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EVALUATION OF MERITS AND DEMERITS OF PRESENT FIXED DOSE COMBINATIONS FOR DAILY ANTITUBERCULAR TREATMENT UNDER REVISED NATIONAL TUBERCULOSIS CONTROL PROGRAMME (RNTCP)

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ABSTRACT:

Introduction: Tuberculosis still accounts for millions of cases of active disease and deaths worldwide. The disease mainly affects the developing countries. Modern Anti-tubercular treatment can cure virtually all patientsprovided correct combination treatment is taken in amount and duration. Treatment of TB has been shifted towards daily regimen with administration of daily fixed dose combination of first-line ATD as per appropriate weight bands.

Objectives:

1. To observe incidence of side effects of RNTCP recommended anti TB FDCs.
2. To study compliance of patients to new Anti TB FDCs and difficulties posed by patients.

Materials and Methods: A Prospective cohort study was conducted involving a total of 830 patients presenting to Department of Respiratory Medicine, Lokmanya Tilak Municipal Medical College and General Hospital, Sion, Mumbai with diagnosed tuberculosis and Registered for CAT I and CAT II anti tuberculosis therapy (ATT). Duration of study was 21 months. Followup was done at the end of intensive phase (2 months) [at the end of maximum 3 months in extrapulmonary TB] and at the end of continuation phase (6 months for Cat I and 8 months for Cat II patients). Outcome of ATT was studied in different weight bands as per RNTCP. (Cure, Failure and treatment completed). Data was analyzed using SPSS version 22.0.

Result: Among treatment categories, most patients (78.6%) were registered under Category I (new patients) as compared to retreatment cases (Category II and Category I Retreatment). Among PTB patients cure rate was 78.2%, while among extra pulmonary tuberculosis (EPTB) patients treatment completion rate was 85.2%. Compliance of patients was better with Fixed drug combination (FDCs) due to reduced pill load, single dose administration, can be conveniently given to patients of all weights as per their weight bands.

Conclusion: Among adverse effects, nausea and vomiting were most common followed byjoint pains. Mean compliance of patients was 84.46% in IP and 84.82 during continuation phase (CP).

Key words: RNTCP, FDC, Merits, Demerits

INTRODUCTION:

Tuberculosis (TB) is one of the major causes of death from a curable infectious disease.[1] The disease mainly affects the developing countries. Modern Anti-tubercular treatment can cure virtually all patients provided correct combination treatment is taken in amount and duration. In India, the standard short-course therapy for all categories of drug-sensitive TB is a 6-month regimen that includes a 2-month intensive phase of four medications (HRZE), namely isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E), at doses of 75/150/400/275 mg, and a 4-month continuation phase of three medications, namely HRE at doses of 75/150/275 mg.[2]

Despite the availability of effective anti-TB drugs, poor drug adherence may lead to treatment failure and may promote drug resistance. Additionally, inadequate doses may also lead to treatment failure and to the emergence of drug resistance.[3] In high-burden countries, lowering non-adherence to ATT may have a greater epidemiological impact on TB incidence than reducing loss to follow-up during treatment.[4] Treatment of TB has been shifted towards daily regimen with administration of daily fixed dose combination of first-line ATD as per appropriate weight bands. The use of fixed-dose combinations (FDCs) of anti-TB drugs and a directly observed treatment short-course strategy (DOTS), as recommended by the World Health Organization (WHO) and other organizations, helps to ensure adequate treatment.[5] Due to various concerns of the patient and healthcare system burden, in 2014, India's National TB Elimination Program (NTEP) adopted daily medication dosing in India replacing the previous thrice-weekly dosing protocol.[6]

Various advantages of FDC include 1) improvements in adherence and ease of drug administration, 2) improvements in drug supply logistics 3) prevention of drug resistance, and 4) reductions in prescription errors 5) reduction in cost & 6) simple treatment plan.[7] With this background present study was conducted to assess the compliance and side effects of daily FDC treatment.

OBJECTIVES:

1. To observe incidence of side effects of RNTCP recommended anti TB FDCs
2. To study compliance of patients to new Anti TB FDCs & difficulties posed by patients.

a. MATERIALS AND METHODS:

Prospective study was conducted involving total of 830 patients presenting to Department of Respiratory Medicine, Lokmanya Tilak Municipal Medical College and General Hospital, Sion, Mumbai with diagnosed tuberculosis and Registeredfor CAT I and CAT II ATT were enrolled into the study. All previously treated patients were registered under Category I Retreatment from 1st January 2019. (As per New RNTCP guidelines from 1st January 2019).

INCLUSION CRITERIA:

All patients of tuberculosis (pulmonary and extrapulmonary) registered for Cat I and Cat II ATT and Cat I Retreatment (from 1stJanuary 2019). aged above 12 year of age and above 25 kg in weight.

EXCLUSION CRITERIA

1. Patients not giving consent
2. Patients already taking ATT at time of enrollment
3. Medically Unstable patients (Admitted and serious patients.)
4. Multi drug resistant (MDR) & Extensive drug resistant (XDR) TB patients.
5. Patient who lost to follow up.

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Statistical Methods and Data Analysis:
Data was entered into Microsoft Excel and analyses were done using the Statistical Package for Social Sciences (SPSS) for Windows software (version 22.0; SPSS Inc, Chicago).

Descriptive Analysis:
Descriptive statistics such as mean and standard deviation (SD) for continuous variables, frequencies and percentages were calculated for categorical Variables were determined. Association between Variables was analyzed by using Chi-Square test for categorical Variables. Level of significance was set at 0.05.

Methodology: All patients presenting to Department of Respiratory Medicine, Lokmanya Tilak Municipal Medical College and General Hospital, Sion, Mumbai with diagnosed tuberculosis and Registered for CAT I and CAT II ATT were enrolled into the study. Cat I ATT was including patients who have never taken ATT or taken ATT less than 4 weeks. Cat II ATT (Retreatment category) was including patients who has previously taken ATT for more than 4 weeks. (will include relapses, treatment failures and defaulters). All previously treated patients were registered under Category I Retreatment. (As per New RNTCP guidelines from 1st January 2019). Informed written consent was taken from all patients. Selected Patients were given anti-tubercular treatment in RNTCP on the basis of their different weight bands. History of patients was taken in terms of chief complains (like fever, cough, weight loss, etc in cases of pulmonary TB and abdominal pain, backache/joint pain, seizures, nodular swelling, urinary complains, etc in cases of extrapulmonary TB). Follow up was done with sputum examination, weight recording, and specific radiological imaging (in case of extrapulmonary TB based on baseline investigations that was done) (e.g. USG in lymph node TB, genitourinary TB, Computed Tomography (CT) in abdominal TB, Magnetic Resonance Imaging (MRI) in spine TB and Central nervous system (CNS) TB, X ray chest in cases of pleural effusion, etc) and systemic examination of system involved.

Incidence of side effects was observed in patients at their follow up visits. (at end of initiation phase(2months) and at the end of continuation phase (6 months for Cat I and 8 months for Cat II) and with telephonic contact at the end of 15 days and 4 months. Expected side effects like GI intolerance, hepatotoxicity, joint pain, blurring of vision, ototoxicity, nephrotoxicity and others was observed and confirmed by relevant investigations in indicated patients.

Compliance of patients was defined on the basis of his/her adherence to daily FDCs consumption, after which he/she has to make phone call on toll free number (given on inside of packet of ATT under each daily dose), which gets notified daily under his/her NIKSHAY ID, so that their regional DOTS provider has data regarding number of Daily FDCs doses taken as well as Missed by patients. Through NIKSHAY App, daily adherence of patients to daily FDCs was retrieved. Compliance of all patients were calculated on the basis of doses taken and missed doses in both IP as well as CP in terms of percentage.

$$\textbf{Compliance in IP or CP} = \frac{\text{No. of doses taken by patients in IP or CP X 100}}{\text{Total no. of doses to be taken in IP or CP}}$$

In such a way, Compliance of patients was determined by daily phone call supervision by NIKSHAY (99DOTS earlier) system in which patients sent a free call each time they take their medications so that providers can monitor adherence records. The calls were toll free, so patients did not have any additional costs.

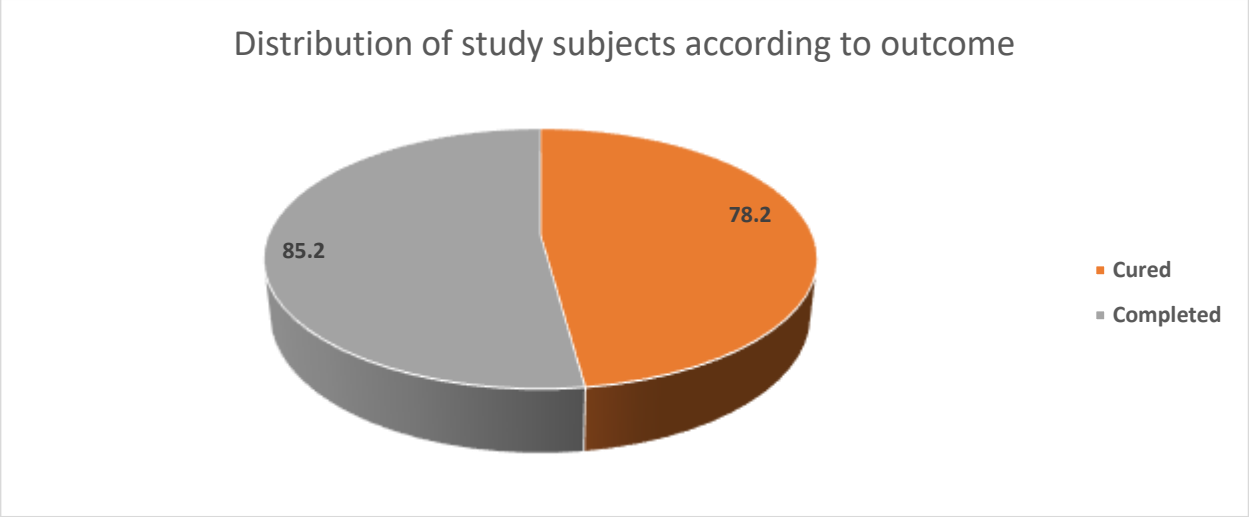
b. Result:

Table No.1: Sociodemographic characteristics of study participants (n=830)

Sr No.	Characteristics	Number of participants	Percentage
1	**Age (in Years)**		
	13-20	138	16.63
	21-30	290	34.94
	31-40	144	17.35
	41-50	138	16.63
	51-60	67	8.07
	>60	53	6.39
	Total	**830**	**100.00**
2	**Gender**		
	Male	452	54.46
	Female	378	45.54
	Total	**830**	**100.00**
3	**Weight Bands**		
	25-39 kg	182	21.93
	40-54 kg	481	57.95
	55-69 kg	163	19.64
	>70 kg	4	0.48
	Total	**830**	**100.00**
4	**Type of TB**		
	PTB	458	55.2
	EPTB	372	44.8
	Total	830	100.00
5	**Number of family members**		
	Lungs	458	55.18
	Lymph Nodes	162	19.52
	Pleural Effusion	158	19.04
	Abdomen	52	6.26
	Total	**830**	**100.00**
6	**Treatment Category**		
	I	652	78.6
	II	82	9.9
	IR	96	11.6
	Total	**830**	**100**

Out of total of 830 patients participated in the study majority were in the age a group of 21-30 years. Total 710 (85.5%) patients were between age group of 13-50 years. Among the study participants 452(54.5%) were males and 378 (45.5%) were females, 458 (55.2%) were suffering from PTB and 372 patients (44.8%) were suffering from EPTB. Among treatment categories, 652 patients (78.6%) were registered under Category I, 82 patients (9.9%) were registered under Category II, 96 patients (11.6%) were registered under Category I Retreatment.

Figure No:1 Distribution of study subjects as per Outcome (N=830)



Out of 458 PTB patients 358 (78.2) patients cured and out of 372 EPTB patients 317(85.2) patients completed treatment.

Table No.2: Distribution of study participants according to the symptoms of adverse effects

Symptoms	No. of Participants	Percentage
Nausea	492	59.3
Vomiting	423	51.0
Pain Abdomen	271	32.7
Itching	143	17.2
Rash	126	15.2
Jaundice	126	15.2
Tingling	119	14.3
Visual disturbance	1	0.1
Joint Pains	336	40.5

Among adverse effects, nausea and vomiting were most common, seen in 492(59.3%) patients and 423 (51.0%) patients, respectively. Other were joint pains seen in 336 (40.5%) patients, pain in abdomen seen in 271 (32.7%) patients, itching in 143 (17.2%) patients, rash in 126 (15.2%) patients, tingling seen in 119 (14.3%) patients, visual disturbances seen in only 1 (0.1%) patient.

Table No.3: Distribution of study participants according to the compliance to treatment (n=830)

Compliance (%)	Intensive phase	Continuation phase
0-20	28 (3.4)	15 (1.8)
20-40	24 (2.9)	53 (6.4)
40-60	57 (6.9)	32 (3.9)
60-80	71 (8.6)	86 (10.4)
80-100	650 (78.3)	644 (77.6)
Mean (SD)	84.46 (21.24)	84.82 (21.29)
Range	0-100	0-100
Mean Difference = -0.364 (19.141)		
Correlation = 0.595		
P Value = 0.584, Not Significant		

It was observed that most of the patients with 80-100% compliance rate has cure rate of 78.3% in intensive phase and 77.6% in continuation phase respectively. Mean difference between compliance of patients during intensive phase and continuation phase was 0.364, which was nonsignificant.

Table No.4: Association between adverse effects and outcome (n=830)

Adverse effects	Total	n	Cured	N	Completed
Nausea	492	286	210 (73.4)	206	166 (80.6)
P Value			0.271		0.429
Vomiting	423	243	173 (71.2)	180	170 (94.4)
P Value			0.179		0.034*
Pain Abdomen	271	167	116 (69.5)	104	80 (76.9)
P Value			0.219		0.579
Itching	143	89	46 (51.7)	54	44 (81.5)
P Value			0.012*		0.091
Rash	126	73	44 (60.3)	53	39 (73.6)
P Value			0.140		0.417
Jaundice	126	68	52 (76.5)	58	48 (82.8)
P Value			0.897		0.870
Tingling	119	65	53 (81.5)	54	42 (77.8)
P Value			0.805		0.632
Visual disturbance	1	1	1 (100.0)	0	0
P Value			0.861		NA
Joint Pains	336	186	139 (74.7)	150	117 (78.0)
P Value			0.605		0.359

It was observed vomiting & itching significantly affected the outcome.

Table No.5: Association between compliance and outcome

Compliance (%)	Total	N	Cured	N	Treated
0-20	28	18	8 (44.4)	10	4 (40.0)
20-40	24	17	7 (41.2)	7	5 (71.4)
40-60	57	33	14 (42.4)	24	16 (66.7)
60-80	71	40	31 (77.5)	31	23 (74.2)
80-100	650	350	298 (85.1)	300	269 (89.7)
P Value			<0.001*		<0.001*
Chi-Square Test, P Value *Significant					

It was observed that proportion of patients cured and treated increased as compliance rate increased from 0-20% to 80-100%.

c. DISCUSSION:

In the present study total 830 patients of tuberculosis (both PTB and EPTB) were studied, majority were in the age group between 21-30 years (range 13-78years). According to India TB report 2019, Majority of TB burden is among the working age group. The89% of TB cases come from the age group of 15-69 years. Thus, commonly affected age group was similar to present study. In present study out of 830 patients, 458(55.2) were PTB (55.2%) and 372(44.8) were EPTB. In the present study treatment success rate among PTB & EPTB cases was 78.2% & 85.2% respectively. Similar findings was observed by Sama, J N et al[8] revealed treatment success rate among PTB & EPTB was 89.0% and 82.5%respectively.

In the present study among adverse effects, nausea and vomiting were most common, seen in 492(59.3%) patients and 423 (51.0%) patients, respectively. Other adverse effects were joint pains seen in 336 (40.5%) patients, pain in abdomen seen in 271 (32.7%) patients, itching in 143 (17.2%)

patients, rash in 126 (15.2%) patients, tingling seen in 119 (14.3%) patients, visual disturbances seen in only 1 (0.1%) patient. Dedun AR, Borisagar GB, Solanki RN. Et al[9] revealed that out of 72 patients, gastro-intestinal upset was the prime complaint noticed in majority (49) patients, followed by giddiness and headache in 37 of the patients. As per bulletin of WHO regarding "Anti-tuberculosis medication side-effects constitute major factor for poor adherence to tuberculosis treatment" [10]

It was observed that patients with 80-100% compliance rate has cure rate of 78.3% in intensive phase and 77.6% in continuation phase respectively. Mean difference between compliance of patients during intensive phase and continuation phase was 0.364, which was nonsignificant. Ester Ndahekelekwa Nepolo et al[11] observed that, treatment success was 278 (88.50%) among patients that complied with their treatment and much lower 1 (10%) among those patients that did not comply with their treatment. While In the continuation phase, treatment success amongst compliant patients seems to increase (95.6%) as does treatment success amongst those non-compliant 16 (42.1%).(statically significant association in both phases of treatment).

In the present study mean compliance of all patients during Intensive phase was 84.46 percent and Mean compliance of all patients during Intensive phase was 84.82 percent

Tesfahuneygn G, Medhin G, Legesse M. et al[12] revealed that overall treatment adherence was 88.5 %.

On enquiry with patients, good compliance of patients is observed to be due to requirement of only daily single dose administration hence it reduced the pill load as compared to separate drug regimen which was more convenient to patients. and also it can be given as different does as per weight bands of patients, hence better tolerated by patients of all weights. (Merits Of FDCs) While few of patients told that pill is difficult to swallow due to its larger size, hence resulting in poor compliance. (Demerits Of FDCs)

CONCLUSION:

Among adverse effects, nausea and vomiting were most common followed by joint pains. Mean compliance of patients was 84.46% in IP and 84.82 during CP. Compliance of patients was better due to reduced pill load, singledose administration, can be conveniently given to patients of all weights as per their weight bands.

'Conflict of Interest Declaration': No conflict of interest

Source of funding: Nil

Ethical Clearance: Approved by institutional ethical committee.

Name-Institutional Ethical Committee Human Research, Lokmanya Tilak Municipal Medical College & General Hospital.

Date-12/01/2018

Reference number-IEC/135/18

d. REFERENCES:

1. Wu JT, Chiu CT, Wei YF, Lai YF. Comparison of the safety and efficacy of a fixed-dose combination regimen and separate formulations for pulmonary tuberculosis treatment. Clinics (Sao Paulo). 2015 Jun;70(6):429-34.

2. National TB Elimination Programme. Guidelines for programmatic management of TB preventive treatment in India 2021 2021. Available from: https://tbcindia.gov.in/WriteReadData/l892s/Guidelines%20for%20Programmatic%20Management%20of%20Tuberculosis%20Preventive%20Treatment%20in%20India.pdf

3. Mitchison DA. How drug resistance emerges as a result of poor compliance during short course

chemotherapy for tuberculosis. Int J Tuberc Lung Dis. 1998;2((1)):10–15.

4. Rajavardhana Thamineni, Ramalingam Peraman, Jayakumar Chenniah, Geethavani Meka, Ashok Kumar Munagala, Vijayakumar Thangavel Mahalingam, Rajanandh Muhasaparur Ganesan. A European Journal of Tropical Medicine & International Health. 2022;(27(11):1011-1023.

5. Moulding T, Dutt AK, Reichman LB. Fixed-dose combinations of anti-tuberculous medications to prevent drug resistance. Ann Intern Med. 1995;122((12)):951–4.

6. Cross A, Gupta N, Liu B, Nair V, Kumar A, Kuttan R, et al. 99DOTS: a low-cost approach to monitoring and improving medication adherence. ACM international conference proceeding series; Association for computing, Machinery, NY; 2019. https://doi.org/10.1145/3287098.3287102.

7. Iftikha S, Sarwar MR. Potential Disadvantages Associated with Treatment of Active Tuberculosis Using Fixed-Dose Combination: A Review of Literature. J Basic Clin Pharma 2017;8: S131-136

8. Sama JN, Chida N, Polan RM, Nuzzo J, Page K, Shah M. High proportion of extrapulmonary tuberculosis in a low prevalence setting: a retrospective cohort study. Public Health. 2016 Sep;138:101-7.

9. Dedun AR, Borisagar GB, Solanki RN. regarding "Impact of adverse drug reaction of first line anti – tuberculous drugs on treatment outcome of tuberculosis under revised national tuberculosis control programme"

10. Awofeso N. Anti-tuberculosis medication side-effects constitute major factor for poor adherence to tuberculosis treatment. Bull World Health Organ. 2008;86(3):1-4.

11. Effects of treatment compliance on treatment outcomes for pulmonary tuberculosis patients on Directly Observed Treatment-short Course in Windhoek District,Namibia. https://etd.uwc.ac.za/xmlui/handle /11394/4908? show=full [Accessed on June 2020]

12. Tesfahuneygn G, Medhin G, Legesse M. Adherence to anti-tuberculosis treatment and treatment outcomes among tuberculosis patients in Alamata district, northeast Ethiopia. BMC Res Notes2015;8:503