

# Assessing Treatment Efficacy and Determinants of Outcome in Isoniazid Mono-resistant Tuberculosis Patients: A Prospective Observational Study in Gujarat

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## Abstract

**Introduction:** There is a high number of isoniazid-resistant tuberculosis (TB) in India; estimates imply that over 25% of TB patients there are isoniazid-resistant. Hence, the study aimed to evaluate the effectiveness of therapy for patients with isoniazid-mono-resistant TB and the negative effects of the H-mono-resistant TB Regime. **Materials and Methods:** It was a hospital-based prospective observational study from September 2021 to August 2022. Hence, 100 patients diagnosed with isoniazid mono-resistance TB enrolled in this study. After obtaining the prior informed consent of all patients willing to approve the collection and publication of their data, including extensive clinical history and radiological, microbiological, and biochemical investigations, this study included all diagnosed cases of isoniazid mono-resistant TB. A descriptive statistical analysis was done for continuous and categorical variables. Differences in characteristics between participants were tested with logistic regression and cross-tabulation.  $P < 0.05$  was considered significant. **Results:** Among 100 patients participated, their mean age was  $50.8 \pm 3.2$  years. About 72 (72%) participants have successful treatment outcomes (cure). Only about 25 (25%) patients had minor adverse drug reactions. Body mass index (16.6 [3.6–74]), substance addiction history (9.5 [3.3–26.9]), previous history of TB (9 [3.3–24.0]), type of lesion (5.3 [1.6–17]), and extent of the lesion (2.6 [1.03–6.07]) in chest X-ray were associated statistically with the treatment outcome. **Conclusion:** The findings suggest that the H-mono-resistance regime is generally well-tolerated, with only a small percentage of patients experiencing nonserious adverse drug reactions, and the overall successful treatment outcome in H-mono patients was 72%. The study also highlights the importance of monitoring drug resistance patterns, particularly for levofloxacin and moxifloxacin, and the need for effective treatment regimens for isoniazid mono-resistant pulmonary TB.

**Keywords:** Adverse effects, H-mono-resistance, risk factors, treatment outcome

## INTRODUCTION

Tuberculosis (TB) is a major public health problem worldwide, with an estimated 10 million new cases and 1.4 million deaths in 2019.<sup>[1]</sup> Despite significant progress in TB control efforts, the emergence of drug-resistant TB (DR-TB) poses a substantial threat to achieving the ambitious targets outlined in the World Health Organization's End TB Strategy. Among the various forms of DR-TB, isoniazid mono-resistant TB (H-Mono TB) has garnered increasing attention due to its unique characteristics and challenges in both diagnosis and treatment. The emergence of DR-TB has further complicated the

management of this disease. Isoniazid (INH) mono-resistance is a common form of DR-TB, defined as resistance to INH but susceptibility to rifampicin (RIF) and other first-line anti-TB drugs. INH mono-resistance is associated with lower TB treatment success rates compared to fully susceptible.<sup>[2–4]</sup>

Achieving successful treatment outcomes among H-Mono TB patients is influenced by a complex interplay of various factors. These factors can be broadly categorized into patient-related,

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health-care system-related, and pathogen-related factors. Patient-related factors include treatment adherence, comorbidities, socioeconomic status, and nutritional status. Health-care system-related factors encompass access to care, quality of health-care services, and availability of appropriate medications. Pathogen-related factors include the presence of additional drug resistance and genetic variations in the mycobacterial strain. Identifying and understanding these factors within the context of Gujarat will help tailor interventions to improve treatment outcomes.

Treatment adherence remains a linchpin in the management of TB, especially drug-resistant forms. Interrupted or incomplete treatment can lead to the development of further drug resistance, treatment failure, and the potential spread of drug-resistant strains within the community. Patient education and support mechanisms are essential to ensure treatment completion. In the context of H-mono TB, where the treatment regimen is adjusted to accommodate isoniazid resistance, adherence becomes even more critical. The findings of this study hold substantial public health implications. Understanding the factors influencing treatment outcomes among H-mono TB patients can inform policy decisions and health-care practices. It can guide the allocation of resources, the development of targeted interventions, and the enhancement of diagnostic and treatment services. Moreover, by addressing the unique challenges faced by H-mono TB patients in Gujarat, we contribute to the global effort to combat DR-TB and work toward achieving the End TB Strategy's ambitious goals.

Hence, the present study aimed to assess the treatment outcome and adverse effects of H-mono mono-resistant TB patients registered under NTEP, Gujarat.

## MATERIALS AND METHODS

### Study design and setting

A hospital-based prospective observational study on H-mono-resistant patients was conducted in Gujarat from September 2021 to August 2022.

### Sample size and sampling technique

Using the formula  $n = 4pq/l^2$ , the sample size was determined by taking into account the considerable prevalence of isoniazid-resistant TB in India, with estimates indicating that about 25% of TB cases are isoniazid-resistant.<sup>[3]</sup> Here, the permitted error L has been set at 9. A 92-person sample has been computed. With a final sample size of 100 and a nonresponsive rate of 5%, the study was concluded. Participants in the research were chosen at random.

### Inclusion criteria

All cases of pulmonary and extrapulmonary TB, both untreated and previously treated, who gave consent were included.

### Exclusion criteria

Drug-sensitive TB patients, multidrug- and RIF-resistant TB patients, patients who are terminally sick, and unwilling individuals are among the exclusion criteria.

### Data collection procedure

The selection of patients was random. Thus, following the prior informed consent of participants who were willing to give their nod of approval for the collection and publication of personal data, including detailed clinical history and radiological, microbiological, and biochemical investigations, a total of 100 patients with isoniazid mono-resistant TB were enrolled in this study. Sputum samples from all patients were taken and initially examined by smear AFB, followed by the first- and second-line probe tests. All patients had monthly clinical and radiological evaluations throughout their course of therapy. Up to the completion of the course of therapy, sputum smear microscopy was done every month. Mycobacterium TB sputum cultures were performed at the end of the 3<sup>rd</sup> month and the conclusion of therapy (the 6<sup>th</sup> month). Patients who had smear/culture-positive results in the 3<sup>rd</sup> month and after therapy were advised to undergo liquid culture DST.

### Ethical declaration

Written informed consent was taken in their vernacular language. Good clinical care guidelines were followed and guidelines as per the Helsinki Declaration 2008. This study was approved by the Institutional Ethical Review Board of our hospital before the start of the study (REF No-38/01/2020).

### Statistical analysis

All data were collected, cleaned, and edited in MS Excel and transferred into the SPSS version 26 (IBM Corporation Armonk, New York, United States) for analyses. We used frequency and percentage indices to describe the sociodemographic and clinical variables of the study, respectively. A descriptive statistical analysis was done for continuous and categorical variables. Differences in characteristics between participants were tested with bivariate logistic regression and cross-tabulation. Odds ratios and their 95% confidence intervals were used to quantify the associations.  $P < 0.05$  was considered significant.

## RESULTS

In the sociodemographic characteristics of participants ( $n = 100$ ), the mean age of the participants was  $50.8 \pm 3.2$  years. About 40 (40%) patients belonged to the age group of  $>45$  years. In regard to gender, males were about 62 (62%). More importantly, about 48 (48%) patients had undernutrition at the baseline assessment. About 42 (42%) had a substance addiction history. Of that, 42 most common substance addictions present smokeless ones (about 76%). About 32 (32%) had having comorbidity history other than TB. The most common comorbidity found to be hypertension (69%) followed by type-2 diabetes mellitus (49%).

In the clinical and radiological characteristics of the study participants ( $n = 100$ ), about 70 (70%) were newly diagnosed. The most common clinical presentation was cough (99%), followed by fever (90%), weight loss (80%), and cough with expectoration (79%).

In regard to radiological parameters, about 62 (62%) patients had cavitary lesions and 55 (55%) patients had extensive lesions in chest X-ray.

Table 1 shows the treatment outcome of the study participants ( $n = 100$ ). In newly diagnosed patients ( $n = 70$ ), 60 (86%) had successful treatment outcome (cure) and 10 (14%) had an unsuccessful treatment outcome (5-treatment defaulter + 5-regime failure). In the same way, in the previously TB-treated group ( $n = 30$ ), 12 (40%) had a successful treatment outcome (cure) and 18 had an unsuccessful treatment outcome (12-defaulter + 6-regime failure), respectively.

Figure 1 shows the distribution of adverse drug reactions (ADRs) among the study participants ( $n = 100$ ); in this study, out of a total of 100 patients, 75 (75%) patients did not have ADR, and 25 (25%) had nonserious ADRs. Out of 25 patients with nonserious ADRs, 12 (48%) patients had GIT related, 4 (16%) patients had hepatic, 4 (16%) patients had articular, 3 (12%) patients had dermatological, and 2 (8%) patients had neurological adverse reactions (giddiness).

**Table 1: Treatment outcome with the H-mono regime**

Treatment history	Outcome			Total, n (%)
	Cured, n (%)	Defaulted, n (%)	Regimen failure, n (%)	
Newly diagnosed	60 (86)	5 (7)	5 (7)	70 (70)
Previously treated	12 (40)	12 (40)	6 (20)	30 (30)
Total	72 (72)	17 (17)	11 (11)	100 (100)

Table 2 shows an analysis of drug resistance patterns among regime failure cases ( $n = 11$ ). From  $n = 11$ , about 4 (36.3%) had levofloxacin resistance, 4 (36.3%) had both levofloxacin and moxifloxacin resistance, and about 3 (27.2) had pyrazinamide resistance.

Table 3 shows the association between sociodemographic, clinical, and radiological characteristics with treatment outcome ( $n = 100$ ). Body mass index (BMI), substance addiction history, previous history of TB, type of lesion, and extent of the lesion in chest X-ray were associated statistically with the treatment outcome of the treatment ( $P < 0.05$ ).

## DISCUSSION

In the present study, out of a total of 100 cases, 62% of cases were male and 38% were female; when comparing this to the study by Varahram *et al.*, 65.6% were male and 34.4% were female.<sup>[5]</sup> In Maguire *et al.*'s study, 70.3% were male and 29.3% were female,<sup>[6]</sup> and in Garg *et al.*'s study, 67.3% were male and 32.7% were female.<sup>[7]</sup>

In the present study, out of a total of 100 cases, 30% of cases were previously treated for TB and 70% of cases were newly diagnosed with H-mono-resistance; when compared with the study by Garg *et al.*, 17% of cases were previously treated for TB and 63% of cases were newly diagnosed.<sup>[7]</sup> In Chien *et al.*'s study, 12.7% of cases were previously treated for TB and 87.3% of cases were newly diagnosed.<sup>[8]</sup> Variability in results is likely to be related to demography, sample size, and clinical and epidemiological differences.

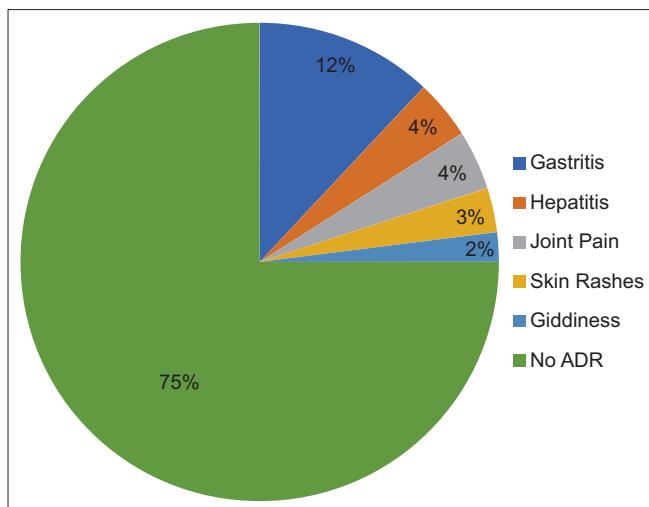
**Table 2: Analysis of drug resistance among failure cases**

Drug-resistant among failure cases	Levofloxacin	Levofloxacin and moxifloxacin	Pyrazinamide	Total
Number of patients with regimen failure (%)	4 (36.3)	4 (36.3)	3 (27.2)	11 (100)

**Table 3: Association between sociodemographic, clinical, and radiological characteristics with treatment outcome ( $n=100$ )**

Variables	Treatment outcome		Total (n=100), n (%)	OR (CI)	P
	Treatment cure (n=72), n %	Treatment failure (n=28), n %			
BMI					
≥18.5	46 (96)	2 (4)	48 (48)	16.6 (3.6–74.6)	<0.001**
<18.5	36 (69)	26 (31)	52 (52)		
Substance addiction					
Present	20 (48)	22 (52)	42 (42)	9.5 (3.3–26.9)	<0.001**
Absent	52 (90)	6 (10)	58 (58)		
Types of lesions on chest X-ray					
Cavitory	38 (61)	24 (39)	62 (62)	5.3 (1.6–17.04)	0.004*
Noncavitory	34 (89)	4 (11)	38 (38)		
The extent of the lesion in chest X-ray					
Limited (<1 lobe)	37 (82)	8 (18)	45 (45)	2.6 (1.03–6.7)	0.04*
Extensive (>1 lobe)	35 (64)	20 (36)	55 (55)		
Previous history of TB					
Yes	12 (33)	18 (77)	30 (30)	9 (3.3–24.0)	<0.001**
No	60 (93)	10 (7)	70 (70)		

$P < 0.05$  - significant,  $P < 0.001$  - highly significant. OR: Odds ratio, CI: Confidence interval, TB: Tuberculosis, BMI: Body mass index



**Figure 1:** The distribution of adverse drug reactions among participants ( $n = 100$ )

In the present study, out of a total of 100 cases, 72% of cases were cured with the H-mono regimen and 11% of cases had regimen failure. This can be compared with other studies: in Sayfutdinov *et al.*'s study, 80% of cases were cured and 8% of cases had regimen failure;<sup>[9]</sup> in Kwak *et al.*'s study, 84.1% of cases were cured and 15.9% of cases had regimen failure;<sup>[10]</sup> and in Cornejo Garcia *et al.*'s study, 77.2% of cases were cured and 3.1% of cases had regimen failure.<sup>[11]</sup> As per the India TB Report 2021, 53% of cases were cured, and 2% of cases had regimen failure<sup>3</sup>; as per the India TB report (Gujarat State), 60% of cases were cured and 8% of cases had regimen failure<sup>3</sup>; variation in result attributed to demography and sample size.

The study found that out of a total of 100 patients, 75 (75%) patients did not have ADRs, and 25 (25%) had nonserious ADRs. Out of 25 patients with nonserious ADR, 12 (48%) patients had GIT related, 4 (16%) patients had hepatic, 4 (16%) patients had articular, 3 (12%) patients had dermatological, and 2 (8%) patients had neurological adverse reactions. These findings can be compared with a meta-analysis of different treatments for isoniazid-resistant TB found that success, mortality, and acquired RIF resistance varied depending on the treatment given.<sup>[12]</sup>

Analysis of drug resistance patterns among regime failure cases shows levofloxacin resistance, and both levofloxacin and moxifloxacin resistance were major reasons for the treatment failure followed by pyrazinamide resistance. This can be compared with a previous study conducted by Explorative Analysis of Treatment Outcomes of Levofloxacin- and Moxifloxacin-based Regimens and Outcome Predictors in Ethiopian multidrug-resistant (MDR)-TB patients, which found that moxifloxacin is more potent than levofloxacin in terms of *in-vitro* drug susceptibility. However, a study conducted by comparison of levofloxacin versus moxifloxacin for MDR-TB found that the choice of levofloxacin or moxifloxacin made no difference to the final treatment outcome among patients with fluoroquinolone-sensitive MDR-TB.<sup>[13,14]</sup>

In a study conducted by a Global Perspective on Pyrazinamide Resistance: Systematic Review and Meta-Analysis, it was reported that PZA resistance is ubiquitous, with an estimated one in six incident TB cases and more than half of all MDR-TB cases resistant to PZA globally.<sup>[15]</sup>

BMI, substance addiction history, previous history of TB, type of lesion, and extent of the lesion in chest X-ray were associated statistically with the treatment outcome of the treatment ( $P < 0.05$ ). This finding can be compared with another study, MDR-TB Treatment Outcome and Associated Factors at the University of Gondar Comprehensive Specialized Hospital: A 10-Year Retrospective Study, which found that patients with a low BMI, comorbidities, HIV infection, a history of past anti-TB drug usage, and pulmonary TB had a higher proportion of unfavorable treatment outcomes than their counterparts.<sup>[16]</sup>

These findings suggest that the H-mono-resistance regime is generally well-tolerated, with only a small percentage of patients experiencing nonserious ADR. The most common nonserious ADRs were GIT related, followed by hepatic, articular, dermatological, and neurological adverse reactions. It is important to note that the study was observational, and further research is needed to confirm these findings. In addition, health-care providers should continue to monitor patients for adverse reactions and take appropriate measures to manage them. Overall, the study provides valuable information on the safety and tolerability of the H-mono-resistance regime, which can be used to inform clinical practice and improve patient outcomes.

### Limitations

- The study was observational, which limits the ability to draw causal conclusions
- The sample size was relatively small, which may limit the generalizability of the findings
- The study did not compare the H-mono-resistance regime to other treatment options, which limits the ability to evaluate its effectiveness relative to other options.

### Recommendations

- Further research is needed to confirm these findings and compare the H-mono-resistance regime to other treatment options
- Health-care providers should continue to monitor patients for adverse reactions and take appropriate measures to manage them
- Patients should be informed about the potential risks and benefits of the H-mono-resistance regime and other treatment options to make informed decisions about their care
- The study also highlights the importance of monitoring drug resistance patterns, particularly for levofloxacin and moxifloxacin, and the need for effective treatment regimens for isoniazid mono-resistant pulmonary TB.

### Conclusion

This prospective observational study of 100 patients with

isoniazid mono-resistant TB in Gujarat found that 72% of patients had successful treatment outcomes with the H-mono-resistant regimen. Among the 72 cured patients, the majority (86%) were newly diagnosed cases. The study also assessed adverse reactions, with 75% of patients experiencing no adverse effects. The remaining 25% had minor nonserious reactions such as GI, hepatic, articular, dermatological, and neurological effects. An analysis of the 11 patients with regimen failure showed that fluoroquinolone (levofloxacin and moxifloxacin) and pyrazinamide resistance were the main factors. The data indicate that lower BMI, substance addiction history, previous TB, cavitary lesions, and extensive lesions were significantly associated with poorer treatment outcomes. These findings contribute to the development of more effective treatment strategies for patients with DR-TB.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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