Management of MDR & XDR Cases

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Greetings from AIIMS, Bhubaneswar

Objectives

- Classification of patients based on drug resistance pattern
- Pre-treatment evaluation
- Classes of Anti TB drugs recommended for the treatment of DR-TB patients
- Newer anti-TB drugs
- Treatment Initiation
- Regimen type (including newer drugs)
- Drug dosages and administration
- Treatment is special circumstances
- Management of adverse drug reactions
- Palliative care

Classification of patients based on drug resistance pattern

- Mono-resistance (MR): A TB patient, whose biological specimen is resistant to one first-line anti-TB drug only.
- Poly-Drug Resistance (PDR): A TB patient, whose biological specimen is resistant to more than one first-line anti-TB drug, other than both H and R.
- Rifampicin Resistance (RR): A TB patient, whose biological specimen is resistant to rifampicin, detected using phenotypic or genotypic methods. It includes any resistance to rifampicin, in the form of mono-resistance, poly-resistance, MDR or XDR.

Classification of patients based on drug resistance pattern

- Multi Drug Resistance (MDR): A TB patient, whose biological specimen is resistant to both isoniazid and rifampicin with or without resistance to other first line drugs.
  - MDR-TB patients may also have additional resistance to *any/all* FQ or *any/all* SLI anti-TB drug.
- Extensive Drug Resistance (XDR): A MDR TB patient whose biological specimen is additionally resistant to at least a FQ(Ofx, Lfx, Mfx) and a SLI anti-TB drug (Km, Am, Cm).

Pre-treatment evaluation

- Referral for pre-treatment evaluation
- Initial counselling

  - information on lab results and reliability of lab results

  - need for additional treatment;

  - importance of rapid initiation of treatment and adherence to prescribed treatment;

  - necessary infection control precautions and

  - re-assurance to the family against panic or unnecessary stigmatization of the patient.

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Health education/counselling to patient and family members

- Nature and duration of treatment
- Importance of adherence to treatment and need for complete and regular treatment
- Possible side effects of drugs
- Consequences of irregular treatment or pre-mature cessation of treatment
- Family planning counselling for female patients

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Pre-treatment evaluation

SN	Pretreatment evaluations	Regimen for H Mono / poly DR-TB	Conv. MDR-TB regimen	Shorter MDR-TB regimen	Regimen for RR-TB with FQ/SLI ± Lzd resistance (without newer drugs)	Newer drugs containing regimen
1	Detailed history (including screening for mental illness, seizure disorder, drug/alcohol abuse, etc.)	✓	✓	✓	✓	✓
2	Previous history of ATT taken especially SLI/FQ	✓	✓	✓	✓	✓
3	Weight & height	✓	✓	✓	✓	✓
4	Thorough clinical examination	✓	✓	✓	✓	✓
5	Complete blood count with hemoglobin & platelets count	✓	✓	✓	✓	✓
6	Blood sugar to screen for Diabetes Mellitus	✓	✓	✓	✓	✓
7	Blood urea and S. Creatinine to assess renal function	✓	✓	✓	✓	✓
8	Urine examination – routine and microscopic	✓	✓	✓	✓	✓
9	UPT (for all women in the child-bearing age)	✓	✓	✓	✓	✓
10	Chest X-ray	✓	✓	✓	✓	✓
11	HIV counselling and testing*	✓	✓	✓	✓	✓
12	Audiogram -	✓	✓	✓	✓	✓
13	Liver function tests#	✓	✓	✓	✓	✓

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Pre-treatment evaluation

SN	Pretreatment evaluations	Regimen for H Mono / poly DR-TB	Conv. MDR-TB regimen	Shorter MDR-TB regimen	Regimen for RR-TB with FQ/SLI ± Lzd resistance (without newer drugs)	Newer drugs containing regimen
14	TSH levels to assess the thyroid function		✓	✓	✓	✓
15	Mental health evaluation		✓	✓	✓	✓
16	Surgical evaluation		✓	✓	✓	✓
17	ECG (if Mfx[h], Dlm, Bdq, Cfz used)			✓	✓	✓
18	Serum electrolytes – potassium, magnesium, calcium					✓
19	Serum proteins, lipase, amylase					✓
20	Ophthalmologist opinion to rule out chorioretinitis /uveitis					✓

**All DR-TB patients will be offered referral for HIV counselling and testing at the nearest centre if the HIV status is not known or HIV test result is negative with results mor than 6 months. If patient is HIV positive, refer to ART centre (if not on ART)*

 # including HBsAg at baseline

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Classes of Anti TB Drugs recommended for treatment of DR-TB

New Grouping of Drugs			
A. Fluoroquinolones		Levofloxacin Moxifloxacin Gatifloxacin	Lfx Mfx Gfx
B. Second-line injectable agents		Amikacin Capreomycin Kanamycin (Streptomycin)	Am Cm Km (S)
C. Other second-line agents		Ethionamide / Prothionamide Cycloserine / Terizidone Linezolid Clofazimine	Eto/Pto Cs/Trd Lzd Cfz
D. Add-on agents (not part of the core MDR-TB regimen)	D1	Pyrazinamide Ethambutol High-dose isoniazid	Z E H^h
	D2	Bedaquiline Delamanid	Bdq Dlm
	D3	p-aminosalicylic acid Imipenem-cilastatin Meropenem Amoxicillin-clavulanate (Thioacetazone)	PAS Ipm/Cls Mpm Amx-Clv (T)

WHO treatment guidelines for DR-TB 2016 update

Newer anti-TB drugs

- The first new drug named Bedaquiline (BDQ) with anti-TB effect was approved for treatment of multidrug resistant TB by US FDA in late 2012

- BDQ was followed by the approval of another new drug Delamanid (Dlm) by the stringent regulatory authority of various countries

Bedaquiline

- New class of drug, diarylquinoline
- Targets mycobacterial ATP synthase
- Strong bactericidal and has superior sterilizing activity
- Highly protein bound (99.9%), metabolized by cytochrome P450 isoenzyme 3A (CYP3A)
- Extensive tissue distribution up to 5.5 months post stopping BDQ
- BDQ concentration reduced by 50% with concurrent Efavirenz and increased two times with concurrent Lopinavir + Ritonavir
- Significant benefits in improving the time to culture conversion in MDR-TB patients.
- Moderate QT interval prolongation (minimize the use of Clofazimine, Delamanid & Fluoroquinolones)
- Cross-resistance with Clofazimine

Lancet Respir Med 2017;5:291-360

Delamanid

- Nitroimidazole group
- Inhibits mycolic acid synthesis and liberates toxic NO within M tuberculosis
- Potent sterilising activity
- Highly protein bound (>99.5%), metabolised by albumin, has a half-life of 34 hrs
- Co-administration with Ritonavir or Efavirenz does not markedly affect Delamanid exposure
- Causes moderate QT interval prolongation
- Has low threshold for resistance development, therefore should be used in combination with drugs having higher genetic barriers to resistance, like Bedaquiline
- Contraindicated in those having allergy to Metronidazole

Lancet Respir Med 2017;5:291-360

Principles of Designing a WHO Recommended MDR-TB Regimen

- In patients with RR or MDR-TB, a regimen with at least ***five effective TB medicines during the intensive phase*** is recommended, including
  - Pyrazinamide and

  four core second-line TB medicines
  - One from group A
  - One from group B and
  - At least two from group C

  If the minimum of effective TB medicines cannot be composed as above, an agent from group D2 and other agents from D3 may be added to bring the total to five.

Lancet Respir Med 2017;5:291-360

Principles of Designing a WHO Recommended MDR-TB Regimen

- SLI (Gr.B) used for >4months after culture conversion and for a min. of 6 months
- Treatment duration is 20 months (low quality evidence)
- Bedaquiline or Delamanid (Gr. D2) usually added when a group A or B drug cannot be used
- Linezolid (Gr. C) can be used particularly in FQ resistant MDR or XDR-TB
- A single drug should not be added to a failing regimen
- Patient's HIV status should be established and ART initiated in all co-infected patients

Lancet Respir Med 2017;5:291-360

Principles of Designing a WHO Recommended XDR-TB Regimen

- Use of ≥4 drugs likely to be effective based on the prevailing patterns of drug resistance
- Backbone of Bedaquiline or Delamanid or both + Linezolid, a later generation FQ and addition of other drugs like, Clofazimine, PAS, Pyrazinamide, high dose INH, depending on susceptibility
- Caution:

  - ECG monitoring for QT prolongation when Bedaquiline and Delamanid used together
- Differential susceptibility to FQ might occur
- Gr. D3 drugs can be used

Lancet Respir Med 2017;5:291-360

Shorter MDR-TB regimen (9-12 months)

- In patients with RR-TB or MDR-TB who were not previously treated with 2nd line drugs
- In whom resistance to FQ and SLI was excluded or is considered highly unlikely
- It includes 3 drugs (Kanamycin, Prothionamide and high dose INH) for 4-6 months with additional drugs (Moxifloxacin, clofazimine, pyrazinamide & ethambutol) given throughout the course of treatment

(Conditional recommendation, very low certainty in the evidence)

WHO treatment guidelines for DR-TB 2016 update

Features of Shorter MDR-TB Regimen

- Treatment duration: 9-12 months
- Indicated for pulmonary & xtra pulmonary case (plural effusion and lymph nodes) RR-TB or MDR-TB patients
- Exclusion criteria:
  - Second-line drug resistance (FQ and/or SLI drugs)
  - Pregnancy
  - Extra pulmonary case (other than plural effusion and lymph nodes)
  - Previous exposure for >1 month to a fluoroquinolone or a second-line injectable medicine which is not in the Shorter MDR-TB Regimen but which may generate cross-resistance is considered an exclusion criterion.

  However, if resistance to both (FQ and/or SLI drugs) has been excluded by a reliable drug-susceptibility test (DST), then the shorter MDR-TB regimen can be used
- DST (Z, H^h, E, Eto, Cfz) is not recommended to base treatment decisions, owing to the unreliable nature of the tests

Justification for shorter MDR-TB regimen

- Observational studies from Bangladesh, Uzbekistan, Swaziland, Cameroon, Niger and 9 sub-Saharan Africa (n=1116)
- Specific inclusion criteria
- Higher treatment success
- Relapses were very low
- Treatment success was lower in patients with additional resistance to Z and/or FQ on shorter MDR-TB regimens.

WHO treatment guidelines for DR-TB 2016 update

Standard regimen for initiating treatment of MDR/RR-TB based on CBNAAT or FL-LPA

Resistance Pattern	Regimen Class	Intensive Phase	Continuation Phase	Principle of regimen design
Shorter MDR-TB Regimen				
R resistant + H sensitive/ unknown **Or MDR -TB**	Shorter MDR-TB Regimen	(4-6) Mfx^{h} Km* Eto Cfz Z H^{h} E	(5) Mfx^{h} Cfz Z E	As per WHO recommendation
Regimen for MDR/RR-TB				
R resistant + H sensitive/ unknown **Or MDR -TB**	Conventional MDR-TB Regimen	(6-9) Lfx Km Eto Cs Z E	(18) Lfx Eto Cs E	1 GpA + 1GpB + 2 GpC + Z + add on 1 GpD1

*If the intensive phase is prolonged, the injectable agent is only given three times a week in the extended intensive phase.

Standard regimen for initiating treatment of MDR/RR-TB or H mono-poly DR-TB based on CBNAAT or FL-LPA

Resistance Pattern	Standard Regimen Class	Intensive Phase	Continuation Phase	Principle of regimen design
Regimen for H mono/poly DR-TB				
H mono/poly DR-TB (R susceptible H resistant TB & DST of SEZ not known)	H Mono-poly DR TB Regimen	(3-6) Lfx Km R E Z	(6) Lfx R E Z	REZ + augment with 1 GpA + 1 GpB drug

DST guided regimen with or without newer drugs for initiating treatment of DR-TB patients with additional resistance to FQ class and/or SLI class based on SL-LPA

Resistance Pattern	DST Guided Regimen class	Intensive Phase	Continuation Phase	Principle of regimen design
Regimen with New drugs for XDR-TB				
XDR-TB (Res to both FQ and SLI[1] class)	XDR-TB	(6-12) Cm[1] Eto Cs Z Lzd[3] Cfz E + (6) Bdq	(18) Eto Cs Lzd[3] Cfz E	0 GpA + 1 GpB[1] + 2 GpC + Z + add on 2 GpC + 1GpD1 + 1 GpD2
Regimen for XDR-TB: (without new drugs)				
XDR-TB (resistance to both FQ and SLI[1] class)	XDR-TB	(6-12) Mfx[h2] Cm[1] Eto Cs Z Lzd[3] Cfz E	(18) Mfx[h2] Eto Cs Lzd[3] Cfz E	1 GpA[2] + 1 GpB[1] + 2 GpC + Z + add on 2 GpC + 1GpD1

1. If only Km resistant (at eis mutation), then add Cm in IP upfront in the regimen design.
2. In patients with MDR/RR + FQ Class resistance, XDR-TB and Mixed pattern resistance where a new drug is not considered in the regimen for any reason, Mfx[h] would be added upfront in the regimen design and the decision to continue or replace it would be taken based on LC-DST results to Mfx (2.0) by NDR-TBC
3. Lzd to be replaced with a suitable drug if found to be resistant on LC-DST. In such situation the patient must be reclassified as mixed pattern DR-TB

Dosage of DR-TB drugs for adults

S.No	Drugs	16-29 Kgs	30-45 Kgs	46-70 Kgs	>70 Kgs
1	Rifampicin(R)[1]	300mg	450mg	600mg	600mg
2	High dose H (H^h)	300 mg	600 mg	900 mg	900 mg
3	Ethambutol(E)	400 mg	800 mg	1200 mg	1600 mg
4	Pyrazinamide(Z)	750 mg	1250 mg	1750 mg	2000 mg
5	Kanamycin(Km) [2]	500 mg	750 mg	750 mg	1000 mg
6	Capreomycin (Cm)	500 mg	750 mg	750 mg	1000 mg
7	Amikacin (Am)	500 mg	750 mg	750 mg	1000 mg
8	Levofloxacin(Lfx) [4]	250 mg	750 mg	1000 mg	1000 mg
9	Moxifloxacin (Mfx) [4]	200 mg	400 mg	400 mg	400 mg
10	High Dose Mfx (Mfx^h) [4]	400mg	600mg	800mg	800mg
11	Ethionamide(Eto) [4]	375 mg	500 mg	750 mg	1000 mg
12	Cycloserine(Cs)[4]	250 mg	500 mg	750 mg	1000 mg
13	Na-PAS (60% weight/vol) [3,4]	10 gm	14 gm	16 gm	22 gm
14	Pyridoxine(Pdx)	50 mg	100 mg	100 mg	100 mg
15	Clofazimine (Cfz)	50 mg	100 mg	100 mg	200 mg
16	Linezolid (Lzd)	300 mg	600 mg	600 mg	600 mg
17	Amoxyclav(Amx/Clv) (In child: WHO 80mg/Kg in 2 divided doses)	875/125 mg BD	875/125 mg BD	875/125 mg (2 morning +1 evening)	875/125 (2 morning +1 evening)
18	Bedaquiline (Bdq)	Week 0–2: Bdq 400 mg daily Week 3–24: Bdq 200 mg 3 times per week			

[1]For H mono/poly resistant TB; [2]For adult more than 60 yrs of age, dose of SLI should be reduced to 10mg/kg (max up to 750 mg) [3]In patient of PAS with 80% weight/volume the dose will be changed to 7.5gm (16-29Kg); 10 gm (30-45 Kg); 12 gm (46-70 Kg) and 16 gm (>70 Kg) [4] drugs can be given in two divided doses in a day in the event of intolerance

Management of DR-TB patients with Treatment Interruptions and Loss to Follow up

- All the missed doses during IP must be completed prior to switching the patient to CP.
- Similarly all missed doses during CP must be administered prior to ending treatment.

Patients who interrupt treatment for less than one month during IP:

- Resume IP treatment, however the duration of treatment will be extended to complete IP. The follow up cultures will be done as per the revised schedule.

Patients who interrupt treatment for less than one month during CP:

- Resume CP treatment, however the duration of treatment will be extended to complete the CP. The follow up cultures will be done as per the revised schedule.

Management of DR-TB patients with Treatment Interruptions and Loss to Follow up

Patients who interrupt treatment continuously for one month or more and return back for treatment:

- Such patients will be given an outcome of "loss to follow up"
- The patient would be subjected to repeat FL-SL LPA and LC as per the diagnostic algorithm to restart with appropriate DST guided regimen with or without newer drug for a fresh episode of treatment

Monitoring treatment response

MONITORING EVALUATION	RECOMMENDED FREQUENCY
Evaluation by clinician	*During the intensive phase*: Every day during the first weeks if hospitalized and at least every week if treated as outpatient, until the treatment is well tolerated. Once stable the patient is seen twice a month or once a month. *During the continuation phase*: Monthly assessments unless there is a medical necessity to see the patient more often. The DOT supporter sees the patient daily between consultations and signals any concerns to the clinician.
Treatment adherence and tolerance	Daily at every DOT encounter by the DOT provider.
Sputum smears and culture	Monitoring smears and culture monthly throughout treatment. (Note: programmes with limited resources may choose to do monthly smears and cultures until conversion and then monthly smears with every other month cultures.)
Weight	At baseline, then every two weeks for first three months and then monthly.
Height	At start of treatment for all (to be able to assess BMI throughout treatment); monthly for children (to assess growth).
Drug susceptibility testing	At baseline for first- and second-line anti-TB drugs. Repeat DST for patients who remain culture-positive or revert after month four (see Chapter 3 for more information on DST).
Chest radiograph	At baseline, and then every six months.

Companion handbook to WHO for programmatic management of DR-TB, 2014

Follow-up schedule for uncomplicated MDR-TB patients

MONTH	CLINICAL CONSULT	WEIGHT	SMEAR	CULTURE	DRUG SUSCEPTIBILITY TESTING	CHEST RADIOGRAPH	LFT	CR, K	TSH	AUDIO-METRY	HIV TESTING
0 (baseline)	√	√	√	√	√	√	√	√	√	√	√
1	Every two weeks	√	√	√				√		√	Repeat if indicated
2		√	√	√				√		√	
3		√	√	√				√	√	√	
4	Monthly	√	√	√	If culture pos.			√		√	
5		√	√	√				√		√	
6		√	√	√	If culture pos.	Optional		√	√	√	
7		√	√	√				√		√	
8		√	√	√	If culture pos.			√		√	
9		√	√	√				If on inj.	√	If on inj.	
10		√	√	√	If culture pos.			If on inj.		If on inj.	
11		√	√	√				If on inj.		If on inj.	
12		√	√	√	If culture pos.	Optional		If on inj.	√	If on inj.	
Until completion			Monthly	Monthly	If culture pos.	Optional			Every three months		

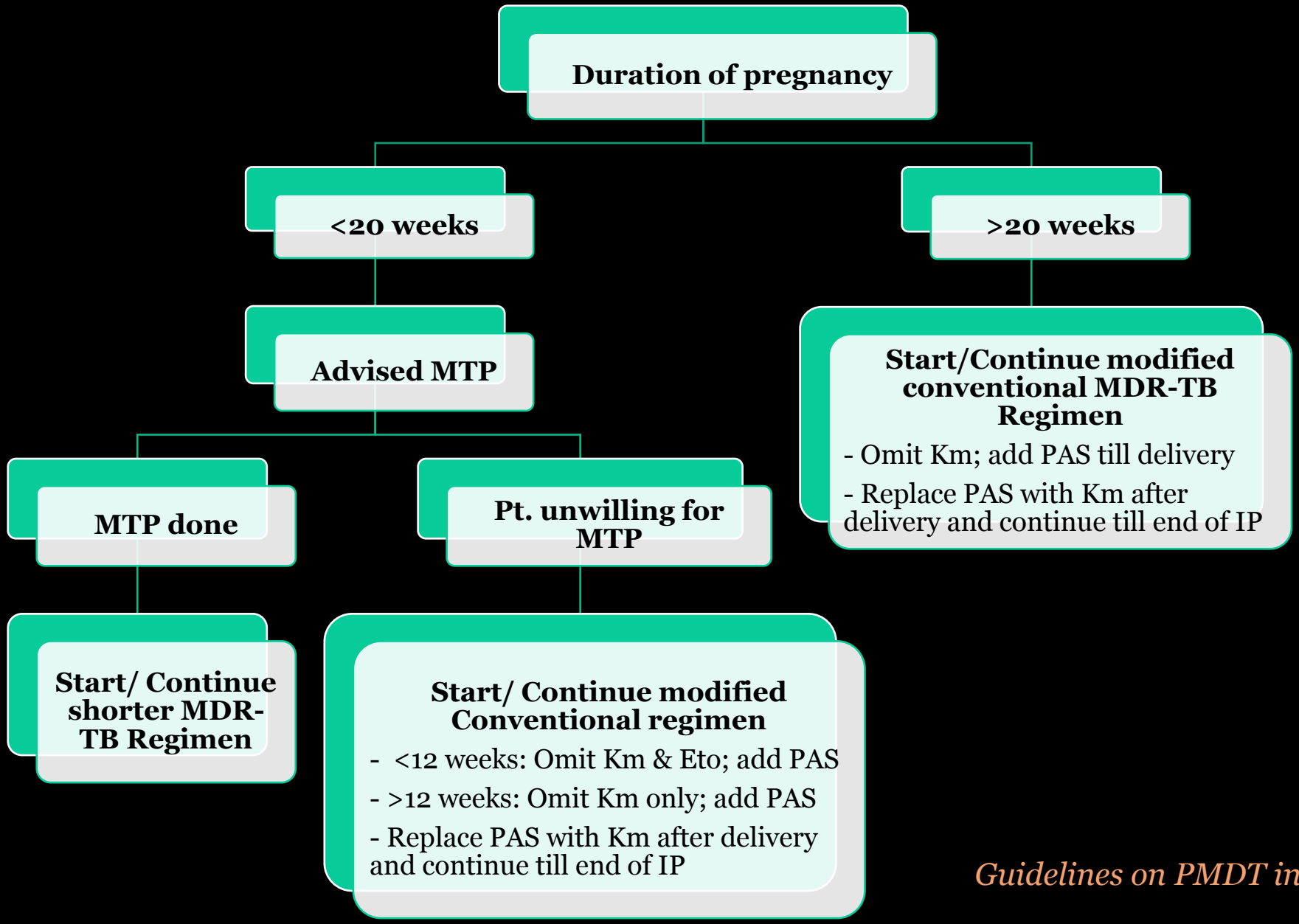
Abbreviations: pos. = positive; inj = injectable drug; LFT = liver function testing (liver enzymes); Cr = creatinine; K = potassium.

Treatment in Special Situations

Contents

- DR-TB in pregnancy
- DR-TB requiring surgery
- DR-TB in patients with renal impairment
- DR-TB in patients with pre-existing liver disease
- DR-TB with seizure disorders
- DR-TB with psychiatric illnesses
- DR-TB in Extra-Pulmonary TB patients
- Management of contacts of DR-TB

Management of DR-TB patients with Pregnancy



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DR-TB in pregnancy

- Avoid aminoglycosides as it is particularly toxic to the developing fetal ear

- Ethionamide can increase the risk of nausea and vomiting associated with pregnancy
  - If the injectable agents & ethionamide/ prothionamide or other drugs were withheld because of the pregnancy, they can be added back postpartum to make a more complete regimen.

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DR-TB in pregnancy

- Patients with mono- and poly-resistant TB who are susceptible to rifampicin:
  - Use of rifampicin interacts with the contraceptive drugs resulting in decreased efficacy of protection against pregnancy
- A woman on oral contraception while receiving rifampicin treatment may choose between two options following consultation with a physician:
  - Use of an oral contraceptive pill containing a higher dose of oestrogen (50 µg)
  - Use of another form of contraception.

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Role of surgery in management of DR-TB

- In DR-TB patients with localized disease, surgery, as an adjunct to chemotherapy, can improve outcomes.
- When unilateral resectable disease is present, surgery should be considered for the following cases:
  - *Absence of clinical or bacteriological response* to chemotherapy despite 6-9 months of treatment with effective anti-tuberculosis drugs
  - *High risk of failure or relapse* due to high degree of resistance or extensive parenchymal involvement
  - *Morbid complications of parenchymal disease* e.g. haemoptysis, bronchiectasis, bronchopleural fistula, or empyema;

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Role of surgery in management of DR-TB

- *Recurrence of positive culture* status during course of treatment
- *Relapse after completion of anti-tuberculosis treatment.*

- If surgical option is under consideration, at least six to nine months of chemotherapy is recommended prior to surgery, to ensure culture conversion.

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DR-TB in patients with renal impairment

- In DR-TB patients, blood urea and serum creatinine should be monitored prior to treatment initiation,
  - monthly for three months after treatment initiation
  - then every three months whilst injection Kanamycin is being administered
- In Mild renal impairment, the dose of aminoglycosides may be reduced.
- In Severe renal failure, the aminoglycoside therapy should be discontinued
  - replaced with other potent non-nephrotoxic anti-tuberculosis drugs.

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Dose adjustment of anti-TB drugs in presence of renal impairment

Drug	Recommended dose and frequency for patients with creatinine clearance < 30 ml/min or for patients receiving haemodialysis (unless otherwise indicated dose after dialysis)
Isoniazid	No adjustment necessary
Rifampicin	No adjustment necessary
Pyrazinamide	25-35 mg/kg per dose three times per week (not daily)
Ethambutol	15-25 mg/kg per dose three times per week (not daily)
Rifabutin	Normal dose can be used, if possible monitor drug concentrations to avoid toxicity.
Rifapentine	No adjustment necessary
Streptomycin	12-15 mg/kg per dose two or three times per week (not daily)[b]
Capreomycin	12-15 mg/kg per dose two or three times per week (not daily)[b]
Kanamycin	12-15 mg/kg per dose two or three times per week (not daily)[b]
Amikacin	12-15 mg/kg per dose two or three times per week (not daily)[b]
Ofloxacin	600-800 mg per dose three times per week (not daily)
Levofloxacin	750-1000 mg per dose three times per week (not daily)
Moxifloxacin	No adjustment necessary

Dose adjustment of anti-TB drugs in presence of renal impairment

Drug	Recommended dose and frequency for patients with creatinine clearance < 30 ml/min or for patients receiving haemodialysis (unless otherwise indicated dose after dialysis)
Cycloserine	250 mg once daily, or 500 mg / dose three times per week[c]
Terizidone	Recommendations not available
Prothinamide	No adjustment necessary
Ethionamide	No adjustment necessary
PAS[a]	4 g/dose, twice daily maximum dose[d]
Bedaquiline	No dosage adjustments required in patients with mild to moderate renal impairment (dosing not established in severe renal impairment, use with caution).
Linezolid	No adjustment necessary
Clofazimine	No adjustment necessary
Amoxicillin/ clavulanate	For creatinine clearance 10-30 ml/min dose 1000 mg as amoxicillin component twice daily; For creatinine clearance <10 ml/min dose 1000 mg as amoxicillin component once daily
Imipenem / cilastin	For creatinine clearance 20-40 ml/min dose 500 mg every 8 hours; For creatinine clearance <20 ml/min dose 500 mg every 12 hours
Meropenem	For creatinine clearance 20-40 ml/min dose 750 mg every 12 hours; For creatinine clearance <20 ml/min dose 500 mg every 12 hours

DR-TB in patients with pre-existing liver disease

- Most of the second line drugs can be safely used in presence of mild hepatic impairment
- Pyrazinamide should be avoided in such patients.
- Differential diagnosis for hepatitis in patients on second line drugs:
  - *viral hepatitis, alcoholic hepatitis, drug induced hepatitis by non-TB drugs etc.*
- DR patients having deranged liver function test (LFT) during pre-treatment evaluation should be strictly monitored through monthly LFTs while on treatment.

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DR-TB in patients with seizure disorders

- Evaluate the patient for H/O seizure disorder or anti-seizure medication
- If the seizures are not under control, initiation or adjustment of anti-seizure medications will be needed prior to the start of DR-TB therapy.
- Among second line drugs, Cycloserine, Ethionamide and fluoroquinolones have been associated with seizures
- Pyridoxine should be given with Cycloserine to prevent seizures.

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DR-TB in patients with seizure disorders

- High dose isoniazid also carries a high risk of seizure and should be avoided in patients with active seizure disorders.
- The prophylactic use of oral pyridoxine (vitamin B6) can be used in patients with seizure disorders to protect against the neurological adverse effects of isoniazid or cycloserine.
- Suggested prophylactic dose
  - for at-risk patients on isoniazid is 10 to 25 mg/day
  - for patients on cycloserine is 25 mg of pyridoxine for every 250 mg of cycloserine daily.

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DR-TB in patients with psychosis

- Counselling- While treating with psychiatric medication, individual counselling and /or group therapy
- Fluoroquinolones and Ethionomide have been associated with psychosis.
- Cycloserine may cause severe psychosis and depression leading to suicidal tendencies
  - Use of Cycloserine is not absolutely contraindicated for the psychiatric patient.
  - Close monitoring is recommended if Cs is used in psychiatric patients.
  - If patient on Cs therapy develops psychosis, anti-psychotic treatment should be started, Cs therapy should be temporarily suspended. Once symptoms resolve it may be resumed.

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DR-TB in patients with psychosis

- Pyridoxine prophylaxis may minimize the risk of neurologic and psychiatric adverse reactions.
- Psychiatric emergencies include psychosis, suicidal ideation, and any situation involving the patients being a danger to him/herself or others
  - Mechanisms to deal with it (often inpatient psychiatric hospital admissions) should be available 24 hrs
  - Proper infection-control measures must be taken for the smear-positive patient who requires any hospitalization.

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Management of DR TB in Extra Pulmonary TB cases

- Management of bacteriologically confirmed Extra-Pulmonary DR-TB patients will be considered
- EP DR-TB patients will undergo all those pre-treatment investigations as done for pulmonary DR-TB
- Ultrasound of abdomen to rule out involvement of other organs and abdominal nodes
- Treatment regimen and schedule for EP DR-TB patients will remain the same as for pulmonary DR-TB.

Guidelines on PMDT in India 2017

Monitoring and follow up

- Clinical monitoring is the most important criteria for the follow up of patients with Extrapulmonary DR-TB
- Bacteriological monitoring:
  - Two specimens from the discharging sinus /pus in the lymph node should be collected, one for smear and one for culture.
  - The specimen should be taken at the end of 3rd month of treatment and then every month (at least 30 days apart) in IP till there is pus /discharge from sinus (in the node).

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Management of contacts of DR-TB

- *If the contact is found to be suffering from pulmonary TB disease, irrespective of the Smear results microbiological confirmation, he/she will be identified as a "Presumptive DR-TB".*

- The patient will be initiated on regimen for new or previously treated patient based on their history of previous anti-TB treatment.

- Simultaneously sputum samples will be transported for culture and DST to a C&DST laboratory; he/she should be evaluated as per the DR-TB diagnostic algorithm.

Guidelines on the management of LTBI, WHO 2015

Preventive therapy in contacts of DR-TB

- Due to lack of evidence there is no consensus about whether close contacts of MDR-TB patients should be given preventive therapy, and if so, which drugs should be given
- Strict clinical observation and close monitoring for the development of active TB disease for at least 2 years is preferred over provision of preventive therapy in contacts of MDR-TB cases
- Serious limitations in the quality of evidence prevent drawing any recommendation

Guidelines on the management of LTBI, WHO 2015

	Standard treatment*	Shortened treatment	Key role	Adverse events and tolerability	Comments
Fluoroquinolone: levofloxacin or moxifloxacin	Yes	Yes	Key bactericidal agent	Generally well tolerated; tendinitis; insomnia; QT prolongation	Optimal dose unclear; little to no sterilising activity
Injectable agent: amikacin, kanamycin, or capreomycin	Yes	Yes	Undefined	Ototoxicity, common and often irreversible; nephrotoxicity; injections painful	No measurable bactericidal activity; no measurable sterilising activity; candidate for replacement in novel regimens because of poor tolerability; should generally be avoided with tenofovir
Ethionamide or prothionamide	Yes	Yes	Treat isolates whose isoniazid resistance is mediated by *katG* mutation	Nausea and vomiting common	Candidate for replacement in novel regimens because of toxicity
Cycloserine or terizidone	Yes	No	Bacteriostatic drug	Neuropsychiatric side-effects common	Candidate for replacement in novel regimens because of toxicity
Linezolid	No	No	Protect against emergence of resistance	Peripheral neuropathy and bone marrow toxicity common	Optimal dose and duration to optimise efficacy and minimise toxicity not defined
Clofazimine	No	Yes	Sterilising drug	Skin discoloration in almost all people; QT prolongation	Synergistic with pyrazinamide; some cross-resistance with bedaquiline
High-dose isoniazid	No	Yes	Treat isolates whose isoniazid resistance is mediated by *inhA* mutation	Peripheral neuropathy, preventable by vitamin B6	Optimal dose unclear Avoid use with stavudine or didanosine to prevent peripheral neuropathy
Pyrazinamide	Yes	Yes	Sterilising drug; synergy with other drugs	Arthralgias common; hepatitis	Synergistic with clofazimine High proportion of MDR isolates are resistant Should be used with caution when combined with other potentially hepatotoxic ART
Ethambutol	No	Yes	Protection against resistance	Optic neuritis, rarely	High proportion of MDR isolates are resistant

*In 2016, WHO recommendations were updated to recommend the following as standard treatment: a fluoroquinolone, an injectable, two of the following—ethionamide or prothionamide, cycloserine or terizidone, linezolid, and clofazimine—and pyrazinamide. Other agents (ethambutol, bedaquiline, delamanid, etc) could be added, if needed, to construct a regimen. Before 2016, linezolid and clofazimine were not components of WHO-recommended standard MDR-TB treatment, but they now are.

K Dheda et al. Lancet Respir Med 2017;5:291-360

Management of adverse drug reactions

- Proper management of adverse effects begins with pre treatment patient education.
- Depending on the severity of ADRs the following actions may be indicated:
  - If the adverse effect is mild and not serious, continuing the treatment regimen, with the help of ancillary drugs if needed, is often the best option.
  - Most of the adverse effects of a number of second-line drugs are dose-dependent. Reducing the dosage of the offending drug or terminating the offending drug is another method of managing adverse effects.
- Psychosocial support is an important component of the management of adverse effects

Principles of treatment support

- Minimise patient travel
- Minimise delay in treatment initiation and follow up
- Minimise Catastrophic expenditure
- Minimise infection in transit
- Maximise patient satisfaction
- Maximise adherence to treatment
- Maximise transparency in operations

Palliative care

- Palliative care is a multidisciplinary approach to medical care for people with serious illnesses.
- It focuses on providing patients with relief from the symptoms, pain, physical stress, and mental stress of a serious illness—whatever the diagnosis
- Challenges - Neither trained health workers nor local community-based palliative care resources are usually available
- Approach – HR and Infrastructure need to provide an extra layer of support
  - Longer duration of stay
  - Airborne infection control
  - Training Community-based workers

Companion handbook to WHO for programmatic management of DR-TB, 2014

Supportive measures in palliative care

- Respiratory rehabilitation: Relief from dyspnoea with oxygen
- Relief from pain and other symptoms: Tramadol, paracetamol
- Infection control measures
- Nutritional support: Small and frequent meals
- Regular medical visits: periodic assessment and management of post treatment sequelae
- Vocational Rehabilitation: socio-economic sufficiency
- Continuation of ancillary medicines: patient comfort
- Preventive measures: Oral care, prevention of bedsores, bathing and prevention of muscle contractures
- Provide psychosocial support: patient and family caregivers
- Respect for patient's beliefs and values at the end of life

Companion handbook to WHO for programmatic management of DR-TB, 2014

Summary

- Key factors critical in improving treatment outcomes like ensuring adherence support, good lab infrastructure, effective management of co-morbidities and a well functioning TB program
- A precision medicine oriented treatment approach should be adopted in which universal access to rapid DST for INH, Rif, SLI and FQ is present to guide individualised treatment
- Patients without resistance to SL drugs should receive the WHO approved shortened regimen and those with resistance would receive novel agents like Bedaquiline or Delamanid or both in combination with other drugs
- Multi-disciplinary management of patients with DR-TB

Thank you