

## **A Study of Outcome Analysis of Treatment in 100 Cases of New Sputum Positive Pulmonary Tuberculosis Under RNTCP**

**Dr. Dharit Shah\***, **Dr. Pratik Patel\*\***, **Dr. Vishakha Kapadia\*\*\***, **Dr. Savita Jindal\*\*\*\***, **Dr. Sanjay Tripathi\*\*\*\*\***, **Dr. Sanskruti Patel\*\*\*\*\***

\* Second Year Junior Resident, \*\*First Year Junior Resident, \*\*\* Assistant Professor, \*\*\*\*Associate Professor, \*\*\*\*\*Professor & Head of the Department, Department of Respiratory Medicine, \*\*\*\*\*First Year Junior Resident, Department of Pharmacology AMCMET Medical College, Sheth L.G. Hospital, Ahmedabad, Gujarat

**KEY WORDS :** Tuberculosis, Fixed Drug Combination, GeneXpert

### **ABSTRACT**

**Introduction:** The United Nation's Sustainable Development Goals (SDGs) along with the World Health Organization's end TB strategy has made global targets for "To End the Global Epidemic of Tuberculosis (TB)." RNTCP launched Fix Dose Combination (FDC) for treatment of patients of drug-sensitive TB. FDC drugs contain the four main molecules - Rifampicin, Isoniazid, Pyrazinamide and Ethambutol—in one pill. RNTCP mandates to take sputum sample for GeneXpert of every Sputum smear positive, so it helps to make early diagnosis.

**Objectives:** To know the treatment outcomes and to find the correlation between the radiological and bacteriological aspects in cases of new sputum positive pulmonary tuberculosis on treatment of Fixed drug combination under RNTCP. **Method:** In this prospective study, we considered 100 new sputum smear-positive pulmonary TB patients aged  $\geq 11$  years diagnosed in our TB unit. Before starting the treatment Sputum AFB by Fluorescent stain was examined. The follow up was done at the end of Second month (End of Intensive Phase) and Sixth months (End of treatment). And the data was analyzed using appropriate statistical tests. P-value less than 0.05 is considered as significant. **Result:** The 89.65% successful treatment outcome of all new sputum positive TB patients observed in our study achieved the target i.e. 90% of RNTCP for the 12th 5 years plan (2012–2017). Poor adherence with treatment and malnutrition were significantly associated with non conversion ( $P = 0.03$ ). Patients with TB and diabetes mellitus were found to be highly significantly associated ( $P = 0.01$ ) with sputum non conversion at end of Intensive Phase.

### **INTRODUCTION**

Despite recent declines in reported tuberculosis (TB) rates in India, the disease remains a major public health challenge.<sup>[1]</sup> In the developing country like India, Tuberculosis (TB) is an important health problem. As per the Global TB report 2018, the estimated incidence of TB in India was approximately 28,00,000 accounting for about a quarter of the world's total number of TB cases.<sup>[2]</sup> Previously in India, the thrice weekly intermittent TB regimen was being used for drug-sensitive TB patients which has been switched to a daily Fixed Drug Combination (FDC) regimen for treatment of all TB patients applicable since 2017. An FDC product is when 2 or more drugs are combined physically into one preparation such as a tablet or pill. Anti TB FDCs are usually combinations of two or more first line anti TB drugs [Rifampicin(R), Isoniazid(H), Pyrazinamide(Z) and Ethambutol(E)]. Reduced risk of emergence of resistant strains, better patient compliance, simplified

drug supply management, shipping and distribution, less risk of medication errors and reduced cost of treatment are some of the potential advantages associated with the use of FDCs.<sup>[3]</sup>

The goal of the national strategic plan is to achieve universal access of quality of TB diagnosis and treatment of all TB patients. And the objective is to achieve and maintain a TB treatment success rate of at least 90% among new sputum positive (NSP) patients.<sup>[4]</sup>

RNTCP recommends periodic sputum smear microscopy during the course of treatment to monitor patient progress and to assess overall program performance.<sup>[5]</sup> With the availability of Cartridge Based Nucleic Acid Amplification Testing (CBNAAT), the diagnosis of TB and Drug resistant TB has significantly reduced. CBNAAT is a rapid molecular assay that detects M. tuberculosis and Rifampicin Resistance. The test is fully automated and provides results within two hours. Thus, treatment of Drug resistant TB can be initiated early.<sup>[6]</sup> The National Strategic

---

**Correspondence Address :** **Dr. Dharit Prashantkumar Shah**  
1/15; Simandhar Flats, Opp. Shaily Flats, B/H. Dharnidhar Derasar, Vasna,  
Ahmedabad – 380007 E-mail : dharit.shah17@gmail.com

Plan is aiming to achieve elimination of TB, by 2025. According to that their expected

outcomes during plan period are 80% reduction in TB incidence, 90 % reduction in TB mortality, 0% patient having catastrophic expenditure due to TB.<sup>[7]</sup>

Thus, this study was conducted with the objectives to analyze the treatment outcome in cases of new sputum positive (NSP) pulmonary tuberculosis and also to find any radiological and bacteriological correlation with treatment outcome.

## MATERIAL AND METHOD

This prospective study was carried out at TB Unit, Sheth L. G. General Hospital, Ahmedabad.

The study was commenced after getting approval from the Institutional Review Board. Informed written consent in vernacular language was taken. All new sputum smear-positive pulmonary TB patients aged  $\geq 11$  years of either sex, registering for directly observed treatment, short course (DOTS) IP under RNTCP from February to November 2018 were enrolled. Sputum negative or clinically diagnosed cases of Pulmonary TB, Extra pulmonary TB cases like pleural effusion, abdominal TB, mediastinal lymphadenopathy etc, Retreatment cases (on category two patients), New sputum smear positive patients who were on alternate regimen (like Chronic liver or kidney diseases etc), New sputum smear positive patients whose Sputum or BAL (Bronchoalveolar lavage) CBNAAT Shows Rif – Resistant, Patients lost to follow up or migrate to another DOTS centre were excluded.

Proper history and detailed clinical examination of all the patients were taken with these few other parameters like age, sex, weight, height, BMI, Diabetes,

HIV status, Area of living and Radiological involvement.

Two sputum samples were collected over two consecutive days.

- One Spot sample on the first day.
- Second early morning sample on next day.

Samples were examined by Fluorescent staining as per the IUATLD/WHO scale 400 x magnifications and categorized as scanty, +1, +2, +3.<sup>[8]</sup>

### Drug Regimen:

All patients were administered anti tuberculosis drugs under DOTS regimen according to

Category 1 - HRZE (75/150/400/275 mg per tablet) for 2 month + HRE (75/150/275 per tablet for 4 month according to weight.<sup>[9]</sup>

Patients with RBS more than 140 evaluated for confirmed case of diabetes and managed with oral hypoglycemic drugs or insulin or both. The sputum for GeneXpert (CBNAAT) was done at the starting of treatment.

Follow up of the cases and smear examination at specified intervals:

- At the End of 2<sup>nd</sup> month(end of intensive phase)
- At the end of 6<sup>th</sup> month(end of treatment)

Adherence to DOTS was considered to be present if the patient had consumed  $\geq 80\%$  of the prescribed drugs during treatment. Patients were examined in between for any worsening of their symptoms or any kind of adverse drug reaction (ADR). Treatment regarding the ADRs like gastritis, joint pain, vomiting etc has been done. In follow-up if sputum smear examination positive again CBNAAT was done.

The collected data were compiled in Microsoft Excel worksheet and analyzed using Statistical Package for Social Sciences software version 18.0. Categorical variables were summarized using percentages and proportions. A *P* value below 0.05 was considered statistically significant. Logistic regression analysis was performed to find the predictors for the delay in sputum smear conversion.

### Definitions:<sup>[9]</sup>

#### □ Treatment outcome:

- **Cure:** A patient whose sputum smear or culture was positive at the beginning of the treatment but who was smear- or culture-negative in the last month of treatment and on at least one previous occasion.
- **Treatment Completed:** A patient who completed treatment but who does not have a negative sputum smear or culture result in the last month of treatment and on at least one previous occasion.
- **Treatment success** is the sum of cure and completed.
- **Failure:** A patient whose sputum smear or culture is positive at 5 months or later during treatment.
- **Default:** A patient whose treatment was interrupted for 2 consecutive months or more.
- **Died:** A patient who dies for any reason during the course of treatment.
- **Transfer out:** A patient who has been transferred to another recording and reporting unit and whose treatment outcome is unknown.
- **Radiological:**
- **Minimal Involvement:** slight to moderate density lesions which includes small part of one or both lungs

and total extent should not exceed volume of lung on one side that occupies the space above second chondrosternal junction and T<sub>4</sub> spine or body of T<sub>5</sub> vertebrae. There are no cavities.

- **Moderately Advanced:** lesions are present in one or both lungs and total extent should not exceed the following limits: disseminated lesions extending throughout total volume of one lung or equivalent in both lung and dense, confluent lesions limited to 1/3<sup>rd</sup> the volume of one lung or cavities with maximum diameter not exceeding 4cm.
- **Far Advanced:** lesions more extensive than moderately advanced lesions.

□ **Sputum conversion rate:**

No. of sputum smear-positive converted to sputum smear negative at the end of Intensive Phase  
 $\times 100$

Total no. sputum smear positive patients initiated on treatment

**RESULTS**

Total 111 patients screened during study duration; 11 sputum positive - Rifampicin resistant cases were excluded. Out of which total 100 patients included for the study analysis, 68% were males and 32% were females constituting the male to female ratio as approximately 3:1 ; 7% adolescent (11-17 year), 56% were young adult (18-40 year, 27% adult (41-64), 10% elderly ( $\geq 65$  year) with mean  $\pm$  SD is  $38 \pm 17.8$  years.

Table I			
Sputum Conversion Rate with Different Parameter	STARTING OF RX	END OF IP	
	POSITIVE	NEGATIVE	POSITIVE
<b>Sputum Status</b>			
SCANTY (n=11)	12	9 (81.81%)	2
SPUTUM +1 (n=20)	26	20 (100%)	0
SPUTUM +2 (n=23)	29	23 (100%)	0
SPUTUM +3 (n=25)	33	23 (92%)	2
Total (n=79) *	100	75 (94.93%)	4
<b>BMI (BODY MASS INDEX) Kg/m<sup>2</sup></b>			
UNDERWEIGHT(<18.5) (n=61)	75	58 (95.08%)	3
NORMAL(18.5-24.9) (n=15)	20	14 (93.33%)	1
OVERWEIGHT(25-29.9) (n=3)	5	3 (100%)	0
OBESE(>30)	0	0	0
Total (n= 79) *	100	75 (94.93%)	4
<b>X-Ray Involvement</b>			
MINIMAL – Advanced (n=50)	63	47 (94%)	3
MODERATE - Advanced (n=19)	23	19 (100%)	0
FAR – Advanced (n=10)	14	9 (90%)	1
Total (n=79) *	100	75(94.93%)	4
<b>Sputum Status of Diabetes</b>			
SCANTY (n=4)	4	3 (75%)	1
SPUTUM +1 (n=3)	3	3 (100%)	0
SPUTUM +2 (n=0)	1	0	0
SPUTUM +3 (n=6)	7	4 (66.66%)	2
Total (n=13) #	15	10 (76.92%)	3

\* 21 patients from whom sputum was not collected due to default / death / transferred out by the end of intensive phase were excluded from the denominator.

# 2 diabetic patients from whom sputum was not collected due to default / death / transferred out by the end of intensive phase were excluded from the denominator

Variable	Converted	Not Converted	P value	Unadjusted OR (95% CI)
Age (years)				
<50	62 (82.6%)	3 (75%)	0.69	1.59 (0.15 – 16.52)
≥50	13 (17.4%)	1 (25%)		
Gender				
Male	50 (66.6%)	2 (50%)	0.50	2.0 (0.26 – 15.04)
Female	25 (33.4%)	2 (50%)		
Domicile				
Rural	20 (26.6%)	3 (75%)	0.94	0.91 (0.09 – 9.33)
Urban	55 (73.4%)	1 (25%)		
Adherence				
Present	65 (86.6%)	1 (25%)	0.03	12.42 (1.20 – 128.67)
Absent	10 (13.3%)	3 (75%)		
Side effects of ATT				
Absent	54 (72%)	1 (25%)	0.08	7.71 (0.75 – 78.39)
Present	21 (28%)	3 (75%)		
Family H/O. TB				
Absent	39 (52%)	2 (50%)	0.93	1.08 (0.14 – 8.09)
Present	36 (48%)	2 (50%)		
Alcohol				
No	40 (53.3%)	1 (25%)	0.29	3.42 (0.34 – 34.47)
Yes	35 (46.6%)	3 (75%)		
Smoker				
No	32 (42.6%)	1 (25%)	0.49	2.23 (0.22 – 22.46)
Yes	43 (57.4%)	3 (75%)		
Diabetes				
Absent	65 (86.6%)	1 (25%)	0.01	19.50 (1.84 – 206.33)
Present	10 (13.4%)	3 (75%)		
Under nutrition				
Absent (BMI >18.5 Kg/m <sup>2</sup> )	58 (36.7%)	1 (25%)	0.03	12.42 (1.20 – 128.67)
Present (BMI < 18.5 Kg/m <sup>2</sup> )	14 (58.2%)	3 (75%)		
Initial Smear Grading				
+2, +1, Scanty	51 (68%)	2 (50%)	0.46	2.12 (0.28 – 16.00)
+3	24 (32%)	2 (50%)		
X-Ray Involvement				
Minimal – Moderate	68 (90.6%)	3 (75%)	0.33	3.23 (0.29 – 35.45)
Far	7 (9.4%)	1 (25%)		

Sputum Status	Treatment Outcome				
	CURED	Death	DEFAULTED	TREATMENT FAILURE	TRANSFERRED OUT
SCANTY n=12	11	0	0	0	1
SPUTUM +1 n=26	20	2	0	0	4
SPUTUM +2 n=29	23	2	0	0	4
SPUTUM +3 n=33	24	1	3	1	4
Total n=87 *	78 (89.65%)	5 (5.74%)	3 (3.44%)	1 (1.14%)	13

\* 13 patients transferred out from our TB Unit to any other TU so not included in treatment outcome analysis.

### **Observations with Different Bacillary Load**

Out of 100 smear positive pulmonary tuberculosis cases, in 21 patients dropped out due to default (n=3) / death (n=5) / transferred-out (n=13) before the end of intensive phase. Remaining 79 patients included in the study, 75 patients were reported as smear negative at the end of IP (Sputum Conversion Rate = 94.93%). In our study, the sputum conversion rate reported is 81.81% (9), 100% (20), 100% (23), 92% (23) according to their sputum status as scanty, +1, +2, +3 respectively. Hence it can be reported that there was a delayed sputum conversion observed with Scanty and with high bacillary load (+3). (Table - 1)

Total five patients died i.e. one with sputum status +1, one with sputum +2 and three with sputum +3.

### **Observation with different Body Mass Index (BMI)**

In this study, the mean with SD BMI is 17.60±3.82 Kg/m<sup>2</sup>. The majority (62%) were underweight as per BMI criteria below 18.5 Kg/m<sup>2</sup>. Delayed sputum conversion seen in patients with Underweight and Normal BMI was noted to be 95.08% and 93.33% respectively (Table - 1). Total five patients died i.e. four of underweight BMI and one with normal BMI.

### **Observation as per X-Ray Involvement**

It was observed that the highest number of patients (63%) fall into the 'minimally involved' category. Delayed sputum conversion is seen with minimally and far advanced patients which is 94% and 90% respectively (Table - 1). Total five patient died - one with minimally involved and four with far advanced lung in chest examination.

### **Observations in Diabetics**

In the study, total 15 patients (05 patients were newly diagnosed and the remaining were already diabetic) identified as TB with Diabetes. Two patients one with sputum +2 and +3 died before the end of Intensive phase. Diabetic patient with sputum smear scanty and +3 showed delayed sputum conversion – 75 % and 66.66 % respectively. The overall sputum conversion rate in diabetic patients is 76.92 %. (Table – I)

### **Factors Influencing Smear Conversion**

After excluding 21 dropouts, the factors (like age, gender, domicile, adherence, side-effects of AKT, family history, addictions like alcohol and smoking, co-morbidities like diabetes mellitus, BMI, initial smear reading and X-ray involvement) influencing the delay in sputum smear conversion were included and the data was analyzed at the end of IP for 79 study participants.

Poor adherence with treatment is associated with non conversion (P = 0.03). Malnutrition was also significant

factor for sputum non conversion (P = 0.03). Patients with TB and diabetes mellitus were found to be highly significantly associated (P = 0.01) with sputum non conversion at end IP (Table - II).

### **Treatment Outcome Analysis**

Total 111 microbiologically confirmed new TB patients notified during the study period, 11(9.90 %) Rifampicin resistant cases were switched to another treatment category. Out of 100 78(89.65%) were cured, 5(5.74%) died during the treatment, 3(3.44%) were reported as defaulter, 1(1.14%) treatment failure after excluding 13 transferred out patients. (Table - III)

One Malnourished (low BMI) Diabetic with high bacillary load and extensive (Far-Advanced) affected patient's sputum examination consistently positive and sputum GeneXpert was Rif Sensitive at end of IP also but at the End of CP it was turn out to be Rifampicin Resistant.

## **DISCUSSION**

- As per the RNTCP, Sputum Conversion Rate (SCR) of at least 85-90% has to be achieved in a well-performing area.[5] The result in our study shows that the Sputum Conversion with daily FDC treatment is about 94.93% which is quite significant. This shift from alternate day regimen to daily FDC treatment regimen not only tends to improve and increase patient compliance to the treatment but is also a milestone in making India TB free. On the other hand, when correlated with the results of studies on alternate day regimen, it was found that the sputum conversion rate was highest 93.20% as reported by Velayutham Banurekha et al.[10] The sputum conversion in patients on alternate day regimen was found to be quite similar, that is, 84% and 81.01% as reported by Bawri et al[11] and Anandraj et al[12] respectively.
- Our study reported a significant association between high bacillary with grade 3+ AFB at the initiation of treatment and low sputum conversion at the end of 2 months of follow-up sputum examination. These findings were in congruence with other studies with alternate day regimen.[10-13] This finding was of significance as initial sputum smear grading can be used to identify patients with higher probability of not converting to sputum negative after 2 months of treatment.
- Out of total 79 patients on FDC regimen included, 13 patients were identified as TB with diabetes. Out of which majority, that is, 10 patients showed sputum conversion of about 76.92%. at the end of intensive phase.
- Diabetics were 20 times (OR=19.50) more prone to have a delayed smear conversion in our study. Studies conducted elsewhere shows early smear conversion



with alternate day regimen.[12] Defects in the immune system of patients with active TB and diabetes lead to reductions in the activation of alveolar macrophages and the capacity to produce interleukins, resulting in delayed smear conversion. Diabetes impairs cell-mediated immunity and poor diabetic control has been shown to affect in vitro innate and type 1 cytokine responses. Poor diabetic control could possibly lead to unfavorable treatment outcomes such as failure and death.

- The present study showed a significant influence of diabetes on sputum conversion and treatment outcome with tuberculosis as patient with high bacillary load with grade 3+ AFB and diabetes showed delayed sputum conversion and treatment failure.
- The present study showed a significant negative influence in under-nourished patients (Low BMI <18.5 Kg/m<sup>2</sup>; OR=12.42) on smear conversion when compared with the results noted by Saulius Diktanas et al (BMI OR=0.81).[13]
- Mortality was seen high with malnourished patients who had High bacillary load and Far advanced involvement with Co-Morbidity like DM.
- The 89.65% successful treatment outcome of all new sputum positive TB patients observed in our study achieved the target i.e. 90% of RNTCP for the 12th 5 years plan (2012–2017)[14] but it was higher (80%) compared to that reported by C. Jackson et al. [15]
- With use of FDC daily regimen it is safe to conclude that with lesser number of tablets to be taken by the patients, the treatment adherence increases which leads to early sputum conversion (p value=0.03).

More Prospective studies on larger number of patients are necessary to substantiate our findings in this study.

## REFERENCES

1. World Health Organization. Global tuberculosis report, 2018. Geneva, Switzerland: WHO, 2018
2. Ministry of Health and Family Welfare. Central TB Division. TB India 2018. Revised National TB Control Programme annual status report. End TB by 2025. New Delhi, India: Ministry of Health and Family Welfare, 2018.
3. Fixed Dose Combinations for Tuberculosis: Lessons learned from Clinical, Formulation and Regulatory Perspective. <https://www.ncbi.nlm.nih.gov/pubmed/15632956> /Accessed March 2019.
4. RNTCP - Government TB Treatment Education & Care NSP; TB FACTS.ORG. <https://www.tbfacts.org/rntcp/> / Accessed March 2019.
5. Government of India. Revised National Tuberculosis Control Programme. Training Course for Program Manager (Modules 1-4). Central TB Division. Directorate General of Health Services. New Delhi: Ministry of Health and Family Welfare; 2011.

6. Revised National Tuberculosis Control Programme; Annual status report; UNITE TO END TB; Central TB Division, New Delhi; TB India 2017.
7. Revised National Tuberculosis Control Programme; Annual status report; UNITE TO END TB; Central TB Division, New Delhi; TB India 2018. <https://tbcindia.gov.in/showfile.php?lid=3314> /Accessed March 2019.
8. REVISED NATIONAL TUBERCULOSIS CONTROL PROGRAMME; Manual for Sputum Smear Fluorescence Microscopy; <https://tbcindia.gov.in/showfile.php?lid=2988> / Accessed March 2019.
9. RNTCP. Technical and operational guidelines for tuberculosis control in India 2016. <http://tbcindia.nic.in/showfile.php?lid=3219> /Accessed March 2019.
10. Velayutham Banurekha, Tarun Bhatnagar, Swaminathan Savithri, Natarajan Dinesh Kumar, Boopathi Kangusamy, and Sanjay Mehendale. Sputum Conversion and Treatment Success among Tuberculosis Patients with Diabetes Treated under the Tuberculosis Control Programme in an Urban Setting in South India. *Indian J Community Med.* 2017 Jul-Sep; 42(3): 180–182.
11. S Bawri, S Ali, C Phukan, B Tayal, and P Baruwa. A Study of Sputum Conversion in New Smear Positive Pulmonary Tuberculosis Cases at the Monthly Intervals of 1, 2 & 3 Month Under Directly Observed Treatment, Short Course (Dots) Regimen. *Lung India.* 2008 Jul-Sep; 25(3): 118–123.
12. Anandaraj R, Anurupa M S, Kavithai P, Rashmi B M, Ranjitha A, Raghavendra S K. Factors influencing delay in sputum smear conversion among new smear-positive pulmonary tuberculosis patients of Davangere tuberculosis unit. *International Journal of Medical Science and Public Health.* Sept-2017, Vol – 6, Issue – 11;1565-1671.
13. Saulius Diktanas, Edita Vasiliauskiene, Katazyna Polubenko, Edvardas Danila, Indre Celedinaite, Evelina Boreikaite and Kipras Misiunas. Factors Associated with Persistent Sputum Positivity at the End of the Second Month of Tuberculosis Treatment in Lithuania. *Tuberc Respir Dis* 2018;81:233-240.
14. Government TB Treatment Education & Care NSP 2012 – 2017. <https://www.tbfacts.org/rntcp/> / Accessed March 2019
15. C. Jackson, H. R. Stagg, A. Doshi, D. Pan, A. Sinha, R. Batra, S. Batra, I. Abubakar, and M. Lipman. Tuberculosis treatment outcomes among disadvantaged patients in India. *Public Health Action.* 2017 Jun 21; 7(2): 134–140.