UAPM
Journal of Respiratory Diseases
and Allied Sciences

Original Article

Treatment Outcomes for Isoniazid-Resistant Pulmonary Tuberculosis Using a Shorter Regimen at a Tertiary Care Centre from the Western Part of India

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Abstract

Background: Drug-resistant tuberculosis has been associated with higher rates of morbidity and mortality. A global total of an estimated 4 lakh people with 'multidrug resistant/rifampicin resistant' tuberculosis (MDR/RR-TB) were detected and notified in 2023. In India, 63,929 MDR/ RR TB cases were diagnosed, with 23,019 patients diagnosed with isoniazid (H)-mono/poly drug-resistant tuberculosis (DR-TB).

Objective: This study analyses the outcome of 'Isoniazid Mono Resistance' Tuberculosis patients and the adverse drug reaction (ADR) among those put on isoniazid (H) mono/poly regimen treatment.

Method: 'Isoniazid-mono-poly' DR TB regimen duration is 6 to 9 months and started according to drug sensitivity testing (DST) among eligible patients. Follow-ups were done every two months for clinical, bacteriological and radiological parameters. Outcomes observed were cure, treatment completed, treatment failure, died, lost to follow-up, not evaluated, switch to another regimen and transfer out, etc., as per standard protocol.

Results: 88 isoniazid-mono/poly patients were enrolled over the last two years. There were 62 male and 26 were females. Outcome for isoniazid mono/poly regimen was cure among 40 (45.5%), treatment completed in 34 (38.6%), lost to follow up in 2 (2.3%), treatment failure in 1 (1.1%), died in 9 (10.2%) and switched to another regimen in 2 (2.3%). The prevalence of *kat*G mutation (High level Isoniazid resistance) was more than *inh*A (Low level Isoniazid resistance). A more favorable treatment outcome was observed among those with minimal/moderate lung disease compared to those with far advance disease with large cavitation ($p = 0.029$). This was also in line with better sputum conversion.

Conclusion: Treating isoniazid 'mono-resistant' TB patients with levofloxacin, rifampicin, ethambutol, and pyrazinamide (LfxREZ) resulted in satisfactory outcomes and low toxicity. Ruling out the isoniazid drug resistance pattern is important for all bacteriologically confirmed TB cases.

Keywords: Tuberculosis, Drug resistance, Isoniazid, Treatment-outcome.

Introduction

Tuberculosis (TB) is a transmissible illness that remains a significant global health burden. In 2023, it reclaimed its position as the world's most fatal single infectious disease after a three-year period in which COVID-19 held that title. Currently, an estimated 25% of the global population is infected with *M. tuberculosis*.[1]

Global TB cases reached 10.8 million in 2023, up from 10.7 million the previous year. This continued increase is attributed to the long-term after-effects of pandemic-related disruptions to healthcare services. In 2023, an estimated

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Access this article online

Quick Response Code

Website: uapmjournal.in

DOI: 10.70192/v3.i1.02

How to cite this article: Chaudhary P, Gupta N, Dixit R, Kuldeep R, Meghwanshi R. Treatment Outcomes for Isoniazid-Resistant Pulmonary Tuberculosis Using a Shorter Regimen at a Tertiary Care Centre from the Western Part of India. UAPM J. Respiratory Diseases Allied Sci. 2026;3(1):7-11.

Received: 12-11-2025, **Accepted:** 10-01-2026, **Published:** 12-02-2026

400,000 people globally developed MDR/RR-TB. Among these, the proportion of TB patients with multidrug-resistant or rifampicin-resistant strains was 3.2% for new cases and 16% for those previously treated.[1]

In India, a total of 63,929 MDR/RR-TB, including 11,749 'pre-XDR-TB', 114 'XDR-TB', and 23,019 'H-mono/poly' DR-TB patients were diagnosed.[2] In 2023, TB resulted in approximately 1.25 million deaths across the globe.[2]

Isoniazid was introduced in 1952. Isoniazid is a prodrug that becomes active only after it is converted by the KatG catalase/peroxidase enzyme (encoded by the *katG* gene). Once activated, it works by inhibiting the synthesis of mycolic acids through the NADH-dependent enoyl-acyl carrier protein (ACP)-reductase, which is encoded by the *inhA* gene.

The two primary molecular mechanisms of Isoniazid resistance involve gene mutations in *katG* and *inhA* or their promoter regions. Isoniazid resistance can be categorized as either "high-level" or "low-level" resistance. Concurrent mutations in the *katG* and *inhA* genes are usually associated with a high level of drug resistance. A mutation limited only to the *inh* A promoter area is usually associated with "low-level" resistance and a higher dose of isoniazid (10-15 mg/kg/day) is likely to add benefit.

This study was planned to study the outcome analysis of isoniazid mono resistance tuberculosis patients put on H mono/poly regimen at treatment completion, apart from assessing the adverse drug reaction (ADR) and to find out the cause resulting in lost to follow up in such cases.

Methods

This was a hospital-based, analytical type of observational study to assess treatment outcome. After approval from the institutional ethical committee, 88 patients enrolled for the H mono/poly regimen for the last two years at our Centre constituted the final study population. A detailed clinical history for each patient was recorded apart from a complete pre-treatment evaluation, i.e., skiagram chest PA view, CBC, LFT, RFT, etc.

All oral H mono/poly DR TB regimen: -

All eligible patients (documented rifampicin (R) resistance not detected and H resistance TB) received a drug regimen containing levofloxacin (Lfx), rifampicin (R), ethambutol (E) and pyrazinamide (Z).

The total duration of 'H mono-poly' DR TB regimen was [(6) Lfx R E Z] for 6 to 9 months, undivided into intensive phase or continuation phase. Treatment was extended to nine months, guided by smear microscopy and clinical monitoring, for patients who had extensive or extra-pulmonary TB, uncontrolled comorbidities, a positive smear at four months, or required regimen modification due to FQ resistance or the need for replacement drugs.

As per the study protocol, all patients received clinical follow-up for symptoms every two months. Smear microscopy was conducted monthly from the third month onwards, with cultures taken at 3, 6, and 9 months (if applicable). Chest X-rays were performed as clinically indicated and upon completion of treatment. Possible adverse events were also assessed as and when required.

Treatment outcomes were classified as 'Cured', 'Treatment completed', 'Treatment failed', 'Died', 'Lost to follow up', 'Transferred out', and 'Regime changed' as per the national elimination tuberculosis program (NTEP), Government of India. In our study, cured and achieved a cure were included in the favorable outcome category, whereas treatment failure, death, loss to follow-up, regime change, not evaluated status, and transfer out were all classified as unfavorable outcomes.

Methods used for drug susceptibility testing included nucleic acid amplification test (NAAT), line probe assay (LPA), and growth-based phenotypic culture methods included automated Liquid culture systems.

Results

Among 88 study patients, the median age was 38 years (range 12–75 years). Most of the patients were males, 62 (70.5%), and only 26 (29.5%) patients were females.

Out of 88 patients, 64 (72.7%) had high isoniazid resistance, while the remaining 24 (27.3%) patients had low isoniazid resistance (Table 1). Table 2 depicts that at the initiation of treatment, 36 (40.9%) patients had minimal disease, 30 (36.6%) patients had moderate disease and 22 (26.8%) patients had far advanced disease on chest skiagram. At the end of treatment, 39 (79.6%) patients had minimal disease, 6 (12.2%) patients had moderate disease and 4 (8.2%) patients had far advanced disease on chest skiagram (Table 3).

About 24 patients (27.3%) out of 88 experienced at least one adverse drug reaction. Figure 1 depicts adverse drug

Table 1: The distribution of study subjects according to the type of isoniazid resistance among patients receiving the H mono/poly regimen

Type of Isoniazid resistance	*H mono/poly regime*	
	N	%
High (*kat*G mutation)	64	72.7
Low (*inh*A mutation)	24	27.3
Total	88	100

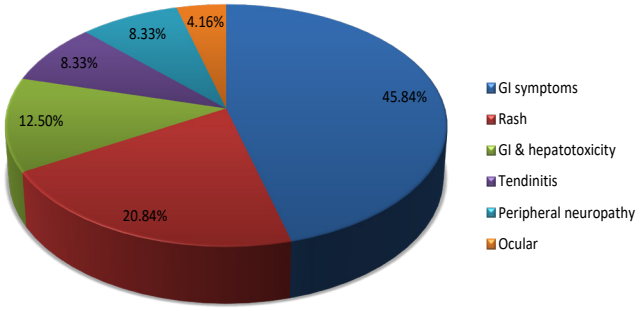

Figure 1: Adverse drug reactions experienced by patients on H mono/poly regimen

reactions experienced by patients on H mono/poly regimen**.** 11 (45.84%) patients experienced gastrointestinal symptoms, 5 (20.84%) patients experienced rashes, 3 (12.5%) patients experienced gastrointestinal & hepato-toxicity, 2 (8.33%) patients experienced tendinitis, Over 2 (8.33%) patients experienced peripheral neuropathy and one (4.16%) patient experienced ocular side effects. The most common ADR associated with the H mono/poly regime was gastrointestinal symptoms.

Table 4 depicts that a total of 27 patients had sputum conversion at 2 months, of which 15 (55.6%) patients had minimal disease, 8 (29.63%) patients had moderate disease and 4 (14.81%) patients had far advanced disease on chest skiagram. About 30 patients had sputum conversion at 3 months, of which 13 (43.3%) patients had minimal disease, 13 (43.3%) patients had moderate and 4 (13.3%) patients had far advanced disease on chest skiagram. At 4 months, 8 patients had sputum conversion, of which 4 (50%) patients had far advanced disease, 3 (37.5%) patients had moderate disease and only 1 (1.5%) had minimal disease on chest skiagram. This indicates that sputum conversion is late among patients with far-advanced disease as compared to those with moderate or minimal disease on chest X-ray. However, no significant association was seen in sputum conversion rate and chest skiagram findings ($p = 0.198$).

Table 2: shows the extent of pulmonary disease on chest X-ray among patients receiving the H mono/poly regimen. (In 39 patients, follow-up chest skiagram information was not available upon completion of therapy due to death/lost to follow-up after treatment completion)

Extent of disease on chest X-ray	*At the initiation of treatment*		*At the end of treatment*	
	N = 82	*%*	*N = 49*	*%*
Minimal/normal	36	40.9	39	79.6
Moderate	30	34.1	6	12.2
Far advanced	22	25	4	8.2
Total	88	100	49	100

Table 3: Type of lesion on chest radiograph among patients receiving H mono/poly regimen

Type of lesion on chest radiograph	*At the initiation of treatment*		*At completion of treatment*	
	N	*%*	*N*	*%*
Cavitatory	32	36.4	9	10.2
Non Cavitatory	50	56.8	40	45.5
Negative	6	6.8	39	44.3
Total	88	100	88	100

Table 5: Final outcomes of patients receiving the H mono/poly regimen

Outcome	*Number of patients*	*Percentage*
Cured	40	45.5
Treatment completed	34	38.6
Lost to follow up	2	2.3
Treatment failure	1	1.1
Transferred out	0	0.0
Died	9	10.2
Switch to others regimen	2	2.3
Total	88	100

Various outcomes of patients receiving an H mono/poly regimen were noted. About 40 (45.5%) patients were declared as 'cured' while 34 (38.6%) patients were declared as 'treatment completed'. Death occurred in 9 (10.2%) patients, while treatment failure occurred in only 1 (1.1%) patient. Two patients were lost to follow-up and 2 (2.3%) patients were switched to another regimen (Table 5).

Table 1 shows the distribution of study subjects according to the type of isoniazid resistance among patients receiving the H mono/poly regimen.

Discussion

This study was an observational study with a total of 88 patients enrolled for the isoniazid mono/poly regimen. Those who attended the outpatient department for follow-up at the Programmatic Management of Drug-Resistant Tuberculosis (PMDT) site were reviewed and follow-up for all three parameters, i.e., clinical, microbiological, and radiological outcomes.

Among the 88 patients with isoniazid mono-resistant tuberculosis, 62 (70.5%) were male, and 26 (29.5%) were

Table 4: Correlation of radiologically classified chest skiagram findings with sputum conversion rate at different intervals for H mono-poly resistance (N= 66)

Extent of disease on chest skiagram	*Sputum conversion at different intervals*								*Total*	
	at '2' months		*at '3' months*		*at '4' months*		*at '5' months*			
	N	*% (N=27)*	*N*	*% (N=30)*	*N*	*% (N=8)*	*N*	*% (N=1)*	*N*	*% (N=66)*
Minimal	15	55.6	13	43.3	1	12.5	0	0	29	36.4
Moderate	8	29.6	13	43.3	3	37.5	0	0	24	36.4
Far advance	4	14.8	4	13.4	4	50.0	1	100	13	19.7
Total	27		30		8		1		66	

female. The mean age (± SD) was 39 ± 16.31 years, with a median age of 38 years. A similar study by Hyun Lee *et al.*[3] in 2016 at Seoul, South Korea, observed 65.7% (92 out of 140) males with a median age of 54 years. This difference in median age may be due to the developed and higher socio-economic country compared to ours and higher life expectancy, i.e., 83 years in South Korea.

Out of 88 patients, 64 (72.7%) had high isoniazid resistance (*katG* mutation), while the remaining 24 (27.3%) patients had low isoniazid resistance (*inhA* mutation) in the present study. A study by Se Hyun Kwak *et al.*[4], mutations in *katG* were the most frequent seen in 54 (56.3%), followed by 34 (35.4%) patients. A study by Kabra *et al.*,[5] revealed that the *katG* gene mutation was the most common form of isoniazid (H) monoresistance observed in 30 (65.2%) patients, followed by the *inhA* gene mutation in 16 (34.8%) patients.

Out of 60, 58 (96.7%) patients on isoniazid mono/poly regimen had clinical improvement and 2 (3.3%) patients had clinical deterioration in the present study. About 22 (36.7%) patients had some residual or persistent symptoms at the end of 6 months of treatment, while 38 (63.3%) patients were asymptomatic following the completion of treatment. Among sputum converted patients in the H mono/poly regimen, out of 66 patients, 64 (97%) patients had favorable outcomes at the end of treatment, while 1 (1.5%) switched to another regimen and 1 (1.5%) was lost to follow-up. In our study, the sputum conversion rate was around 75%.

In minimal lung disease on chest skiagram, 34/36 (94.4%) patients had a favorable outcome, in moderate lesions, 25/30 (83.3%) had a favorable outcome and in those with far advanced lesions, 15/22 (68.2%) had a favorable outcome following the treatment completion. Among patients with minimal lesions, 2/36 (5.6%) patients had an unfavorable outcome, in moderate lesions, 5/30 (16.7%) patients, and in far-advanced lesions, 7/22 (31.8%) had an unfavorable outcome at the end of treatment. Chest skiagram lesions were significantly associated with outcomes of the disease in the H mono/poly regimen in the present study. A study done by JY Chien *et al.*[6] in Taiwan observed that those with minimal lesions, 86.1% had a favorable outcome, in moderate disease, 79.7% patients, and in those with extensive disease, 75% patients had a favorable outcome. These results closely align with our study. In the same study, unfavorable treatment outcome was observed in 13.9% patients with minimal disease, 20.3% patients with moderate disease and 25% patients with far-advanced disease. Cavitary lesions were linked to a significant increase in relapse (4.1 *vs.* 0.0%, $p = 0.006$). Relapse occurred in 25.0% of patients receiving 6-month treatment, whereas those receiving extended therapy for 7–9, 10–12, or >12 months had lower relapse rates of 3.2, 0, and 3.7%, respectively in their study. "Based on these observations, it appears crucial to maintain rifampicin treatment throughout and to extend the duration of therapy for cavitary disease in order to improve outcomes for patients with isoniazid mono-resistant TB.

Over 32 (36.4%) patients had cavitary lung disease and 56 (63.6%) patients had non cavitary lung disease on chest skiagram in present study. A trial by Andrew J Nunn *et al.*[7] (STREAM study) found 184/239 (76.9%) had at least one cavitary lesion. They also observed minimal disease in 11%, moderate in 52% and advanced disease in 35% patients. This difference was probably due to large sample size in their study.

Of the 88 patients in our study, 24 (27.3%) experienced at least one adverse drug reaction. Out of 24 patients, 11 (45.84%) experienced GI symptom, 3 (12.5%) had GI & hepato-toxicity, 5 (20.84%) had rashes, 2 (8.33%) had tendinitis, 2 (8.33%) had peripheral neuropathy and 1 (4.16%) experienced ocular side effects. Most common ADR associated with H mono/poly regimen was GI symptoms. A study by Kamila Romanowski *et al.*[8] found almost similar result. The STREAM trial[7] observed grade 3 or higher adverse events in 48.2% of participants. Specifically, 11.0% experienced a QT/corrected QT interval (Fridericia's formula) prolongation to 500 msec, which required close monitoring and medication adjustments.

In H mono regimen out of 88 patients, 40 (45.5%) patients were declared as 'cured' and 34 (38.6%) patients were assigned outcome as 'treatment completed' thereby constituting favorable outcome in 84.1% patients in the present study. In other studies, favorable outcome was observed in 85% by Yan Shao *et al.*[9], 84.1% by Se Hyun Kwak *et al.*[4] and in 91.3% by Kabra *et al.*[5] In a study by Ayse Feyza Aslan *et al.*[10] 51.6% patients were cured and 41.0% completed the treatment. In another study, Khan S, *et al.*[11] observed favorable treatment outcomes in 87% subjects, including treatment completion in 52% and cure in 35%. These results are almost similar to our study findings. 'India TB report 2024' also mentions that 87% patients had treatment success in isoniazid resistance TB patients on 'H mono/poly' regimen.[2]

Among 88 patients receiving the 'H mono/poly' regimen, two (2.3%) were lost to follow-up during this study. Severe ADR led to treatment discontinuation for one patient and other one left the treatment due to misbelief that the treatment received was not effective. A study by Barbara Manyame-Murwira *et al.*[12] from Zimbabwe observed that 2.9% patients were lost to follow up, which is similar to our study. In 'India TB report 2024' the figure of reported lost to follow up was 5%.[2]

In H mono/poly regimen, out of 88 patients 1 (1.1%) patient was assigned outcome as a treatment failure in our study. The same findings were seen by Kamila Romanowski *et al.*[8] at British Columbia in 1.1% patients. On the other hand, the 'India TB report 2024'[2] reported treatment failure in 2%. Similar results were seen with other studies by Ayse Feyza Aslan *et al.*[10] in 2.7% and by Sumaiya Khan S *et al.*[11] in 2.3%. In H mono/poly regimen, out of 88 patients 9 (10.2%) were assigned outcome as 'died' during the treatment in present study whereas, 'India TB report 2024'[2] mentions 5% patients declared as 'died'. The all-cause mortality was seen in 6 (3.6%) patients from Canada[8]. "These findings imply that successful

treatment outcomes in isoniazid-resistant cases are potentially linked to early detection and disease extent, as well as patient adherence and comorbid illnesses.

There were few limitations in the present study. This was an observational, single-center study where patients received treatment at peripheral DOTS centers, and several DOTS providers failed to mention important details i.e. sputum status, ADRs, radiological and symptoms improvement, reason for lost to follow up etc. therefore, this information was not accurately analyzed. Secondly, not all the patients came for follow up, as a result of which their clinical, microbiological and radiological progress/status could not be monitored efficiently. Moreover, potential confounding variables and effect modification could not be controlled/assessed.

But despite these limitations, this study explores treatment outcome of isoniazid resistant TB in low resource countries under programmatic conditions from this vary part of country. Most patients were male and sex distribution did not appear to influence treatment outcome. The prevalence of *kat*G mutation was more than *inh*A, however, outcome was almost similar in both type of resistance and not statistically significant. The minimal and moderate lung disease had more favorable outcome and sputum conversion than those with far advance disease ($p = 0.029$). The non-cavitary lung disease had better outcome than cavitary disease ($p < 0.001$). About 24 patients (27.3%) experienced at least one adverse drug reaction with most common ADR as GI symptoms. High-quality studies are the need of the hour to assess the effectiveness of standardized regimens, paying special attention to trials that use fluoroquinolones. There is need of constant monitoring and review of treatment guidelines for 'isoniazid mono-resistant' TB in view of currently available data.

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