

# Treatment Outcomes of Isoniazid Mono-resistant Pulmonary Tuberculosis Patients Under RNTCP

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## Abstract

**Background:** Mono-resistance to isoniazid (INH) is emerging as one of the major causes of treatment failure and increasing the probability of multidrug resistant TB (MDR TB). With the revised treatment regimen, possibility of better outcomes along with factors influencing it need further evaluation.

**Methods:** An observational, prospective study was conducted from 1st September 2017 to 31st May 2019 among 85 newly diagnosed INH mono-resistant pulmonary tuberculosis (PTB) patients at RBIPMT, Delhi, fulfilling inclusion criteria.

**Result:** Out of the total 85 patients enrolled, 8 were cured, 53 completed their treatment, 13 were lost to follow-up, 6 patients died and 5 had a treatment failure. 14 (77.8%) were current smokers, 14 (51.8%) had a current history of alcohol intake, 18 (78.3%) were contacts of a TB case, 17 (92.9%) were household contacts of MDR TB, 21 (55.3%) were of lower socio-economic class, 12 (80%) had increased TLC, 8 (80.0%) had deranged LFT, 4 (80.0%) had deranged KFT, 17 (73.9%) had BM1 < 17.5 Kg/m<sup>2</sup>, 16 (94.1%) had far advanced disease, 16 (64.0%) had cavity, and 15 (88.2%) had extensive disease on chest X-ray were significantly associated with unsuccessful outcome. 47 (90.4%) had sputum smear status < 1+ and at follow-up, increased weight, sputum smear negative status, minimal lesion on chest X-ray and improved symptoms were significantly associated with successful outcome.

**Conclusion:** Early detection, identification of risk factors and adequate treatment of INH mono-resistant TB, along with appropriate lifestyle modifications were associated with better treatment outcomes.

**Keywords:** Pulmonary tuberculosis, drug resistance, and risk factors.

## Introduction

TB remains an important public health problem due to the long period of 6 months or more of treatment, the potential of infectivity, risks of mortality, and crippling economic impact<sup>1</sup>.

INH and rifampicin are the main drugs for successful treatment of drug sensitive (DS) TB in short duration regimen (6 months to less than a year). Inability to prescribe INH due to resistance complicates the outcome, probably due to amplification of drug resistance<sup>2</sup>. Approximately 25% of MDR-TB suspects were found to have first-line mono- and poly-drug resistance under the revised national tuberculosis control program (RNTCP)<sup>2</sup>.

Presence of various forms of resistance to first-line anti-TB drugs is an important cause for unfavorable outcomes including failure of treatment, amplification of drug resistance and death. Early identification of patterns of drug resistance, either by culture followed by drug susceptibility or by genotypic methods is important for deciding treatment regimen<sup>3</sup>.

In 2017, among all cases of TB, the average global frequency of INH resistance without concurrent rifampicin resistance was 7.6% (95% CI 6.3% - 8.5%). In new and previously treated cases, the global averages were 7.1% (95% CI: 6.2 - 8.0%) and 7.9% (95% CI: 5.9 - 10%), respectively<sup>1</sup>.

In March 2016, the Revised Technical and Operational guideline for Tuberculosis declared a new regimen for INH mono-resistant tuberculosis that included kanamycin, levofloxacin, rifampicin, ethambutol and pyrazinamide in the intensive phase for 3 - 6 months and followed by continuation phase of levofloxacin, rifampicin, ethambutol and pyrazinamide for 6 months<sup>3</sup>. WHO came up with treatment recommendations for scrapping of the injectable drug kanamycin altogether, due to the unacceptably high incidence of adverse effects. These recommendations have been adopted by the Indian RNTCP too, w.e.f. January 2019<sup>4</sup>. However, as the start of this study was prior to this new update, every patient received kanamycin injection.

The purpose of this study was to ascertain the outcomes of this newly introduced regimen for INH mono-resistant TB and to see whether this regimen was associated with

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improved outcomes we also wanted to identify possible factors which may predict success or failure of the treatment among these patients.

## Material and Methods

**Study site:** Kingsway Chest Centre (KCC) OPD and in-Patient Department of Rajan Babu Institute for Pulmonary Medicine and Tuberculosis (RBIPMT), North Delhi Municipal Corporation, GTB Nagar, Delhi-110009. The report of INH resistance was obtained via Line Probe Assay (LPA) testing from IRL situated at New Delhi TB centre, Delhi.

**Study population:** Newly diagnosed INH mono-drug resistant PTB patients attended at RBIPMT for initiation of treatment with newly introduced treatment regimen during the intake period who met the inclusion criteria were offered to participate in the study, irrespective of age and gender.

**Study design:** It was an observational, prospective longitudinal study.

**Study duration:** Intake was from 1st September 2017 to 31st May 2018, i.e., total of 9 months. Final date of follow-up was 31st May 2019.

**Sample size:** As per the National Drug Resistant Surveillance (NDRS) survey in 2015, the prevalence of INH resistance was 16%<sup>2</sup>. The formula used to calculate sample size in prospective studies was-  $N = 4 pq/d2$ . Sample size was calculated as 96 for 1 year of intake. Since this was a time bound study with intake of 9 months and accounting for dropouts and patients refusing consent, the sample size was determined to be 50.

**Sampling technique:** Every consecutive patient who fulfilled inclusion and exclusion criteria was included.

### Inclusion criteria

1. Patient of PTB who tested INH mono-resistant by LPA or sputum culture followed by Drug Sensitivity Testing (DST) from IRL.
2. All patients who had given written consent and were willing for regular follow-up, diagnostic evaluation and if indicated, hospitalisation
3. Age above 14 years, irrespective of gender.

### Exclusion criteria

1. Not willing to give consent.
2. Patients of rifampicin resistance, MDR, pre-XDR and XDRTB.
3. Extra pulmonary TB cases.
4. Patients not belonging to Delhi.

5. All patients below 14 years of age.

### Consent and ethical consideration

The study was carried-out after obtaining approval from the Institutional Human Ethics Committee. An informed written consent was obtained from all patients.

### Flow chart of methodology

Study subjects enrolled after informed consent.

History and clinical examination was done. Investigation- Body weight (BMI<sup>5</sup>), haematology, biochemistry, sputum smear examination, chest X-ray<sup>6</sup>.

Patients were started on regimen for INH resistant TB as per newly revised guidelines. Three monthly follow-up with symptoms, body weight, sputum smear examination and chest X-ray was carried out.

Assessment was based on successful or unsuccessful outcomes<sup>3</sup> and comparison with various factors for possible significance.

The radiological extent of the disease was based on the guidelines of National Tuberculosis Association of USA as:

1. Minimal: These lesions include those that are of slight-to-moderate density but do not contain demonstrable cavitation. They may involve a small part of one or both lungs, but the total extent, regardless of distribution, should not exceed the volume of lung on one side.
2. Moderately advanced: These lesions may be present in one or both lungs, but the total extent should not exceed the following limits: disseminated lesions of slight moderate density that may extend throughout the total volume of one lung or the equivalent in both lungs; dense and confluent lesions limited in extent to one-third of the volume of one lung; total diameter of cavitation, if present must be less than 4 cm.
3. Far advanced: Lesions more extent than moderately advanced<sup>7</sup>.

Minimal and moderately advanced lesions were grouped into less extensive group and far advanced lesions were grouped into more extensive group.

### Statistical analysis

Descriptive statistics was analysed with SPSS version 21.0 software. The various risk factors and predisposing conditions were expressed as frequencies and percentages.

Nominal categorical data between the groups was compared using Chi-square test. For all statistical tests, a p-value less than 0.05 was taken to indicate a significant difference.

## Results

Out of the total 85 patients enrolled, 8 patients completed the RNTCP definition for cure, 53 patients completed their treatment and were grouped under successful outcomes (group A). 13 were lost to follow-up, 6 patients died and 5 had a treatment failure in the form of microbiological positivity or change of regimen, all of them were termed under unsuccessful outcome (group B).

As shown in Table I, out of 85 patients, 34 (82.9%) patients who were between 21 - 40 years of age had significantly successful outcome. Majority of patients were males 60 (70.6%). Cough and sputum production were most common symptoms presented by 83 (97.6%), and 80 (94.1%) patients, respectively. Breathlessness ( $p = 0.03$ ), haemoptysis ( $p = 0.001$ ), chest pain ( $p = 0.002$ ) or loss of appetite (0.005) individually were significantly associated with unsuccessful outcome. Out of 67 never/former smokers 57 (85.1%) had successful outcome while out of 18 current smokers, 14 (77.8%) had unsuccessful outcome. Out of 60 patients with no history of alcohol intake, 48 (82.7%) patients had successful outcome, while out of 27 with current history of alcohol intake, 14 (51.8%) had unsuccessful outcome. 21 (55.3%) out of 37 patients of lower socio-economic class had unsuccessful outcome, while 44 (93.6%) who belonged to upper and middle class had successful outcome.

**Table I: Comparison of treatment outcomes in various demographic characteristics.**

Demographic characteristics		Group A	Group B	p-value
	No. (%)	No. (%)		
Age (Range in years)	≤ 20	9 (64.3)	5 (35.7)	0.49
	21 - 40	34 (82.9)	7 (17.1)	<b>0.02</b>
	41 - 60	15 (62.5)	9 (37.5)	0.23
	> 60	3 (50.0)	3 (50.0)	0.21
Gender	Male	41 (68.3)	19 (31.7)	0.27
	Female	20 (80.0)	5 (20.0)	
Symptoms	Fever	42 (67.7)	20 (32.3)	0.17
	Cough	59 (71.1)	24 (28.9)	0.36
	Sputum	58 (72.5)	22 (27.5)	0.54
	Breathlessness	10 (52.6)	9 (47.4)	<b>0.03</b>
	Hemoptysis	2 (18.2)	9 (81.8)	<b>0.001</b>
	Chest pain	2 (25.0)	6 (75.0)	<b>0.002</b>
	Loss of appetite	12 (50.0)	12 (50.0)	<b>0.005</b>
Loss of weight	28 (66.7)	14 (33.3)	0.30	
Smoking Status	Never and former smokers	57 (85.1)	10 (14.9)	<b>0.00001</b>
	Current smokers	4 (22.2)	14 (77.8)	
Alcohol Intake	Never	48 (82.7)	10 (17.2)	<b>0.0009</b>
	Current or stopped one year ago	13 (48.1)	14 (51.8)	
Socio-Economic Class	Lower	17 (44.7)	21 (55.3)	<b>0.001</b>
	Upper and middle	44 (93.6)	3 (6.4)	

18 (78.3%) patients out of 23 who had contact with TB case and 17 (92.9%) out of 20 who were household contact of MDR-TB case were significantly associated ( $p = 0.0001$  and  $0.001$  respectively) with unsuccessful outcome while 38 (92.7%) out of 41 who took full course of ATT treatment were significantly associated (0.001) with successful outcome as shown in Table II. 36 (97.3%) out of 37 patients with normal haemoglobin levels, 54 (77.1%) out of 70 with normal platelet level, and 47 (90.4%) out of 52 with sputum smear status < 1+ were significantly associated ( $p = 0.001$ ,  $0.01$  and  $0.0002$ , respectively) with successful outcomes while 12 (80%) out of 15 with increased TLC ( $> 9.06 \times 10^3/\text{mm}^3$ ), 8 (80.0%) out of 10 patients with deranged LFT, 4 (80.0%) out of 6 with deranged KFT and 17 (73.9%) out of 23 with  $\text{BMI} < 17.5 \text{ Kg/m}^2$  were significantly associated (0.001, 0.001, 0.008, < 0.0001 respectively) with unsuccessful outcomes as shown in Table III.

**Table II: Comparison of treatment outcomes with history of contact with a case of TB and drug resistant TB according to presumptive DR-TB suspect criteria.**

History of contact of TB/ past history of ATT intake		Group A	Group B	p-value
		No. (%)	No. (%)	
Contact of TB case	Yes	5 (21.7)	18 (78.3)	<b>0.0001</b>
	No	56 (90.3)	6 (9.7)	
Presumptive DR TB suspect criteria	Any TB patient who is a household contact of MDR-TB case	3 (7.1)	17 (92.9)	<b>0.001</b>
	Other DR-TB suspect criteria	58 (15.0)	7 (85.0)	
Past history of ATT	Present	42 (66.7)	21 (33.3)	<b>0.07</b>
	Absent	19 (86.4)	3 (13.6)	
Number of times ATT taken	Once	15 (65.2)	8 (34.8)	<b>0.85</b>
	More than once	27 (67.5)	13 (32.5)	
Full course of treatment taken	Yes	38 (92.7)	3 (7.3)	<b>0.001</b>
	No	4 (18.2)	18 (81.8)	

**Table III: Comparison of treatment outcomes according to laboratory parameters and BMI of patients.**

Laboratory Parameters		Group A	Group B	p-value
		No. (%)	No. (%)	
Haemoglobin (g/dl)	Reduced (< 12)	25 (52.1)	23 (47.9)	<b>0.001</b>
	Normal (12 - 16)	36 (97.3)	1 (2.7)	
TLC ( $10^3/\text{mm}^3$ )	Reduced (< 3.54)	3 (50.0)	3 (50.0)	<b>0.001</b>
	Normal (3.54 - 9.06)	55 (85.9)	9 (14.1)	
	Increased (9.06)	3 (20.0)	12 (80.0)	
Platelets ( $10^3/\text{mm}^3$ )	Reduced (< 165)	7 (46.7)	8 (53.3)	<b>0.01</b>
	Normal (165 - 415)	54 (77.1)	16 (22.9)	
LFT	WNL	59 (78.7)	16 (21.3)	<b>0.001</b>
	Deranged	2 (20.0)	8 (80.0)	

KFT	WNL	60 (75.0)	20 (25.0)	<b>0.008</b>
	Deranged	1 (20.0)	4 (80.0)	
Baseline sputum smear status	< 1+	47 (90.4)	5 (9.6)	<b>0.0002</b>
	> 1+	14 (42.4)	19 (57.6)	
BMI(Kg/m <sup>2</sup> )	< 17.5	6 (26.1)	17 (73.9)	<b>&lt;0.0001</b>
	> 17.5	55 (88.7)	7 (11.3)	

As shown in Table IV, 16 (94.1%) out of 17 patients with far advanced disease, 16 (64.0%) out of 25 with cavity and 15 (88.2%) out of 17 with more extensive disease on baseline chest X-ray were significantly associated (0.0001) with unsuccessful outcomes.

**Table IV: Comparison of treatment outcomes according to baseline chest X-ray findings.**

Chest X-ray findings		Group A	Group B	p-value
		No. (%)	No. (%)	
Baseline chest X-ray findings	Minimal	32 (100.0)	0 (0.0)	<b>0.0001</b>
	Moderately advanced	28 (77.8)	8 (22.2)	
	Far advanced	1 (5.9)	16 (94.1)	
Cavity	Present	9 (36.0)	16 (64.0)	<b>0.0001</b>
	Absent	52 (86.7)	8 (13.3)	
Extent of disease	Less extensive	59 (86.8)	9 (13.2)	<b>0.0001</b>
	More extensive	2 (11.8)	15 (88.2)	

At the end of 3 months follow-up, compared to baseline parameters, 42 (97.7%) out of 43 patients with increased weight, 58 (93.5%) out of 62 with sputum smear-negative status, 58 (98.3%) out of 59 with minimal lesion on chest X-ray and 46 (97.9%) out of 47 with improved symptoms were significantly associated ( $p = 0.0004, 0.0001, 0.00001, 0.00001$  respectively) with successful outcome. At the end of 6 months follow-up among 68 patients who followed-up, 50 (98.0%) out of 51 with increased weight and 56 (96.6%) out of 58 with improved symptoms were significantly associated ( $p = 0.00001$ ) with successful outcomes. 61 (96.8%) out of 63 patients with negative sputum smear status and 61 (98.4) out of 62 with minimal lesion on chest X-ray were also associated with successful outcome as seen in Table V.

**Table V: Comparison of various parameters between the groups at 3 months and 6 months follow-up, compared to baseline for patients who continued treatment.**

Parameters		No. of patients (n= 85)			p value
		Group A	Group B		
		No. (%)	No. (%)	No. (%)	
At 3 Months Weight	Reduced or Same	28 (39.4)	19 (67.8)	9 (32.1)	<b>0.0004</b>
	Increased	43 (60.5)	42 (97.7)	1 (2.3)	

Sputum smear status	Negative	62 (87.3)	58 (93.5)	4 (6.5)	<b>0.0001</b>
	Positive	9 (12.7)	3 (66.7)	6 (33.3)	
CXR findings	Minimal	59 (83.1)	58 (98.3)	1 (1.7)	<b>0.00001</b>
	Moderately advanced and Far advanced	12 (16.9)	3 (25.0)	9 (75.0)	
	Symptoms	Improved	47 (66.2)	46 (97.9)	1 (2.1)
	Same or Worsen	24 (33.8)	15 (62.5)	9 (37.5)	
At 6 Months Weight	Reduced or Same	17 (25.0)	11 (64.7)	6 (35.3)	<b>0.00001</b>
	Increased	51 (75.0)	50 (98.0)	1 (2.0)	
Sputum smear status	Negative	63 (92.6)	61 (96.8)	2 (3.2)	N.A.
	Positive	5 (7.4)	0 (0.0)	5 (100.0)	
CXR findings	Minimal	62 (91.2)	61 (98.4)	1 (1.6)	N.A.
	Moderately advanced and far advanced	6 (8.8)	0 (0.0)	6 (100.0)	
	Symptoms	Improved	58 (85.3)	56 (96.6)	2 (3.4)
	Same or worsen	10 (13.2)	5 (50.0)	5 (50.0)	

## Discussion

Even in the 21st century with rapid and lifesaving revolutionary advances in medical science and technology, TB continues to remain a disease with high burden and significant morbidity and mortality. In 2017, worldwide, an estimated 9.96 million new people developed TB and 1.3 million died from it. In India alone, there were 2.6 million new cases<sup>1</sup>.

When there is resistance to any drug, the regimen needs to be modified and increased in duration based on the pattern of resistance<sup>8</sup>. On an individual level, patients with INH mono-resistant disease are at a theoretically greater risk of developing MDR than those with drug-sensitive TB due to the requirement for only a single additional resistance mutation, with the associated risk of a need for more expensive, toxic and lengthy treatment regimens<sup>9</sup>. This study was conducted to determine the outcomes of the regimen for INH mono-resistant TB.

In the present study, 71.8% of patients had successful outcomes, out of which 9.4% of patients completed the RNTCP definition of cure and 62.3% of patients completed their treatment. 28.2% of patients had unsuccessful outcomes, out of which 15.3% patients were lost to follow-up, 7.1% patients died and 5.9% patients had a treatment failure in the form of microbiological positivity or change of regimen. In the study done by Gegia *et al*, successful outcomes were found in 71% of the patients<sup>10</sup>.

Patients of age groups 21 - 40 years had successful outcomes. Gegia *et al*, reported that treatment outcomes

were worse for older patients, among those who had INH mono-resistance<sup>10</sup>.

In the present study, cough and sputum were the most common symptoms. Breathlessness, hemoptysis, chest pain and loss of appetite were significantly associated with unsuccessful outcomes as these chest symptoms are related to severity of the disease, increased lung involvement and higher bacillary load.

27.1% of patients had contact with a case of TB and had significant association with unsuccessful outcomes. Báez-Saldaña *et al* stated that there was significant association between unsuccessful outcomes and patients having contact with a case of TB<sup>11</sup>. It may be explained by the fact that contact with a case of TB has a chance of increased transmission of resistant bacilli.

There was a significant association of unsuccessful outcomes among patients who did not complete their full course of ATT. Gegia *et al* stated that unsuccessful outcome was significantly associated with patient with a history of previous treatment<sup>10</sup>. There is an increased chance of emergence of drug resistant bacilli in patients who are lost to follow-up and higher chances of treatment failure. In this study, there was significant association of unsuccessful outcomes and patient with any household contact case of MDR-TB.

Patients who were current smokers were significantly associated with unsuccessful outcomes. In a similar study done by Chien *et al* smoking was significantly associated with unsuccessful outcomes<sup>12</sup>. This may be because smoking affects lung functions and hampers the defense mechanism of airways thus, increasing the symptoms and decreased health status, affecting compliance of the patients towards treatment.

History of alcohol intake was also significantly associated with unsuccessful outcomes. Báez-Saldaña *et al* stated that alcohol intake was an independent factor for unsuccessful outcomes<sup>11</sup>. Majority of anti TB drugs are metabolised by the liver and have adverse effect on liver, thus decreasing metabolism of ATT drugs.

Lower socio-economic class was significantly associated with unsuccessful outcomes. This may be due to unemployment/low family income, people may have limited and delayed access to healthcare services and under-nutrition is also associated with poor outcomes.

Patients with BMI of less than 17.5 Kg/m<sup>2</sup> in all age groups were significantly associated with unsuccessful outcomes. This may be explained by the fact that under-nutrition leads to protein deficiency, which causes inefficient transport of anti-TB drugs in the body. Also, protein deficiency causes immune-compromised state which further deteriorates the health condition of the patient.

A significant association of unsuccessful outcomes was found with deranged biochemical parameters of patients. Deranged biochemical parameters lead to decrease tolerance to medicines and decreased metabolism of ATT, thus increasing the chances of side-effects. In a few patients, due to kanamycin injection, adverse effects like pain at injection site and decreased hearing were observed.

The patients with sputum AFB direct smear 2+ or more were significantly associated with unsuccessful outcomes. In a similar study done by Karo *et al*, sputum smear positivity was associated with unsuccessful outcomes<sup>13</sup>. This suggests that chances of treatment failure and death increases with the increase in initial bacillary load.

Patients with cavity and bilaterally extensive disease on baseline chest X-ray were significantly associated with unsuccessful outcomes. In a similar study done by Kim *et al*, cavity and bilateral extensive lesions on chest X-ray were commonly found in patients who exhibited treatment failure<sup>14</sup>. It can be explained by the fact that extensive lesions had more bacillary load, cause more symptoms and are difficult to treat.

71 out of the total 85 patients continued treatment till 3rd month of follow-up. 68 out of 71 patients continued treatment till 6th month of follow-up and 62 out of the remaining 68 patients till 9th month of follow-up. Rest of the patients, at each follow-up, had unsuccessful outcomes. The patients who were lost to follow-up were non-compliant with medications due to long duration of treatment, requirement of intake of multiple drugs and daily visit to the health facility.

A significant association of increase in weight and improvement of symptoms at 3rd and 6th month was established with successful outcome. Increase in weight and improvement of symptoms were surrogate markers of successful outcome and response to medication.

Negative sputum smear status at 3rd month had significant association with successful outcomes. In 6th month of follow-up sputum smear-positivity had unsuccessful outcomes. There was significant association between minimal lesions on chest X-ray at 3rd month follow-up with successful outcomes.

## Conclusion

Early diagnosis of INH resistance and proper treatment along with education, emphasis and early attention to medical care, adequate nutrition, proper hygienic and ventilated living conditions, avoiding any addiction, compliance to regular complete treatment with required follow-up with social and economic support leads to successful management of patients with better outcome.

**Disclosures:** Funds was not required nor taken to conduct this study and there were no conflicts of interest.

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