB patients not eligible for the newly WHO-recommended shorter regimen.

Results: A total of 49 cases of MDR TB were included in the study. At the end of 4th month, 2.04% population had positive culture conversion. In 5th month there is no positive culture conversion. At the end of the 6th month, 4.08% population had positive culture conversion. At the end of the 4th, 5th, and 6th month; 95.91%, 93.90%, and 87.75% of patients' sputum culture converted to negative respectively. In the study, we can see that in both the 9th month & and 12th month 1(2.04%) patients got positive culture conversion. Also, 44(89.79%) in 9th month and 43(87.75%) in 12th month got negative culture. In the 9th month, 4 patients got expired/lost to follow-up, and 5 patients got expired/lost to follow-up in the 12th month.

Conclusion: This study found that patients who were on bed aquiline-based OBR had more smear/culture conversion to negative. In addition, the time required for the same was less. Of the patients, 95.91% underwent smear and culture conversion in only three months. In addition, we did not find any single case of default. This is because drug tolerance was better than that of the previous regimen. The introduction of Bedaquiline in Shorter Regimen has also implicated a step towards an injection-free DR-TB regimen.

Keywords: Bed aquiline-based Optimized Background Regimen (OBR), multidrug-resistant tuberculosis, sputum conversion

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Introduction

Tuberculosis (TB) has inflicted considerable suffering and mortality, establishing itself as the most significant infectious bacterial disease in history, a global pandemic with profound and far-reaching consequences for its victims, particularly among marginalized individuals with lower socioeconomic status. This malady has roots deeply embedded in both the historical and contemporary facets of humanity. TB, a communicable disease, stands as a major contributor to poor health globally, ranking among the top 10 causes of death worldwide and claiming the leading spot as the

cause of death from a single infectious agent, surpassing even HIV/AIDS. [1] The Global Tuberculosis Report of 2020 indicates that TB's estimated global burden in terms of incidence and mortality stands at 26% and 32%, respectively. [2] Alarming statistics reveal that two out of every five Indians carry the TB bacillus, with a significant 10% likelihood of developing TB during their lifetime. [2] TB manifests in various organs, with pulmonary TB being the predominant form, often accompanied by or resulting in extra-pulmonary TB. The progression of the disease is contingent

upon an individual's immunity, with 90% of healthy individuals resisting its advancement. Among the remaining 10%, half may develop active TB within two years, while the other half may succumb later in life. [3] Despite a gradual global decline in TB incidence, the disease remains uncontrolled in numerous regions, compounded by the emergence of Drug-Resistant Tuberculosis (DR TB). The Global TB Report of 2020 highlights that 3.3% of new cases and 18% of previously treated cases in 2019 exhibited drug-resistant TB, with India accounting for 27% of these cases. In India, efforts to eradicate TB have intensified through the implementation of the National Strategic Plan (2017-2025) over the past three years. [4] The National TB Programme underwent a transformation, now known as the National Tuberculosis Elimination Programme (NTEP), reflecting a dedicated resolve to eliminate TB from the country.

Furthermore, drug-resistant Tuberculosis (TB) remains an ongoing menace to global health. In 2016 alone, there were 600,000 reported cases of new rifampin-resistant TB (RR-TB), among which 490,000 were classified as multidrug-resistant TB (MDR-TB) [5]. The protracted treatment regimen for MDR-TB spans 20 to 24 months and involves the use of several highly toxic drugs, including kanamycin, capreomycin, and amikacin, which are known to pose the risk of causing deafness [6]. Clinicians are cognizant of the prolonged treatment duration, the elevated toxicity associated with anti-TB drugs, and the frequent complications observed in patients. Consequently, devising an effective treatment regimen proves challenging, requiring the careful selection of at least 4 to 5 active drugs [5, 7, 8]. Moreover, despite these efforts, the treatment outcomes for MDR-TB remain notably suboptimal, with a global treatment success rate of only 54% [5]. In recent times, the introduction of two novel drugs, namely bedaquiline and delamanid, has marked a significant advancement in the treatment of multidrug-resistant Tuberculosis (MDR-TB). Bedaquiline, classified under a novel category of anti-TB drugs called diarylquinolines, operates by inhibiting mycobacterial adenosine triphosphate synthases [9]. A phase II trial has demonstrated that bedaquiline yields improved treatment outcomes [10]. Moreover, findings from compassionate use programs indicate promising new treatment possibilities for individuals with incurable MDR-TB and bleak prospects of recovery [11,12]. With this background, we in the current study tried to evaluate the interim outcome of Bedaquiline in combination with the recommended Drug Resistant TB treatment regimen in terms of Smear and culture conversion

Material and Methods

This prospective study was conducted in the

Department of Pulmonology study Participants were selected from patients coming to the Tertiary Healthcare Centre of South Gujarat and participants were enrolled as per below mentioned criteria. Verbal and written consent were taken from all the participants before starting the interview. Institutional Ethical approval was obtained for the present study. The study period was of 15 months (June 2020-August 2021) in which patients were enrolled or recruited for 3 months (June 2020- August2020). Enrolled patients were followed up for 12 months. The method of sampling used in the current study was convenient sampling.

Inclusion Criteria

1. All those patients were put on the Bedaquiline-based OBR during the study period.
2. Those who are willing to participate in the study by giving written informed consent.

The criterion for patients to receive Bedaquiline as approved by the Drug Resistant TB Committee guidelines:

1. Adults aged > 18 years having pulmonary DR-TB
2. Additional requirements:
 - Non-pregnant females or females not on effective hormonal birth control methods are eligible.
 - Patients with controlled stable arrhythmia can be considered after obtaining cardiac consultation.

Bedaquiline is indicated in adult Multi Drug Resistant TB patients not eligible for the newly WHO- WHO-recommended shorter regimen. These may include

1. Multi-drug resistant/Rifampicin Resistant TB patients with resistance to any / all Fluoroquinolones OR any/all Second line injectables. (Pre-XDR TB patients)
2. Extensive Drug Resistant Tuberculosis patients.
3. Mixed pattern resistant TB patients.
4. Treatment failures of Multi-Drug Resistant TB with Fluoroquinolones/Second Line Resistance OR Extensive Drug Resistant TB.

Exclusion Criteria

1. Currently having an uncontrolled cardiac arrhythmia that requires medication.
2. Patients < 18 years of age
3. Patients having evidence of chorioretinitis, optic neuritis, or uveitis at screening which precludes long-term linezolid therapy

Out of all newly diagnosed DR TB patients at the center, we selected the patients who were eligible

for the Bedaquiline-based Optimized Background Regimen. Then we explained and informed the patient regarding the study. The patients who gave verbal and written consent were enrolled in this study. After all baseline routines and other needed work-ups, we started the treatment with regular monthly follow-up till the first 6 months of treatment. After 6 months, three monthly follow-ups are done according to guidelines. We noted the baseline investigations, references, and clinical

status. During the mentioned follow-ups, patients were examined for the efficacy of treatment, side effects caused by the drug, and clinical and radiological aspects according to guidelines. Side effects to be studied are Gastrointestinal complaints, Hepatorenal Toxicity, Peripheral Neuropathy, Hearing disturbances, Depression and other psychological illnesses, Visual disturbances, QT prolongation, seizures, hypothyroidism, etc.

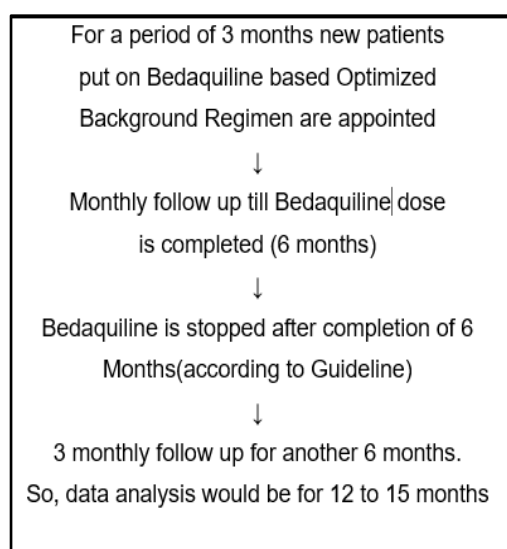


Figure 1: Illustrating the framework of the study

Investigations Required: Detailed history, Previous history of ATT taken, weight and Height Thorough clinical examination, Complete Blood Count with hemoglobin & and platelets count Blood sugar to screen for Diabetes Mellitus, Liver function test, Blood Urea and serum Creatinine to assess renal function, Urine examination- routine and microscopic, Serum electrolytes- potassium, magnesium, calcium, Serum amylase, lipase, proteins, TSH levels to assess the thyroid function, Urine Pregnancy test (for all women in childbearing age), HIV counselling and testing, Chest X-ray, ECG, Audiogram, Mental health evaluation, Ophthalmologist opinion

Statistical Analysis: The data were inputted into Microsoft Excel software and analyzed using SPSS-21 with coded representations. Categorical variables are represented as percentages, and

continuous variables are expressed as mean and standard deviation. Paired t-tests were employed to assess categorical variables. Statistical significance was considered for p-values less than 0.05.

Results

A total of 49 cases were included in the study out of which 31(63.27%) were males and 18(36.73%) were females. The age-wise distribution of patients in the study is given in Table 1. It shows that young adults (aged 18-27) are disproportionately affected by MDR TB in this study population. This age group represents nearly 40% of the cases, highlighting a concerning trend of MDR TB occurring in younger individuals. The gradual decline in frequency with increasing age suggests that MDR TB is less common in older adults in this cohort.

Table 1: Age Distribution of Patients included in the study

Age Group	Frequency (N=49)	Percentage
18-27	19	38.78
28-37	11	22.45
38-47	06	12.25
48-57	10	20.40
58-67	02	4.08
68-77	00	0.00
78-87	01	2.04

In our study, 26(53%) patients are underweight, followed by 18(37%) patients having healthy weight and 5(10%) patients are overweight (Table 2).

Table 2: BMI and Weight Status of Patients

BMI	Weight Status	Frequency (N=49)	Percentage
Below 18.5	Underweight	26	53
18.5-24.9	Healthy Weight	18	37
25-29.9	Overweight	5	10
30.0 and above	Obesity	0	0

In our study, 28(57.14%) patients had a history of Tuberculosis in the past, and 21(42.86%) had no history of tuberculosis.

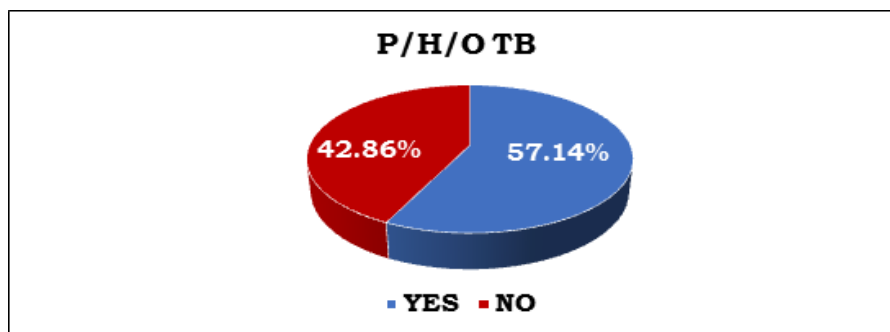


Figure 2: Showing the history of tuberculosis in the patients of the study.

Table 3 summarizes the **past anti-tubercular treatment (ATT) history of 49 MDR TB patients**. Treatment completion status: Completed ATT for DSTB (drug-sensitive TB): 23 patients (46.93%) had completed treatment for non-MDR

TB in the past. Completed ATT for DRTB (drug-resistant TB): 7 patients (14.28%) had previously completed treatment for MDR TB itself. Defaulted ATT: 3 patients (6.12%) defaulted on DRTB treatment.

Table 3: Interpretation: Anti-Tubercular Treatment History of MDR TB Patients

	No of Patients (N=49)	Percentage
Completed ATT for DSTB	23	46.93
Completed ATT for DRTB	7	14.28
Defaulted ATT for DSTB	-	-
Defaulted ATT for DRTB	3	6.12

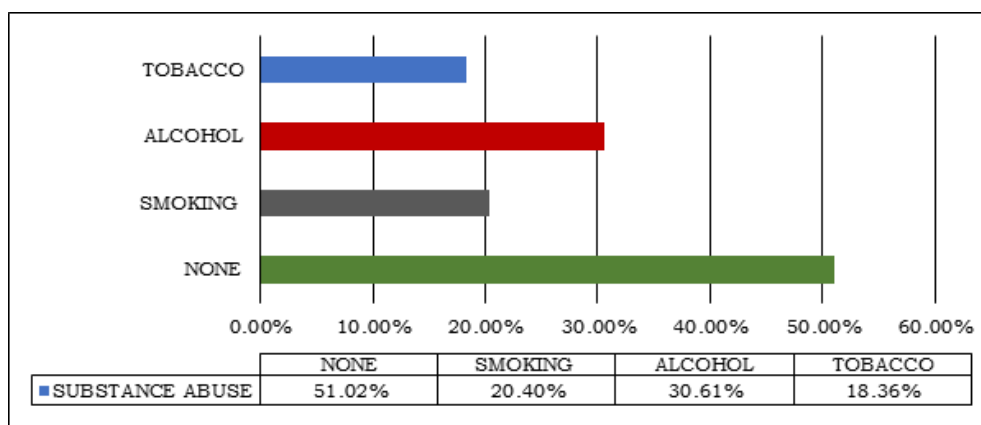


Figure 3: Showing substance abuse distribution in the patients of the study

In this study, out of 49 patients about 15 (30.61%) had a history of contact with tuberculosis, as the family member is having the disease. Out of 49 patients, a history of alcoholism was present in 15 (30.61%), smoking in 10(20.40%) and tobacco

chewing in 9(18.36%) depicted in Figure 3. In our study out of 49 patients, 13(26.53%) had pallor, and 36(73.47%) patients did not have any of the above general examination findings.

Table 4: Socioeconomic status of MDR TB patients

Socio-Economic Status	No of Patients (N=49)	Percentage
Upper Class	-	-
Upper Middle Class	14	28.60
Lower Middle Class	17	34.68
Upper Lower Class	8	16.32
Lower Class	10	20.40

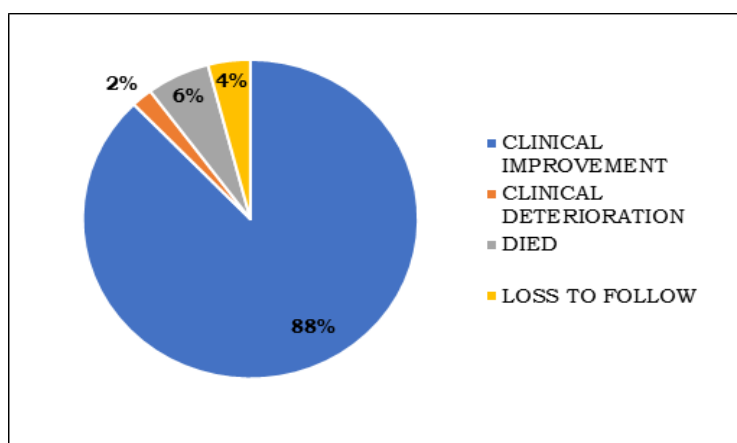
The majority of patients 17(35%) have up to primary education, followed by 14(29%) patients having up to secondary education. Only 3(6%) patients are graduated. Table 4 demonstrates the socioeconomic status (SES) distribution of 49 MDR TB patients, as determined by the Modified Kuppuswamy Scale. No patients fall within the Upper-Class category, suggesting an absence of MDR TB cases from the highest SES group in this study population. The majority of patients (63.28%) belong to the Middle Class categories:

Upper Middle Class: 14 patients (28.60%), Lower Middle Class: 17 patients (34.68%). The remaining patients fall within the Lower Classes: Upper Lower Class: 8 patients (16.32%) Lower Class: 10 patients (20.40%). In our study, we can see that 24(48.97%) patients have a non-vegetarian diet, followed by 18(36.73%) vegetarian and 7(14.30%) mixed diet. In the study, we find that 2(4.09%) patients are HIV Positive, and 47(95.91%) patients are HIV Negative.

Table 5: Showing CXR of MDR TB patients

CXR	No of Patients (n=49)	Percentage
NAD	0	00.00
Pulmonary Infiltrate	29	59.18
Cavitary Lesion	26	53.06
Consolidation	5	10.20
Milliary Findings	3	6.12
Mediastinal or Hilar Lymphadenopathy	3	6.12
Blunting Of Castophrenic Angle	1	2.04
Old Lesions	20	40.81

In the present study, we observed that 33(67.34%) patients were put on BDQ-based OBR on DST Based Criteria, and 16(32.66%) patients on Non-DST Based Criteria. DST-based criteria include resistance to drugs. Non-DST-based criteria include Clinical failure, Defaulted previous ATT, Clinical judgment, and non-compliance for a shorter regimen.

**Figure 4: Showing the clinical assessment at the end of 12 months in the patients of the study.**

In the present study, we can see that 43(87.75%) patients showed clinical improvement during twelve months of the treatment. During treatment 5(10.20%) patients died/lost to follow up and 1(2.04%) suffered clinical deterioration. In the present study, we find that 47(95.91%) patients' smears converted to negative, and 1(2.04%) patient

had still a positive smear after three months of ATT. One patient got expired within three months of starting ATT. By 4th month of ATT, one patient got expired/lost to follow-up, at 5th month of ATT three patients got expired/lost to follow-up, at 6th month of ATT four patients expired/lost to follow-up.

Table 6: showing smear conversion at the end of the 4th, 5th, and 6th Months

Smear	4 TH Month		5 TH Month		6 TH Month	
	Patient (n=49)	Percentage	Patient (n=49)	Percentage	Patient (n=49)	Percentage
Positive	1	2.04	1	2.04	2	4.08
Negative	47	95.91	45	91.63	43	87.75

Table 6 shows that at the end of the 4th, 5th, and 6th month; 95.91%, 91.63%, and 87.75% of patients' sputum smear converted to negative respectively. At the end of the 4th, 5th, and 6th month; 2.04%, 2.04%, and 4.08% of patients' sputum smears were positive.

Table 7: showing culture conversion at the end of 4th - 12th month

Culture	4 TH Month		5 TH Month		6 TH Month		9 TH Month		12 TH Month	
	(n=49)	%	(n=49)	%	(n=49)	%	(n=49)	%	(n=49)	%
Positive	1	2.04	0	0	2	4.08	1	2.04	1	2.04
Negative	47	95.91	46	93.90	43	87.75	44	89.79	43	87.75

Table 7 shows that at the end of the 4th month, 2.04% population had positive culture conversion. In 5th month there is no positive culture conversion. At the end of the 6th month, 4.08% population had positive culture conversion. At the end of the 4th, 5th, and 6th month; 95.91%, 93.90%, and 87.75% of patients' sputum culture converted to negative respectively. In the study, we can see that in both the 9th month and 12th month 1(2.04%) patients got positive culture conversion. Also, 44(89.79%) in 9th month and 43(87.75%) in 12th month got negative culture. In the 9th month, 4 patients got expired/lost to follow-up, and 5 patients got expired/lost to follow-up in the 12th month.

Discussion

In this study, we analyzed 49 patients with drug-resistant pulmonary tuberculosis who underwent treatment with a bedaquiline-based Optimized Background Regimen (OBR) in South Gujarat. Interim results over 12 months revealed favorable outcomes, including clinical and radiological improvement, minimal observed adverse drug reactions, and early sputum conversion. Key observations included a male predominance (63.26%), a median age of 30 years, and a significant proportion of patients with a BMI below 18.5, indicating underweight individuals. The study focused on South Gujarat, identifying urban areas, particularly Surat Municipal Corporation, as more susceptible to tuberculosis than rural regions, with Vyara having the least cases and Dang district reporting none. The socioeconomic status was 34.68% from the lower middle class and 28.60% from the upper middle class. Occupations varied: 30.61% homemakers, 26.53% skilled workers, and 22.44% unskilled workers. Approximately 48.97% of the participants had a nonvegetarian diet. Interestingly, the study found no clear association between occupation and diet, drug-resistant tuberculosis, and treatment outcomes. HIV co-

infection was present in only 4.09% of the patients in this study. In the present study, the mean age of the cohort was 30 years (range of 23.5 – 79 years). In a similar study by Gao et al. [13], the mean age at prevalence was 36 years 28 – 50 years. Mbuagbaw L et al. [14] 36.4 years age range they found was 24.8 – 48.2 years. In the present study, we found that half of the patients (53%) were underweight and 37% had a healthy weight status. The remaining 10% of the patients were overweight. The present study found a history of tuberculosis was present in 57.14% of the patients. Oлару et al. [15] found that the history of tuberculosis in patients with MDR was 59%, and Borisov et al. [16] found a history of tuberculosis in 78% of the cases in their study. In the present study, we included 10 patients (n=49, 20.41%) with a history of drug-resistant TB; hence, they were exposed to second-line ATT. Among them, 7 patients (14.28%) had completed the treatment previously and 3 patients (6.12%) had defaulted it. Franke et al. [17] reported that 75% of patients had a history of second-line drugs, and 86.3% in the study by Mbuagbaw et al. [14] Tuberculosis recurrence and a history of drug-resistant tuberculosis were prevalent risk factors, while alcoholism, smoking, and tobacco chewing were identified in 30.61%, 20.40%, and 18.36% of patients, respectively.

In the present study, of 49 patients, 13(26.53%) had pallor and 36(73.47%) had no general examination findings. In the present study, 24(48.97%) patients had a non-vegetarian diet, followed by 18(36.73%) vegetarians, and 7(14.30%) mixed diets. The present study found 4.09% of cases of drug-resistant tuberculosis had HIV co-infection SE Borisov et al. [16] found HIV co-infection in 22.1% of cases and Mbuagbaw L et al. [14] found 25.7% of drug-resistant tuberculosis cases. In the present study, we observed that 33(67.34%) patients were placed on BDQ-based OBR on DST-based criteria and 16(32.66%) patients on non-DST-based criteria. In the present study, smear, and

culture conversion rates, in 3rd month are 95.91% and 95.91% respectively, at 4th month are 95.91% and 95.91% respectively, at 5th month are 93.90% and 93.90% respectively, at 6th month are 87.75% and 87.75% respectively. culture conversions in the 9th and 12th months were 89.79% and 87.75%, respectively. We collected these data according to the guidelines for DR TB under the NTEP. Kim JH et al. [18] in Korea found that bedaquiline elicited more rapid culture conversion. The results of this Korean subpopulation study demonstrated that bedaquiline addition to the background regimens yielded good therapeutic results. Furthermore, the observed 75% culture conversion rate at week 120 and 70% cure rate. Other studies have shown that the median time to culture conversion in the bedaquiline treatment group was 83 days, while others have reported 85 days [10, 11]. Culture conversion is comparable to the 65% rate reported by the C208 study [10]. In the C209 study, the culture conversion and cure rates were 72.2% and 61.0 %, respectively. Franke MF et al. [17] found that 85% of the patients experienced a favorable interim outcome (i.e. conversion of sputum from positive to negative) within 6 months. Mbuagbaw et al. [14] found that the culture conversion rate at the end of the 6 months was 78.0%. In addition, Oлару et al. [15], 79.5% of culture conversion occurred at the end of the 6th month.

Conclusion

In the present study, we observed 49 patients who received a bedaquiline-based optimized background regimen for drug-resistant pulmonary tuberculosis in South Gujarat. We considered the interim outcome of the treatment, which is 12 months from the beginning of the treatment to the twelfth month of treatment. It was found that patients who were on bedaquiline-based OBR had more smear/culture conversion to negative. In addition, the time required for the same was less. Of the patients, 95.91% underwent smear and culture conversion in only three months. In addition, we did not find any single case of default. This is because drug tolerance was better than that of the previous regimen. The introduction of Bedaquiline in Shorter Regimen has also implicated a step towards an injection-free DR-TB regimen. This goal of Govt. in India is clinically welcomed. Ultimately, our focus is on an acceptable and adherent drug-resistant TB regimen for the patients. We conclude that this new molecule, bedaquiline, plays a pivotal role in the treatment of drug-resistant tuberculosis.

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