Original Article

Treatment outcome of multidrug-resistant tuberculosis with modified DOTS-plus strategy: A 2 years' experience

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ABSTRACT

Background: Multidrug-resistant tuberculosis (MDR-TB) is a global health problem with notoriously difficult and challenging treatment. This study determined treatment outcome in patients of MDR-TB with modified DOTS-Plus strategy. **Methods:** Ninety-eight consecutive MDR-TB patients treated with standardized regimen according to modified DOTS-Plus strategy aligned to the existing national DOTS-Plus guidelines with relevant modifications proposed by Chennai consensus were analyzed prospectively. Treatment included monthly follow-up with clinical, radiological, and bacteriological assessment (sputum smear advised monthly till conversion then quarterly; culture for *Mycobacterium tuberculosis* at 0, 4, 6, 12, 18, and 24 months), ensuring adherence, intense health education, and monitoring of adverse events (AEs). Patients' outcome was considered as cure when at least two of the last three cultures (all three or last two) were negative and as failure when the same were positive. **Results:** Favorable and unfavorable outcomes in this cohort were reported to be 71/98 (72.4%) and 27/98 (27.6%) (failure – 10 [10.2%], default – 7 [7.1%], and expiry – 10 [10.2%]), respectively. Sputum smear and culture conversion rate were 75/81 (92.5%) and 71/81 (87.7%), respectively. Major AEs were experienced in only 17.4% of patients. **Conclusions:** MDR-TB can be cured successfully with modified DOTS-Plus strategy and requires much effort from both the patients and health-care workers. It can be an alternative model for treating MDR-TB patients in private sector.

KEY WORDS: Drug resistant, individualized, programmatic management of multidrug-resistant tuberculosis, regimen, standardized, tuberculosis

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INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) has become a major public health problem worldwide and considered to be an obstacle for effective global TB control.[1] The management of patients with MDR-TB in India is being undertaken by the Revised National Tuberculosis Programme (RNTCP) under the Programmatic Management of Multidrug-Resistant Tuberculosis (PMDT), formerly known as DOTS-Plus. It is a comprehensive management strategy for MDR-TB patients by providing a standardized treatment regimen based on common drug sensitivity testing (DST) profile of the prevalent MDR-TB strains.[2] DOTS-Plus has been implemented phase wise in India since 2006, with complete geographical coverage achieved in 2013. Out of 130,000 MDR-TB cases emerging annually in India (22% of global burden), 79,000

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were among the notified cases of TB in 2015.[3] Among 79,000 MDR-TB cases, only 36% were diagnosed with suboptimal treatment success rate of 46%. Nearly 64% of cases remained uncovered leading to amplification of resistance in the community. Therefore, these large number of uncovered MDR-TB patients will have to consult private health sector for treatment. Another issue is that the standardized approach provided by DOTS-Plus programs in resource-limited settings has also confronted significant difficulties in the enrollment, diagnosis, and management of MDR-TB patients.[4-7] Retention and adherence to therapy remains a major challenge in the treatment of MDR-TB patients as treatment course is expensive, is consisting of more toxic second-line drugs (SLDs), and is lengthy with frequent follow-up cultures. An innovative method based on the local availability of resources is required in order to be devised to address these unmet needs. A modified approach was introduced in order to support the existing national DOTS-Plus program by overcoming these challenges that are encountered in the management of MDR-TB cases.[8,9] Therefore, the present study has been conducted to determine the treatment outcome in patients of MDR-TB with an alternative approach known as modified DOTS-Plus strategy at Lucknow, India.

METHODS

Study design and setting

It was a prospective cohort study performed among 132 consecutive patients of pulmonary TB referred from Lucknow and other districts of Uttar Pradesh (UP), India, between June 2009 and February 2010 to the Department of Pulmonary Medicine having an established DOTS center and the Department of Microbiology, King George Medical University, Lucknow, India, which is a WHO-recommended Intermediate Reference Laboratory certified by the RNTCP of India.

Inclusion and exclusion criteria

All patients provided informed consent before participating in the study. These patients were cases of pulmonary TB with proven culture positive for *Mycobacterium tuberculosis* and resistant to at least isoniazid (INH) and rifampin (RIF) and having age >18 years. Patients were excluded from the study if they had (1) non-MDR-TB pattern according to drug susceptibility testing (DST) results, (2) taken SLDs >1 month before confirmation of diagnosis, (3) pregnancy, (4) age <18 years, and (5) concurrent major medical or psychiatric illnesses at baseline. These exclusions were according to the RNTCP guidelines prevailing at the time of study.[8]

Diagnosis

Pretreatment investigations included sputum smear for acid-fast bacilli (Ziehl–Neelsen staining), culture for *M. tuberculosis* (conventional method using Löwenstein–Jensen medium) and DST (proportion method), complete hemogram, chest X-ray, renal and liver function tests, and thyroid profile. All patients were routinely tested for human immunodeficiency virus (HIV) infection before the initiation of treatment. The BACTEC method (Becton Dickinson, Sparks, MD, USA) for culture and DST for SLDs were also used whenever possible. DST for SLDs was performed when subsequent cultures after 6 months of treatment remained positive. Care was taken to interpret the culture results cautiously along with clinicoradiological data although our laboratory setup underwent regular surveillance for external quality assurance. The minimum inhibitory concentration of the first-line drugs and SLDs used was as follows: streptomycin 16 μg/ml, INH 0.5 μg/ml, RIF 128 μg/ml, ethambutol 8 μg/ml, pyrazinamide (PZA) 50 μg/ml, kanamycin (KM) 30 μg/ml, and levofloxacin or ofloxacin (OFX) 2 μg/ml.[10]

Management protocol according to the modified DOTS-Plus strategy

A committee consisting of clinicians (6), laboratory technicians (2), domiciliary DOT-providers (3), TB health workers (2), health educator (1), and microbiologists (2) was constituted at Lucknow center. One domiciliary DOT-provider from each DOTS center of 18 districts (Kanpur, Basti, Gorakhpur, Allahabad, Faizabad, and Varanasi divisions) was selected and also included in the committee. Operational guidelines as framed by the modified DOTS-Plus strategy were implemented in this study. Modified DOTS-Plus strategy is essentially DOTS-Plus Protocol of the RNTCP based on the WHO guidelines prevailing at that time with relevant modifications according to the Chennai consensus.[8,9,11] The protocol of the modified DOTS-Plus strategy is described in Table 1. All members of the committee underwent 1 month of training regarding implementation of this strategy. Emphasis was given on training of all domiciliary DOT-providers and TB health workers in order to ensure adherence to treatment as well as to access adverse events (AEs) associated with antitubercular therapy. Sample collection of sputum for smear examination and culture inoculation were done daily on an outpatient department basis (excluding Sundays and other holidays). Prior intimation was given to patients for sputum sample deposition at a specified date in order to avoid inconvenience. Regular supply of consumable and nonconsumable staining and culture material was ensured at our established DOTS center. Regular supply of quality-assured drugs was also ensured in collaboration with the Central Tuberculosis Division Ministry of Health and Family Welfare, Government of India, and Uttar Pradesh State Tuberculosis Association. Care was taken to safeguard standardized quality of health care for patients. A subcommittee comprising two clinicians, one microbiologist, and one laboratory technician was framed and assigned to take care of this issue. This subcommittee continued to follow up patients with the prevailing DOTS-Plus guidelines of the RNTCP, particularly in terms of the frequency of culture monitoring, treatment outcomes, as well as monitoring of any AEs. This supervision was performed in order to detect any discrepancy in management with adopted the modified DOTS-Plus strategy as compared to the standard RNTCP guidelines.

Table 1: Characteristic features of the modified Directly Observed Treatment Short-Course-Plus strategy

Components of the modified DOTS plus strategy	
Component characteristics	**Management strategies**
Regimen used	Standardized regimen provided under supervision IP with six drugs - KM, OFX or LFX, ETO, CS, PZA, EMB CP with four drugs - OFX, ETO, CS, and EMB Duration: IP for a minimum of 6 months extended up to 9 months in patients in case culture positive at the 4th month of treatment followed by CP for a minimum of 18 months leading to a total duration of 24-27 months of treatment Dosage according to weight band: Patients weighing<45 kg - KM (500 mg), ETO (500 mg), CS (500 mg), OFX (600 mg) or LFX (500 mg), PZA (1250 mg), and EMB (800 mg) and patients weighing ≥45 kg - KM (750 mg), ETO (750 mg), CS (750 mg), OFX (800 mg) or LFX (750 mg), PZA (1500 mg), and EMB (1200 mg) Drugs provided free of cost to the patients every month Ensuring regular supply of quality-assured drugs in collaboration with the CTD, MOHFW, Government of India, and Uttar Pradesh State TB Association
Treatment monitoring	Smear examination: Baseline, every monthly during IP and then quarterly during CP Culture examination: 0, 4, 6, 12, 18, and 24 months of treatment Daily sample collection of sputum for smear examination and culture inoculation on an OPD basis (excluding Sundays and other holidays) Monthly follow-up to the outpatient clinic to complete self-administered treatment Total duration of follow-up at least 2 years after the initiation of treatment Prior intimation or reminder given to patients for sputum sample deposition at a specified date Ensuring regular supply of consumable and nonconsumable staining and culture material
Surveillance of AEs	Clinical symptoms and AEs recorded at each visit under the supervision of a clinician AEs recording based primarily on clinical evidence under the supervision of clinician further supported by laboratory investigations AEs considered only when reflected at least by one abnormal laboratory value confirmed by a repeat test AEs considered major, if required change in the regimen, i.e., stoppage of offending drug or substitution with other drug PAS as a substitute drug for any one bactericidal (KM, OFX, ETO, and PZA) or two bacteriostatic drugs (CS and EMB) in case of occurrence of AEs
Health education and family counseling	Provision of counseling and intense health education to all patients and their family members prior to treatment initiation and during all follow-up visits Counseling about the disease, DOTS-plus treatment, importance of treatment adherence, TB transmission, coughing etiquette, proper disposal of sputum, and use of contraception in order to avoid pregnancy during treatment and nutrition Encouragement to maintain personal hygiene and were asked to keep doors and windows open during day time Provision of opportunities to discuss about emotional needs and problems Counseling to family members to provide love and care to the patient Motivation of patients and their family members not to stop treatment despite all its discomforts as it is the last resort that stands between life and death
Adherence	Checking empty blister packs on every follow-up visits Provision of contact numbers of committee members to patients for reporting any issues including AEs Appointment for consultation by clinician to fix issues at the earliest for ensuring treatment adherence Arrangement of home visits if any patient was reported to be absent for periodic follow-up Provision of medicines at residence by DOT provider if patient is unable to collect from the center
Treatment outcome	Cure: At least two of the last three cultures at 12, 18, and 24 months (either all the three or the last two) were negative Failure: At least two of the last three cultures at 12, 18, and 24 months (either all the three or the last two) were positive Death: Patient died for any reason during the course of MDR-TB treatment Still on treatment: When for any reason, was receiving the treatment at the time of preparation of treatment outcome report Lost to follow-up or default: When initiated on prescribed regimen but did not turn up for follow-up during any stage of the study Smear conversion: Two negative consecutive sputum smears after treatment initiation Time to smear conversion: Time interval between the date of MDR-TB treatment initiation and the date of the first of two negative consecutive smears Culture conversion: Two negative consecutive cultures after treatment initiation Time to culture conversion: Time interval between the date of MDR-TB treatment initiation and the date of the first of two negative consecutive cultures
Data collection	Maintaining systematic records of demographic profile including address, contact number, treatment regimen, doses, duration, adverse events, investigation results, and treatment outcome for all patients initiated on second-line treatment Recording of data recorded in a predesigned proforma

TB: Tuberculosis, IP: Intensive phase, KM: Kanamycin, OFX: Ofloxacin, LFX: Levofloxacin, ETO: Ethionamide, CS: Cycloserine, PZA: Pyrazinamide, EMB: Ethambutol, CP: Continuation phase, CTD: Central TB division, MOHFW: Ministry of Health and Family Welfare, OPD: Outpatient department, PAS: Para-amino salicylic acid, DOT: Directly observed treatment, DOTS: DOT short-course, MDR-TB: Multidrug-resistant tuberculosis, CP: Continuation phase, AEs: Adverse events

Data analysis

Data were single entered on Microsoft Excel 2007 sheet, and the accuracy of the entry was verified against the original paper forms. The data were further checked for any errors and then analyzed using descriptive statistics. Absolute and relative frequency counts and measures of central tendency (mean) were calculated. Measure of dispersion such as standard deviation was also calculated. Chi-square test, Fisher's exact test, Student's *t*-test, and Mann–Whitney *U*-test were used for univariate

analyses. Cumulative survival was compared by using the Kaplan–Meier method with the log-rank test. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using Epi Info software version 3.5.3 (Centre for Disease Control and Prevention; Atlanta; Georgia; USA).

Ethical clearance

The ethical committee of King George Medical University approved the present study.

RESULTS

Out of 132 patients, a total of 98 patients proved to be cases of MDR-TB by culture were enrolled for treatment. All the patients were categorized under re-treatment cases. Thirty-four patients were excluded from the study (non-MDR susceptibility – 13, >1 month treatment of SLDs before diagnosis – 8, migrated/not traced –3, unwillingness for treatment – 2, major medical/psychiatric illnesses at baseline – 6, and expiry before the initiation of treatment – 2). All patients were HIV seronegative after testing. Of them, 68 (69.4%) were males and 30 (30.6%) were females. The mean age and weight were 29.3 ± 9.3 years and 42.9 ± 9.1 kg, respectively. The clinical and demographic profile of the patients is illustrated in Table 2. Fifty-six of 98 (57.2%) patients were from areas in and around Lucknow, whereas 42/98 (42.8%) cases were referred from other districts as the DOTS-Plus program was not implemented in UP. The mean duration of total illness was 4.8 ± 3.6 years. Radiologically, 5 (5.1%) patients had unilateral disease, whereas 93 (94.9%) had bilateral disease. The average duration of anti-TB treatment received by the cohort as a whole prior to referral was 26 ± 12.3 months. The cohort was resistant to a mean of 3.17 ± 1.06 drugs. The intensive phase (IP) was extended to 9 months in 30 (30.6%) patients with proven culture positivity at the 4th month. Mean smear and culture conversion time were 3.4 ± 2.1 months (1–11) and 4.6 ± 2.5 months (4–12), respectively. Sputum smear and culture conversion rates were 75/81 (92.5%) and 71/81 (87.7%), respectively, with only ten (10.2%) patients remained culture positive as shown in Table 3. Seven patients were resistant to SLDs during the course of treatment among which four were either resistant to KM or OFX in addition to MDR-TB, while the remaining three met the revised WHO diagnosis of extensively drug-resistant (XDR)-TB. These patients were treated either with individualized or standardized regimens for XDR-TB (CAT V under the RNTCP). The clinical characteristics of patients showing unfavorable outcome after treatment with MDR-TB therapy are described in online Supplementary Table S1. A wide range of AEs was observed during the treatment, some requiring discontinuation of the offending drug as shown in Tables 4 and 5. Seventeen (17.4%) patients had major AE requiring drug substitution or permanent discontinuation of drugs. Seven (7.1%) patients required admission to hospital for the occurrence of AE. None of the patients had to discontinue their complete regimen permanently due to major AE. The offending drugs responsible for

Table 2: Clinical and demographic characteristics of the cohort of 98 patients treated with multidrug-resistant tuberculosis therapy

Characteristics	*n* (%)
Age distribution (years)	
≤20	13 (13.3)
21-30	51 (52.1)
31-40	24 (24.4)
≥41	10 (10.2)
Sex distribution of patients	
Male	68 (69.4)
Female	30 (30.6)
Geographical distribution	
Urban	44 (44.9)
Rural	54 (55.1)
Weight (kg)	
≤30	8 (8.2)
31-40	33 (33.7)
41-50	38 (38.8)
51-60	16 (16.2)
≥61	3 (3.1)
Total duration of illness (years)	
<1	6 (6.1)
1-2	42 (42.8)
3-4	38 (38.8)
>5	12 (12.3)
Number of episodes of pulmonary TB for which treatment taken	
Two	54 (55.1)
Three	30 (30.6)
More than three	14 (14.3)
Contact history with TB patients	20 (20.4)
Previous TB treatment taken from	
Public sector (supervised)	14 (14.3)
Private sector (unsupervised)	21 (21.4)
Public and private both	63 (64.3)
Risk factors	
Drug addiction	5 (5.1)
Alcoholism	13 (13.3)
Diabetes mellitus	4 (4.1)
Radiological assessment	
Unilateral	5 (5.1)
Bilateral	93 (94.9)
Consolidation	70 (71.4)
Infiltrate	38 (38.8)
Cavitation	57 (58.2)
Fibrotic areas	8 (17.1)
Calcification	2 (2.1)
Pyo-pneumothorax	3 (3.1)
Effusion	1 (1.1)
Culture sensitivity pattern	
RIF, INH	36 (36.7)
RIF, INH, EMB	13 (13.3)
RIF, INH, EMB, PZA	10 (10.2)
STM, RIF, INH, EMB, PZA	12 (12.3)
STM, RIF, INH	8 (17.1)
STM, RIF, INH, EMB	18 (18.4)
STM, RIF, INH, PZA	1 (1.1)
Any RIF	98 (100)
Any INH	98 (100)
Any EMB	53 (54.1)
Any PZA	23 (23.5)
Any STM	39 (39.8)

TB: Tuberculosis, RIF: Rifampin, INH: Isoniazid, EMB: Ethambutol, PZA: Pyrazinamide, STM: Streptomycin

Table 3: Bacteriological response of 98 patients treated with multidrug-resistant tuberculosis therapy over 2 years

Characteristics	Treatment duration (%)					Nonconverter (%)
	4 months	6 months	12 months	18 months	24 months	
Lost to follow-up	1 (1.1)	2 (2.1)	4 (4.1)	5 (5.1)	7 (7.1)	
Expired	6 (6.1)	6 (6.1)	7 (7.1)	10 (10.2)	10 (10.2)	
Patient continuing on treatment	91 (92.8)	90 (91.8)	87 (88.8)	83 (84.7)	81 (82.6)	
Smear conversion rate						
Best scenario	63/91 (69.2)	80/90 (88.9)	81/87 (93.1)	77/83 (92.8)	75/81 (92.5)	6 (6.1)
Worst scenario	63/98 (64.3)	80/98 (81.6)	81/98 (82.7)	77/98 (78.6)	75/98 (76.5)	
Patient still smear positive	28 (28.6)	10 (10.2)	6 (6.1)	6 (6.1)	6 (6.1)	
Culture conversion rate						
Best scenario	61/91 (67.1)	75/90 (83.3)	78/87 (89.7)	74/83 (89.2)	71/81 (87.7)	10 (10.2)
Worst scenario	61/98 (62.2)	75/98 (76.5)	78/98 (79.6)	74/98 (75.5)	71/98 (72.4)	
Patient still culture positive	30 (30.6)	15 (15.3)	9 (9.2)	9 (9.2)	10 (10.2)	

Best scenario: Excluding patients with unfavorable outcome in denominator, Worst scenario: Including patients with unfavorable outcome in denominator

Table 4: Frequency of adverse events among 98 patients receiving multidrug-resistant tuberculosis treatment

Grouped AEs	Specific AEs	Frequency of AEs (%)	Offending drugs
Gastrointestinal	Nausea/vomiting	24 (20.2)	ETO, CS, PZA, OFX
	Anorexia	9 (7.6)	ETO
	Gastritis	8 (6.7)	ETO, PAS
	Hepatitis	3 (2.5)	ETO, PZA
	Diarrhea	2 (1.7)	ETO, PAS
	Abdominal pain	1 (0.8)	ETO, PAS
	Constipation	1 (0.8)	ETO
Ototoxicity	Deafness	12 (10.1)	KM
	Vertigo	10 (8.4)	KM, CS, OFX
	Tinnitus	6 (5.1)	KM
Neurological	Dizziness	10 (8.4)	KM, CS, OFX
	Headache	8 (6.7)	CS, KM
	Peripheral neuropathy	3 (2.5)	ETO, KM, CS
Psychiatric	Psychosis	5 (4.2)	CS
	Depression	1 (0.8)	CS
Others	Arthralgia	9 (7.6)	PZA
	Visual disturbance	3 (2.5)	EMB, ETO
	Rash	2 (1.7)	OFX
	Hypothyroidism	1 (0.8)	ETO, PAS
	Renal failure	1 (0.8)	KM
Overall AEs		119	

Sum of column percentages may exceed 100% because a patient may experience more than one adverse event. EMB: Ethambutol, PZA: Pyrazinamide, KM: Kanamycin, CS: Cycloserine, ETO: Ethionamide, OFX: Ofloxacin, PAS: Para-aminosalicylic acid, AEs: Adverse events

these major AE were injectable KM (deafness/renal failure), CS (psychosis), ETO (gastrointestinal tolerance), and PZA (arthralgia/hepatitis). No mortality occurred due to major AE in our cohort. Sixteen of thirty (53.3%) female patients were of childbearing age. None of these female patients included in the study conceived during treatment as they were counseled either to avoid intercourse or to use contraception (barrier methods – 8, intrauterine device – 3). Of the total 98 patients included in this study, 81 (82.7%) completed the treatment, with 71 (74.5%) declared successfully cured and 10 (10.2%) failed, whereas 7 (7.1%) defaulted and 10 (10.2%) died at the completion of treatment. The reason behind default in all cases was migration due to social reasons. The causes for mortality among the ten patients were found to be acute respiratory failure due to extensive disease (4), accidental trauma (2), viral hemorrhagic fever with multiorgan failure (2), acute coronary syndrome (1), and complicated malaria (1). No significant discrepancy was observed in treatment outcome with reduced frequency of monitoring with culture under modified strategy as reported by the subcommittee in online Supplementary Table S2. Figure 1 shows Kaplan–Meier plot of the probability of survival among MDR-TB patients from the time of diagnosis. Overall median survival of 98 MDR-TB patients was 26.5 months (95% confidence interval [CI]: 25.6–27.4), with 27 months (95% CI: 25.9–28.1) and 26 months (95% CI: 25.2–26.8) for males and females, respectively. No significant difference in survival rate was observed based on gender ($P = 0.37$, log–rank – Mantel–Cox test). The association of clinical and demographic variables with treatment outcome for MDR-TB patients is described in Table 6. Patients were more likely to have poor outcomes if they were drug addicts (odds ratio [OR] 0.11; 95% CI: 0.01-0.77; $P = 0.03$), had a previous history of TB episodes >2 (OR 0.14; 95% CI: 0.11-0.39; $P < 0.001$), and had resistance to both KM and OFX (OR 0.15; 95% CI: 0.01-0.98; $P = 0.05$). All patients with successful outcome were observed for 1 year after completion of treatment with no relapse.

DISCUSSION

India constitutes a considerable burden of MDR-TB patients. National programs in developed countries with adequate laboratory facilities may monitor treatment outcome frequently with cultures without constraints. However, in a resource-poor country like India, performing frequent cultures is cumbersome, considering the long waiting period for the results, lack of skilled workforce, and poor quality control of laboratories both in the public and private sectors. A study reported major constraints influencing the outcome such as difficulty in arranging daily DOT for 2 years particularly at peripheral centers, ensuring compliance especially on Sunday and other holidays, lack of access to specialized laboratory facilities, and managing major AEs in field conditions.[5] Taking

Table 5: Frequency of major adverse events and suspected agents among the 98 patients receiving multidrug-resistant tuberculosis treatment

Agents	Specific major AEs observed	Number of patients experiencing major AEs (%)	Number of patients requiring substitution with other drug	Number of patients requiring discontinuation of drugs
KM	Deafness	4 (4.1)	1	3
	Tinnitus	1 (1.1)	1	0
	Renal failure	1 (1.1)	0	1
CS	Psychosis	4 (4.1)	0	4
PZA	Arthralgia	2 (2.1)	1	1
	Hepatitis	2 (2.1)	1	1
ETO	Nausea	1 (1.1)	1	0
	Vomiting	1 (1.1)	1	0
	Hypothyroidism	1 (1.1)	0	1
Total		17/98 (17.4)		

PZA: Pyrazinamide, KM: Kanamycin, CS: Cycloserine, ETO: Ethionamide, AEs: Adverse events

Table 6: Summary of association of clinical and demographic variables with treatment outcome for multidrug-resistant tuberculosis patients

Characteristics	Patients with favorable outcome - successfully cured (*n*=71)	Patients with unfavorable outcome - defaulted/expired/failure (*n*=27)	Unadjusted OR (95% CI)	*P*
Mean age (years)	29.17±9.61	29.71±7.74	0.54 (−3.56-4.64)	0.79
Sex (male), *n* (%)	54 (76.01)	22 (81.48)	0.72 (0.24-2.20)	0.57
Mean weight	42.62±8.48	40.76±9.65	1.86 (−5.82-2.10)	0.35
Alcohol abuse, *n* (%)	9 (12.68)	4 (14.81)	0.83 (0.23-2.98)	0.78
Drug addiction, *n* (%)	1 (1.41)	4 (14.81)	0.11 (0.01-0.77)	0.03
Diabetes mellitus, *n* (%)	2 (2.82)	2 (7.41)	0.36 (0.05-2.71)	0.32
Total duration of illness (years)	4.63±3.52	4.79±3.15	0.16 (−1.38-1.70)	0.84
Previous number of episodes of TB, *n* (%)				
2	48 (67.61)	6 (22.22)	1	
>2	23 (32.39)	21 (77.78)	0.14 (0.11-0.39)	<0.001
Previous contact history with TB, *n* (%)	14 (19.72)	6 (22.22)	0.86 (0.29-2.53)	0.78
Cavitary lesions on chest X-ray, *n* (%)	42 (59.15)	15 (55.55)	1.16 (0.47-2.83)	0.75
Resistance to KM, *n* (%)	0 (0.00)	2 (7.41)	0.11 (0.01-1.54)	0.09
Resistance to OFX, *n* (%)	0 (0.00)	2 (7.41)	0.11 (0.01-1.54)	0.09
Resistance to KM and OFX (XDR-TB), *n* (%)	0 (0.00)	3 (11.11)	0.15 (0.01-0.98)	0.05

CI: Confidence interval, TB: Tuberculosis, KM: Kanamycin, OFX: Ofloxacin, XDR: Extensively drug-resistant, OR: Odds ratio

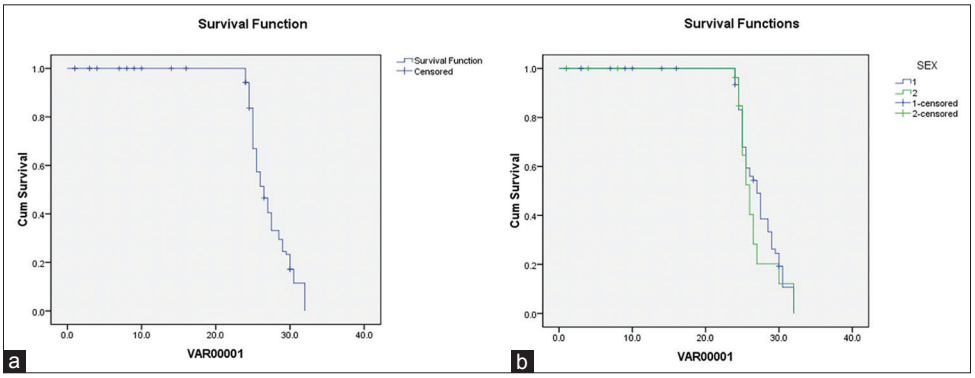

Figure 1: (a) Kaplan–Meier plot of the probability of survival among 98 multidrug-resistant tuberculosis patients from the time of diagnosis. (b) Probability of survival based on gender (*P* = 0.37, log-rank – Mantel–Cox test)

note of this huge discrepancy, the Chennai consensus was framed in order to overcome these limitations.[9] Meanwhile, laboratory services should be strengthened for adequate and timely diagnosis of MDR-TB, and DOTS-Plus should be scaled up as per the target set by the Global Plan to Stop TB 2011–2015.[12]

The present study has reported successful treatment outcome in 71 (72.5%) and unsuccessful treatment outcomes in 27 (27.5%) patients (failure – 10 [10.2%], treatment default – 7 [7.1%], and death – 10 [10.2%]). Several studies including systematic reviews and meta-analyses revealed variable results, with treatment

success rate for MDR-TB patients worldwide ranging from 21% to 83% with considerable unsuccessful treatment outcomes ranging from 29% to 39% (failure or relapse: 6% to 7.6%, treatment default: 12% to 15%, and death: 11% to 13%).[3,13-17] The treatment outcome remains variable even among different regions of India as shown in online Supplementary Table S3. This may be attributed to heterogeneity in the demographic profile of cohorts, frequency of associated comorbid illnesses, settings, methodology, regimens, and definition of outcomes. The success rate was high in our cohort with lower default rate indicating that the modified DOTS-Plus strategy might be effective in improving success outcomes as emphasis was given on patient-centric care, timely management of AE related to SLDs, intense health education, counseling, and psychosocial support apart from reducing follow-up cultures.

In our study, the culture conversion rate was 87.7%, which was in accordance with previous studies reporting conversion rates ranging from 74% to 92%,[5,6,18-26] suggesting that adoption of the modified DOTS-Plus strategy might be a cost-effective strategy, particularly in high MDR-burden resource-limited setting like India. Reduction in culture examinations in the continuation phase can also help in diversion of available resources in further expansion of the existing program to cater to unmet populations.

Certain characteristics were responsible for poor treatment outcome in this study such as drug addiction, previous history of TB episodes >2, and resistance to KM as well as OFX, as reported in other studies.[18-27] Many studies with diversity in demographic profile, setting, and methodology have reported other characteristics such as alcoholism, diabetes, extensive cavitary lesions, and HIV seropositivity with poor outcome, although not observed in our study due to limited sample size and no HIV seropositivity in our cohort.

Overall, 119 AEs were reported in 46 (46.9%) patients. The most commonly grouped AEs were gastrointestinal followed by ototoxicity and arthralgia as reported similarly in other studies.[28-33] Major AEs were reported in 17.4% of patients, which is lower in comparison to other studies.[28-33] Among major AEs, the most common was deafness induced by KM and psychosis by CS. This lower incidence may be attributed to the adopted methodology for active surveillance and systematic periodic follow-up.

A major issue of concern still remains that 21/132 (15.9%) patients were excluded from our study as 8 (6.1%) were exposed to SLDs >1 month and 13 (9.8%) showed non-MDR resistance patterns. These subset of patients could lead to amplification of drug resistance in households and community if left untreated. There could also be a high probability of either suboptimal treatment outcome with standardized regimen or baseline resistance to SLDs at initiation of treatment responsible for failure detected during the course of treatment. Appropriate individualized regimens based on DST pattern would be preferred for treating these subset of patients. Several studies from urban sector reported remarkable treatment success rate with individualized regimens ranging from 48.4% to 68%.[15,22,23,25-27] A systematic review and meta-analysis reported that individualized regimens had better outcome (successful rate – 67.2%; unsuccessful rate – 30.8%) than standardized regimens (successful rate – 56.9%; unsuccessful rate – 43%) as prescribed under the DOTS-Plus programs.[15] However, treatment with individualized regimens remains challenging in resource-limited settings requiring support of quality-assured laboratory facilities and expertise in interpretation of results with prescription of appropriate regimens.

There is expanding evidence over the last decade regarding the management of MDR-TB patients under national PMDT program. Additional SLD's resistance even at baseline, created by irrational use of drugs especially in private sector, has significantly increased and has become a major issue.[17,25-27] Majority of TB patients seek consultation from private sector, but the quality of care remains suboptimal with undernotification of cases, wide variations in knowledge, poor adherence to guidelines, and misuse of SLDs leading to increase in drug resistance.[34-37] The introduction of genotypic diagnostic tests (GeneXpert, line probe assays) providing rapid diagnosis and individualized regimens fortified with newer drugs (bedaquiline and delamanid) has created revolution in the management of DR-TB patients. The recently released national PMDT guidelines focus on the active surveillance of disease and AE, re-classification of drugs, individualized regimens according to the most recent pattern of DST, patient-centric approach, universal DST, and engagement of private sector.[38]

Current national guidelines primarily rely on culture reports for treatment regimen optimization, i.e., shift from IP to continuation phase (CP) and decision to define the outcome of treatment. Monitoring with follow-up cultures entails time, travel, and work loss costs for the patient and because culture result by the conventional method is not available before a lag period of approximately 6–8 weeks, there is a delay in decision-making by health-care professionals.[5] It is observed that culture conversion which reflects the viability of tubercle bacilli is more sensitive and is considered necessary to monitor progress in MDR-TB patients. There was no significant difference between smear conversion rate and culture conversion rate at 4 months (69.2% vs. 67.1%; 95% CI:-11.3 − 15.4; $P = 0.76$), 6 months (88.9% vs. 83.3%; 95% CI:-4.7 − 15.9; $P = 0.28$), and 12 months (93.1% vs. 89.7%; 95% CI:-5.4 − 12.4; $P = 0.43$). The trend of diagnostic accuracy of smear examination with reference to culture as gold standard during the course of treatment is described in online Supplementary Table S4. This supports findings from a previous study showing the potential role

of the smear conversion rate as a surrogate of culture conversion, especially in resource-limited high-burden countries like India as early decision regarding transition from IP to CP can be made resulting in reduction in cost of drugs to health system as well as patients, duration of hospitalization, and AEs related to drugs.[39] However, findings of smear examination need to be interpreted cautiously as it has less sensitivity than culture and does not differentiate between live and dead bacilli or other species such as atypical mycobacterial species leading to false positives. Reducing follow-up cultures might delay the confirmation of bacteriological conversion and could delay the diagnosis of possible treatment failure before conversion.[40] Therefore, these findings need to be confirmed with more studies involving larger number of samples. Our study has adopted modified DOTS strategy and reported satisfactory treatment outcome of MDR-TB patients at that point of time when the national DOTS-Plus program was in expansion phase and genotypic tests were to be included for diagnosis. However, the study was hospital based involving small number of patients. Further community-based studies are required to validate these findings.

CONCLUSION

There is no doubt that the current PMDT program has expanded its services throughout the nation and is rigorously providing every effort to manage more and more DR-TB cases effectively by scaling up laboratory facilities with genotypic tests and appropriate regimens including newer drugs. Despite this effort, an enormous burden of DR-TB cases in high-burden countries like India, especially in private sector, still remains uncovered. This can be considered to be a great hurdle in achieving the ambitious goal of elimination of TB by 2025.[41] The modified DOTS-Plus strategy adopted in our study can support national programs in the reduction of burden of DR-TB cases in resource-limited settings, especially in private sector. It should be made flexible as well as less stringent according to local needs but should be kept aligned to the existing national PMDT guidelines. A systematic approach is required for curbing down the epidemic of DR-TB cases by implementing cost-effective and sustainable interventions in the near future.

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Conflicts of interest
There are no conflicts of interest.

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ONLINE SUPPLEMENTARY TABLES

Online Supplementary Table S1: Clinical characteristics of patients showing unfavorable outcome after treated with multidrug-resistant tuberculosis therapy

n	Sex	Age	Weight	DST pattern		Time in months		Comorbid illness/risk factor if any	Outcome
				Baseline	Additional resistance (months of treatment)	Culture conversion	Culture reversion		
1	Male	45	50	RIF, INH, PZA	Nil	4	18	Diabetes	Failure
2	Male	32	45	RIF, INH	KM (6)	No	No		Failure
3	Male	28	31	RIF, INH, EMB	KM (6) OFX (6)	No	No		Failure
4	Female	38	55	RIF, INH	Nil	6	18	Drug addiction	Failure
5	Male	51	38	STM, RIF, INH	KM (6)	No	No		Failure
6	Female	54	45	STM, RIF, INH, EMB, PZA	OFX (6)	4	24		Failure
7	Female	22	36	STM, RIF, INH, EMB	Nil	4	12	Drug addiction	Failure
8	Female	54	67	RIF, INH, PZA	KM (6) OFX (6)	4	6		Failure
9	Male	38	50	STM, RIF, INH, EMB, PZA	KM (12) OFX (12)	4	12		Failure
10	Female	57	39	RIF, INH	OFX (6)	No	No		Failure
11	Male	25	45	RIF, INH	Nil	4	24	Drug addiction	Default
12	Male	30	41	STM, RIF, INH, EMB, PZA	Nil	No	No		Default
13	Male	46	51	RIF, INH	Nil	6	18	Alcoholism	Default
14	Female	40	36	STM, RIF, INH	Nil	4	12	Drug addiction	Default
15	Male	20	44	RIF, INH, PZA	Nil	No	No	Alcoholism	Default
16	Female	23	55	RIF, INH, EMB	Nil	4	12	Alcoholism	Default
17	Female	35	42	STM, RIF, INH, PZA	Nil	No	No		Default
18	Female	21	40	STM, RIF, INH, EMB	Nil	4	No		Expiry
19	Female	26	46	STM, RIF, INH, EMB, PZA	Nil	4	12		Expiry
20	Female	20	32	RIF, INH, PZA	Nil	4	No		Expiry
21	Male	45	42	RIF, INH	Nil	No	No		Expiry
22	Male	52	35	RIF, INH, EMB	Nil	No	No	Alcoholism	Expiry
23	Male	61	40	RIF, INH	Nil	No	No		Expiry
24	Male	43	48	STM, RIF, INH, EMB, PZA	Nil	No	No		Expiry
25	Female	25	59	RIF, INH, PZA	Nil	6	No		Expiry
26	Female	39	44	STM, RIF, INH, EMB, PZA	Nil	No	No	Diabetes	Expiry
27	Female	45	38	STM, RIF, INH, EMB, PZA	Nil	No	No		Expiry

RIF: Rifampin, INH: Isoniazid, EMB: Ethambutol, PZA: Pyrazinamide, STM: Streptomycin, DST: Drug sensitivity testing, KM: Kanamycin

Online supplementary Table S2: Bacteriological response of the 98 patients treated with multidrug-resistant tuberculosis therapy over 2 years (expanded version)

Characteristics	Treatment duration (months) (%)														Nonconverter (%)
	1	2	3	4	5	6	7	8	9	12	15	18	21	24	
Lost to follow-up	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (1.1)	0 (0.0)	1 (1.1)	0 (0.0)	1 (1.1)	0 (0.0)	2 (2.1)	0 (0.0)	
Expired	2 (2.1)	1 (1.1)	2 (2.1)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	3 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	
Patient continuing on treatment	96 (97.9)	94 (95.9)	92 (93.8)	91 (92.9)	91 (92.9)	90 (91.8)	89 (90.8)	88 (89.8)	87 (88.8)	87 (88.8)	83 (84.7)	83 (84.7)	81 (82.6)	81 (82.6)	
Smear conversion rate															
Best scenario	1/96 (1.1)	2/94 (2.1)	28/92 (30.4)	63/91 (69.2)	75/91 (82.4)	80/90 (88.9)	79/89 (88.7)	80/88 (90.9)	79/87 (90.8)	81/87 (93.1)	78/83 (93.9)	77/83 (92.8)	75/81 (92.6)	75/81 (92.6)	6 (6.1)
Worst scenario	1/98 (1.1)	2/98 (2.2)	28/98 (28.6)	63/98 (64.3)	75/98 (76.5)	80/98 (81.6)	79/98 (80.6)	80/98 (81.6)	79/98 (80.6)	81/98 (82.7)	78/98 (79.6)	77/98 (78.6)	75/98 (76.5)	75/98 (76.5)	
Patient still smear positive	95 (96.9)	92 (93.8)	64 (65.3)	28 (28.6)	16 (16.3)	10 (10.2)	10 (10.2)	8 (8.2)	8 (8.2)	6 (6.1)	5 (5.1)	6 (6.1)	6 (.1)	6 (6.1)	
Culture conversion rate															
Best scenario	0/96 (0.0)	1/94 (1.1)	26/92 (28.3)	61/91 (67.1)	73/91 (80.2)	75/90 (83.3)	73/89 (82.1)	76/88 (86.4)	77/87 (88.5)	78/87 (89.7)	75/83 (90.4)	74/83 (89.2)	71/81 (87.7)	71/81 (87.7)	10 (10.2)
Worst scenario	0/98 (0.0)	1/98 (1.1)	26/98 (26.5)	61/98 (62.3)	73/98 (74.5)	75/98 (76.5)	73/98 (74.5)	76/98 (77.6)	77/98 (78.6)	78/98 (79.6)	75/98 (76.5)	74/98 (75.5)	71/98 (72.4)	71/98 (72.4)	
Patient still culture positive	96 (97.9)	93 (94.8)	66 (67.3)	30 (30.6)	18 (18.4)	15 (15.3)	16 (16.3)	12 (12.3)	10 (10.2)	9 (9.2)	8 (8.2)	9 (9.2)	10 (10.2)	10 (10.2)	

The analysis performed by the subcommittee has been combined in addition to that of modified DOTS-Plus strategy. DOTS: Directly Observed Treatment Short-Course

Online Supplementary Table S3: Characteristics of important studies from India showing bacteriological response and outcome of multidrug-resistant tuberculosis

Author (study year)	Location	Study period	Total number of enrolled MDR-TB cases	Type of regimen used	HIV positive (%)	Culture sensitivity pattern	Bacteriological response (culture±smear conversion)	Outcome of treatment for MDR-TB
Subhash *et al*., 2003[1]	Vellore, Tamil Nadu	1997-1999	100	Individualized	2/28 (7) (tested for HIV - 28)	RIF+INH - 100% EMB - 66% STM - 69% CS - 11% ETO - 17% CFX - 22%	Smear available - 49/55 (89.1%) Smear conversion - 26/49 (53.1%) Culture available - 26/55 (47.3%) Culture conversion - 16/26 (61.5%)	Responders - 26/55 (47.3%) Failure - 23/55 (41.8%) Defaulted - 45/100 (45%)
Prasad *et al*., 2006[2]	Lucknow, Uttar Pradesh	February 1998-October 2002	46	Individualized		RIF+INH - 8 RIF+INH+1 drug - 21 RIF+INH+2 drugs - 17	Smear and culture Conversion - 29/39 (74.3%) Mean - 4.4 months	Cured - 29 (74.3%) Died - 2 (5.1%) Defaulted - 6 (20.6%) Failure - 2 (5.1%) Among cured ones Relapse - 2/29 (6.9%) Defaulted - 4/29 (13.8%) Remained smear -ve - 23/29 (79.3%)
Arora *et al*., 2007[3]	New Delhi	January 2002-March 2005	66	Standardized		RIF+INH only - 23 (34.8%) RIF+INH+1 drug - 23 (34.8%) RIF+INH+two drugs - 17 (25.8%) RIF+INH+three drugs - 3 (4.5%)	53 (80.9%) culture conversion within 9 months Among 53 patients 3 months - 77.4% 6 months - 92.5%	Estimated for 52 patients Cured - 36 (69.2%) Defaulted - 6 (11.5%) Died - 6 (11.5%) Treatment failure - 4 (7.7%)
Dhingra *et al*., 2008[4]	New Delhi	August 2002-December 2004	27	Individualized	2	RIF+INH - 8 RIF+INH+1 drug - 9 RIF+INH+2 drugs - 5 RIF+INH + ≥ 3 drugs - 5	Mean smear conversion - 2.3 months Mean culture conversion - 4.4 months	Cured - 13 (48.1%) Defaulted - 10 (37.1%) Died - 1 (3.7%) Still on treatment - 1 (3.7%) Referred for surgery - 2 (7.4%)
Thomas *et al*., 2007[5]	Chennai, Tamil Nadu	May 1999-December 2003	66	Individualized		RIF+INH - 12 (18%) RIF+INH+1 drug - 26 RIF+INH+2 drugs - 20 RIF+INH+3 drugs - 6 RIF+INH + > 3 drugs - 2 XDR-TB - 1	Smear conversion at 3 months - 23/25 (92%) Culture conversion 3 months - 16/25 (64%)	Cured - 25 (37.8%) Failure - 17 (25.7%) Defaulted - 16 (24.3%) Died - 8 (12.2%)
Singla *et al*., 2009[6]	New Delhi	January 2002-December 2006	126	Standardized		RIF+INH only - 50 (40%) RIF+INH+1 drug - 41 (33%) RIF+INH+2 drugs - 25 (20%) RIF+INH+3 drugs - 10 (8%)	100 (79%) culture conversion within 8 months 3 months - 82% 6 months - 98%	Cured - 76 (61%) Defaulted - 22 (17%) Died - 24 (19%) Treatment failure - 4 (3%)
Jana *et al*., 2009[7]	West Bengal	January 2003 -January 2008	31	Individualized				Cured - 64.5% Relapse - 12.9% Failure - 19.4%

Contd...

Online Supplementary Table S3: Contd...

Author (study year)	Location	Study period	Total number of enrolled MDR-TB cases	Type of regimen used	HIV positive (%)	Culture sensitivity pattern	Bacteriological response (culture±smear conversion)	Outcome of treatment for MDR-TB
Datta *et al*., 2009[8]	Srinagar, Jammu and Kashmir	March 2003-February 2007	52	Individualized		RIF+INH only - 7 (13.4%) RIF+INH+1 drug - 16 (30.8%) RIF+INH+2 drugs - 16 (30.8%) RIF+INH+3 drugs - 5 (9.6%) RIF+INH + > 3 drugs - 8 (15.4%)	Smear conversion 3 months - 30 (57.7%) 6 months - 44 (84.6%) Culture conversion 3 months - 23 (44.1%) 6 months - 44 (84.6%)	Cured - 37 (77.1%) Died - 11 (21.1%) Defaulted - 4 (7.6%) Failure - 8 (15.3%) (All XDR-TB)
Joseph *et al*., 2011[9]	Tamil Nadu	Jane 2006-September 2007	38	Standardized		RIF+INH only - 3 RIF+INH+1 drug - 15 RIF+INH+2 drugs - 15 RIF+INH+3 drugs - 4 RIF+INH+4 drugs - 1 OFX - 5 KM - 1 ETO - 12	Smear 3 months - 33 (87%) 6 months - 33 (87%) Culture 3 months - 32 (84%) 6 months - 33 (87%) Culture conversion - 82% in 2 months or less	Cured - 25 (65.8%) Defaulted - 5 (13.2%) Died - 3 (7.9%) Treatment failure - 5 (13.2%) XDR-TB among treatment failures- 2/5 (40%)
Isaakidis *et al*., 2011[10]	Mumbai, Maharashtra	May 2007-May 2011	58	Individualized or Standardized	100	MDR-TB suspect - 13 Pure MDR (RIF+INH) - 2 RIF+INH+other FLD - 15 RIF+INH+SLD - 26 XDR-TB - 2	Baseline smear positive - 25 Smear conversion at 4 months - 13/25 (52%) Baseline culture positive - 44 Culture conversion at 4 months - 23/44 (52%)	Cured - 8 (14%) Completed treatment - 5 (9%) Died - 13 (22%) Defaulted - 7 (22%) Failure - 2 (3%) Still on treatment - 23 (40%)
Nagaraja *et al*., 2012[11]	Bengaluru, Karnataka	January 2005-December 2008	224	Individualized	5	STM+RIF+INH+EMB - 146 (65.2%) STM+RIF+INH - 39 (17.4%) RIF+INH+EMB - 19 (8.5%) RIF+INH - 20 (8.9%)	SRHE - 40.3 SRH - 48.2 RHE - 51.3 RH - 55	Cured - 145 (64.7%) Treatment failure - 5 (2.2%) Died - 10 (4.4%) Defaulted - 64 (28.5%)
Kapadia and Tripathi, 2013[12]	Ahmedabad, Gujarat	August 2007-June 2012	63	Standardized	2 (3.2)	STM+RIF+INH+EMB- 12 (57%) STM+RIF+INH - 4 (19.1%) RIF+INH+EMB - 2 (3.2%) RIF+INH - 3 (14.3%) Line probe assay RIF+INH - 37 (90.3%) RIF only - 5 (9.7%)	Smear conversion at 3 months - 32/48 (66.7%) Mean smear conversion - 4.2±2.1 months Culture conversion at 3 months - 27/48 (57.3%) Mean culture conversion - 4.3±2.4 months	Treatment completed - 23 Cured - 9/23 (39.2%) Still on treatment - 28 Failure - 3 OFX- 2/XDR-TB - 1 Defaulted - 10 Died - 13
Dholakia and Shah, 2013[13]	Mumbai, Maharashtra	August 2006-November 2010	29	Individualized	3	Mono-resistant - 3 (11%) MDR-TB with EMB/PZA/EMB, PZA - 20 (69%) Pure MDR-TB - 4 XDR-TB - 1 Resistance to at least one SLD - 13 (44.8%)	Average - 7.8 (3-11) months	Cured - 14 (51%) Died - 5 (18%) Failure - 2 (7%) Defaulted - 5 (18%) Migrated - 1 Still on treatment - 2
Isaakidis *et al*., 2013[14]	Mumbai, Maharashtra	July 2007-January 2013	11	Individualized + standardized	100	RIF+INH - 100% EMB - 7/9 (78%) FQ - 6/8 (75%) Injectable - 1/8 (13%)		Cured - 1 Still on treatment - 3 Died - 4 (36.5%) Defaulted - 3 (27%)

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Online Supplementary Table S3: Contd...

Author (study year)	Location	Study period	Total number of enrolled MDR-TB cases	Type of regimen used	HIV positive (%)	Culture sensitivity pattern	Bacteriological response (culture±smear conversion)	Outcome of treatment for MDR-TB
Jain *et al*., 2014[15]	Ahmedabad, Gujarat	January 2009-December 2009	130	Standardized		STM, RIF, INH, EMB - 61 (47%) STM, RIF, INH/RIF, INH, EMB - 14 (10%) STM, RIF/RIF, INH - 49 (38%), RIF - 6 (5%)	89 (68%) within 9 months 3 months - 73 (82%) 6 months - 84 (94%)	Cured - 51 (39%) Treatment completed - 7 (5%) Failure - 17 (13%) Defaulted - 30 (23%) Died - 25 (19%)
Udwadia and Moharil, 2014[16]	Mumbai, Maharashtra	May 2006-May 2010	78	Individualized		RIF, INH - 100% STM - 74.4% EMB - 51.3% PZA - 15.4% OFX - 43.6% PAS - 24.4% KM - 17.9% ETO - 32.1%		Cured - 53 (68%) Failure - 12 (15%) Defaulted - 13 (16%)
Kapadia and Tripathi, 2014[17]	Ahmedabad, Gujarat	August 2007-March 2010	66	Standardized	1 (1.5)	STM, RIF, INH, EMB - 31 (63.3%) STM, RIF, INH- 9 (18.4%) RIF, INH, EMB- 2 (4.3%) RIF, INH - 7 (14.3%) Line Probe Assay RIF, INH- 13 (76.5%) RIF only - 4 (23.5%)	Mean smear conversion - 4.2 2.2 months mean culture conversion - 4.3±2.5 months	Cured - 25 (37.87%) Failure - 4 (6.1%) OFX - 2/XDR-TB - 2 Defaulted - 17 (25.75%) Died - 17 (25.75%) Treatment completed - 3 (4.54%)
Yadav *et al*., 2016[18]	Jaipur, Rajasthan	2012	115	Standardized		RIF, INH - 86 (74.8%) RIF alone - 29 (25.2%)	3 months - 68 (59.1%) 6 months- 68.4%	Cure - 63.5% Failure - 9.6% Defaulted - 15.7% Died - 11.3%
Patel *et al*., 2016[19]	Vadodara, Gujarat (Western India)	March 2010-January 2013	145	Standardized	2	STM, RIF, INH, EMB - 87 (60%) STM, RIF, INH - 29 (20%) RIF, INH - 18 (12.4%) STM, RIF - 2 RIF, INH, EMB - 6 (4.1%) RIF, EMB - 1 RIF - 1		Cured- 48 (33.1%) Treatment completed - 8 (5.5%) Treatment failure - 9 (6.2%) Died - 43 (29.7%) Defaulted - 32 (21.1%) Transferred - 3 (2.1%) Switched to CAT V - 1 Still on treatment (30 months) - 4 (2.8%) Compliancy to treatment- 81 (55.9%)
Nair *et al*., 2016[20]	Tamil Nadu	Conventional DST September 2010-September 2011 Rapid diagnostic September 2012-September 2013	Conventional DST - 135 Rapid diagnostic- 389	Standardized	Only among rapid diagnostic group - 18 (5)	Conventional DST RIF, INH - 127 (94%) RIF only - 7 (5%) Rapid diagnostic RIF, INH - 216 (56%) RIF only - 169 (43%)	Conventional DST 6 months - 69 (51%) Rapid diagnostic 6 months - 208 (54%)	Conventional DST Cured - 31 (23%) Treatment completed - 9 (7%) Died - 24 (18%) Failure - 5 (4%)

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Online Supplementary Table S3: Contd...

Author (study year)	Location	Study period	Total number of enrolled MDR-TB cases	Type of regimen used	HIV positive (%)	Culture sensitivity pattern	Bacteriological response (culture±smear conversion)	Outcome of treatment for MDR-TB
								Loss to follow-up - 45 (33%) Transfer out - 2 (2%) Switched to XDR-TB treatment - 0 (0.0%) Stopped due to reasons other than ADR - 0 (0.0%) Missing data - 19 (13%) Rapid diagnostic Cured - 110 (28%) Treatment completed - 50 (13%) Died - 75 (20%) Failure - 1 (0.3%) Loss to follow-up - 120 (31%) Transfer out - 13 (3%) Switched to XDR-TB treatment - 7 (2%) Stopped due to reasons other than ADR - 1 (0.3%) Missing data - 12 (3%)
Neeta *et al*., 2016[21]	Bellary, Karnataka	December 2012-April 2013	43	Standardized		RIF, INH- 33 (76.7%) RIF- 10 (23.3%)	6 months - 20 (45.5%) 12 months - 34.9%	Cured- 9 (44.2%) Defaulted - 12 Died - 9 Failure - 1 XDR-TB evaluation - 2
Dole *et al*., 2017[22]	Solapur (Western Maharashtra)	September t 2012-December 2014	146	Standardized	6		130 (89%) within 3 months	Cured - 39 (27%) Treatment completed - 45 (31%) Died - 20 (14%) Defaulted - 28 (19%) Failure (Switch to CAT-V) - 14 (9%)
Suryawanshi *et al*., 2017[23]	Maharashtra	January 2011-December 2012	4024	Standardized	138 (3.4)			Cured - 828 (20.6%) Treatment completed - 340 (8.4%) Died - 857 (21.3%) Lost to follow-up - 768 (19.1%) Failure - 98 (2.4%) Switched to CAT V treatment for XDR-TB - 190 (4.7%) Still on treatment - 239 (5.9%)

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Online Supplementary Table S3: Contd...

Author (study year)	Location	Study period	Total number of enrolled MDR-TB cases	Type of regimen used	HIV positive (%)	Culture sensitivity pattern	Bacteriological response (culture±smear conversion)	Outcome of treatment for MDR-TB
Janmeja *et al.*, 2017[24]	Chandigarh, Punjab	January 2012-December 2014	140	Standardized	4 (2.7)		3 months - 98 (70%) 6 months - 112 (81.4%)	Cure - 77 (55%) Treatment completed - 11 (7.8%) Died - 23 (16.4%) Defaulted - 13 (9.2%) Failure - 5 (3.5%) Switched to CAT V (XDR-TB) - 11 (7.8%)
Waghmare *et al.*, 2017[25]	Mumbai, Maharashtra	August 2012 - December 2013	194	Standardized Individualized in cases of Pre-XDR and XDR-TB	8.8	MDR-TB - 59 (30.4%) MDR TB with additional FQ resistance (pre-XDR [FQ]) - 124 (64%) MDR TB with additional AM resistance (preXDR [AM]) - 11 (5.6%) XDR TB - 10 (5.1%)	Available for 133/194 3 months - 92 (69%) 6-11 months- 125 (93.9%)	Cured - 68 Treatment completed - 26 Failure - 22 (11.3%) Died - 39 (20.15%) Defaulted - 23 (11.8%) Treatment completed with outcomes unknown - 26 (13.4%) Transferred out - 13 (6.7%) Treatment stopped due to ADRs - 3 (1.5%)
Parmar *et al.*, 2018[26]	7 states of India	August 2007-March 2011	3712	Standardized	58 (1.6)	RIF only - 187 (5.0%) RIF, INH only - 1058 (28.5%) RIF, INH combination - 2407 (64.8%) RIF combination - 50 (1.4%) Gujarat sub-group OFX resistance - 62 (59.6%) KM resistance - 8 (7.7%) ETO resistance- 28 (26.9%) XDR-TB - 6 (5.8%)	2735 (73.6%) Median time- 100 days	Outcome defined for 2264/3712 (60.9%) Cured - 781/2264 (34.5%) Died - 644/2264 (28.4%) Lost to follow up - 670/2264 (29.6%) Treatment failure or changed to XDR-TB treatment - 169/2264 (7.5%) Still on treatment - 1448/3712 (39%)
Gupta and Jorwal, 2018[27]	New Delhi	2009-2013	819	Standardized	18 (2.2)	RIF and INH- 100% EMB - 167 (58%) STM - 222 (76.8%) OFX - 45 (78.9%) KM - 9 (69.2%)		Cured - 415 (52%) Treatment completed - 23 (3%) Default - 199 (24%) Died - 130 (16%) Switched to CAT V - 27 (3%) Transferred out - 12 (1%) Treatment failure - 13 (1%)

MDR-TB: Multidrug-resistant tuberculosis, RIF: Rifampin, INH: Isoniazid, EMB: Ethambutol, PZA: Pyrazinamide, STM: Streptomycin, CS: Cycloserine, ETO: Ethionamide, OFX: Ofloxacin, XDR: Extensively drug-resistant, CAT V: Category V, DST: Drug sensitivity testing, ADR: Adverse drug reaction, FQ: Fluoroquinolone, AM: Amikacin, KM: Kanamycin

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Online Supplementary Table S4: Diagnostic accuracy of smear with culture as reference during the course of multidrug-resistant tuberculosis treatment

Duration of treatment (months)	Smear + Culture +	Smear + Culture −	Smear − Culture +	Smear − Culture −	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
0	98	0	0	0	98	0	98	0
4	15	13	15	48	50.0	78.7	53.6	76.2
6	10	0	5	75	66.7	100	100	93.8
12	6	0	4	77	60	100	100	95.1
18	7	0	2	75	77.8	100	100	97.4
24	7	0	0	75	100	100	100	100

Six patients were smear +/culture+at 12 months of treatment. The PPV of smear was high at start as most smear+are culture +, but with treatment, it decreased as chance of dead bacilli increased and smear+could be culture −. However, at 6 months, PPV again approached 100%, leading to satisfactory corroboration between sputum and culture positivity as majority of the dead bacilli were excreted. The NPV of smear was high after 4 months of treatment as smear−reflects culture in most situations. The NPV approached to 93% or more from 6 months onwards. The specificity of smear test gradually increased during treatment and from 6 months onward the specificity was 100%, indicating that after the 6th month, the probability of false positivity with smear would be less. The sensitivity of smear was variable with higher values at the beginning and near the end of treatment with variability in between, indicating that the false negatives were low during this period. PPV: Positive predictive value, NPV: Negative predictive value