

Update on Management of DR TB

Definitions



Presumptive MDR-TB

 A patient suspected of drug-resistant TB, based on RNTCP criteria for submission of specimens for drug-susceptibility testing

MDR-TB Case

- A TB patient:
 - whose sputum is culture positive for *Mycobacterium tuberculosis* and
 - is resistant *in-vitro* to isoniazid and rifampicin with or without other anti-TB drugs
 - based on DST results from an RNTCP-certified C & DST Laboratory

Definitions



XDR-TB Case

- **A MDR-TB patient** whose recovered *M. tuberculosis* isolate is resistant to
 - at least isoniazid, rifampicin,
 - a fluoroquinolone (ofloxacin, levofloxacin, or moxifloxacin) and
 - a second-line injectable anti-TB drug (kanamycin, amikacin, or capreomycin)
- at a RNTCP-certified Culture & DST Laboratory.

Case finding strategy



- MDR-TB suspect should be identified based on predecided suspect criteria, which are:
 - All failures of New TB cases
 - Previously treated (PT) Smear +ve cases who remain S+ve at 4th month onwards
 - All Pulmonary TB cases who are contacts of known MDR TB case.
 - All Smear +ve Previously treated Pulmonary TB cases at diagnosis
 - Any Smear +ve follow up in New or PT cases
 - Any Smear -ve Previously treated Pulmonary TB cases at diagnosis
 - HIV infected presumptive TB cases, HIV co-infected TB cases

Diagnostic Technology



The different diagnostic technologies are:

- 1. Solid C-DST (LJ)
 - DST is performed for streptomycin (S), isoniazid (H), rifampicin (R) and ethambutol (E) only
- 2. Liquid C-DST (MGIT)
- 3. Line Probe Assay (LPA)
 - DST is performed for Isoniazid (H) and Rifampicin (R) only
- 4. Rapid molecular automated nucleic acid amplification test (NAAT) (Gene-Xpert)
 - > DST is performed for Rifampicin (R) only

Sputum Collection and Transport

For diagnosis : Two sputa samples collected, ideally,

- an early morning sample
- Supervised spot sample

For follow up : Only one sample collected (preferably morning)

- Sputa collected in Falcon tubes
- Samples can be collected and transported in cold chain as soon as possible (maximum within 72 hours to the lab)

SIHEN

- Consists of recently discharged material from bronchial tree
- Volume of 3-5 ml of mucoid or muco-purulent material

In special situation:

- Collecting 2 spot specimens with a gap of at least one hour (60 minutes)
 - if the patient is coming from a long distance or
 - there is a likelihood that the patient may default to give a second specimen

Referral of a confirmed MDR-TB case to indoor facility at the DR-TB Centre

- Once confirmed, the MDR-TB patients and those with <u>any Rifampicin resistance</u> are referred to the RNTCP designated DR-TB Centre:
 - with their DST result (Annexure I)
 - Request for Category IV treatment form (Annexure V)
- MDR-TB patients referred to the RNTCP designated DR-TB Centre for:
 - Pre-treatment evaluation, and
 - Initiation of Regimen for MDR TB

Pre-Treatment Evaluation



The following investigations/assessments are done at DR-TB Centre before initiation of Treatment for MDR patients

- 1. Detailed history (including screening for mental illness, drug/alcohol abuse etc.)
- 2. Weight
- 3. Height
- 4. Complete Blood Count
- 5. Blood sugar to screen for Diabetes Mellitus
- 6. Liver Function Tests
- 7. Blood Urea and S. Creatinine to assess the Kidney function
- 8. TSH levels to assess the thyroid function
- 9. Urine examination Routine and Microscopic
- 10. Pregnancy test (for all women in the child bearing age group)
- 11. Chest X-Ray
- 12. HIV counseling and testing
- 13. Counseling to patient, family members, Females on family planning



For XDR-TB Patients, Pre-treatment evaluation will be done as for MDR-TB as well as:

- an ECG,
- Serum electrolytes, and
- Surgical evaluation

At the DR-TB Centre in-door facilit

- DR-TB Centre committee will consider all the clinical and biochemical results before starting the patient on an RNTCP Regimen for MDR-TB.
- The patient will then be counselled and their treatment card opened.
- If clinically appropriate the patient may be discharged 7 days after the treatment is initiated, or later if appropriate.



RNTCP Category IV Regimen

IP: It consists of 6 **CP: It consists of 4** drugs in Intensive drugs in Phase for 6-9 **Continuation Phase** for 18 months months Levofloxacin, Ethionamide, Kanamycin, **Ethambutol** Levofloxacin, Cycloserine The treatment is Ethionamide, given in 2 phases **Pvrazinamide Éthambutol** MDR-TB for **Cycloserine** patients **[Reserve/Substitute** drugs: PAS, Mfx, Cm1



RNTCP Category V Regimen



Dosage and Weight Band Recommendations



- **Drug-dosages for Treatment are provided as** per weight band
- MDR patient : There are 5 weight bands drugdosages recommended for providing treatment:
 - Less than 16Kg
 - \wedge 16-25 Kg
 - 26-45 kg
 - 46-70 Kg
 - \triangleright More than 70 Kg
 - XDR patient : only 2 weight bands
 - less than 45
 - more than 45 kg \triangleright



Regimen for Cat IV

For Regimen of MDR TB

S.No	Drugs	16-25 Kg	26-45 Kg	46-70 Kg	>70kg
1	Kanamycin(500&1G) (IP)	500 mg	500 mg	750 mg	1G
2	Levofloxacin (250 & 500mg) (IP/CP)	250 mg	750 mg	1000 mg	1000mg
<u>3</u>	Ethionamide (250mg) (IP/CP)	375 mg	500 mg	750 mg	1000mg
4	Ethambutol (200 & 800mg) (IP/CP)	400 mg	800 mg	1200mg	1600mg
<u>5</u>	Pyrazinamide (500 & 750mg) (IP)	500 mg	1250 mg	1500 mg	2000mg
<u>6</u>	Cycloserine (250mg) (IP/CP)	250 mg	500 mg	750 mg	1000mg
<u>7</u>	PAS (80% Bioavailability)	5 gm	10 gm	12 gm	12gm
8	Pyridoxine (100mg) (IP/CP)	50 mg	100mg	100mg	100mg

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 $^{^2}$ In case of PAS with 60% weight/volume the dose will be increased to 7 gm (16-25 Kg); 14 gm (26-45 Kg) and 16 gm (> 45 Kg)



Regimen for Cat V

For Regimen of XDR TB

S.No	Drugs	< 45kg	>45kg		
1	Capreomycin (750&1G) (IP)	750 mg	1G		
2	Moxifloxacin (400mg) (IP/CP)	200 mg	400mg		
<u>3</u>	Isoniazid (300mg) (IP/CP)	600mg	900mg		
<u>4</u>	Clofazimine (200 mg) (IP/CP)	200 mg	200mg		
<u>5</u>	Linezolid (600mg) (IP/CP)	600 mg	600mg		
6	Amoxyclav (875/125mg) (IP/CP)	875/125 mg (BD)	875/125 mg (BD		
<u>7</u>	PAS (80% Bioavailability)	10 gm	12gm		
<u>8</u>	Pyridoxine (100mg) (IP/CP)	100 mg	100mg		
Reser	ve/Substitute Drug				
1	Clarithromycin (500mg)	500mg (BD)	500mg (BD)		
2	Thiacetazone (150mg)	150mg	150mg		

Treatment strategy



- If a patient Gains or Loses 5 kgs or more in weight during treatment and crosses the weight-band range
 - the DOTS–Plus site committee may consider moving the patient to the higher weight-band drug dosages
- The new higher/lower dosages are provided whenever the patient is due for the next supply of drugs in the normal course of treatment and not as soon as change of weight is noted
- Separate Dosages of 2nd line drugs for MDR TB cases in paediatric age group weighing < 16 Kg
- Additional dosages of some 2nd line drugs for MDR TB cases in patients weighing > 70 kg

Transfer of MDR TB patients

Patient migrating to any other district <u>NOT</u> being served by the same DR-TB Centre:

- Patient may be formally transferred out:
 - with 7 days of drugs for transit period where he/she proposes to move
 - in consultation with the DTO of that district, and
 - under intimation of the DR-TB Centre.
- Patient at the DR-TB Centre catering to the receiving district:
 - Registered with a new PMDT TB number
 - Old PMDT TB number mentioned in the remarks column for future reference.
 - The patient will be continued on the same treatment on the new PMDT TB numbe
- Following records of patient from the DR-TB Centre will be sent to the district and the DR-TB Centre receiving the patient by the DTO who initiated the transfer out process:
 - the referral for treatment form
 - the copies of the PMDT treatment cards
 - a transfer note
 - a copy of the clinical information booklet
- The details of the patient will be updated in the PMDT treatment register at the DR-TB Centre for future reference
- Receiving DTO / DR-TB Centre to send a feedback to former district / DR-TB centre

Treatment Duration for Regimen fo

- Total duration of treatment: 24 27 months
- Duration of IP: 6 9 months
- Duration of IP: 18 months
- <u>IP to CP</u>:
 - Review patients after 6 months of treatment
 - treatment changed to CP if the 4th or 5th month culture result in solid or liquid culture is negative respectively

Treatment Procedure



- All drugs given in a single daily dosage under directly observed treatment (DOT)
- All patients receive drugs under direct observation on 6 days of the week
- On the 7th day (Sunday) the oral drugs will be administered unsupervised whereas injection kanamycin will be omitted
 - If intolerance occurs to the drugs, Ethionamide, Cycloserine and PAS may be split into two dosages
 - □ morning dose administered under DOT
 - evening dose will be self-administered

Monitoring Process during Treatmen

It is to be done by MO:

Clinical Evaluation:

- At monthly interval during IP
- At 3 monthly interval during CP (until the end of treatment)
- assess clinical, microbiologic, and radiologic response to treatment

Screening of patients

- For clinical improvement
- For adverse reactions
- Body weight monitoring at every visit

Follow-Up Investigations during Treatment



Chest radiograph:

- during pre-treatment evaluation
- At the end of IP
- At the end of treatment
- When clinically indicated

Serum Creatinine

- every month for the first 3 months
- every 3 months thereafter till patient is receiving inj Kanamycin
- Liver / Thyroid function tests
 - as & when indicated clinically

Follow up schedule

	mc	onthly exami	IP follow nation	/ up Is	Extension of IP (1-3 months)				ex	CP Quarterly follow up xamination in months					
	1 st FU	2 nd FU	3 rd FU	4 th FU				q	l tr	ll qtr	lli qtr	IV qtr	V qtr	VI qtr	
No IP extension	 3	4	5	6	-	-	-	7	9	12	15	18	21	24	
IP extension 1 month	 3	4	5	6	7	-	-	8	10	13	16	19	22	25	
IP extension 2 months	 3	4	5	6	7	8	-	9	11	14	17	20	23	26	
IP extension 3 months	 3	4	5	6	7	8	9	10	12	15	18	21	24	27	

• 1 sputum sample collected and examined by smear and culture at least 30 days apart from the 3rd to 7th month of treatment and at 3-monthly intervals from the 9th month onwards till the completion of treatment

•Wherever available, follow-up sputum culture should be done using liquid culture for *all IP follow-up cultures* and for the last 6 months of CP

1 specimen for culture will be collected and transported in Falcon tubes in cold chain

How to identify presumptive XDR TB

- DRTB case on cat IV termed as 'presumptive XDR case' when
 - No culture conversion at 6th month i.e. pt. continues to be culture +ve
 - Culture reversion (culture negative pt. becomes culture +ve)
 - Failure of Cat IV



RNTCP Category V Regimen

- The treatment is given in 2 phases for XDR-TB Patients
- It consists of <u>7</u> drugs in Intensive Phase for 6-12 months
 - ✤ Capreomycin, Moxifloxacin, Clofazimine, High dose INH, Linezolid PAS Amoxyclav
- It consists of <u>6</u> drugs in Continuation Phase for 18 months
 - PAS,
 Clofazimine,
 Linezolid

Moxifloxacin, High dose INH, Amoxyclav

[Reserve/Substitute drugs: Clarithromycin, Thiacetazone]



Regimen for XDR TB dosage and weight band recommendations

Drnes	Dos	age/day			
2.42	≤45 Kgs	> 45 Kgs			
Inj. Capreomycin (Cm)	750 mg	1000 mg			
PAS	10 gm.	12 gm			
Mosiflosacin (Mfx)	400 mg	400 mg			
High dose INH (High dose-H)	600 mg	900 mg			
Clofazimine (Cfz)	200 mg	200 mg			
Linezolid (Lzd)	600 mg	600 mg			
Amosyclav(Ams/Clv)	875/125 mg BD	875/125 mg BD			
Pyridoxine	100 mg	100 mg			
Reserve/Substitute drugs					
Clarithromycin (Clr)	500 mg BD	500 mg BD			
Thiacetazone (Thz)*	150 mg	150 mg			

Depending on availability, not to be given to HIV positive cases

Reserve/Substitute drugs: {Clarithromycin, Thiacetazone}



The reserve/substitute drugs would be used in the following conditions:

- In case the patient was on PAS, PAS will be replaced with one of the reserve drugs in the regimen for XDR TB
- If the patient is unable to tolerate one or more of the drugs
- If the patient is found to be resistant to Capreomycin



The Regimen for XDR TB would be of 24-30 months duration, with 6-12 months Intensive Phase (IP) and 18 months Continuation Phase (CP).

The change from IP to CP will be done only after achievement of culture conversion i.e. 2 consecutive negative cultures taken at 48 least one month apart.

In case of delay in culture conversion, the IP can be extended from 6 months up to a maximum of 12 months.

In case of extension, the DR-TR Centre Committee, which will be responsible for initiating and monitoring the Regimen for XDR TB, can decide on administering Capreomycin injection intermittently (3 times/week) for the months 7 to 12.



No difference to follow-up Sputum Culture for patients on regimen for MDR TB and XDR TB

XDR TB : Differences in Management

- Admission preferably for one month in DR TB ward (at least for a week)
- In addition to routine PTE
 - Serum Electrolytes
 - ECG &
 - Surgical consultation is to be taken

Follow up of the patient



Direct observation of treatment remains even more crucial, as this is the last chance at successful treatment that these patients will have. Because of the use of drugs with different toxicity profiles, XDR TB requires more intensive monitoring during followup.

Complete Blood Count with Platelets Count:

• weekly in first month, then monthly to rule out bone marrow suppression and anaemia as a side effect of Linezolid

Kidney Function Test-

 monthly creatinine and addition of monthly serum electrolytes to the monthly creatinine during the period that Inj Capreomycin is being administered

Liver Function Tests: monthly in IP and 3 monthly during CP

CxR every 6 months

Management of treatment interruptions and default for M/XDR TB patients who return within 6 months

Figure 7.2: Algorithm for management of M/XDR patients who default and return for treatment within 6 months of discontinuing Regimen for M/XDR TB



Management of treatment interruptions and default for M/XDR TB patients who return after 6 months

Figure 7.3: Algorithm for management of M/XDR patients who default and return for treatment after 6 months



Silfw

Treatment outcome - definition

- 1. Cure
- 2. Treatment completed
- 3. Died
- 4. Treatment failure
- 5. Treatment default
- 6. Transfer out
- 7. Treatment stopped due to adverse drug reactions
- 8. Treatment stopped due to other reasons
- 9. Switched to Category V treatment
- **10. Still on treatment:**

Adverse effects of 2nd line Anti-TB drugs



- Gastrointestinal disturbances
 - Diarrhoea, Nausea, vomiting, and abdominal pain
- CNS Disorders-
 - Seizures / Fits
- Difficulty in breathing
- Anxiety, Hallucinations, depression, altered behaviour and suicidal tendencies
- Visual disturbance Blurring of vision, pain in the eyes, disturbance in colour vision
- Ototoxicity- Ringing in the ears , problems with hearing, Dizziness
- Numbness, Tingling, Pain in hands and feet
- Unusual bruising or bleeding
- Joint pains
- Jaundice (yellow eyes or skin, Dark coloured urine)
- Skin rashes with or without itching
- Nephrotoxicity Puffiness of face, swelling on the feet, decreased urine output

Information system and data management



- Electronic HMIS being established
- Records and Reports
 - PMDT TB Register, Culture & DST Register, Identity Card and Treatment Card
 - Quarterly reports on Case Finding, Culture Conversion and Treatment Outcome
 - Six Monthly and twelve monthly Interim report on outcome
 - Drug and lab consumables
- All patients initiated on treatment will be accounted for outcomes
- Project monitoring and evaluation
 - Supervision and regular monitoring of activities

RI	NTCP Request	for Culture and D	rug Sensiti	vity Te	esting	(<u>A</u>	nnexu	<u>re-l</u>)	Refe	erral No):	/ Date	:
Nikshay ID/	J_ J_J	IRL ID-		_//_			PI	NDT ID)		./_/_		
Pa	atient Information	n				Mole	cular T	B/DS	T Resul	ts			
Patient Name Patient Address with landmark			Test Test validi	ty	Lin	e Probe / id	Assay(l	.PA)	Inva	CBN/	AAT	·	
Patient Mobile No. or other Contact No	Sex : Male	/ Female	M. Tuberc	ulosis		tected				-detec	ted		
Sputum-Date of collection	Sample 1:		Rifampicir Isoniazid	1	Re Re	sistant sistant			Sen	sitive sitive		Not Not	Available Available
Name of referring fac Tuberculosis Unit (TU District:	ility (PHI/DMC/DI	R-TB Center/other):	Notes: Date tested	l:		Reporte	ed by (N	lame 8	Signatu	ıre):			
HIV Status: (Iveg / Pos	7 Not Kilowilj					11/1	iauid C	ulture	results				
DIAGNOSI	eason for Testing S	FOLLOW-UP	Date received	Speci men	Speci men	Smear result	Neg	Pos	Culture	Result	t * (che	eck one) + Conta	minated/
MDR Suspect Criteria		PMDT Registration Number:		A	No.				col			other	results
Failure	s(+) at 4 th month		Notes:	D	I								
Contact of known S(+) at diagnosis, r	MDR-TB case	Treatment month of Follow-up:	Result Dat	e:		Report	ed by (Name	& Signa	iture):			
Any follow-up S(+)				J / Liqui	d culture	DST Res	ults: (N	ote: 'S	' if susc	eptible	e, 'R' if	resistant)	
S(-) at diagnosis, re	e-treatment case		Date DST Initiated	Specin No	nen S	н	R	E	Z	Kn	n Of	(Eto	Other
HIV/TB-case RNTCP TB Reg No, Cat	tegory & Type:	DR-TB Centre Name:	Result Dat	e:	Rei	orted by	(Nam	e & Sia	gnature):			
(or Not Applicable)												

KNICP PMD1 Referral for Treatment F	orm Annexure v
(Fill in duplicate. Send one copy to the respective facility rec	eiving the patient, and keep the duplicate copy on file)
Name and address of Referring unit (District TB Centre/DR-T	B Centre)
Email address of referring unit	
Name of DR-TB Centre / District TB Centre to which the patie	ent is referred
Name of patient	AgeSex M 🗆 F 🗅
Complete Address	
Details of treatment taken by the patient at the ti	me of diagnosis of MDR and reason for suspecting
Latest Regimen: 🗆 New 🗆 Previously treated 🗅 MDR 🗅 XD	R 🗆 Private Rx Latest TB No
Disease Classification: 🗖 Pulmonary 📮 Extra Pulmonary (Sit	e)
Type: 🗆 New 🗆 Relapse 🗆 TAD 🗆 Failure 🗖 Others	
Reason for Suspecting MDR TB:	
A: 🗆 Failure 🗆 Re-treatment case S+ at 4 th month 🗅 Cont	act of known MDR TB case
B: 🗆 S+ at diagnosis, re-treatment case 🗆 Any follow up Sr	mear +ve
C: 🗆 S- at diagnosis, re-treatment case 🛛 HIV TB c	ase
Soutum Culture and DST details	Details of M/XDR TB treatment
Section Contraction Dol retains	PMDT TB number
Date of sputum collection://	FMD1 1D number
Date of culture result: /////	Name of DR-TB Centre:
Date of DST/LPA/CB-NAAT result://	Date M/XDR regimen started:
DST/LPA/CB-NAAT result*:S 🗆 H 🗆 R 🗆 E 🗖 O 🗆 K 🗖	Number of doses taken:
Tick the drugs to which resistance is shown	
Date of regimen change and details of change:	
ast Exposure to Second Line Anti TB Drugs: Drug	Duration
IV Status: Pos / Neg / Not Known Date of CPT initiation:	Date of ART initiation:
Date of referral to DR-TB Centre / DTC: Day	Month Year 20
Referred for:	
 Initiation of treatment 	
Adverse drug reaction (give details)	
Iransier out (give details) Ambulatory treatment (if the patient is referred t	• DTC)
Any other (give details)	

<u>Reminder for the health facility where the patient has been referred</u> Please send an email to the referring unit, informing the referring doctor of the date that the above named patient reported at the receiving health facility.





RNTCP PMDT Treatment Card Annexure VIII

Tick appropriately

DR-TB Centre DTC TU PHI DOT Provider

Patient's Name:	Name, Designation & Contact Details of DOT provider:												
State / District:	Name	of TU:			Name	of PHI	:						_
Sex: M F Age	PMDT	TB N	umbe	r:									
Date of registration://	Rea:	s on for Failure	Suspe Re-f	ecting l reatmen	IDR T	B: (Tic at 4th n	k) 10nth □	Contac	t of kno	wn MD	R TB ca	se	
Address:	B: □ C: □ L at/	B: □ S+ at diagnosis, re-treatment case □ Any follow up Smear +ve C: □ S- at diagnosis, re-treatment case □ HIV TB											
Contact Telephone No		STID	no., 11	any:									
Initial home visit: Data Ry	Date	of Sta	rting l	Ionthl	y Box:	(DD/M	M/YY)					
Initial nome visit. DateBy	IP 1 2 3 4 5 6 7 8 9 10 11								11	12			
DR-TB Centre:		1	2	3	4	5	б	7	8	9			
	СР	10	11	12	13	14	15	16	17	18			

DR-TB Centre Committee meetings – dates and decisions*

Date	Decision	Next Date

* Enter details of decisions regarding change of IP to CP, completion of Rx, severe adverse reactions, change of treatment etc.



Patient's name: _____

Month		Culture Resu	lts
Month	Date	Sample No.	Culture
Diagnosis			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			



*All dates in both tables are the dates the sputum was collected from the patient

DRUG SUSCEPTIBILITY TESTING RESULTS: Enter 'R' for Resistant 'S' for Susceptible

Date	Type of culture test					Second line drugs ^{\$} (if required)							
	(Molecular/LJ/Liquid/Other specify)	S	H	R	E	0	K	Cs	Cm	PAS	Amk		

\$ write the name of second line drugs



Patient's name:	
-----------------	--

Initial Weight (kgs): _____Kgs <16kg □ 16-25kg □ 26-45kg □ 46-70kg □ >70kg Height (cm): _____

Date of Starting Continuation Phase: Date of Starting Intensive Phase: _____

Date of regimen change and details of change:

Date	Change in regimen	Reason

ADMINISTRATION OF DRUGS (one line per month):

Month	D	DAY																														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	Wt (kg), Lab, X-ray
Mark in the boxes: ✓ = directly observed; (✓) = Unsupervised; O = drugs not taken																																

Mark in the boxes: ✓ = directly observed; (✓) = Unsupervised; O = Recording of CP should start from fresh line.



Patient's name:

Administration of drugs (continued) Month 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 Wt (kg), Lab, X-ray

Mark in the boxes: \checkmark = directly observed; (\checkmark) = Unsupervised; O = drugs not taken

Date and Details of adverse drug	Details of default retrieval action]	Treatment outcome	Tick	Date
reaction and action taken				one	
			Cured		
			Treatment completed		
]	Died		
]	Failed		
]	Defaulted		
]	Transferred out		
			Treatment stopped due to adverse drug reaction		
			Treatment stopped due to other reason		
			Switched to Regimen for XDR TB		



Unite to End TB WORLD TB DAY 24TH MARCH Thank you