

# Resistance to Isoniazid and Rifampicin and Factors Associated with Resistance Among MDR TB Patients Visiting DOTS PLUS Site

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## Abstract

**Introduction:** Multidrug-Resistant (MDR-TB) is defined as M tuberculosis resistant to isoniazid and rifampicin with or without resistant to other drugs. Drug resistant TB is known to occur from time of introduction of antituberculosis drugs. MDR TB has become a significant health problem and an obstacle to effective TB control<sup>1</sup>. Resistance of M. tuberculosis to anti-TB drugs is caused by chromosomal mutations in genes encoding drug targets. Multidrug-resistant strains of M. tuberculosis (MDR-TB) evolve due to sequential accumulation of mutations in target genes. The WHO cites TB as the single most important fatal infection, with around 8.8 million new cases and 1.4 millions deaths per year, 95% in developing countries. According to Global TB report 2015 data of MDR TB as follows<sup>2</sup>. 50% successfully completed treatment (cure or treatment completed), 16% died, 16% defaulters, 10% treatment failure, 8% without outcome. The MDR-TB is also threatening World Health Organization's target of tuberculosis elimination by 2050. Study conducted by NIRT and NTI suggest MDR level of 1% to 3% in new cases and around 12% in retreatment cases and revealed an overall emergence to rifampicin in only 2% of patients, despite a high level (18%) of initial resistance to isoniazid, either alone in or in combination with other anti tuberculosis drugs+. **Aims and Objectives:** 1. To Study the drug resistance to isoniazid and rifampicin among the MDR TB patients visiting DOTS PLUS CENTRE. 2. To Study the various factors associated with resistance to Isoniazid and rifampicin among MDR TB patients. **Material and Methods:** Present study was conducted at DOTS PLUS Centre in tertiary health care centre. Total 140 of newly diagnosed cases of MDR-TB were included in the present study after satisfying the inclusion and exclusion criteria. Written informed consent was taken from the study participants. Patients' demographic details were noted such as name, age, sex, occupation, socioeconomic status, education. Patients were asked detailed history about smoking, alcohol, tobacco chewing, diabetes mellitus, hypertension, COPD (chronic obstructive pulmonary disease), HIV Status. Details about past history of tuberculosis, treatment history were noted, If the patient was found to have defaulted previous antituberculous treatment, detailed evaluation was done to find out reasons for defaulting the treatment, History of MDR TB contact was noted. The drug resistance pattern of isoniazid and rifampicin was noted. **Results:** Of the 140 drug resistance tuberculosis patients, MDR Pulmonary tuberculosis was more common in economically productive age group of 21-40 years, distribution of male (60%) and female (40%), 35% patients were found to have defaulted previous antituberculous treatment. Main reasons for defaulting were, becoming asymptomatic, feeling better 40.8% followed by medication side effects 32.65% **Conclusion:** Isoniazid and rifampicin resistance (74.28%) is more than rifampicin monoresistance (25.72%), there is significant association between addiction of patient and defaulting the previous antituberculous treatment, analysis of patients various factors for drug resistance showed that MDR-TB is more commonly seen in males, age between 21 to 40 years, low socioeconomic status, past history of ATT, Alcoholic and tobacco user.

**Keywords:** Co morbidities, Defaulter, MDR TB, Resistance

## 1. Introduction

Multidrug-Resistant (MDR-TB) is defined as M tuberculosis resistant to isoniazid and rifampicin with

or without resistant to other drugs. Drug resistant TB is known to occur from time of introduction of antituberculosis drugs. MDR TB has become a significant health problem and an obstacle to effective TB control<sup>1</sup>.

Resistance of *M. tuberculosis* to anti-TB drugs is caused by chromosomal mutations in genes encoding drug targets. Multidrug-resistant strains of *M. Tuberculosis* (MDR-TB) evolve due to sequential accumulation of mutations in target genes.

MDR TB is a manmade phenomenon. The causes of MDR TB are disease related, patient related and physician related. Use of inadequate regimens, poor adherence to treatment, inappropriate Directly Observed Treatment (DOTS), delayed diagnosis of MDR TB leads to increase in the drug resistant levels in the community. The MDR TB patients' lives no. of years before succumbing to the disease. Undiagnosed and improperly treated patients, diagnosed but refused MDR treatment patients, MDR defaulters are a source of ongoing transmission of resistant strains. Many undiagnosed MDR patients treated with first line antiTB drugs/Short Course Chemotherapy causes amplifier effect. When Short Course Chemotherapy is use continuously over a long period in MDR patients, the resistant strains in bacterial population are selected repeatedly & these become the dominant strains and leads to development of MDR TB<sup>1</sup>

The WHO cites TB as the single most important fatal infection, with around 8.8 million new cases and 1.4 millions deaths per year, 95% in developing countries. According to Global TB report 2015 data of MDR TB as follows<sup>2</sup>. 50% successfully completed treatment (cure or treatment completed), 16% died, 16% defaulters, 10% treatment failure, 8% without outcome. The MDR-TB is also threatening World Health Organization's target of tuberculosis elimination by 2050. Moreover, the problem of extensively drug resistant (XDR)strains has recently been introduced<sup>3</sup>.

Prevalence of acquired drug resistance varies according to the drug regimen used and efficacy of control programme With proper implementation of DOTS, MDR rates are likely to be much lower<sup>4</sup>.

Study conducted by NIRT and NTI suggest MDR level of 1% to 3% in new cases and around 12% in retreatment cases and revealed an overall emergence to rifampicin in only 2% of patients, despite a high level (18%) of initial resistance to isoniazid, either alone in or in combination with other anti tuberculosis drugs<sup>5</sup>.

## 2. Aims and Objectives

- To study the drug resistance to isoniazid and rifampicin among the MDR TB patients visiting DOTS PLUS CENTRE.
- To study the various factors associated with resistance to Isoniazid and rifampicin among NDT TB patients.

## 3. Material and Methods

Present study was conducted at DOTS PLUS Centre in tertiary health care centre. Total 140 of newly diagnosed cases of MDR-TB were being included in the present study after satisfying the inclusion and exclusion criteria. Written informed consent was taken from the study participants. Patients demographic details were noted such as name, age, sex, occupation, socioeconomic status, education.

Patients were asked detailed history about smoking, alcohol, tobacco chewing, diabetes mellitus, hypertension, COPD (Chronic Obstructive Pulmonary Disease), HIV Status. Details about past history of tuberculosis, treatment history were noted. If the patient was found to have defaulted previous antituberculous treatment, detailed evaluation was done to find out reasons for defaulting the treatment, History of MDR contact were noted. The drug resistance to isoniazid and rifampicin was noted. Results were tabulated and analysed. Being an observational study, no tests for statistical significance were applied.

## 4. Results

### 4.1 Distribution of Study Participants According to Age

Among 140 study subjects the majority (57.85%) are in age group 21 to 40 years. 25% in age group 41 to 60 years. It was observed that 82.85% of the patients were from economically productive age group (21 to 60 years).

### 4.2 Distribution of Study Participants According to Gender

The Sex wise distribution among 140 study subjects were 84 (i.e., 60%) are Male and 56 (i.e., 40%) are Female.

### 4.3 Distribution of Study Participants According to Educational Status

Out of 140 MDR-TB patients, 73(52.15%) patients had primary education, 35(25%) with secondary education, 24(17.14%) patients were illiterate, 5(3.57%) graduate and 3(2.14%) with higher secondary education.

### 4.4 Distribution of Study Population According to Socioeconomic Status

According to Revised of Prasad's SES classification 2014, out of 140 MDR-TB Patients, 84(60%) patients were from

socioeconomic status class IV,24(17.14%) patients from class III.

#### 4.5 Distribution of Study Participants According to Co-morbidities

The most common co-morbidity was diabetes mellitus followed by HIV.

**Table 1.** Co morbidities among MDR TB patients

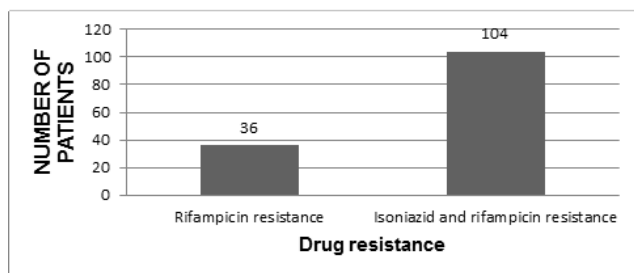
Co-Morbidities	Patients	Percentage (N=140)
Diabetes mellitus	20	14.28
HIV	11	7.85

#### 4.6 Distribution of Study Participants According to Addiction

Among 140 MDR-TB patients,65 (46.43%) patients were non addict, 40(28.57%) patients were tobacco chewer, 25(17.85%) patients were alcoholic and 18(12.85%) patients were smoker, 5 patients were both alcoholic and tobacco chewer, 3 patients were both smoker and tobacco chewer

#### 4.7 Drug Resistance Pattern

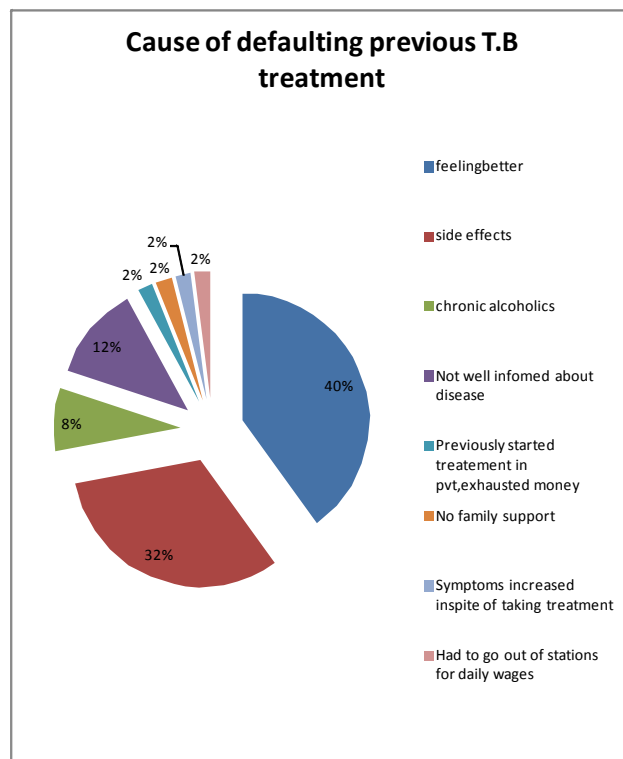
Of the 140 drug resistant tuberculosis patients whose drug sensitivity test was analysed, it was found that Rifampicin mono-resistance was less than Isoniazid and Rifampicin resistance (both).



**Figure 1.** Drug resistance of INH and Rifampicin.

#### 4.8 Reasons of Defaulting Previous T.B Treatment

Among 140 drug resistant tuberculosis patients, 49 (35%) were found to have defaulted previous antituberculous treatment.



**Figure 2.** Causes of default among MDR TB.

The most common reasons of defaulting were patients feeling better after few days of treatment, Side effects of antituberculous treatment.

**Table 2.** Association of socioeconomic status with treatment defaulter

Socioeconomic status	Defaulter column %	Non Defaulter Column%	Total No. Patients
Upper class (S.E.S I & II)	3(6.122%)	11(12.1%)	14
Middle class (S.E.S III)	8(16.33%)	16(17.6%)	24
Lower class (S.E.S IV & V)	38(77.55%)	64(70.30%)	102
<b>Total</b>	<b>49(100%)</b>	<b>91(100%)</b>	<b>140</b>

For the present study purpose, Prasad socioeconomic classification upper class (S.E.S I & II), Middle class (S.E.S III) and lower class (S.E.S IV & V) is used.

No significant association was found between socioeconomic status and defaulter

$X^2 = 1.391$ ,

Degrees of Freedom = 2

p-value = 0.4989 (Not Significant)

**Table 3.** Association of educational status with treatment defaulter

Education	Defaulter Column %	Non Defaulter Column%	Total No. patients
Illiterate	8(16.36%)	16(17.6%)	24
Primary and secondary education	40(81.6%)	68(74.70%)	108
11 <sup>th</sup> standard onwards	1(2.04%)	7(7.7%)	8
<b>Total</b>	<b>49(100%)</b>	<b>91(100%)</b>	<b>140</b>

No significant association was found between educational status and defaulter

$X^2 = 2.007$ ,

Degrees of Freedom = 2

p-value = 0.3667 (Not Significant)

**Table 4.** Association of addiction with treatment defaulter

Addiction	Defaulter column %	NonDefaulter Column%	Total No.patients
YES	36(73.46%)	39(42.86%)	75
NO	13(26.54%)	52(57.14%)	65
<b>Total</b>	<b>49(100%)</b>	<b>91(100%)</b>	<b>140</b>

$X^2 = 12$ ,

Degrees of Freedom = 1

p-value = 0.0005320(Significant)

## 5. Discussion

MDR TB is a major public health problem in developing as well as developed countries. MDR TB levels are higher in areas with poor TB control and the proportion of retreatment cases is high.

Treatment of MDR-TB often possesses serious challenge to patients and majority of such patients are usually referred to tertiary care. These patients are already resistant to most of the first line drugs and require

judicious and optimal combinations of second line drugs as second line drugs are very expensive and having more side effects.

This prospective study was conducted in tertiary care centre and included 140 patients of MDR pulmonary Tuberculosis admitted in DOTS PLUS CENTRE during the period August 2013 to December 2015.

Our study showed majority of patients (58.1%) were in age group of 21 to 40 years and 83.7% of patients were from economically productive age group of 21 to 60 years. This was comparable to the findings of the study conducted by Mahadev et al.,<sup>6</sup> and Global tuberculosis control: WHO report 2011.

Our study shows an distribution of male (60%) and female (40%) patients as compared to study by Mahadev et al.,<sup>6</sup> which had a ratio of 3:1. This is more likely to be due to increased awareness of Tuberculosis and hence more number of patients getting themselves screened for Tuberculosis.

All the Patients were screened for associated co-morbid illnesses 28% patients had Diabetes as a co- morbid illness followed by 7.85% patient had HIV. These findings are comparable to the study carried out by Dheeraj Gupta et al.<sup>7</sup> and V. K. Dhingra et al.,<sup>8</sup> where Diabetes mellitus was the commonest comorbidity. A study conducted by Wipa et al., Shringarind hospital, Thailand<sup>9</sup> showed commonest comorbidity was HIV.

All the patients of the study i.e., 100% presented with Fever, Cough and Weight loss followed by loss of appetite (i.e., 70%) and remaining presenting symptoms were breathlessness on exertion (40%) and haemoptysis (20%). This is comparable to the study findings carried out by Dheeraj Gupta et al.,<sup>7</sup> and Dr. Javed Malik et al.,<sup>10</sup> which also has shown fever, cough and weight loss to be the commonest symptom among these patients.

It was observed that Among 140 MDR TB patients, 49 (35%) patients had history of defaulted previous antituberculous treatment. Feeling better after taking Anti-TB medications for few months and medication side effects were most common causes for defaulting the previous antituberculous treatment in our study. Similar observations were found in the other studies conducted by K. Jaggarajamma et al.<sup>11</sup>, B. Castelnuovo et al.<sup>12</sup>. Among 49 defaulter patients, there is significant association between defaulter and addiction of the patient.

One Patient among 49 defaulter patient had no family support, in such case DOTS provider should counsel the family and provide psychosocial support.

One patient was defaulted the ATT (private daily ATT) because of exhaust of money, hence there is need

for motivating private practitioners for referral of non-affording patients to RNTCP for treatment.

So proper treatment as per the guidelines is very important to prevent the development of resistant disease in future.

## 6. Conclusion

- Drug resistance seen in isoniazid and rifampicin resistance (HR) is more than rifampicin monoresistance (R).
- Analysis of various factors for drug resistance showed that MDR-TB is more commonly seen in males, age between 21 to 40 years, low socioeconomic status, past history of ATT, alcoholic and tobacco user patients.
- Diabetes Mellitus is the common associated comorbidity in patients with multi drug resistant Pulmonary Tuberculosis.
- Large number of patients had history of defaulting previous ATT. The most common reason for defaulting previous ATT were feeling better after few days of treatment followed by side effects of drugs followed by not well informed about disease and treatment duration.
- Among defaulter patients, there is significant association between addiction of patient and defaulting the antituberculous treatment.
- DOTS provider should counsel the family and provide psychosocial support.

As MDR-TB is a man-made phenomena so proper counselling of patients, increasing awareness about disease, its spread, treatment duration and side effects during treatment will reduce the prevalence and incidence of MDR-TB

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