

# Follow up of Drug-Resistant Pulmonary Tuberculosis Patients in a DRTB Center in First Fifteen Months of Treatment

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## Abstract

**Background and Objective:** Multidrug-resistant tuberculosis (MDR-TB) is defined as resistant to both INH and Rifampicin with or without resistance to other first-line antitubercular drugs. The aim of the study was to assess the sputum culture conversion rate during first 12 months of treatment in drug-resistant TB patients, to assess the impact of comorbid illnesses and other factors on culture conversion by following up the patients up to 15 months after initiation of treatment.

**Materials and Methods:** This was a prospective study comprising of 142 diagnosed patients of drug-resistant TB admitted in this center from April 2014 to March 2015 for treatment initiation, excluding extrapulmonary TB and already diagnosed extensively drug-resistant tuberculosis (XDR-TB). After pretreatment evaluation, standard second-line antitubercular drug (CAT-IV) was started. Patients were followed up in first 15 months of treatment. Results of sputum culture for mycobacteria at 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 7<sup>th</sup>, 9<sup>th</sup> and 12<sup>th</sup> months after treatment initiation were analyzed.

**Results:** Sputum culture for mycobacteria was converted negative within one year in 95 cases (67%); whereas 18 patients died during follow up, 27 defaulted and 2 patients switched over to CAT-V after development of extended drug-resistance during follow up.

**Conclusion:** Though drug-resistant tuberculosis (DRTB) is one of the biggest challenges to public health program in India, treatment with standardized second-line drugs under RNTCP have a favorable outcome as indicated by sputum culture conversion of as many as 67% of patients within one year in this study.

**Keywords:** Drug-resistant tuberculosis, Multidrug-resistant tuberculosis, Sputum culture conversion

## Introduction

Drug-resistant-tuberculosis (DRTB) is a global concern in recent years posing a major challenge to tuberculosis control. India with one-fourth tuberculosis burden of the world is also facing the menace. Around 71,000 cases of multidrug-resistant tuberculosis (MDR-TB) have emerged annually from notified pulmonary TB in India.<sup>1</sup> MDR-TB is defined as resistant to both INH and Rifampicin with or without resistance to other first line antitubercular drugs. The prevalence of MDR cases in India is 3% in new cases and 12–17% in retreatment cases.<sup>1</sup> Around 6% retreatment cases failed with CAT II regimen under Revised National Tuberculosis Control Programme (RNTCP).<sup>3</sup> Under RNTCP, drug-resistance is

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detected by solid or liquid culture DST or by DNA-PCR using either LineProbeAssay (LPA) or Cartridge Based Nucleic Acid Amplification Test (CBNAAT). Under RNTCP, usually INH and Rifampicin resistance are tested and in some cases only Rifampicin resistance is screened by CBNAAT. Standard CAT-IV treatment comprising Kanamycin, Levofloxacin, Ethionamide, Cycloserine, Ethambutol, Pyrizinamide is given to all patients having resistance to Rifampicin and INH or patients having detected only Rifampicin resistance. Each patient is admitted in DRTB center for pretreatment evaluation and initiation of treatment and then discharged to take supervised drugs at home. Patients are followed up by sputum culture and the culture results guide the course of treatment. Sputum culture conversion is defined as two consecutive negative sputum cultures taken at least 30 days apart.<sup>2</sup> There are a few studies which showed that sputum culture conversion within 9 months indicate successful treatment outcome.<sup>4,5</sup> There is evidence that delay in sputum culture conversion may be associated with several factors like alcoholism, immunosuppression and comorbid illness all of which resulting in amplification of resistance.<sup>6</sup> In the present study, all patients who had initiated standard second-line treatment in a DRTB center were followed up in the first 15 months of therapy with monthly sputum culture from 3 to 7 months and then at 9 and 12 months and the factors that may affect culture conversion were assessed.

### Aims and Objectives

The aim of the study was to assess the sputum culture conversion rate during first 12 months of treatment in drug-resistant TB patients, to assess the impact of different comorbid illnesses and other factors on culture conversion by following up the patients up to 15 months after initiation of treatment.

### Materials and Methods

This was a prospective study conducted in DRTB center attached to a government medical college at Kolkata, incorporating all the drug-resistant TB patients who were admitted in this center from April 2014 to March 2015 for initiation of treatment, subject to valid consent to be included in this study. Patients having extrapulmonary TB and those already diagnosed to have XDR-TB were excluded from this study. Patients who were transferred out to other DRTB centers during follow up were also excluded. Ethical clearance was obtained from institutional ethical committee. Each patient was subjected to thorough review of history and clinical examination with special attention to history of comorbidities. Weight and height of each patient

was measured and body-mass index (BMI) calculated. Pretreatment evaluation was done according to RNTCP guidelines with chest radiography, complete hemogram, blood sugar, urea, creatinine, liver function tests, HIV, TSH and urine routine analysis. After pretreatment evaluation, standard second-line ATD (CAT-IV) was started. Patients were followed up in the first 15 months of treatment. Results of sputum culture for mycobacteria at 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 7<sup>th</sup>, 9<sup>th</sup> and 12<sup>th</sup> month after initiation of treatment were analyzed using standard statistical method.

### Results

Our study comprised a total of 142 diagnosed cases of drug-resistant pulmonary tuberculosis (DRTB) with male female ratio 1.53:1 and the most common age group between 21 and 40 years. Sputum culture for mycobacteria was converted negative within one year in 95 cases (67%); whereas 18 patients died during follow up, 27 defaulted and 2 patients switched over to CAT-V after development of extended drug-resistance during follow up. 86(61%) of our patients were male with 58% (50 cases) sputum culture conversion rate within one year, whereas out of 56 female 45 (80%) had achieved conversion. Sputum culture conversion in different age groups is shown in Fig. 1. 116 (82%) patients of this study were from rural area and among them 74 (64%) achieved sputum culture conversion within one year. Out of 26 urban patients, 21 (81%) cases achieved this. The number of alcohol-addicted patients was 48 (33%) and all were male. In this alcoholic group, 22 (46%) became culture-negative in one year, but out of 94 non-alcoholic patients 73 (78%) became negative in that time. Sputum culture conversion of patients with different comorbid illnesses is shown in Table 1. 138 cases (97%) have received ATD before and 91 (66%) among them achieved culture conversion in one year while all four cases that had never taken ATD before achieved this (i.e. 100% conversion rate in primary drug-resistance). In this study, 79 cases (56%) had low BMI (<18.5) and rest had average BMI (18.5-24.5). The culture conversion of these two groups is shown in Table 2, which also shows sputum culture conversion in extensive diseases as indicated by bilateral lesion in chest radiography and high colony count (+3 or 4+) in initial sputum culture. Among 142 cases, 21 cases were only Rifampicin-resistant and 16 (76%) such Rifampicin-resistant cases achieved culture conversion in one year as compared to 79 (65%) out of 121 cases that were resistant to both Rifampicin and INH. Cumulative sputum culture conversion at different months during first year of treatment is shown in Fig. 2. Adverse drug-reactions encountered by patients are shown in Table 3. No patient had to quit treatment due to drug-related toxicity.

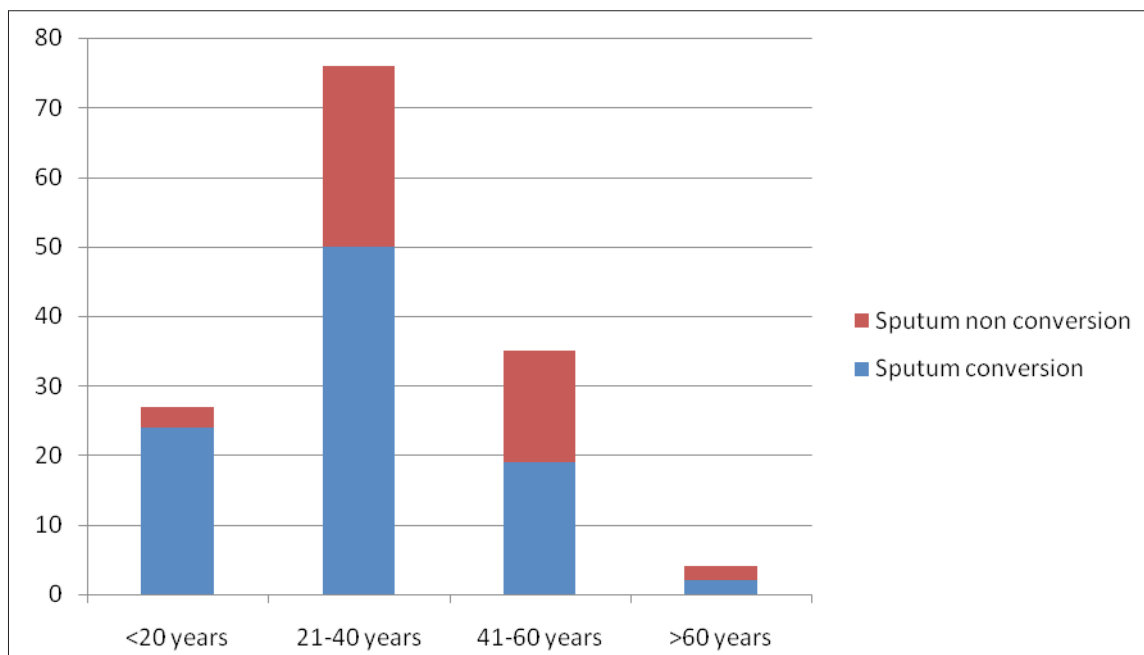


Figure 1.Culture Conversion in Different Age Groups

Table 1.Sputum Culture Conversion Rate in Different Comorbid Conditions

|                                | Total No. | Sputum Culture Conversion in One Year | Percentage |
|--------------------------------|-----------|---------------------------------------|------------|
| Total No. of patients in study | 142       | 95                                    | 66.9       |
| HIV                            | 5         | 1                                     | 20         |
| Diabetes mellitus              | 13        | 6                                     | 46.15      |
| Hypothyroidism                 | 5         | 3                                     | 60         |
| Renal failure                  | 14        | 5                                     | 35.7       |
| Liver disease                  | 7         | 2                                     | 28.6       |
| Preexisting lung disease       | 15        | 5                                     | 33.3       |
| Cardiac disease                | 6         | 1                                     | 16.7       |

Table 2.Sputum Culture Conversion in Low BMI vs. Average BMI Patients and Extensive vs. Less Extensive Disease

|  | Total No. | Sputum Culture Conversion in One Year | Percentage |
|--|-----------|---------------------------------------|------------|
| Low BMI                                | 79        | 42                                    | 53%        |
| Average BMI                            | 63        | 53                                    | 84%        |
| High (3+ and 4+) colony count          | 64        | 27                                    | 42%        |
| Low (1+ and 2+) colony count           | 78        | 68                                    | 87%        |
| Unilateral lesion in chest radiography | 64        | 53                                    | 82%        |
| Bilateral lesion in chest radiography  | 78        | 42                                    | 54%        |

Table 3.Adverse Drug Reaction in Study Population

|                       | No. of patients (n=142) | Percentage |
|-----------------------|-------------------------|------------|
| Gastrointestinal      | 78                      | 55         |
| Peripheral neuropathy | 16                      | 11         |
| Hepatic               | 12                      | 8.5        |
| Renal                 | 18                      | 13         |
| Ototoxicity           | 9                       | 6          |
| Psychological         | 10                      | 7          |
| Arthralgic            | 14                      | 10         |

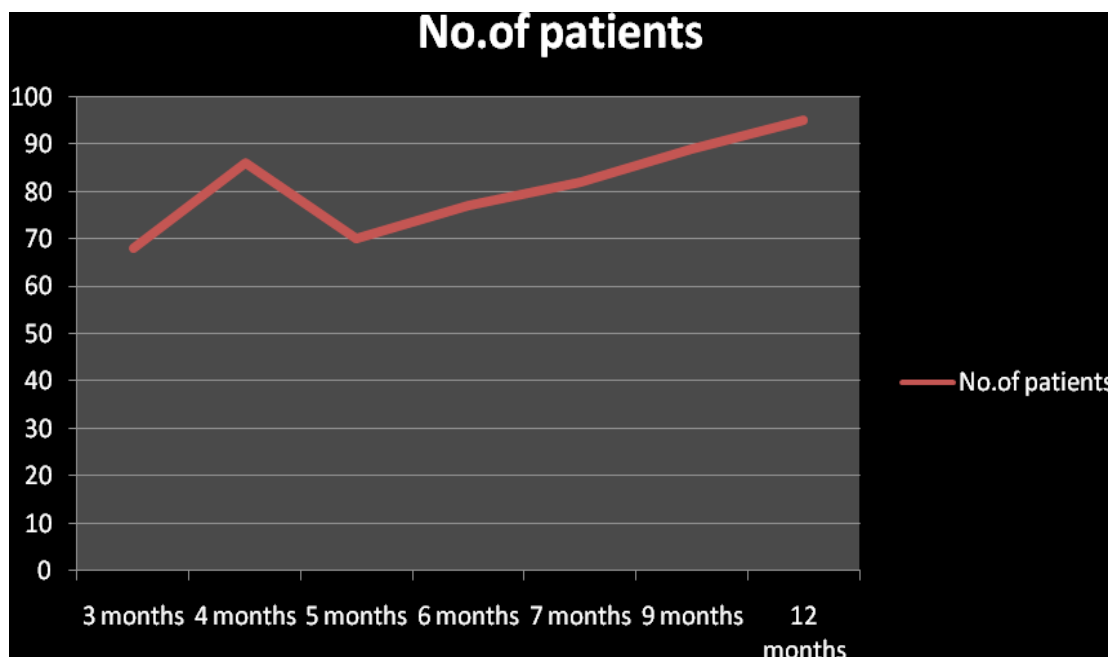


Figure 2. Cumulative Sputum Culture Conversion Rate in Different Months of First Year of Treatment

### Discussion

Drug-resistant TB is a serious challenge to TB control program in India and RNTCP has started to treat drug-resistant TB for the last few years. Sputum culture conversion is a very important parameter in follow-up of these patients as it has been seen that 84% of patients who have achieved sputum conversion have favorable treatment outcome.<sup>7</sup> In several East European countries, median culture conversion time was found to be around 3 months.<sup>[7,8]</sup> One report from Bangladesh found that 88% MDR patients turned culture-negative after 3 months of therapy.<sup>[9]</sup> In our study, we followed up the patients for first 15 months to assess the culture status during first one year as most of the patients who had successful treatment were converted in this period. We have found that 67% of our patients achieved culture conversion within one year. One previous study with MDR-TB patients on DOTS-plus regimen under RNTCP found 74% culture conversion within one year.<sup>10</sup> We have also found that though 61% of our patients were converted within 4 months, but some again turned culture-positive later. But reversion also occurred and hence the conversion rates at 6<sup>th</sup> and 9<sup>th</sup> month were 56% and 62% respectively (Fig. 2). In a previous study, reversion was noted in 11% patients. The culture conversion of Rifampicin-resistant patients was only marginally higher than those with both INH and Rifampicin resistance.<sup>7</sup> In this study, culture conversion rate was higher in younger age group with highest (88.88%) in less than 20 years group and lowest (50%) in aged over 60 years. Previous studies also showed that patients with <40 years of age have higher rate of successful treatment.<sup>5,8</sup> Alcoholic patients had poor culture conversion than non-alcoholic in our study (46% vs 78%) and as all the alcoholics were male, overall conversion rate of male was also lower than female (58% vs 80%). A

previous study from India also favored our findings.<sup>5</sup> We have found that patients having low BMI and high bacillary load had much lower conversion than those having average BMI (53% vs 84%) and low bacillary load (42% vs 87%) as also patients with bilateral disease than unilateral one (54% vs 82%). This observation was also noted in other studies.<sup>7,8</sup> Patients having HIV, diabetes mellitus, liver and renal diseases and pre-existing lung diseases had poor conversion rate (20%, 46%, 29%, 36%, 33% respectively). But the number of patients in each group was too small. Majority of patients (55%) had gastrointestinal adverse effect due to drugs but no patient had to stop treatment for adverse drug reaction.

### Conclusion

Though drug-resistant tuberculosis is one of the biggest challenges to public health programs in India, treatment of drug-resistant tuberculosis with standardized second-line drugs under DOTS has a favorable outcome as indicated by sputum culture conversion of as many as 67% of patients within one year in this study. 61% of the patients were converted as early as 4 months but reversion to culture-positive and subsequent reversion occurred to some (16 patients). Old age, alcoholism, low BMI, high bacillary load, presence of bilateral radiological lesion, comorbid illness like HIV, diabetes mellitus, pre-existing lung, liver and renal diseases – all were a poor determinant in sputum culture conversion within one year. In spite of having difficulties to be implemented in a population-inflated country like India, the RNTCP program with DOTS-PLUS regimen is creating a landmark towards control of tuberculosis in Indian perspective. Successful program implementation with public awareness is key towards our effort.

**Conflict of Interest:** None

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