

# Comparison of Extremely Drug Resistant Tuberculosis Versus Multidrug Resistant-Tuberculosis Patients Attending a Tertiary Care Center Delivering DOTs Plus Regime

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## Abstract

**Background:** Extremely drug resistant tuberculosis (XDR-TB) is a very difficult clinical problem currently faced by many of the developing and some of the developed nations of the world. It is associated with considerable morbidity and mortality. Less effective medications with frequent side effects makes the scenario all the more worse. In Kerala, the Revised National Tuberculosis Control Programme (RNTCP) has implemented the Programmatic management of drug resistant tuberculosis by providing standardized treatment for XDR-TB under the CAT-V regime and CAT-IV regime for MDR TB patients under the DOTs plus strategy which is a nationwide TB control programme currently existent throughout the whole of India.

**Aim:** To compare the clinical profile and mortality trends of XDR versus MDR TB patients attending a tertiary care setting.

**Methodology:** All patients who got enrolled for the CAT-IV & CAT-V regime as per RNTCP for MDR & XDR-TB respectively at the DOTs plus centre, Kozhikode from June 2012 till the second quarter of June 2014 were included for the descriptive analysis.

**Results:** There were 4.14 & 0.22 cases per lakh population of MDR/XDR-TB cases reporting to this centre during this period. Majority were males, smokers among both the groups. 38.8% of MDR TB patients and 45% of XDR TB patients were diabetics. 50-60% mortality was observed for XDR TB patients during this period as compared to 16-25 % mortality in MDR TB patients.

**Conclusion:** This study showed that XDR TB as compared to MDR TB was more difficult to manage and had more than double mortality rates. Hence stress should be more on early diagnosis and proper management of drug sensitive cases and MDR-TB cases and reducing incidence of XDR TB cases.

**Key words:** Extremely drug resistant tuberculosis (XDR-TB), MDR-TB (multi drug resistant tuberculosis), DOTs plus, mortality, Category -IV (CAT-IV) & Category -V (CAT-V) regimes.

## INTRODUCTION

Extremely drug resistant tuberculosis (XDR-TB) is defined as resistance to at least INH, RIF, a fluoroquinolone, and one of the 3 second line injectable agents (AK, KM, or CM).<sup>1</sup> Pre-XDR TB is defined as multidrug

resistant-TB (MDR-TB) patients with resistance to either fluoroquinolone or second-line injectable drug. A few scattered reports reveal the prevalence ranging from 2.4% to 33.3%.<sup>2-4</sup> By 2010, according to the World Health Organization (WHO), XDR-TB patients were reported from a total of 58 countries with at least one case. The proportion of XDR-TB among MDR-TB was 5.4% from pooled data. Velayati *et al.* introduced the term super XDR-TB, for strains with resistance to all available first and second line medications which are also known as total drug resistance (TDR).<sup>5</sup> In a study conducted in KwaZulu Natal, South Africa, from 1428 presenting to the district hospital with signs and symptoms of TB, the probability of having MDR-TB was 13% and XDR-TB 2%.<sup>6</sup> In Kerala, a

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study by Joseph *et al.* revealed that ancestral East-African Indian lineage comprised the majority of circulating MTB genotypic clones.<sup>7</sup>

Treatment of the patients with XDR-TB is challenging because of the lack of potent anti-TB drugs, frequency of adverse reactions, and poor treatment outcomes.<sup>8,9</sup> In a 2010 systematic review and meta-analysis by Jacobson *et al.*, evaluating 13 observational studies including 560 patients, the pooled treatment success rate was 43.7% with a mortality of 20.8%.

Worldwide the reported proportion of MDR-TB was 4.9% among new cases and around 22% cases in retreatment cases in 2015. Kerala being a linear strip of land along the Arabian coast with 14 districts and estimated 32 million population, DOTs plus services were instituted for the southern seven districts with the DOTs plus site at Thiruvananthapuram in December 2008. The northern seven districts have their DOTs plus site located at Kozhikode which started functioning in February 2009. This study is a comparative analysis of XDR and MDR-TB patients started on CAT-IV/CAT-V regime from the DOTs plus site of a tertiary care center aimed to know the profile and mortality trends in these patients.

## MATERIALS AND METHODS

### Aim of the Study

This paper is aimed to analyze the various trends noted while managing this dreaded disease as per the current PMDT Guidelines. This would definitely give insights regarding the severity and helps in predicting the possible outcome in many of these patients.

### Study Methodology

#### Design

Study methodology design was STROBE - descriptive analysis.

#### Setting

DRTB Centre, Institute of Chest Diseases, Government Medical College, Kozhikode, Kerala, India.

#### Time of analysis

This study was conducted from June 2012 to June 2014, Second quarter.

### Protocol

#### Inclusion criteria

All patients who got enrolled for the CAT-IV and CAT-V regime as per Revised National TB Control Programme (RNTCP) for MDR and XDR-TB, respectively, in this DRTB Centre from June 2012 till the second quarter of

June 2014 were included in the study group and none were excluded from the study.

### Study Proper

Patient data were recorded in structured format that included the demographic data, comorbidities, contact history, and other relevant details including HIV screening from a VCTC. The checklist for investigations should include, blood routine, urine routine, chest X-ray PA view, LFT, RFT, FBS/PPBS, HbA<sub>1c</sub> (optional), TFT, ECG, uric acid (optional), and pregnancy test in females in the reproductive age group. All the patients who were diagnosed as XDR-TB based on the culture report provided from the Intermediate Reference Laboratory at Thiruvananthapuram were started on a standardized weight based regime, Category V. The regime is for 24-30 months.

Drugs dosage/day (<45 kg/>45 kg) is as follows:

- Injection capreomycin (CM) 750 mg/1000 mg,
- PAS 10 g/12 g,
- Moxifloxacin (MFX) 400 mg,
- High dose INH 600 mg/900 mg,
- Clofazimine (CFZ) 200 mg,
- Linezolid (LZD) 600 mg,
- Amoxycylav(Amx/Clv) 875/125 mg BD,
- Pyridoxine 100 mg

(Reserve/substitute drugs: Clarithromycin 500 mg BD, thiacetazone 150 mg).

Intensive phase (6-12 months) Cm, PAS, MFX, high dose-H, CFZ, LZD, AMX/CLV followed by.

Continuation phase (18 months) PAS, MFX, high dose-H, CFZ, LZD, AMX/CLV.

All MDR-TB patients received CAT-IV regime as follows:

6(9) Km Z E LFX Eto Cs/18 E Lfx Eto Cs

KM: Kanamycin, Z: Pyrazinamide, E: Ethambutol, LFX: Levofloxacin, ETO: Ethonamide, CS: Cycloserine.

The profile and mortality trend of the XDR-TB patients were analyzed and compared against the MDR-TB patients enrolled in the DRTB Centre at that point of time.

## RESULTS

There were a total of 785 patients enrolled for the second line regimes in the DOTs plus site of Kozhikode at this point of time. Out of this, 745 (94.9%) were MDR-TB patients and 40 were XDR-TB (5.1%) Figure 1.

Upon finer scrutiny, it was seen that out of the 40 XDR-TB patients enrolled for CAT-V regime, 37.5% (15/40) cases came under the definition of true XDR-TB, 60% (24/40) came under the Pre-XDR-TB group and one patient was started on CAT-V following failure of CAT-IV regime Figure 2. This works out to 4.14 and 0.22 cases per lakh population for MDR/XDR-TB cases, respectively.

There was a clear gender preponderance noticed among the XDR-TB patients with males dominating the picture with a male to female ratio of 3.4:1, Table 1. A similar picture was seen in case of MDR-TB patients where the male to female ratio was 3.7:1, Table 2. The clear gender predominance in either groups points toward the fact that males are more prone to develop serious forms of pulmonary TB which could be due to poor adherence to treatment and increased mobility of the male gender exposing themselves to the higher risk of acquiring the disease through airborne transmission related to his job or due to his addictions or associated comorbidities which might be compromising these patients' immune system.

The body weight of both MDR and XDR-TB patients showed that there were a large proportion of

patients belonging to >45 kg weight band in either group, Tables 3 and 4.

A huge number of smokers were seen among MDR-TB patients and by the time they got transformed to XDR-TB the number of smokers dropped drastically to about 50% of smokers as seen among the MDR-TB patients, Table 5.

When the number of diabetics in both groups was compared, it was seen that 38.8% of MDR-TB and 45% of XDR-TB patients were diabetics, thus making diabetes a major risk factor in converting drug-sensitive organisms to a drug-resistant variety.

Hence, addressing diabetes by concurrently offering specialized care for diabetes control could curtail to a great extent the development of this menace, and currently,

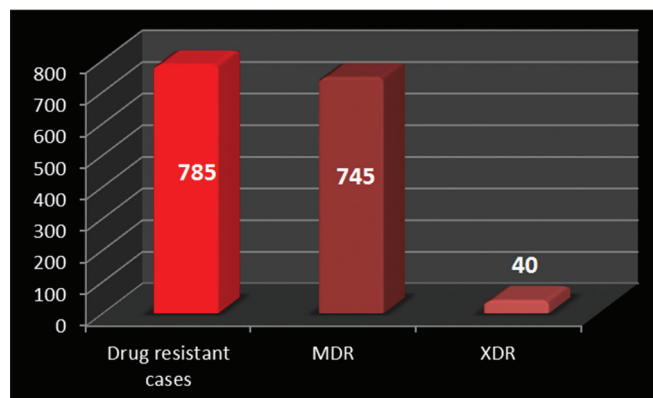


Figure 1: Total number of multidrug resistant tuberculosis and extremely drug resistant tuberculosis patients

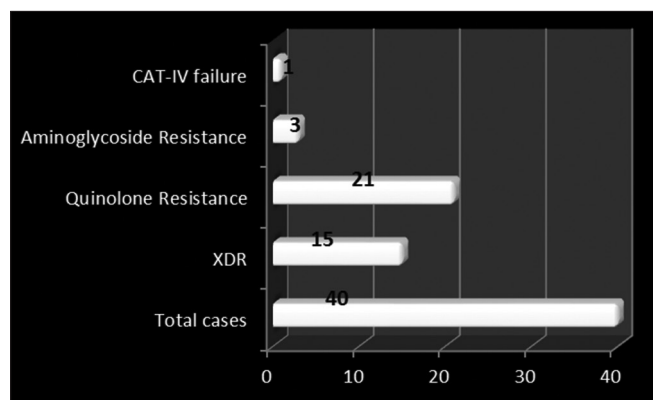


Figure 2: Profile of extremely drug resistant tuberculosis patients

Table 1: Gender profile of XDR-TB patients

Males	31
Females	9
Total	40

XDR-TB: Extremely drug resistant tuberculosis

Table 2: Gender profile of MDR-TB patients

Males	585
Females	160
Total	745

MDR-TB: Multi drug resistant tuberculosis

Table 3: Body weight of XDR-TB patients

Weight	Number
>45 kg	14
<45 kg	26
Total	40

XDR-TB: Extremely drug resistant tuberculosis

Table 4: Body weight of MDR-TB patients

Weight	Number
<45 kg	321
>45 kg	524
Total	745

MDR-TB: Multi drug resistant tuberculosis

Table 5: Smoking status of MDR and XDR-TB patients

Variables	MDR-TB	XDR-TB
Total patients	745	40
Smokers	448	13
%	60.2	32.5

MDR-TB: Multi drug resistant tuberculosis, XDR-TB: Extremely drug resistant tuberculosis

all the smear positive cases coming under RNTCP are screened for both retro positive statuses as well as for the presence of uncontrolled diabetes, Tables 6-9. Fortunately, the proportions of retro positive patients among MDR and XDR-TB patients are not alarming at present.

About 17.6% cases among the MDR-TB patients and 24% cases of XDR-TB cases had adverse events warranting admission. Arthralgia due to hyperuricemia, sensorineural deafness attributable to aminoglycosides, hypothyroidism due to thioamides and PAS, psychiatric abnormality and peripheral neuropathy due to cycloserine and bone marrow suppression due to LZD were among the serious side effects encountered in our center. However, it was interesting to note that despite having high incidence of GI intolerance which was a common manageable side effect on an OP basis, only very few patients had hepatic derangement requiring inpatient care.

Three consecutive years of treatment success was analyzed for MDR-TB patients and it was found to be around 58-60% which conforms to the existing reported success rates in well-managed DOTs plus centers elsewhere in the world, Table 10.

**Table 6: Diabetic status of MDR and XDR-TB patients**

Variable	MDR	XDR
Total patients	745	40
Diabetics	289	18
Percentage	38.8	45

MDR-TB: Multi drug resistant tuberculosis, XDR-TB: Extremely drug resistant tuberculosis

**Table 7: Gender status of MDR-TB diabetics**

MDR diabetics	n=289 (%)
Males	202 (69.9)
Females	87 (30.1)

MDR-TB: Multi drug resistant tuberculosis

**Table 8: Gender status XDR-TB diabetics**

XDR diabetics	Total (18)	%
Males	15	83.3
Females	3	16.7

XDR-TB: Extremely drug resistant tuberculosis

**Table 9: HIV status XDR-TB patients**

Variables	MDR	XDR
Total	745	40
HIV +	14	0
%	1.9	0

MDR-TB: Multi drug resistant tuberculosis, XDR-TB: Extremely drug resistant tuberculosis

A similar attempt was done to assess the treatment success trends of XDR-TB patients during the same period. It was noted that the treatment success rate was as low as 30-50% in case of XDR-TB patients (Table 11) which clearly points toward the fact that this could be a setback for the success of the DOTs plus program unless the number of XDR-TB cases are drastically reduced by placing proper stress on managing drug sensitive TB and MDR-TB cases and to offer tailored regime based on the second line drug sensitivity pattern for XDR-TB cases.

When we looked into the mortality trends of these dreaded disease, it was seen that MDR-TB has a mortality of 16-25% which skyrocketed to the alarming rates of 50-60% in cases of XDR-TB (Tables 12 and 13).

## DISCUSSION

In India, the RNTCP offers standard regime for all MDR and XDR-TB patients under the DOTs plus strategy. 2 years beyond sputum conversion is the standard treatment duration recommended for XDR-TB. Results from the 2013 meta-analysis by Falzon *et al.*, reported treatment success was highest if at least 6 drugs were used in the intensive phase and four in the continuation phase. It was

**Table 10: Success rates of MDR-TB patients**

Year	2012	2013	2014-2 <sup>nd</sup> quarter
Total MDR registered	153	112	56
Treatment success	90	68	34
Success rate (%)	58.80	60.70	60.70

MDR-TB: Multi drug resistant tuberculosis

**Table 11: Success rates of XDR-TB patients**

Year	2012	2013	2014-2 <sup>nd</sup> quarter
Total XDR registered	6	8	10
Treatment success	3	4	3
Success rate (%)	50.00	50.00	30.00

XDR-TB: Extremely drug resistant tuberculosis

**Table 12: Mortality trend of MDR-TB patients**

Year	2012	2013	2014-2 <sup>nd</sup> quarter
Total MDR registered	153	112	56
Death	25	18	14
Death rate (%)	16.30	16.10	25

MDR-TB: Multi drug resistant tuberculosis

**Table 13: Mortality trend of XDR-TB patients**

Year	2012	2013	2014-2 <sup>nd</sup> quarter
Total XDR registered	6	8	10
Death	3	4	6
Death rate (%)	50	50	60

XDR-TB: Extremely drug resistant tuberculosis

also noted that addition of a newer quinolone resulted in more success despite the strain showing resistance to an earlier quinolone *in vitro*. This study was performed as an effort to compare the clinical profile as well as the mortality trends in MDR and XDR-TB patients attending our center.

In our study, male gender, uncontrolled diabetes, and smoking status were associated with more number of MDR and XDR-TB patients which has to be further evaluated as potential risk factors for the development of drug-resistant TB. In one study, super-XDR-TB (total drug resistance) patients ( $n = 15$ ), the male to female ratio was more than threefold, with statistical relevance ( $P < 0.05$ ).<sup>5</sup> There were a considerable number of pre XDR-TB patients who were started on CAT-V regime owing to quinolone resistance in our study. Hence, routine use of quinolones without ruling out TB should not be encouraged in any case of lower respiratory tract infection. Recent studies report that approximately 30% of OFX-resistant strains are still susceptible to MFX. Jacobson *et al.* reported that use of a later generation fluoroquinolone in the setting of XDR-TB was associated with better treatment outcomes. In a 2014 retrospective study from the Republic of Korea by Jo *et al.*, MDR-TB patients with OFX-resistant disease had significantly better treatment outcomes when the isolate was MFX-susceptible (treatment success in 73% vs. 42%).

In two randomized studies, XDR-TB patients treated with LZD had higher culture conversion and treatment success than those in control arms. However, in both studies, 82% of the patients had clinically significant adverse events. In a systematic review (11 studies, 148 patients), any adverse event was 62% with 36% discontinuing LZD due to adverse events. Hence, there was evidence for the fact that LZD was responsible for about 58% of adverse events leading to discontinuation of an XDR regime which indirectly adds to the increased mortality and low success rate of XDR-TB management. High rates of myelosuppression and neurologic toxicity (with peripheral and optic neuropathy which were often not reversible) were encountered with regimes comprising higher doses of LZD.

Alternate choices such as ethionamide and prothionamide with PAS increased gastric intolerance and induced hypothyroidism more rapidly. CFZ containing regimens have been associated with a higher percentage of culture conversion (40% vs. 29%) and an independent predictor of conversion and survival in patients with XDR-TB. In a small randomized controlled trial, sputum culture conversion and cavity closure occurred earlier in patients in the CFZ-containing regimen, and treatment success was higher (74% vs. 54%). Five of six patients with severe XDR-TB converted cultures to negative with a regimen containing meropenem plus amoxicillin/clavulanate which indicates that it could be effective in selected cases.

In a double-blind randomized controlled trial of high-dose INH (16-18 mg/kg) versus placebo in addition to second-line drugs, those who received high-dose INH were 2.38 times more likely to convert cultures to negative than those on placebo and they had a 2.37 times higher rate of being culture negative at 6 months. There was a higher frequency of peripheral neuropathy in the high-dose INH arm. Bedaquiline (BDQ) is a diarylquinoline drug hyped as a wonder drug with significant *in vitro* and *in vivo* activity against MTB. At 6 months of treatment, culture conversion was achieved in 97%. 7 patients (20%) experienced a  $\geq 60$  ms increase in QT interval leading to discontinuation in 2 (6%). Diacon *et al.* reported death of 7 patients during the trial at a median of 386 days after the last dose. When an effective WHO-recommended regimen in adult MDR-TB patients comprising 4 second line drugs in addition to PZA cannot be designed and when there is documented evidence of resistance to any fluoroquinolone, alternate newer drugs are being evaluated as intensive phase drugs. BDQ as a replacement for the injectable agent in MDR-TB is currently approved for clinical use by FDA. Delamanid (DLM) is a nitro-dihydro-imidazooxazole derivative which was approved for the treatment of MDR-TB by the European Medicines Agency but has not yet received FDA approval. RCT by Gler *et al.*, in 481 patients who were randomized to receive DLM 100 mg twice daily, 200 mg twice daily, or placebo for 2 months in combination with a WHO-recommended regimen observed that sputum culture conversion in liquid broth occurred in 45.4% of the patients taking DLM at 2 months compared with 29.6% on the placebo regimen. There are currently no safety data on the concurrent use of DLM and BDQ.

When it comes to comorbid illnesses, Lai *et al.* showed diabetes mellitus to be the most frequent underlying disease (60%), followed by chronic pulmonary disease (20%) and lung cancer (10%), along with end-stage renal disease (10%).<sup>10</sup> In the study conducted in Japan, patients with XDR-TB were more likely to have diabetes mellitus (OR 2.095% CI: 0.34-11.85) and a history of malignancy (OR 5.25, 95% CI: 0.52-61.86) although not statistically relevant.<sup>11</sup> In another study, diabetes mellitus is still the condition that is more prevalent (18.7%).<sup>12</sup> HIV had a predictive value for the diagnosis of XDR-TB, being 2.5-fold higher.<sup>13</sup> In many studies, no HIV-positive patients were found. In one study, the population was specifically HIV-negative.<sup>14,15</sup> However in our study, also HIV was not encountered as a major association but 38.8% of MDR and 45% XDR-TB patients had diabetes. Several studies showed that the positive predictive value for the diagnosis of XDR-TB was significantly high with increased duration and multiple courses of the previous treatments (OR 1.2, 95% CI: 1.11-2.30).<sup>3,16,17</sup>

Many potential factors might contribute to treatment failure; the most relevant in many studies being male gender and HIV-

coinfection.<sup>18</sup> Reported factors for treatment noncompliance among XDR-TB patients were alcoholism (10.1%), drug addiction (42%), or both (47.8%).<sup>19</sup> Shah *et al.* also reported 28 and 30 patients under incomplete or partial DOT, respectively.<sup>13</sup> Fluoroquinolone resistance is the result of previous MDR treatment rather than its use in the community. This reinforces the need for routine fluoroquinolone susceptibility testing before starting standardized regimen.<sup>20</sup>

Adverse drug reactions and comorbid illnesses hence may lead to discontinuation of CAT-IV and CAT-V regimens in these patients, and this could be the additional reasons other than disease severity for higher mortality in these groups of patients as compared to drug sensitive TB.<sup>21,22</sup>

## CONCLUSION

The increasing mortality rate in XDR-TB (50-60%) as compared to MDR-TB (16-25%) points to the fact that we have to be extremely cautious while treating these cases as we have only very few choices left against these diseases at this point of time. Bedaquiline is currently available for use in selected cases under RNTCP after approval from the state TB center with concurrence from the central TB division on a case to case basis. Reported cardiac side effect makes it not a routine choice. Another drug being tried is delamanid and is not approved for use in Kerala currently. Hence, all efforts to see that the number of MDR/XDR-TB cases never rises beyond the existing proportion and in fact efforts aiming for its declining trends in incidence and mortality should be set as a TB control goal and a performance indicator of the program.

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