

Initial Higher Sputum Graded Patients Treated Under Category-II RNTCP (DOTS) with Low Weight Gain Tend to Have More Relapse Rate

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Abstract: DOTS strategy, as recommended by the WHO after declaring tuberculosis as a global emergency in 1993, is a very important landmark in the history of tuberculosis control. Supervised, intermittent chemotherapy was found to be operationally impracticable under National Tuberculosis Control Program. Hence Cost effective strategy 'directly observed intermittent chemotherapy' for tuberculosis control under RNTCP has been formulated and implemented. It has long been proved to be effective in various trials in India. Under DOTS strategy, the main emphasis is on diagnosing and treating sputum smear positive patients, thus the stress on sputum microscopy. The patients are categorized into two categories according to status of the disease and previous treatment history. Various published reports indicate a very high efficacy of treatment regimens with cure rates of 80-100% under RNTCP. However follow up reports of relapse rate on patients who have completed treatment under RNTCP are very few. Relapse rate, an important indicator of success of any treatment regimen, has not been measured under program condition. Follow up study of 203 patients was done to examine the rate of relapse among sputum smear positive pulmonary tuberculosis patients who have successfully completed treatment and declared either cured or treatment completed. Majority of 21/32 (65.6%) relapses were occurred in those who gained less than 4 kg weight gain during treatment. Further the maximum number 64% (16/25) among Category-I patients and 71.43% (5/7) among Category-II patients relapsed within first 6 month of follow up period.

Keywords: Tuberculosis, RNTCP, DOTS, Cured, Relapse, Category-I, Category-II, Weight Gain

1. Introduction

Tuberculosis, known since 10,000 BC but the organism Mycobacterium Tuberculosis was discovered by Robert Koch in 1882[1]. It primarily affects lungs but can also affect other parts of body. It still continues to be a major health hazard till today, despite the development of highly effective drugs and vaccine [2], [3].

India accounts for 1/4th of global incidence of TB and tops the list of 22 high TB burden countries [4]. The tuberculosis problem in India was first recognized through a resolution passed in the All India Sanitary Conference, held at Madras in 1912. WHO and UNICEF took keen interest in providing assistance for introducing mass BCG vaccination with low cost in 1951[5].

Karel Styblo had calculated 1 percent ARTI would correspond to about 50 cases of infectious TB [6]. Estimated average annual risk of tuberculosis infection (ARTI) in India has been computed to be 1.5/1000 implying that 150 per 100000 population newly acquired TB infections each year [7]. The annual decline estimated from the first to the third survey was 6% [8]. ARTI was more in North India; further seem to be more in urban population (3.3%) than in rural population (1.5%) [9]. Each infectious source approximately infect 10 -15 new cases annually [10]. There are two peaks in incidence observed, first in the one to four age groups and the second in adolescents and young adults [11]. Children are at higher risk of contracting disease from the infected pool of adult cases [12].

Keeping in view of recommendations by World Health Organization (WHO) The Indian Government established

Revised National Tuberculosis Control Programme (RNTCP) using directly observed treatment, short course (DOTS) strategy to ensure that trained observers watch patients swallow their medications.

At least one third of patients who do not receive directly observed treatment stop taking drugs, or don't take medicines regularly. It is difficult to foresee regarding who will default. There will be poor treatment outcome and high death rates in the absence of direct observation. Direct observation of treatment ensures the best possible results in treatment of TB. Hence DOTS can ensure efficient and economical with no reduction in efficacy [13] the adequate drugs, in the adequate doses, at the adequate intervals and for the adequate duration to the patients [14]. Unfortunately, in the private sector TB is ineffectively treated [15] it also results in diagnostic inaccuracy/delay, prolonged infectiousness, resistance to medicine, unfavourable treatment outcomes and high rates of relapse [16]. DOTS has a definite role in the field setting with high Default and relapse rate. [17]

Studies from India have shown that six months of chemotherapy compared with longer terms of treatment for new sputum positive TB patients gives favourable results whereas eight months of treatment is adequate for retreatment TB patients. The shorter time period makes direct observation more feasible and improves patient adherence to treatment [14]. Short-course regimens achieve smear and culture conversion within 2-3 months in most patients. a favourable response of 97-100% culture negativity at the end of treatment with many regimens. The challenge to identify practical regimens with lower (<5%) relapse rates remained [18].

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Majority of relapses after SCC occur within two years after treatment initiation. Presently, there are hardly any operational studies in India that specifically address these issues. Follow up reports on the patients completing treatment under RNTCP DOTS strategy declared cured or treatment completed to assess relapse rate are very few. With this in view, new sputum smear positive pulmonary tuberculosis patients were followed up prospectively to evaluate their treatment outcome. In addition, the associated socio-demographic and treatment related factors were also studied.

2. Material and Method

Study design

A prospective study was designed to elicit the rate of relapse among sputum smear positive patients who had successfully completed treatment and were declared Cured or treatment completed under Revised National Tuberculosis Control Programme.

Case Definition

Standard RNTCP recommended definitions were used to define treatment outcome:-

Cured: "Initially sputum smear positive patient who has completed treatment and had negative sputum smears on two occasions with one of which was at the end of treatment" [19].

Treatment completed: "Sputum smear-positive patients who has completed treatment with negative smears at the end of the intensive phase but none at end of treatment" [20].

Relapse: "a patient who has been declared cured or treatment completed by a physician, but who reports back to the health service and now found to be sputum smear positive". [21], [22]

Why is This Study Planned

The objectives of RNTCP were:

- To detect at least 70% of estimated new cases of sputum smear-positive TB
- To achieve cure rate of 85% [23] through intermittent thrice a week Supervised Short Course Chemotherapy or "DOTS"

Both cured and completion of treatment is recorded as "treatment successes." Under Revised National Tuberculosis Control Programme, follow up is not required for patient who has completed treatment and has been declared cured. Hence there is no check for TB recurrence/relapses. Only a few studies have investigated the long-term outcomes of treatment. Such data are needed to prove whether DOTS can contain the menace of TB globally. In this study, TB relapses in sputum smear positive patients declared cured or treatment completed treated under revised national tuberculosis control programme in the first quarter of 2007 i.e. 1, January, 2007 to 31, March, 2007 registered in Tuberculosis Unit (both indoors and outdoors) and coming

under the area covered by Tuberculosis Unit, which is located within the premises of Department of Tuberculosis and Respiratory diseases, Government Medical College, Amritsar was worked out.

Criteria for Selection

- Sputum smear for AFB positive pulmonary tuberculosis Patients with or without history of anti tubercular treatment in the past who were declared cured or treatment completed after DOTS.
- Only Patients of Amritsar or nearby to Amritsar were included in the study.
- Sputum smear for AFB positive, pulmonary tuberculosis patients declared failure were excluded.

3. Clinical Assessment

Study was carried out on those who fulfilled the above criteria. The detail history was taken with special reference to cough, fever, loss of appetite, loss of weight, haemoptysis, chest pain, alcoholism, smoking and breathlessness along with the duration of symptoms. History of previous anti TB treatment taken by the patients and the regimen prescribed was noted. A thorough physical examination was carried out followed by an elaborate examination of the system involved and relevant physical findings were recorded.

Two Sputum specimens (early morning and spot), from each patient at three time points from the date of declared cured or treatment completion during follow up: 1) after the end of 2nd month, 2) after the end of 6th month, 3) after the end of 12th month was examined. The sample was collected before breakfast cleaning the mouth early in the morning. Care was taken that sputum sample is least contaminated by the salivary secretions. The sputum sample was also taken in between if patient develop any symptoms suggestive of tuberculosis. X-ray chest was done in all symptomatic patients. After reporting, those found sputum smear positive for AFB were considered as relapse.

Data collected after this follow up study has been analyzed and relapse rate has been calculated. Also various risk factors found to be associated in relapse patients in this study has been taken into account and analyzed.

4. Observation and Results

A total of 203 Sputum smear for AFB positive, pulmonary tuberculosis Patients declared cured or treatment completed after DOTS in the first quarter of 2007 i.e. 1, January, 2007 to 31, March 2007 at TU-DTC, in the Department of Tuberculosis and Respiratory diseases, Amritsar were included in this study to evaluate rate of relapse. Out of 203 two of the patients died, seven (5 male, 2 female) could not be traced due to address change or improper address. One female had shifted out after marriage. Rests of the 193 patients were followed up and Data in respect of important characteristics was tabulated and recorded as follows:

Table 1: Sex Wise / Category Wise Distribution Of Cases.

	No. of CAT 1 cases	%age	No. of CAT 2 cases	%age	Total Patients
Male	109	66.0 %	28	73.7%	137
Female	56	33.9 %	10	26.3%	66
Total	165	100.00	38	100.00	203

(Table 1) Out of 203 patients there were 165 (81.28%) patients of DOTS category I and 38 (18.72%) patients of DOTS category II. This is comparable with RNTCP expected re-treatment cases less than 30% [24]. In the

present study there was preponderance of male cases i.e. 137 (67.49%) males against 66 (32.5%) females. male patients ratio was seen higher among Cat II patients (73.7%) as compared to Cat I Patients (66.0%). Almost all such studies conducted in the past have shown a preponderance of male over female cases in the prevalence of Tuberculosis probably thought to be due to the fact that males have more exposure at work. Also adverse social factors are found to affect males more severely than females [25], [26], [27].

Table 2: Age and Sex Distribution
 $Chi(x^2)=16.14, df=3, p<=0.001^{**}$

Sex	Males			Females			Total (%age)		
	No. of Cases			No. of Cases					
	Cat 1	Cat 2	Total	Cat 1	Cat 2	Total	Cat 1	Cat 2	Total
Age groups (years)									
10-19	9	2	11	15	2	17	24 (14.6%)	4 (10.5%)	28 (18.0%)
20-39	58	12	70	32	3	35	90 (54.6%)	15 (39.5%)	105 (51.7%)
40-59	35	12	47	5	5	10	40 (24.2%)	17 (44.7%)	57 (28.1%)
>60	7	2	9	4	0	4	11 (6.7%)	2 (5.6%)	13 (6.4%)
Total	109	28	137 (68%)	56	10	66 (33%)	165	38	203

(Table 2) Maximum number of cases 105(51.72%) in male versus female ratio of 2:1 were seen in the productive younger 20-39 years age group. While least number of 13 (6.4%) cases were of above 60 years. Data was found to be

similar among Cat 1 while in Cat II Maximum numbers of patients 17 (44.74%) were in the little elder age group 40-59 years. The data statistically found to be significant ($Chi(X^2)=16.14, df=3, p<=0.001$).

Table 3: Weight Gain in Kilograms at the End of Treatment

Gain in weight (Kg.)	0-2	2-4	4-6	6-8	Not reported	Total
No. of cases	42 (21.8%)	52 (26.9%)	60 (31.1%)	10 (5.2%)	49	203

(Table 3) Initial Weight at the start of treatment and then at the end of treatment was checked and recorded. Majority of the patients 60(31.09%) had weight gain between 4-6kg, 52 (26.94%) patients in the range of 2-4 Kg, 42 (21.76%) and

10 (5.18%) patients showed weight gain in the range of 6-8 kg at the end of treatment. Earlier studies also found that 95% patients during ATT tend to gain weight [28].

Table 4 Initial Sputum Grading Of Selected Patients

Initial sputum grading	Male			Female			Total		
	Cat I	Cat II	Total	Cat I	Cat II	Total	Cat I	Cat II	Total
Scanty+	6	6	12	3	1	4	9 (5.5%)	7 (18.4%)	16 (7.9%)
1+	18	6	24	9	3	12	27 (16.4%)	9 (21.1%)	36 (17.7%)
2+	21	4	25	11	2	13	32 (19.4%)	6 (15.8%)	38 (18.7%)
3+	64	12	76	33	4	37	97 (58.8%)	16 (42.1%)	113 (55.7%)
Total	109 (66%)	28	137	56 (34%)	10	66	165	38	203

$Chi(X^2)=0.009, df=3, p>0.05$

(Table 4) Out of total 203 pts Maximum no. of patients 113(55.67%) were with initial sputum grading 3+, Followed by 38(18.72%), 36(17.73%) and 16(7.88%) with initial sputum grading 2+, 1+, scanty+ respectively. Of 165 Cat I patients maximum no. of patients 97(58.79%) were with initial sputum grading 3+. Followed by 32(19.39%), 27(16.4%) and 9(5.45%) with initial sputum grading 2+, 1+, scanty+ respectively. Of the 38 Cat II maximum no. of patients 16(42.11%) were with initial sputum grading 3+. Followed by 9(21.1%), 7(18.42%) and 6(15.8%) with initial sputum grading 1+, scanty+ and 2+ respectively.

Table 5: Sex Wise Distribution of Relapses

Sex	Male	Female	Total
No. of cases	137	66	203
Relapses	22	10	32
Relapses % age	16.06%	15.15%	15.76%

$Chi(X^2)=0.15, df=1, p>0.05$

(Table 5) There were 32(15.76%) relapses among the total 203 cases. The percentage of the relapses were slightly more among male patients i.e. 22/137 (16.06%) male patients relapsed; whereas females patients had 10/66 (15.15%) relapses during a follow up study period.

Table 6: Category Wise Distribution of Relapses

Category	I	II	Total
No. of cases	165	38	203
Relapses	25	7	32
Relapse percentage	15.15%	18.42%	15.76%

$Chi(X^2)=0.615, df=1, p>0.05$

(Table 6) The percentage of the relapses was higher among Category-II patients. Out of the 38 Category-II cases 7(18.42%) had relapsed whereas out of 165 Category-I

cases 25(15.15%) had relapsed during a follow up study period. These findings are comparable to various earlier findings where relapse was found to be 7-25% after anti tubercular treatment [29], [30], [31], [32], [33] [34] [35] [36], [37], [38]. But our findings are higher than expected 3-5% relapse under RNTCP [24].

Table 7: Initial Sputum Grading Status among Patients Who Relapsed

Initial sputum grading	Male			Female			Total, n=32		
	Cat I	Cat II	Total	Cat I	Cat II	Total	Cat I n=25	Cat II n=7	Total
Scanty+	1	0	1	0	0	0	1 (4%)	0	1 (3.125%)
I+	2	1	3	0	0	0	2 (8%)	1 (14.3%)	3 (9.4%)
2+	3	2	5	2	1	3	5 (20%)	3 (42.9%)	8 (25%)
3+	11	2	13	6	1	7	17 (68%)	3 (42.9%)	20 (62.5%)
Total n=203	17 (10.3%)	5 (17.9%)	22 (16.1%)	8 (4.9%)	2 (20%)	10 (15.2%)	25 (15.2%)	7 (18.4%)	32 (15.8%)

Chi(X²) = 0.98 d.f = 3, p > 0.05

(Table 7) Out of 32 relapses Maximum no. of 20 (62.5%) were seen among patients with initial sputum smear 3+ followed by 8(25%), 3(9.4%), and 1(3.1%) relapses were among patients with initial sputum smear 2+, 1+ and scanty+ respectively. Maximum relapses were seen among male patients with initial sputum smear 3+. There were no relapses seen among female patients with initial sputum smear 1+ and scanty+ respectively. Similar trends were seen among Cat 1 patients with Overall more relapses among male patients i.e.17(10.3%) as compared to 8(4.85%) relapses among female patients in category-1. There were equal no. of relapses i.e. 3(7.89%) were seen among Cat II patients with initial sputum smear 3+ and 2+ respectively. There were slight difference with a little more relapses in female patients (20%) as compared to male patients 17.86%) in Cat II . More relapses among sputum smear 3+ is consistent with earlier studies [39] [40].

Table 8 Relation of Initial Sputum Status to the Sputum Status at Relapse in Category 1 Patients

Initial Sputum Grading	SPUTUM STATUS AT RELAPSE				Total
	Scanty+	I+	2+	3+	
Scanty+	0	1	0	0	1 (4 %)
I+	0	1	0	1	2 (8 %)
2+	1	1	2	1	5 (20 %)
3+	3	3	6	5	17 (68 %)
Total	4 (16%)	6 (24%)	8 (32%)	7 (28%)	25

(Table 8) Majority of patient who relapsed within category-1 were 8/25 (32%) with sputum smear 2+ followed by 7(28%), 6(24%) and 4(16%) with sputum smear 3+ 1+ and Scanty+ respectively. It was also evident from table that maximum 17/25 (68 %) relapses were among those patients who were having higher initial 3+ sputum grading.

Table 9: Relation of Initial Sputum Status to the Sputum Status at Relapse in Category-II Patients.

Initial Sputum Grading	SPUTUM STATUS AT RELAPSE				Total
	Scanty+	I+	2+	3+	
Scanty+	0	0	0	0	0
I+	0	1	0	0	1 (14.3 %)
2+	0	0	1	2	3 (42.9 %)
3+	0	1	0	2	3 (42.9 %)
Total	0	2 (28.6%)	1 (14.3%)	4 (51.2%)	7

(Table 9) Whereas majority of patients who relapsed within Category-II were 4/7 (51.2%) occurred with sputum smear 3+ followed by 2(28.6%), and 1(14.3%) with sputum smear 1+ and 2+ respectively. None of the patient within Category-II relapsed with sputum smear scanty+. It was also evident that 6/7 (86 %) relapses were seen among patients who had higher initial sputum grades i.e. 3/7 (43%) each among sputum grades 3+ and 2+ respectively. None of the patients with initial grading as scanty+ had relapsed during follow up period.

Table 10: Weight Gain in Kilograms among those Who Relapsed

Gain in weight (Kg.)	0-2	2-4	4-6	6-8	Not reported	Total
No. of Relapses	8 (25%)	21 (65.6%)	1 (3.1%)	0	2 (6.3%)	32

(Table 10) Most of the Relapses 29/32 (91%) was seen among those who gained weight less than 4 kg. Majority of relapses were in those who gained 2-4 Kg i.e. 21(65.6%), followed by 8(25%) in those who gained weight 0-2 Kg. Minimum no. of relapses 1 (3.1%) were seen among those who gained weight between 4-6 Kg. None of cases had relapsed among who gained weight above 6 kg. Underweight at baseline and failure to gain weight on therapy can be simple, useful and easily measurable prognostic tools to monitor TB relapse. At two year follow up by Will Boggs in 2006, 61 patients (7.1%) had relapsed in patients with low median weight [41].

Table 11: Relation of Category and Time Period of Relapse

		0-2	2-4	4-6	6-8	8-10	10-12	Total
<i>Cat I</i>	<i>M</i>	2	5	3	3	3	1	17 (53.1%)
	<i>F</i>	1	4	1	1	0	1	8 (25%)
<i>Cat-II</i>	<i>M</i>	1	1	2	0	0	1	5 (15.6%)
	<i>F</i>	1	0	0	1	0	0	2 (6.3%)
Total		5 (15.63%)	10 (31.3%)	6 (18.8%)	5 (15.6%)	3 (9.4%)	3 (9.4%)	32

(Table 11) highest of the 10(31.3%) relapses occurred during 2-4 month period. During follow up period relapse was found to be 5/32 (15.6%) at 2 months, 21/32 (65.6%) at 6 months. It was also evident that with each passing interval after first 6 months the rate of relapse declined gradually. Whereas 64% (16/25) of relapses among Category-I patients occurred within 6 months but it was further higher in Category-II patients i.e. 71.43% (5/7) relapses over the same period of time. Similar findings of more relapse within 6 months had been observed by various authors in their studies in different part of world [42] [43] [44] [45].

5. Discussion

Before the advent of treatment, complete cure of pulmonary tuberculosis was seen only rarely. Pathologist and clinicians maintained that the disease practically never healed in strict sense of the term, but could only be arrested, become stabilized, or rendered inactive. Since bacilli almost always persisted in the residua of tuberculosis lesions, relapse was common, and that was the reason for adoption of a policy of lifelong follow up of patients who had completed treatment. Relapses were mostly discovered on account of symptoms rather than during routine follow up examination. The dramatic success of modern treatment called into question the usefulness of indefinite follow up and prompted demand for the reassessment of this policy [46].

The phenomenon of 'persisters' explains to some extent why all bacilli are not killed during treatment. Relapse or endogenous reactivation may be due to bacilli that have persisted in residual lesions for a long time in a semi-dormant / dormant state. At the end of two months therapy, bacilli cannot be cultured from the sputum, the patient's clinical symptoms have disappeared but the symptoms and the microbe reappear if treatment is discontinued at this stage. These organisms remain unaffected by most drugs; only Rifampicin or Pyrazinamide may attack them effectively under certain conditions [47].

Possible causes for relapses are poor patient compliance due to alcoholism, homelessness, drug addiction, psychiatric disorders; prescription errors with inadequate treatment durations; concurrent AIDS disease, or use of a three-drug combination despite primary drug resistance. High risk patients in particular, home care visits by a TB nurse in addition to consultations by primary care physicians are necessary to ensure directly observed therapy (DOT) in order to prevent defaults, relapses and treatment failures [48].

A current short-course regimen uses an initial 2 months intensive phase of 'bactericidal activity' of anti-tuberculosis treatment, focuses on rapid killing of organisms. This is followed by a longer continuation phase of 'sterilizing

activity' of fewer drugs with the ability to kill the more slowly growing 'persisters'. The measure of the sterilizing activity of a regimen is reflected by the relapse rate after successful treatment. Of these two phases, it is the sterilizing activity of a regimen that is more important because the better the sterilizing activity of a regimen, shorter the duration of treatment. Six months of therapy is required to overcome the 'relapse' factor indicating the continued presence of a residual bacterial population termed 'persisters' during the treatment period [49]. Studies in the 1980^s that evaluated regimens with a treatment duration of less than 6 months demonstrated high relapse rates (11–40%) in patients with sputum smear-positive pulmonary tuberculosis [50]. Contrary to the previously observed treatment failure due to the appearance of resistant mutants, cultures isolated from relapsed Patients were seen to be 'drug sensitive' [51].

Relapse rate is high (almost 10%) in India which is higher than international studies. Majority of relapse cases present soon after completion of treatment (first six months). Risk factors for relapse included drug irregularity, initial drug resistance, smoking and alcoholism Sex and weight were not risk factors in India. The outcome of relapse cases put on retreatment regimen is positive but less effective than new cases. There are sound arguments and sketchy evidence that DOTS Category 2 treatment may not be adequate for retreatment patients [52].

Even though results are encouraging and cure rates achieved are high in RNTCP, clinicians often raised queries regarding effectiveness of RNTCP regimens [53]. These concerns could convincingly be taken care through scrutiny of treatment outcome, bacteriological support along with drug susceptibility status, besides the long-term follow-up to observe bacteriological relapses under programme conditions. Bacteriological relapse after stopping chemotherapy is the best measure of the efficacy of short course chemotherapy was demonstrated by Aber et al [54].

With the advent of highly effective chemotherapeutic regimens with practically 100% efficacy, bacteriological relapse has become the most crucial factor in determining the relative merits of chemotherapeutic regimens. The speed of sputum conversion and relapse rates are thus good measures of the bactericidal and sterilizing activity of regimens and drugs.

Among 273 Category-I patients 'defaulted' 23% and among 112 'failure' cases 68% were re-registered. After 'successful treatment completion' of 1796 cases 6.5% were re-registered as relapse. Patients declared as 'successful treatment completion' should be encouraged to report if chest symptoms recur [55].

Overall there was wide variation in recurrence after successful treatment, ranging from 0% to 14%. Considerable heterogeneity across studies precluded the systematic assessment of factors contributing to tuberculosis recurrence. Despite DOTS (directly observed treatment, short course) being implemented for more than 10 years and millions of patients treated for tuberculosis, few studies have assessed the ability of standard DOTS regimens to result in lasting cure for patients treated under routine programmatic conditions [56].

After seven years 64.1% are healthy, work and earn; 29.8% report residual respiratory problems; 0.3% of symptomatic patients were diagnosed with smear positive pulmonary tuberculosis. Relapse calculated as worst case scenario for full target population (dead and migrated inclusive) is 9.27% [57].

Patients who were sputum smears positive after 2 months of treatment and those who received DOT were likely to have 3% relapse as compared to those who did not receive DOT they had 26% relapse [58].

6. Conclusion

The majority of patients Default/left the treatment due to feeling well. This can be tackled by effective counselling. Higher percentage of the patients showed weight improvement following DOTS treatment [59]. Worst affected are low weight gainers who tend to have relapse later on . Recurrence was not associated with age, sex, occupation, marital status and level of education. High recurrence rate occurred among smear-positive patients cured under DOTS. The relapse rate of intermittent chemotherapy was similar to the relapse rate with daily regimen by self-administration [60]. Patients who took treatment irregularly were twice more likely to have a relapse than adherent patients. Other independent predictors of relapse were initial drug resistance to isoniazid and/or rifampicin and smoking. The relapse rate under the DOTS programme may be reduced by ensuring that patients take their treatment regularly and are counselled effectively about quitting smoking [61]. More emphasis was to be given toward existing TB patients to get successful results of RNTCP along with quality diet to enhance weight gain. Further studies are required to identify factors contributing to high recurrence rates to improve disease free survival of TB patients after treatment [62].

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