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OUTCOME OF CAT IV ATT FROM DOTS-PLUS SITE: GOVT FEVER HOSPITAL, GUNTUR, ANDHRA PRADESH, INDIA.

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ABSTRACT: India is one of the high burden countries for tuberculosis as well as drug-resistant tuberculosis. Standardized treatment regimen (STR) for management of multi-drug resistant tuberculosis (MDRTB) has been approved by RNTCP national DOTS-plus committee. **OBJECTIVE:** Study was done at Government fever hospital/Guntur medical college, Guntur, to know the effectiveness, adherence and the outcome of DOTS-plus. **METHODOLOGY:** A total of 106 patients who were confirmed to have MDRTB and came for pre-treatment evaluation were enrolled in to this prospective study conducted from October 2009 to March 2012. Patients were treated with DOTS-plus and were followed up mainly on out-patient basis. **RESULTS:** At the end of 3rd month 61(57.5%) patients were culture converted and at the end of 6th month 68(64%) patients were culture converted. At the end of treatment, 57 were cured, 25 defaulted, 13 failed, 11 died. 5 failure cases were converted to extensively drug resistant (XDR) TB during the treatment. 92 patients were complained of adverse drug reactions (ADR) and change of medication needed in 13(12%) patients with severe ADR. **CONCLUSION:** The treatment outcome results of patients treated with DOTS-plus was not up to the mark. Defaulters are main obstacle to the success of DOTS-plus. Patient as well as family counselling, close attention to the timely recognition and treatment of ADRs will improve the adherence to the treatment and thus the cure rate.

KEYWORDS: Drug-resistant tuberculosis, Out-patient basis, Treatment outcome, Guntur.

INTRODUCTION: India is one of the high burden countries for tuberculosis as well as drug-resistant tuberculosis. As per WHO's "Global Tuberculosis Report, 2012", India account for an estimated 64000 patients out of 310000 cases of Drug Resistant TB estimated to have occurred amongst the notified cases of TB across the globe in a year.⁽¹⁾

In 1999, WHO and partners launched "DOTS-Plus for MDR-TB" to manage MDR-TB with second-line drugs in resource-limited settings. In the absence of data, this new approach needed rapid assessment of its feasibility and effectiveness under programme conditions. ⁽²⁾ As part of this strategy, a novel partnership known as the Green Light Committee (GLC) was created to foster access to, and rational use of, second-line drugs.⁽²⁾

In India the Programmatic Management for Drug Resistant TB (PMDT) services for quality diagnosis and treatment of drug resistant TB cases were initiated in 2007 in Gujarat and Maharashtra.⁽³⁾

As on February 2013, PMDT services were available in all 35 states of the country across 638 districts covering a population of 1089 million (92%). Treatment of Drug Resistant TB under the programme is based on drug susceptibility testing (DST) results. Initial hospitalization at drug resistant TB (DR-TB) Centres is followed by ambulatory care. Standardized treatment regimen (STR) for MDR TB has been approved by RNTCP national DOTS-plus committee.⁽⁴⁾

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DOTS plus site was started in Guntur, Andhra Pradesh at Govt Fever Hospital in the year of 2009 covering patients from four districts around Guntur. A prospective study was carried out at Govt. fever hospital/Guntur Medical College, Guntur, to know the adherence & effectiveness of DOTS-plus for MDR TB patients and their outcome was reported from October 2009 to March 2012.

METHODS & METHODOLOGY: This is a prospective study, patients who were confirmed MDR TB and admitted for pre-treatment evaluation for cat IV drugs enrolled into this study and patients were followed for entire course of treatment on an out-patient basis.

Pre-treatment evaluation as per the guidelines of DOTS plus committee includes ICTC, complete blood picture, liver & renal profiles, thyroid profile, complete urine analysis, blood sugars, chest X ray, mental status examination & gynecological examination for female patients. Patients with major psychiatric disorders and severe medical illness were not included in this study. Patients were admitted for 1 week for the pre-treatment evaluation and monitoring of treatment during early period. Patients were monitored for any adverse effects during the initial short periods and then drugs were made available at patients nearest DOTS provider. Patients and their family members were educated well regarding the treatment regularity and minor side effects of the drugs before discharge.

Dosage and weight band recommendations:

Sl. No.	Drugs	16-25 Kg (Daily dose)	26-45 Kg (Daily dose)	>45 Kg (Daily dose)
1.	Kanamycin(Km)	500mg	500mg	750mg
2.	Levofloxacin (LvX)	200mg	500mg	750mg
3.	Ethionamide (Eto)	375mg	500mg	750mg
4.	Ethambutol (E)	400mg	800mg	1000mg
5.	Pyrazinamide (Z)	500mg	1250mg	1500mg
6.	Cycloserine (Cs)	250mg	500mg	750mg
7.	PAS (80% Bioavailability)	5gm	10gm	12gm
8.	Pyridoxine	50mg	100mg	100mg
The standardized treatment regimen under DOTS-plus: Intensive phase (IP): 6 (9) Km LvX Eto Cs Z E Continuation phase (CP): 18 LvX Eto Cs				

At the end of 6 months of treatment, if the fourth month culture remained positive, the IP was extended for a further 3 months. Each day drugs were packed in a separate polythene packs for easy administration by DOT provider.

Patients attended GFH once a month for treatment monitoring and also whenever necessary. Chest X ray, complete haemogram, liver and renal function tests were done whenever indicated. Two sputum samples sent for microscopy, culture and sensitivity every month starting from the 3rd month up to 12th month followed by once for every 3 months.

Outcome was measured in terms of sputum culture conversion, number of patients cured, number of failures, defaults and deaths as per the RNTCP guidelines.

RESULTS: This study included a total of 106 patients who were admitted in DOTS plus site, Govt. fever hospital, Guntur for pre-treatment evaluation of MDR TB during the period between October 2009 to

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December 2012. These patients were hospitalised for 1 week and are followed up for rest of treatment period.

The baseline characteristics were described in table 1. Of the 106 cases, 75 were males and 31 were females. Most of them (42) belong to the age group 31 to 40 years. 57 patients were weighed less than 45 kg. Majority of the patients are from rural background. 6 patients were positive for HIV and are already on ART (Anti-Retroviral Therapy) and 5 patients were diabetics, using oral hypoglycaemic agents. Most of the cases were resistant to all four drugs (RHES) followed by resistance to R&H.

Table1:

Baseline characteristics of total MDR TB cases who received standard treatment under RNTCP		
Patient characteristics		No.
Age (in years)	15-30	35
	31-45	42
	46-60	22
	>60	7
Sex	Male	75
	Female	31
Weight (in KGs)	<45	57
	>45	49
Resident area	Urban	45
	Rural	61
HIV	Positive	6
Diabetes	Present	5
Resistance patterns	R only	6
	R&H	27
	RHE	7
	RHS	12
	RHES	54
XDR TB	RH+Km+Ofx	0

The culture conversion rates are 57.5% and 64% at the end of 3rd and 6th months respectively. 38 patients who were culture converted remained persistently culture negative for the rest of the treatment period. 10 patients had one or two cultures positive between 6th to 12th months but remained negative thereafter and were declared cured.

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Time (in months) of treatment	End of 3 rd month	End of 6 th month
No. of culture converted patients	61	68

Table 2

A total of 25 cases were defaulted. Among them 9 cases were defaulted in the first month itself due to personnel reasons and also due to drug intolerance. 7 of those 9 cases were interested in private treatment and they went for it. Remaining 16 out of 25 cases were defaulted at different times after 3 months of treatment due various reasons like drug intolerance, migration and unknown reasons. Details were given in the table 3.

Sl. No.	Age /Sex	Time of Default from the start of treatment (in months)	Culture converted at (month)	Reason for discontinuation of treatment
1.	40/M	1	-	Private treatment
2.	36/M	1	-	Private treatment
3.	55/M	3	-	Skin reaction
4.	45/M	3	-	Absconded
5.	39/M	5	5	Nausea
6.	55/M	9	3	Not known
7.	46/M	1	-	Private treatment
8.	38/M	3	-	Not known
9.	18/M	1	-	Not known
10.	66/M	1	-	Skin reaction
11.	50/F	5	5	Absconded
12.	51/M	1	-	Nausea
13.	46/M	1	-	Not known
14.	65/F	1	-	Giddiness
15.	36/F	12	No	Local medicine
16.	25/M	14	3	Private treatment
17.	25/F	21	4	Private treatment
18.	32/F	21	3	Hearing loss
19.	40/M	3	3	Giddiness
20.	47/M	4	No	Not known
21.	40/M	6	3	Not known
22.	31/F	1	-	Private treatment
23.	38/F	5	5	Joint pains
24.	30/F	4	3	Anorexia
25.	35/M	13	3	Private treatment

Table 3: Details of the defaulters

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The details of patients who died (11) are given in table 4. Of the 11 died patients, 10 were TB deaths and one was non-TB death. 2 were known HIV positive cases using ART and are died due to TB. One patient was diabetic died due to cause other than TB. Most of the died patients are having weight less than 45 Kg (n=9) and are from rural background (n=7). 3 patients were died within the first month of treatment due to the extensive disease.

No.	Age (yr.)/sex	Weigh t (kg)	Residence	Resistant to	Culture Converted	Culture Reverted to positive	HIV	Diabetes	Time of death from treatment start (months)
					Month				
1	37/F	<45	Rural	RHE	No	-	-	-	1
2	58/M	<45	Rural	RHE	9	13	-	-	23
3	34/M	>45	Urban	RHES	No	-	+	-	3
4	36/F	<45	Rural	RHES	3	4	-	-	5
5	24/M	<45	Urban	RH	No	-	-	-	5
6	45/M	<45	Urban	RHES	3	4	-	-	22
7	22/M	<45	Rural	RHES	3	10	-	-	16
8	36/M	<45	Rural	RH	No	-	-	-	1
9	30/M	<45	Urban	RHES	No	-	-	-	1
10	45/M	<45	Rural	RHS	4	-	+	-	22
11	53/M	>45	Rural	RHES	23	-	-	+	23

Table 4: Details of patients who died

There are 6 HIV sero-positive patients in this study and all of them had an unfavourable outcome (Table 5). 2 patients were died, 2 were defaulted and 2 were failures. One of the failure patients was later converted to XDR TB.

No.	Age/Sex	Weight (Kg)	Residence	Resistant to	Culture converted	Culture reverted to positive	MDR outcome	XDR conversion
					Month			
1	34/M	>45	Urban	RHES	No	-	Died	-
2	50/M	<45	Urban	RHES	3	14	Failure	-
3	36/F	>45	Urban	RHS	No	-	Default	+
4	25/F	<45	Rural	RHES	4	14	Default	-
5	45/M	<45	Rural	RHS	4	-	Died	-
6	30/M	<45	Urban	RH	3	21	Failure	-

Table 5: Details of HIV patients and their outcome

Adverse drug reactions (ADR) noted during the treatment are given in the table 6. 8 patients did not complain of any adverse effects. Some patients were complained of more than one side effect.

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ADRs were considered mild if the patient made 1 or 2 complaints during the 12 month period and only required symptomatic treatment, moderate if the complaint was repeated or of prolonged duration but still could be managed with symptomatic drugs, and severe if either a reduction of dosage or termination of the offending drug(s) was warranted. Severe drug reactions were noted in 14 patients (13.2%). Of these 4 had terminated pyrazinamide, 2 had kanamycin, 2 had ofloxacin, 1 each had cycloserine, ethambutol. Kanamycin dose was adjusted in 2 patients, pyrazinamide in 2 patients, ofloxacin in 1 patient.

Adverse effect	Severity		
	Mild	Moderate	Severe
Gastro-intestinal	32	17	2
Arthralgia	15	2	2
Giddiness	12	2	1
Depression	0	0	1
Convulsions	0	0	2
Visual	2	0	0
Auditory	4	1	2
Cutaneous	2	2	1
Jaundice	0	1	3
Total	67	25	13

Table 6: List of adverse drug reactions

The final outcome of DOTS-plus mentioned in the table below.

Final outcome at the end of treatment	
Cured	57
Defaulted	25
Failure	13
Died	11

Table 7: Final outcome of the study

DISCUSSION: When two cheap and effective drugs (Isoniazid and Rifampicin) have been lost to resistance, treatment is complicated, prolonged, expensive and more toxic and results in predictably poorer outcomes.⁽⁵⁾ Drug resistant TB ultimately develops from the inadequate treatment.⁽⁵⁾ MDR TB is nothing but Man Developed Resistant TB. There is also a significant proportion of patients who acquire drug resistant disease because they live in an environment with a high prevalence of drug resistant disease.⁽⁶⁾ WHO estimates that there were about 0.5 million new MDR-TB cases in the world in 2011. About 60% of these cases occurred in Brazil, China, India, the Russian Federation and South Africa alone ("BRICS" countries).⁽⁷⁾

In our study, the treatment outcome for MDRTB was low with a cure rate of 53.7% is considered significant. The results of our study were in between the results obtained from similar studies conducted at New Delhi.⁽⁸⁾ and Peru.⁽⁹⁾ with a success rate of 61% and 48% respectively using

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standard treatment regimen for MDRTB. These results are in contrast to the study conducted at Tuberculosis research centre, Chennai, by Joseph et al.⁽¹⁰⁾ where in the cure rate was high (66%).

Culture conversion rates are good with 57.5% at the end of 3rd month and 64% at the end of 6th month. 38 of the culture converted patients remained culture negative for the rest of 18 months. But these findings are in contrast to the results of study conducted at Tuberculosis research centre, Chennai, by Joseph et al.⁽¹⁰⁾ where the culture conversion rates were high i.e., 84% and 87% at the end of 3rd and 6th months respectively.

In our analysis, we found that the defaulters are very high (25%) which needs more attention to the patient education and prompt treatment of ADRs to bring back patients to treatment. These results are in contrast to those obtained from study conducted by Joseph et al.⁽¹⁰⁾ and James C. Johnston et al.⁽¹¹⁾ where the defaulters were 13% of the study population. The rate of defaulters was far higher in the study by V.K. Dhingra et al.⁽¹²⁾ where 10 out of 27 study subjects i.e., 37% were defaulters. Moreover, this default appears to be a global phenomenon, with rates over 15% in several countries, including Korea (32%), Taiwan (29%), Russia (20%), Italy (17%), Spain (16%), South Africa (29%), Argentina (20%), and Peru (19%). With the advent of DOTS and DOTS-Plus strategies, MDRTB rates have improved in some high prevalence countries, such as Latvia. Yet under these improved circumstances, published default rates were above 10%.⁽¹³⁾

An important finding in our study was the direct association between poor treatment outcome and co-morbid conditions like low body weight, diabetes and HIV. Among the total 11 patients died, 9 had body weight less than 45 KGs. Also majority of patients with low body weight have unfavourable outcome even though they are provided with drugs according to the weight band. These results can be compared with similar results obtained from the studies by Joseph et al.⁽¹⁰⁾ TRC, Chennai and James C. Johnston et al.⁽¹¹⁾

Patients with Diabetes mellitus (n=5) also have unfavourable outcome with 1 failure and one death. These results are in contrast the study by Joseph et al.⁽¹⁰⁾ and James C. Johnston et al.⁽¹¹⁾ where the outcome results of diabetics are similar to non-diabetics. The treatment outcome of patients with HIV was disappointing. All the 6 HIV patients had unfavourable outcome (2 died, 2 failure and 2 defaulted). Only few studies were conducted and the data was sparse on outcome of MDRTB in HIV patients. Thus the patients with co-morbid conditions like low body weight, HIV and Diabetes needs close monitoring.

Another important observation of our study is that 4 of the total cases converted to XDR TB during the course of treatment. We don't know whether they were initially resistant or the resistance was developed during the course of treatment. It is because, in the programme, drug susceptibility testing was done only to first line ATT. The incidence of XDR-TB among MDR-TB in our study is approximately 5% after excluding the defaulters. But according to WHO updates on MDRTB 2013, about 9% of MDR-TB cases also have resistance to two other classes of drugs, or extensively drug-resistant TB (XDR-TB).⁽⁷⁾ Of the 4 XDRTB cases, one patient was sero-positive for HIV. All the 4 cases were shown failure to Cat IV. Two cases were culture converted in the 3rd month and culture reverted to positive in the 4th month itself. Two patients did not culture convert yet all.

Adverse drug reactions are very common with DOTS plus. Severe drug reactions are found in 13.2% of patients which required withdrawal of the offending drug or dose adjustment. Mild to moderate side effects can be treated symptomatically without stopping the treatment. These results are in contrast to the results of Joseph et al.⁽¹⁰⁾ study where the severe ADR were developed in 58% of

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cases. These differences may be due to the high rate of defaults in our study. Timely recognition and treatment of ADRs can improve the treatment adherence by decreasing the default rates.

Though the success rate of DOTS plus for MDRTB is low, there are reasons to be hopeful. Default from treatment is a major challenge in the MDRTB treatment. Newer plans to reduce number of defaulters like education of patients and their families and prompt treatment of ADRs are crucial in the MDRTB treatment. Newer/modified inventions should be developed towards research in the development of less toxic, patient friendly drugs and also less duration of the therapy. And above all, it is wise to take steps to prevent MDR TB rather than treating it.

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