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"ADHERENCE TO 2ND LINE ANTI-TUBERCULAR DRUGS IN DRUG-RESISTANT TUBERCULOSIS CASES"

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ABSTRACT:
India aims to end tuberculosis (TB) by 2025.So we need to have high adherence to anti-TB drugs. We conducted this study to know the adherence to second line drugs for drug-resistant TB. It was a prospective-observational study conducted from November 2022 to May 2024. After obtaining informed consent from the patients, we noted their demographic profile and treatment was started by the chest physicians (not the investigator) as per the guidelines of Revised National TB Control Program PMDT (programmatic management of drug-resistant TB). Patients were followed on a monthly basis for six months, either telephonically or whenever they came for collecting monthly medicines. To assess the level of adherence, we used the eight-item Morisky Medication Adherence Scale (MMAS-8) questionnaire. 228 patients were registered as drug-resistant TB cases at our institute. Of these, 199 were enrolled in the study as per the inclusion and exclusion criteria. There were 9 drop-outs and only 190 patients were considered for final statistical analysis. We found that with the advancement of time, the adherence to second line drugs for drug-resistant TB decreased despite all follow-ups. We concluded that proper patient counseling is important during follow-ups or during monthly visits of patients for collection of their medications. We need to have strategies which are adaptable and people-centered so as to increase the adherence to these drugs and can add to a better outcome.

KEYWORDS: adherence, drug-resistant tuberculosis, Morisky medication adherence scale

INTRODUCTION:

India aims to end tuberculosis (TB) by 2025.[1]To achieve this goal, we need to have a high adherence rate among people on drugs for TB. This study was done to know the adherence to second line drugs for drug-resistant TB. Globally, tuberculosis (TB) has been a huge public health problem. TB holds the second rank as the leading cause of death worldwide (only after HIV and AIDS) after the COVID-19 pandemic.[2]

It has been a long time since the causative organism for TB was discovered and drugs were developed for its cure. [3-6] But there has been an acquisition of resistance to anti-tubercular drugs.[7] Drug-resistant TB is becoming more prevalent in the whole world.[8] Globally, the estimated annual number of people who developed MDR/RR-TB in 2022 was 410 000.[9]

Among the eight countries that account for almost two thirds of all tuberculosis cases, India ranks first and according to the WHO, tuberculosis is one of the top 10 causes of mortality in India.[10]

For the treatment of drug-resistant TB, second-line antitubercular drugs are necessary, which are costly and toxic and must be used for a longer period of time. A variety of drugs are used for the chemotherapy of drug resistant tuberculosis – bedaquiline, linezolid, cycloserine, clofazimine, levofloxacin, delamanid, to name a few.[11]

The second-line drugs for TB do have adverse effects. Diverse studies have been conducted to provide differing insights on adverse reactions linked to the usage of drugs for multi drug resistant tuberculosis.[8] These adverse drug reactions may significantly affect the adherence to anti-tubercular medication, which highly impact patients' treatment outcomes and quality of life. Drug resistant TB is a man-made phenomenon - poor treatment, poor drugs and poor adherence leads to development of multi-drug resistant TB. [11-12]

Adherence is the extent to which a patient takes medicine as directed by the physician. The current definition of treatment adherence, as given by the WHO, is “the extent to which a person's behavior taking medication, following a diet, and/or executing lifestyle changes- corresponds with the agreed recommendations from a healthcare provider”.[13]

Despite the research and development of a number of drugs, the causative organism still persist and has developed resistance to many anti-TB drugs.[7] We wanted to know if there is any association between second line drugs for TB and adherence to medication. Is it non-adherence that has resulted in development of resistance for second-line drugs? A good deal of work has been done on tuberculosis in India but there is limited data available for adherence to TB medication in the state of Madhya Pradesh (MP). This work was designed to find out the adherence of patients to 2nd line drugs for drug resistant tuberculosis (DR-TB) at a tertiary care hospital in MP.

METHODS:

The study was a prospective observational study carried out at the Gandhi Medical College and associated hospitals in Bhopal, the capital of Madhya Pradesh (M.P). The Institutional Ethics Committee's permission was obtained before beginning the study. The study was conducted in accordance with the ethical principles originating from the Declaration of Helsinki. Written informed consent was taken from the all the patients before enrolling them in the study.

Study Site- The study was carried out in the Department of Pharmacology and Department of Respiratory Medicine, Gandhi Medical College and associated hospitals, Bhopal (M.P).

Sample size- Patients who met the inclusion criteria and were registered between November 2022 and November 2023 were included in the study. The study included 199 patients once the inclusion and exclusion criteria were applied.

Study duration-It was carried out in the period between November 2022 up to May 2024. The six-month follow-up period was a part of the study period.

Inclusion criteria:

1. Newly registered patients with proven Drug-resistant TB at Respiratory Medicine Department of the tertiary care hospital.
2. Age group: up to 18 years of age.

Exclusion criteria:
1. Patients admitted to DR-TB center for fewer than seven days.
2. Every pregnant and lactating female.
3. Patients who are seriously and mentally ill.
4. Patients with drug-resistant tuberculosis who are allergic to second line drugs.

Materials-
1. Validated consent form
2. Proforma (self-developed and validated).
3. Modified Morisky Adherence Scale (MMAS-8) Questionnaire.

Methodology-
All participating patients provided written informed consent after being chosen based on inclusion and exclusion criteria. The type and site of tuberculosis, age, gender, case registration, and medication regimen were among the study variables that were recorded. The investigator did not administer treatment; instead, the chest physicians followed the Revised National TB Control Program PMDT (programmatic management of drug-resistant TB) guidelines.

Follow-up: The patients were initially observed daily till they continued to be admitted after the physicians started a DR-TB treatment. Patients received monthly monitoring and follow-up after being discharged. The patients were monitored by phone or digitally whenever they came to collect monthly medications. The follow-up was done for a maximum of six months.

Eight-item Morisky’s Medication Adherence Scale (MMAS-8) Questionnaire

Adherence was determined using an eight-item Medication Adherence Scale of Morisky (MMAS-8) The MMAS-8 is a self-reported general evaluation tool with eight items that measures medication taking behavior and determines non-adherence to drug regimens. The first seven items in the questionnaire have a binary response (yes/no) that denotes either adherent or non-adherent behavior.

The first question is, "Do you ever forget to take your medication?"
Question 2 asks, " People sometimes miss taking their medicines for reasons other than forgetting. Thinking over the past two weeks, were there any days when you didn’t take your medicine?”
Question 3 is “Have you ever cut back or stopped taking your medicine without telling your doctor because you felt worse when you took it?”
Question 4 is “When you travel or leave home do you sometimes forget to take your medicine along?” Question 5 asks “Did you take all your medicines yesterday?” Question 6 asks “When you feel that your symptoms are under control, do you sometimes stop taking your medicine?” Question 7 is “Taking medicine every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?” Question 8 is “How often do you have difficulty in remembering to take all your medicines?” Patients can use a 5-point Likert scale to indicate how often they fail to take their medications when responding to question 8.

For questions 1 through 7, a score of 1 is awarded for "no" as an answer. Question 5 is rephrased, so a score of 1 is assigned for "yes" as a response. The total score goes from 0 to 8. [14]

Accordingly, a patient may be classified as having high, medium, or low adherence to therapy if their total scores are 8, 7, and 6 or fewer than 6.[15-17]
Medium or low therapy adherence was regarded as nonadherence in this study. Following a month of therapy, the outcomes were ascertained at baseline and at every follow-up.

The mean, standard deviation, and percentages were computed using Microsoft Excel 2019, which was also utilized to create graphs, tables, and charts.
Statistical analysis was done using Epi Info Software version 7.1.4.0. Continuous variables were expressed as mean± SD, while categorical variables were expressed as absolute numbers or percentages that were compared using the Chi square test.

RESULTS:
Over the course of the study, 228 patients were enrolled at the Department of Respiratory and Chest Diseases; however, only 199 of them met the inclusion and exclusion criteria suitable for the study.

Table 1: Age and Sex distribution of DR-TB patients

Age group (in years)	**Malen**	**Female n**	**Total N (%)**
≤20	5	13	18 (9.0)
21-40	59	46	105 (52.8)
41-60	30	10	40 (20.1)
>60	18	3	21 (10.6)
Total	112	87	199 (100.0)

There were 87 females and 112 males in the study, ages ranging from 18 to 74 (mean 35±14.32). Male patients ranged in age from 18 to 74 years old, with a mean age of 39±14.32 years, while female patients had an average age of 30.17±11.10 years, ranging in age from 18 to 71 years. Male patients made up the majority of patients (52.8%), who were primarily in the age range of 21 to 40 years. As people aged, the number of patients in both genders gradually decreased.

Table no. 2: Adherence to treatment medication for DR-TB patients

Follow-up period	**Adherentn (%)**	**TotalN**
Baseline (at the end of 1 month)	171 (85.95)	199
At the end of 2 months	186 (94.42)	197
At the end of 3 months	158 (80.61)	196
At the end of 4 months	93 (48.19)	193
At the end of 5 months	69 (36.13)	191
At the end of 6 months	48 (25.26)	190

n=number of patients who were adherent to treatment.
N=total number of patients in the study
The above table shows the trend in adherence to treatment medication for DR-TB. There was a decline in the percentage of patients who were adherent to treatment as the follow-up progressed.

Figure No. 1: Adherence to treatment medication for DR-TB patients

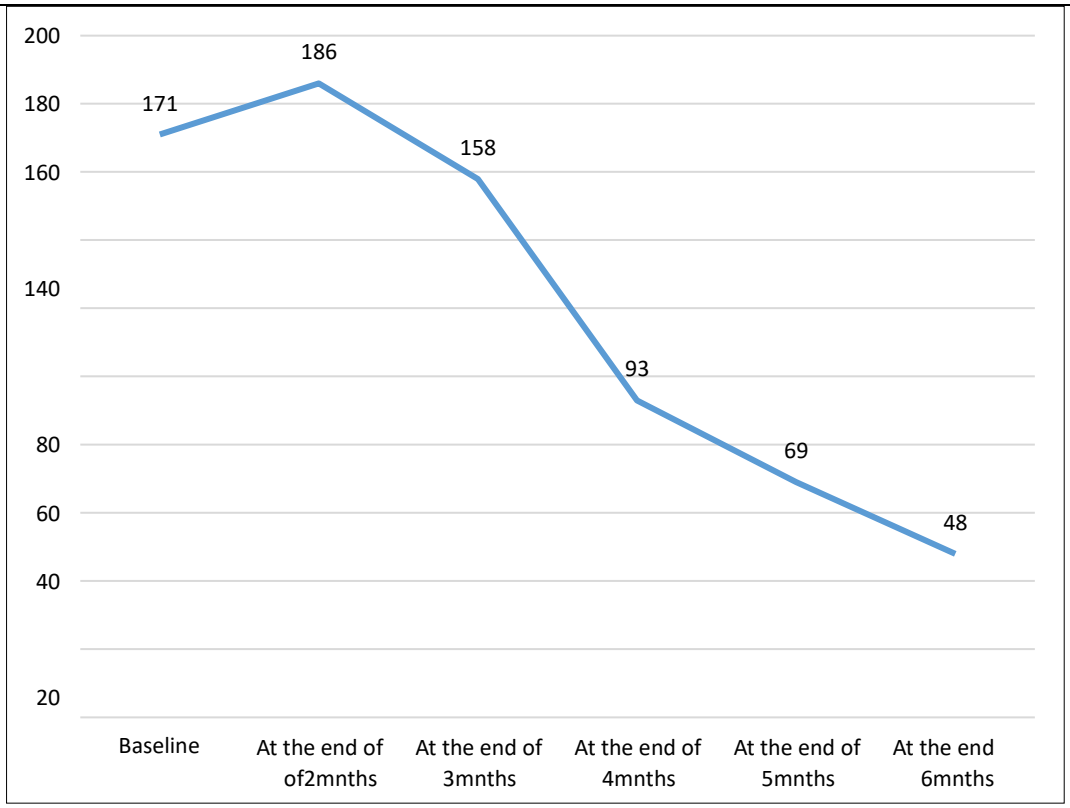

Table 3: Baseline Demographic Characteristics based on gender distribution ofpatients

Parameter	**Male (n=112)**	**Female(n=87)**		
	n (%)	n (%)		
Age (years) (Mean± SD)	39±14.32	30.17±11.10	χ^2	**P-value**
Initial weight (in kg)				
<50	64 (57.14)	48 (55.17)	8.99	0.003*
≥50	48 (42.86)	12 (13.79)		
History				
New cases	21 (18.75)	28 (32.18)	4.76	0.03*
Retreatment	91 (81.25)	59 (60.92)		
Comorbidity				
HIV	6 (5.36)	1 (1.15)	1.31	0.52
DM	2 (18.75)	6 (6.90)		
HTN	7 (6.25)	4 (4.60)		
Habits				
Alcoholic	12 (10.71)	1 (1.15)	73.82	0.00001*
Smoker	58 (51.79)	2 (2.30)		
Nil	41 (36.61)	83 (95.40)		
Site of TB				
PTB	105 (93.75)	81 (93.10)	0.03	0.85
EPTB	7 (6.25)	6 (6.90)		

Type of Regimen				
H. mono/poly	10 (8.93)	9 (10.34)	0.74	0.86
AOS	5 (4.46)	6 (6.90)		
AOL	87 (77.67)	64 (73.56)		
Modified AOL	10 (8.93)	8 (9.20)		

***p<0.05 is considered statistically significant.**

H. mono/poly=Regimen for Isoniazid monoresistance or poly resistance
AOS=Shorter oral Bedaquiline-containing MDR/RR-TB regimen
AOL=Longer oral M/XDR-TB regimen
The disease was found to be more common in retreatment cases, in both genders.

Table no. 4: Association between TB treatment adherence and sociodemographic characteristics (Baseline)

Variable	**Treatment Outcome**		χ^2	**P-value**
	Adherent (N=171)	Non-adherent (N=28)		
	n (%)	n (%)		
Gender				
Male	89 (52.05)	23 (82.14)	8.86	0.003*
Female	82 (47.95)	5 (17.86)		
Marital Status				
Married	110 (64.34)	23 (82.14)	3.44	0.063
Single/Divorced/Widowed	61 (35.67)	5 (17.86)		
Occupation				
Employed	92 (53.80)	25 (89.28)	12.51	0.0004*
Non-employed	79 (46.20)	3 (10.71)		
Level of Education				
Illiterate	4 (2.34)	1 (3.57)	1.57	0.66
Primary/College	7 (4.09)	1 (3.57)		
Secondary	147 (85.96)	22 (78.57)		
Graduate	13 (7.60)	4 (14.28)		

***p<0.05 is considered statistically significant.**

Above table shows that as the education level progressed, the adherence became better.Males were more adherent to treatment than females (52.05%) at the baseline.

Table no. 5 : Association between socio-demographic factors and adherence to TB treatment medication (at the end of 6 months follow-up)

Variable	**Treatment Outcome**		χ^2	**P-value**
	Adherent (N=48)	Non-adherent (N=142)		
	n (%)	n (%)		

Male	21 (43.75)	84 (59.15)	3.44	0.06
Female	27 (56.25)	58 (40.85)		
Married	32 (66.67)	95 (66.90)	0.00	0.98
Single/Divorced/Widow	16 (33.33)	47 (33.10)		
Employed	25 (52.08)	84 (59.15)	0.73	0.39
Non-employed	23 (47.92)	58 (40.84)		
Illiterate/Primary	1 (2.08)	10 (70.04)	1.62	0.20
Secondary/College	47 (97.92)	132 (92.96)		

***p<0.05 is considered statistically significant.**

Above table shows that males became less adherent at the end of follow-up period(43.75%) compared to females (56.25%).

DISCUSSION:

The present study was done to evaluate the adherence to second-line drugs used for the treatment of drug-resistant tuberculosis. A total of 228 patients were enrolled at the Department of Respiratory and Chest diseases during the study duration. Only 199 patients were eligible to be included in the study as per the inclusion criteria and exclusion criteria. Of the 199 patients,190 patients were considered for final analysis. 8 patients died and 1 defaulted during the follow-up period, and hence data of these patients were not considered for final analysis.

Table 1 reveals that, out of the 199 patients, 87 (44%) were females, and 112 (56%) were males. The percentages for males were somewhat higher (65.74% males and 34.25% females) in a study conducted by **Baig et al**. Our study was comparable to one by **Massud et al.** (51.3% males, 48.7% females).[18-19]

The majority of patients (52.8%) were in the age range of 21–40 years, and 59 patients were male on average (Table 1). Male patients ranged in age from 18 to 74 years old, with a mean age of 39±14.32years, while female patients had an average age of 30.17±11.10 years, ranging in age from 18 to 71 years. Our patients' mean baseline age was lower than that of the studies conducted by **Matreja et al.** (mean age of males 48±18, and females 42±16) and **Ravichandran et al.** (mean age 45±17).[20-21]

The youngest patient enrolled in the study was 18 years old and the oldest was 74 years old (not shown). **Dhamotharaswamy et al** had conducted a study in which the geriatric population ranged from 65 to more than 85 years of age. This shows that the disease is prevalent in all age groups.[22]

Of the patients who were male, 57.14% (n = 64) weighed less than 50 kg, and 42.86% (n = 48) weighed greater than or equal to 50 kg. Of the females, 13.79% (n=12) weighed less than 50 kg and 55.17% (n=48) weighed more than 50 kg. (Table 3) At baseline, the average weight of all patients was 45.29±11.08 kg (not indicated). Comparing this to the research by **Kalva et al**., the mean baseline weight of all patients (n = 726) was 48.2 ±10.3 kg.[23]

81.25% (n=91) of the study population's male cases were retreatment (failure, default, relapse) cases, while 18.75% (n=21) of the male patients were newly diagnosed cases (Table 3). Of the females, 28 (32.18%) were new instances, and 59 (60.92%) were cases of retreatment. A statistically significant result was obtained, $X^2(1,190) = 4.76$, $p=0.03$. It was discovered that the illness was more prevalent

in both genders' retreatment cases. In contrast, **Chen et al.**'s study found that this was less frequent. (A 4.8-year median follow-up showed that 3% of patients experienced an MDR-TB relapse.)[24]

HIV positivity rates were 1.15% (n=1) in females and 5.36% (n=6) in males. (Table 3) The results differed from **Yang et al.**'s study (51% of participants tested positive for HIV). 6.90% (n=6) of the females and 18.75% (n=21) of the males had diabetes mellitus. The results were significantly lower than those of studies by **Hochberg et al.** (35.2% had diabetes) and **Boadu et al.** (global prevalence=15.3%).[25-27]

The prevalence of hypertension was 6.25% (n=7) in men and 4.60% (n=4) in women, $X^2(1, N=199) = 1.31$, $p=0.52$, which was statistically non-significant (Table 3). According to a study by **Salindri et al.**, 58.5% of individuals with latent tuberculosis infection had hypertension. In the **Mandieka et al.** study, persons with tuberculosis infection had a significant frequency of hypertension (59%).[25–29]

Gender and habits showed a strong correlation (Table 3). Men were more likely than women to smoke or drink alcohol. $X^2(1,199) = 57.83$, $p=0.00001$ This was comparable to research by **Tewatia et al**. (the majority of smokers were men), **Hochberg et al.** (80.7% of alcohol users), **Thomas et al**. (smoking and alcohol usage among women was minimal).[27,30,31]

93.10% (n=81) of the female patients and 93.75% (n=105) of the male patients had PTB, while the remaining 13 patients had EPTB (Table 3). This has resemblance to the earlier research conducted by **Modi et al**. and **Sharma et al**. Gender did not significantly affect the site of TB.[16,32]

85.95% (n=171) of the patients were adherent to their treatment plan at baseline (Table 2) (Figure 1). This was higher than the 71% treatment adherence found in the **Nellums et al** trial, and our results were comparable to those of **Stephens et al's** South African study (81-98% fully adherent across all measures).[33,34]

At the conclusion of the follow-up period, the mean MMAS-8 score dropped from 7.86±0.35 at baseline to 6.84±0.94 (not shown). Compared to the study conducted by **Matreja et al**., where the baseline MMAS-8 score was 4.09±1.33, the MMAS-8 score at baseline was lower.[20]

There was a significant relationship between treatment adherence and the gender distribution. Males were more likely than females to show adherence to treatment at the baseline, $X^2(1, N=199) = 8.857$, $p=0.003$ (Table 4).

As we progressed through the follow-up period, the number of patients who were adherent to treatment medication declined. (Table no.8) (Figure no. 3)

Strengths of the Study:

The study had used standard tool (MMAS-8 questionnaire) to assess medication adherence. The work was done to find out the adherence of DR-TB patients. This study will add to the outcome and implementation of Programmatic Management of Drug-resistantTuberculosis which works under National Tuberculosis Elimination Program.

Limitations of the study:

1. The issues with patient self-report regarding medication adherence include possible misinterpretation of the questions asked from the tool or maybe longer intervals between appointments.
2. The follow-up period was short compared to the longer treatment duration followed for drug-

resistant TB.
3. It was a single centric study done at a tertiary care hospital; hence the findings cannot be generalized.

CONCLUSION:

Overall, 52.8% of the adult population belonged to the age-group of 21-40 years. In this study, the majority of the main work force of the country belonged to this group, hence the disease is of major concern. Also, the females in the child bearing age were affected. This can have a major impact on the future generation and should raise concern over drug-resistant tuberculosis.

There was a decline in adherence from the baseline in every month as the treatment progressed till the end of follow-up period. It became poorer irrespective of age, marital status, employment or literacy level. In the MMAS-8 questionnaire, patients most commonly answered “yes" to the question- “Have you ever cut back or stopped taking your medicine without telling your doctor because you felt worse when you took it?”

The study showed that the adherence to treatment medication for drug-resistant TB decreased despite all follow-ups. Hence proper patient counseling is important during follow-ups or during monthly visits of patients for collection of their medications.

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CONFLICT OF INTEREST:

There was no conflict of interest.

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