DRUG RESISTANT TUBERCULOSIS

Drug Resistant TB - Definitions

Mono-Resistance:

Resistance to **ONE** first-line drug (Rifampicin, Isoniazid, Pyrazinamide or Ethambutol)

Rifampicin Resistance (RR):

Resistance to Rifampicin, with our without resistance to other TB medicines. This may be mono, poly, multi, or extensive drug resistance.

Poly-Resistance:

Resistance to **TWO** or more first-line drugs, but **NOT** both Isoniazid and Rifampicin

Multi-Drug Resistance (MDR):

Resistance to at least **BOTH Isoniazid and Rifampicin**

Extensive-Drug Resistance (XDR):

Resistance to **Isoniazid and Rifampicin PLUS a fluoroquinolone** (ciprofloxacin, levofloxacin, moxifloxacin) **PLUS** one or more **2nd line injectable drug** (kanamycin, amikacin or capreomycin).

Source: South Africa National Tuberculosis Management Guidelines, 2014

Treatment of Mono/Poly Resistant TB

Drug resistance pattern	Suggested regimen	Minimum duration	Comments
H	Regimen I or II intensive phase for full duration (except for H). In practice it is easier to use fixed dose combinations, but these are not available for children < 8 years for this purpose. Treat with R+Z+E single doses.	6 – 9 months based on symptomatic response to treatment, weight gain, and sputum culture combination. A minimum of 6 months treatment after culture conversion is adequate.	Monitor the patient with sputum smear microscopy and culture on monthly basis throughout treatment. Monthly clinical assessment required. Refer to MDR TB expert if patient is not responding well to treatment.
R (+/- any other 1st line drug than H)	Standardised MDR-TB regimen PLUS INH	18 months after culture conversion	These patients will need confirmation of diagnosis if diagnosed through GXP; however, LPA is a confirmatory diagnosis.
Poly-resistant TB cases			Refer to MDR-TB expert for regimen based on resistance pattern and history of anti-tuberculosis drugs used.

Source: Management of Drug-Resistant Tuberculosis Policy Guidelines, Updated Jan 2013

Standard MDR-TB and XDR-TB Regimens

MDR-TB

Intensive phase: **Km(Am)-Mfx-Eto-Trd-Z**

Kanamycin (Amikacin) - Moxifloxacin - Ethionamide - Terizidone - Pyrazinamide

Minimum duration of 6 months; continue for 4 months after culture conversion

Continuation phase: **Mfx-Eto-Trd-Z**

Moxifloxacin - Ethionamide - Terizidone - Pyrazinamide

Continuation phase ends 18 months after culture conversion

XDR-TB

Intensive phase: **Cm-Mfx-Eto-Trd-Z-PAS-Clofazimine**

Capreomycin - Moxifloxacin-Ethionamide-Terizidone-Pyrazinamide-PAS-Clofazimine

Minimum duration of 6 months; continue for 4 months after culture conversion

Continuation phase: **Mfx-Eto-Trd or Cs-Z-PAS/Clofazimine**

Moxifloxacin-Ethionamide-Terizidone or Cycloserine-Pyrazinamide-PAS/Clofazimine

Continuation phase ends 18 months after culture conversion

Source: South Africa National Guidelines. Management of MDR-TB Policy Guidelines, 2011

Dosing of Standard M(X)DR-TB Regimen in Adults

MDR-TB Standardized Treatment Regimen for Adults and Children > 8 Years — Intensive Phase: Treatment taken at least 6 times weekly for at least 6 months, guided by TB culture conversion				
Drug	**Dose (<33kg)**	**Dose (33-50kg)**	**Dose (51-70 kg)**	**Dose > 70kg**
Kanamycin	15-20mg/kg	500-750mg	1000mg	1000mg
Moxifloxacin	400mg	400mg	400mg	400mg
Ethionamide	15-20mg/kg	500mg	750mg	750-1000mg
Pyrazinamide	30-40mg/kg	1000-1750mg	1750-2000mg	2000-2500mg
Terizidone	15-20mg/kg	750mg	750mg	750-1000mg

MDR-TB Standardized Treatment Regimen for Adults and Children > 8 Years — Continuation Phase: Treatment taken at least 6 times weekly for at least 18 months following culture conversion				
Drug	**Dose (<33kg)**	**Dose (33-50kg)**	**Dose (51-70 kg)**	**Dose > 70kg**
Ethionamide	15-20mg/kg	500mg	750mg	750-1000mg
Pyrazinamide	30-40mg/kg	1000-1750mg	1750-2000mg	2000-2500mg
Moxifloxacin	400mg	400mg	400mg	400mg
Terizidone	15-20mg/kg	750mg	750mg	750-1000mg

Pyridoxine 150 mg (max 200 mg) daily to paitents on Terizidone. Levofloxacin if not tolerating Moxifloxacin at 750 mg for patients < 51 kg and 1000 mg if > 51 kg

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Dosing of Standard M(X)DR-TB Regimen in Adults

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XDR-TB Standardized Treatment Regimen — Intensive Phase: Treatment taken daily for at least 6 months, guided by TB culture conversion				
Drug	**Dose (<33kg)**	**Dose (33-50kg)**	**Dose (51-70 kg)**	**Dose > 70kg**
Capreomycin	15-20mg/kg	500-750mg	1000mg	1000mg
Moxifloxacin	400 mg	400mg	400mg	400mg
Ethionamide	15-20 mg/kg	500mg	750mg	750-1000mg
Terizidone	15-20 mg/kg	500mg	750mg	1000mg
Pyrazinamide	30-40 mg/kg	1000-1750mg	1750-2000mg	2000-2500mg
PAS	150 mg/kg	8000mg	8000mg	8000mg
Clofazimine	3-5 mg/kg	200mg	300mg	300mg

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Dosing of Standard M(X)DR-TB Regimen in Adults

Continued

XDR-TB Standardized Treatment Regimen — Continuation Phase: Treatment taken daily for at least 18 months following culture conversion				
Drug	**Dose (<33kg)**	**Dose (33-50kg)**	**Dose (51-70 kg)**	**Dose > 70kg**
Moxifloxacin	400 mg	400mg	400mg	400mg
Ethionamide	15-20 mg/kg	500mg	750mg	750-1000mg
Terizidone	15-20 mg/kg	500mg	750mg	1000mg
Pyrazinamide	30-40 mg/kg	1000-1750mg	1750-2000mg	2000-2500mg
PAS	150 mg/kg	8000mg	8000mg	8000mg
Clofazimine	3-5 mg/kg	200mg	300mg	300mg

Source: South Africa National Guidelines. Management of MDR-TB Policy Guidelines, 2011

Dosing of Standard MDR—TB Drugs in Children < 8 Years

Dosing of Standard MDR-TB Drugs in Children < 8 Years				
Drug	**Formulation**	**Range (mg/kg)**	**Frequency**	**Maximum daily dose**
Amikacin	Vials: 500 mg, 1 g	15 – 22.5	Once Daily	1g
Levofloxacin (for children under 8 years)	Tablets: 250, 500, 750 mg	7.5 – 10	Once Daily	
Ethionamide	Tablets: 250 mg	15 – 20	2x daily initially aim for 1x daily	1g
Terizidone	Capsules: 250 mg	10 – 20	Once daily	1g
Pyrazinamide		30 – 40		

NB: Ethambutol may be given at the dosage of 20-25 mg/kg

Source: Guidelines for the Management of Tuberculosis in Children 2014

Dosing of Additional Second-line TB Drugs in Paediatrics

Dosing of Additional MDR/XDR TB Drugs in Paediatrics				
Drug	**Formulation**	**Daily dose mg/kg/day**	**Frequency**	**Maximum daily dose**
Streptomycin	Vials: 500 mg, 1g	15 – 30	Once Daily	1g
Kanamycin	Vials: 500 mg, 1g	15 – 30	Once Daily	1g
Capreomycin	Vials: 1g	15 – 30	Once Daily	1g
Moxifloxacin (for children older than 8 years and adults)	Tablets: 400mg	7.5 – 10	Once Daily	
Prothionamide	Tablets: 250 mg	15 – 20	Twice daily	1g
PAS	PAS granules 4g packets	150	Twice daily	12g

Source: Guidelines for the Management of Tuberculosis in Children, 2014

Common Side Effects During MDR-TB Treatment

Drug	Complaint/Side Effect
Aminoglycosides	Hearing loss, Vestibular toxicity, Hypokalemia, Hypomagnesemia, Rash
Amikacin	Ototoxicity*: dizziness and hearing loss, Renal failure*
Capreomycin	Hearing loss, Vestibular toxicity, Hypokalemia, Hypomagnesemia, Rash
Fluoroquinolones	Seizures, Headache, GI complaints, Rash
Clofazimine	GI complaints, Rash
Cycloserine	GI complaints, Behavioural Changes including depression and anxiety*, Rash, Peripheral neuropathy, Seizures*, Headache*, Psychosis
Ethambutol	Visual changes, Rash, Headache
Ethionamide	GI complaints (nausea, anorexia)*, Hypothyroidism*, Hepatotoxicity*, Behavioural Changes, Rash, Peripheral neuropathy*, Headache
Isoniazid	Hepatotoxicity, Behavioural Changes, Visual changes, Rash, Bone Marrow Suppression, Peripheral neuropathy, Seizures, Headache
Linezolid	Visual changes, Rash, Bone Marrow Suppression, Peripheral neuropathy

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Common Side Effects During MDR-TB Treatment

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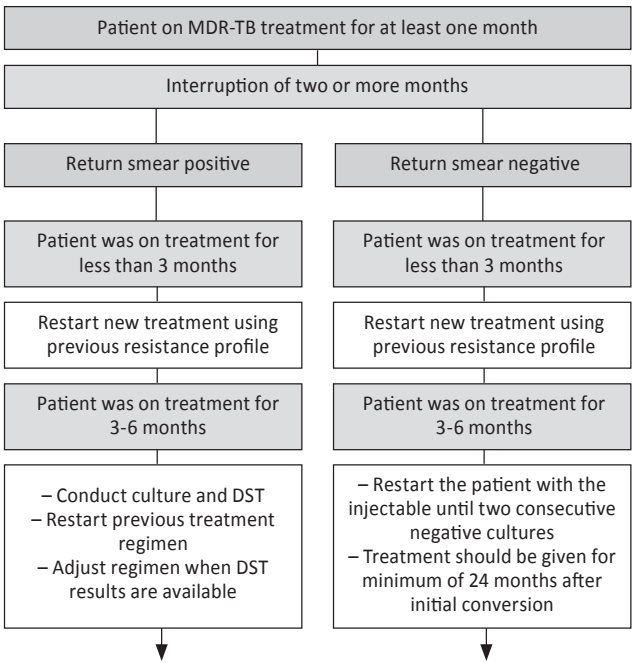
Drug	Complaint/Side Effect
Para-Aminosalicylic Acid	GI complaints, Hyperthyroidism, Hepatotoxicity, Rash
Pyrazinamide	Hepatotoxicity, Rash
Rifampicin	Hepatotoxicity, Rash, Bone Marrow Suppression
Rifabutin	Visual changes, Rash

** Most common*

Source: South Africa National Guidelines. Management of MDR-TB Policy Guidelines, 2011

Management of Patients Who Default MDR-TB Treatment



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Management of Patients Who Default MDR-TB Treatment

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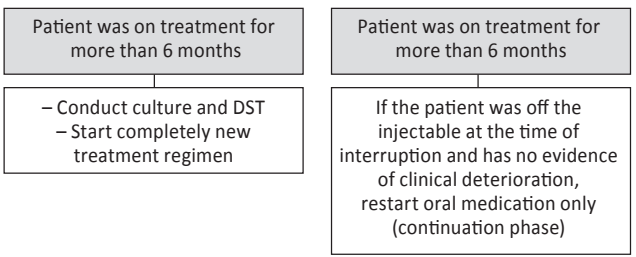

Source: South Africa National Guidelines. Management of MDR-TB Policy Guidelines, 2011; Adapted from the PIH Guide to the Medical Management of Muldtidrug-Resistant Tuberculosis International Edition, Partners in Health, 2003

Monitoring During M(X)DR-TB Treatment

Monitoring	Recommended Frequency
Sputum smear	At baseline, monthly
TB culture	Baseline, monthly until conversion then at least every other month
Drug Susceptibility Testing	On admission and if no improvement (patient TB culture positive on treatment) within 3-6 months
Liver Function Tests	Every 1-3 months if on Pyrazinamide or at risk/symptoms of hepatitis (children: if symptomatic, every 6 months if on ART)
Serum Creatinine	Baseline, monthly while on injectable
Serum Potassium	Monthly while receiving injectable
TSH	Baseline, every 6 months if receiving ethionamide and/or PAS, monthly monitoring for signs of hypothyroidism (children: every 2 months)
HIV and Pregnancy Tests	Baseline and repeat as indicated
Chest X-ray	Baseline, every 6 months, at treatment completion, when requested by clinician (children: every 2-3 months during intensive phase)
Lung CT-Scan	When indicated

Source: South Africa National Guidelines. Management of MDR-TB Policy Guidelines, 2011

Clinical Follow-Up During M(X)DR-TB Treatment

Clinical Follow-Up	Recommended Frequency
Evaluation by Clinician (if outpatient)	At baseline and at least monthly until culture conversion, then at least every 2-3 months
Weight	At baseline, weekly during intensive phase, then monthly
BMI	Baseline, then monthly
Height	Baseline
Side Effects Monitoring	On-going
Signs and Symptoms of hypothyroidism	Monthly
Audiometry	Baseline, monthly during injectable, 3 months after injectable stopped
Eye Test	Baseline, when indicated

Source: South Africa National Guidelines. Management of MDR-TB Policy Guidelines, 2011