Ministry of Health

NATIONAL TUBERCULOSIS CONTROL PROGRAMME FORMULARY

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Dr. Sam Madula
Principal Secretary
Ministry of Health

FOREWORD

Tuberculosis (TB) remains one of the major causes of ill health and death in Malawi. Strategies to control the spread of tuberculosis include active case finding, timely and appropriate management and effective treatment. Active case finding involves health workers screening patients at the facility and in the community. Management involves counselling families as well as the patient, tracing household contacts, patient follow-up and ensuring adherence. Effective TB treatment involves ensuring that patients receive appropriate antimicrobial treatment for the correct duration of therapy, particularly for patients on antiretroviral therapy (ART) and those suspected of having drug-resistant tuberculosis. The availability of medicines and their rational use requires guidelines to ensure that standards of treatment are maintained.

This formulary has been developed with the aim of providing guidance on prescription, dispensing and administering anti-TB medicines to ensure that they are taken in accordance with the National TB Control Programme's (NTP) recommendations.

The formulary shall therefore strengthen TB control services throughout the existing TB management structures. The Ministry of Health, through NTP, shall work with other relevant stakeholders to ensure proper use of this formulary. This formulary will enable the health workers to prescribe the correct dose of TB treatment for correct duration of time and manage any adverse effects appropriately.

The Ministry of Health shall continue to offer support and assistance to

ensure proper use of the formulary as well as in monitoring of anti-TB medicine usage in Malawi.

Honourable Dr. Peter Kampalume, MP
Minister of Health

LIST OF ABBREVIATIONS

3TC	lamivudine
ABC	abacavir
Am	amikacin
Amx/Clv	amoxicillin/ clavulanic acid
ART	antiretroviral therapy
AZT	zidovudine
Bdq	bedaquiline
Cfz	clofazimine
Cln	cilastatin
Clr	clarithromycin
Cm	capreomycin
Cs	cycloserine
DOT	directly observed treatment
E	ethambutol
EFV	efavirenz
Et	ethionamide
FDC	fixed-dose combination
H	isoniazid
Imp	imipenem
Km	kanamycin
Lfx	levofloxacin

LPV/r	lopinavir/ ritonavir
Lzd	linezolid
MDR-TB	multidrug-resistant tuberculosis
Mfx	moxifloxacin
Mpm	meropenem
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NSAID	nonsteroidal anti-inflammatory drug
NTP	National Tuberculosis Control Programme
NVP	nevirapine
Ofx	ofloxacin
PAS	para-amino salicyclic acid
PI	protease inhibitor
Pto	prothionamide
R	rifampicin
Rfb	rifabutin
RTV	ritonavir
S	streptomycin
TB	Tuberculosis
TSH	thyroid stimulating hormone
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis
Z	pyrazinamide

INTRODUCTION

Tuberculosis (TB) treatment—which is tailored to the patient with the right regimen, dose, and duration—are crucial for the effective management of TB and for preventing its ongoing transmission.

Appropriate treatment of drug-sensitive TB entails a 4-drug intensive phase and a 2-drug continuation phase. Fixed-dose combinations (FDCs) of at least three drugs during the intensive phase of treatment, and at least two drugs in the continuation phase of treatment, are available for first-line anti-tuberculosis therapy in Malawi, in line with World Health Organization (WHO) recommendations.

Ensuring the correct treatment is indispensable to preventing the development of drug resistant tuberculosis. Treatment duration for drug-sensitive TB varies from 6 to 12 months, depending on the type and site of the infection. Malawi utilizes directly observed treatment (DOT) strategy. To ensure compliance, patients are directly observed while swallowing the tablets. DOT supervisors can be health workers, guardians, or community members.

This document provides quick guidelines for prescribing, dispensing, and administering anti-tuberculosis medicines. Health workers should refer to the National Tuberculosis Control Programme manual and other relevant documents for further details on tuberculosis prevention and management.

GOAL

- To guide health professionals when they prescribe, dispense, and administer anti-TB medicines.

OBJECTIVES

- To guide the service provider in selecting the appropriate anti-TB medicine regimen.
- To ensure correct prescribing practice of anti-TB medicines.
- To ensure that the service provider fully understands how to properly use each prescribed medicine.
- To provide knowledge to the service provider on how to manage any adverse effects suffered by the patient after administering anti-TB medicines.

TUBERCULOSIS CATEGORIES AND RECOMMENDED REGIMENS

A : ADULTS

Table 1: Adult TB Categories and Recommended Regimens

Category	Description	Treatment Regimens
New patient: smear positive, or GXP+pulmonary TB smear negative/Xpert negative PTB EPTB, except TB meningitis and osteoarticular TB	A patient who has never been treated for TB, or has taken anti-TB medicines for less than one month; new patients may have a positive or negative bacteriology and may have the disease at any anatomical site.	2 RHZE/4RH
TB meningitis	Mycobacterium tuberculosis: infection of the meninges—the system of membranes which envelop the central nervous system.	2 SRHZE /7RH
Relapse	A patient who has previously been treated and completed treatment and has now developed bacteriologically confirmed active tuberculosis.	2 SRHZE/1 RHZE/5 RHE
Failure	A newly diagnosed tuberculosis patient who is sputum-smear positive 5 months or more after the start of chemotherapy.	2 SRHZE /1 RHZE /5 RHE
Treatment interrupted (treatment after default)	A patient who interrupted treatment for more than 2 months after at least one month of chemotherapy and is subsequently found to have bacteriologically confirmed tuberculosis.	2 SRHZE /1 RHZE/5 RHE
Others	All other forms of TB	2 SRHZE/1 RHZE/5RHE
Multidrug resistant (MDR-TB) tuberculosis	Multi-drug resistance implies resistance to at least Rifampicin and Isoniazid.	8Cm-Lev-Cs-Eto- Z/16Lev-Et-Cs

Category	Description	Treatment Regimens
Extensively-drug resistant TB (XDR-TB).	XDR-TB is defined as MDR-TB that is also resistant to any fluoroquinolone, and at least one of the three injectable second line anti-TB medicines (capreomycin, kanamycin, and amikacin).	XDR-TB regimen (Note: refer to medical specialist)

B: PAEDIATRICS

Table 2: Paediatric TB Categories and Recommended Regimens

Site or Type of TB Disease	RHZE Treatment Duration	RH Treatment Duration	Total Length of Treatment
TB meningitis, Miliary TB, osseous/bone TB (spine, joints)	2 months	10 months	12 months
Pulmonary TB, TB lymphadenitis, ALL other forms of TB	2 months	4 months	6 months

Children with proven, or suspected, pulmonary TB or tuberculous meningitis caused by multidrug-resistant bacilli can be treated with a fluoroquinolone in a well-functioning MDR-TB control programme and within an appropriate MDR-TB regimen. A clinician experienced in managing paediatric TB should make the decision to treat.

FIRST LINE ANTI-TB MEDICINES

RIFAMPICIN (R)

Rifampicin is a semisynthetic derivative of rifamycin, an antibiotic produced by Streptomyces mediterranei used in the treatment of tuberculosis caused by Mycobacterium tuberculosis. Rifampicin is well absorbed after oral administration; it is excreted mainly through the liver into bile.

Indications:

- Tuberculosis, in combination with other drugs. Tuberculosis, as a single formulation when a patient reacts to another constituent of the fixed dose combination.

Cautions:

- **Hepatic impairment (monitor liver function regularly);**
- **Renal impairment (if above 600mg daily);**
- **In pregnancy and breast-feeding;**
- **In acute porphyria;**
- ***Important*: advise patients on hormonal contraceptives to use additional means; and**
- Rifampicin discolours soft contact lenses; tears, sweat and urine may become orange coloured.

Interactions:

For interactions with ARV drugs, see appendix E.

Hepatic disorders

Patients or their caregivers should be told how to recognise signs of liver disorder; they should be advised to discontinue treatment and seek immediate medical attention if symptoms, such as persistent nausea, vomiting, malaise, or jaundice develop.

Contraindications:

If patient has jaundice; rifampicin hypersensitivity; acute porphyria—

Side effects:

- Gastro-intestinal symptoms, including anorexia, nausea, vomiting, or diarrhoea (antibiotic-associated colitis reported);
- Headache, drowsiness;
- Side effects occurring mainly on intermittent therapy include influenza-like symptoms (with chills, fever, dizziness, bone pain), respiratory symptoms (including shortness of breath), collapse and shock, haemolytic anaemia, acute renal failure, and thrombocytopenic purpura;
- Alterations of liver function, jaundice;
- Flushing, urticaria, and rashes;
- Other side effects reported include oedema, muscular weakness and myopathy, exfoliative dermatitis, toxic epidermal necrolysis, pemphigoid reactions, leucopenia, eosinophilia, menstrual disturbances;
- Urine, saliva, and other body secretions coloured orange-red; and
- Thrombophlebitis reported, if infusion is used for prolonged period.

For management of side effects see appendix A.

Dosage and administration: See tables 3–7.

ISONIAZID (H)

Isoniazid is the most active drug for the treatment of tuberculosis caused by Mycobacterium tuberculosis. It is readily absorbed from the gastrointestinal tract and diffuses into all body fluids and tissues.

Indications:

- Tuberculosis, in combination with other drugs.
- Tuberculosis, as a single formulation when a patient reacts to another constituent of the fixed dose combination.
- Prophylactic treatment for children under-five contacts of index cases and all HIV positive clients with no active tuberculosis.

Cautions:

- Hepatic impairment (monitor liver function regularly and particularly frequently in first 2 months);
- Renal impairment;
- Epilepsy;
- History of psychosis;
- Alcohol dependence, malnutrition, diabetes mellitus, HIV infection (risk of peripheral neuritis);
- Pregnancy and breastfeeding; and
- Porphyria.

Interactions:

For interactions with ARVs, see appendix E.

Contraindications:

In drug-induced liver disease—

Side effects:

- Nausea, vomiting, constipation, dry mouth;
- Peripheral neuritis with high doses (pyridoxine prophylaxis is required), optic neuritis, convulsions, psychotic episodes, vertigo;
- Hypersensitivity reactions, including fever, erythema multiforme, purpura;
- Blood disorders, including agranulocytosis, haemolytic anaemia, aplastic anaemia;
- Hepatitis (especially over age of 35 years); and
- Systemic lupus erythematosus–like syndrome, pellagra, hyperreflexia, difficulty with micturition, hyperglycaemia, and gynaecomastia reported.

For management of side effects, see appendix A.

Dosage and administration: See tables 3–7.

PYRAZINAMIDE (Z)

Pyrazinamide is a relative of nicotinamide; it is stable and slightly soluble in water; used in the treatment of tuberculosis caused by Mycobacterium tuberculosis.

Indications:

- Tuberculosis, in combination with other drugs.
- Tuberculosis, as a single formulation when a patient reacts to another constituent of the fixed dose combination.

Cautions:

- Pregnancy;
- Hepatic impairment (monitor hepatic function);
- Diabetes; and
- Gout (avoid in acute attack).

Interactions:

For interactions with ARVs, see appendix E.

Contraindications:

Porphyria

Side effects:

- Hepatotoxicity, including fever, anorexia, hepatomegaly, splenomegaly, jaundice, liver failure;
- Nausea, vomiting, flushing, dysuria, arthralgia, sideroblastic anaemia, rash and occasionally photosensitivity.

For management of side effects see appendix A

Dosage and administration: See tables 3–7.

ETHAMBUTOL (E)

Ethambutol is a synthetic, water-soluble, heat-stable compound used in the treatment of tuberculosis caused by ***Mycobacterium tuberculosis***.

Indications:

- Tuberculosis, in combination with other drugs.
- Tuberculosis, as a single formulation when a patient reacts to another constituent of the fixed dose combination.

Cautions:

- Renal impairment;
- In the elderly;
- In pregnancy;
- Test visual acuity before treatment and warn patients to report visual changes; and
- In young children, routine ophthalmological monitoring is recommended.

Contraindications:

- Optic neuritis, poor vision.

Side effects:

- Optic neuritis, red/green colour blindness, peripheral neuritis; rarely rash, pruritus, urticaria, and thrombocytopenia.

Dosage and administration: See tables 3–7.

STREPTOMYCIN (S)

Strepromycin belongs to the aminoglycosides class of drugs. It is active against susceptible strains of Mycobacterium tuberculosis. Streptomycin penetrates into cells poorly and is active against extracellular bacilli, but it crosses the blood-brain barrier and achieves therapeutic concentrations with inflamed meninges.

Indications:

Tuberculosis, in combination with other drugs.

Cautions:

- Pregnancy;
- Renal impairment;
- Neonates, infants, and elderly;
- Avoid prolonged use;
- Conditions characterised by muscular weakness; and
- Obesity.

Interactions:

For interactions with ARV drugs, see appendix E.

Contraindications:

Myasthenia gravis

Side effects:

- Ototoxicity, nephrotoxicity;

- Rarely, hypomagnesaemia on prolonged therapy, antibiotic-associated colitis, stomatitis; and
- Also reported, nausea, vomiting, rash, blood disorders.

For management of side effects, see appendix A.

Dosage and administration: See tables 3–7.

DOSAGE AND ADMINISTRATION OF FIRST LINE DRUGS

Table 3: Isoniazid Preventive Therapy

Weight	Target Dose (OD)	INH 100mg tabs	INH 300mg tabs
Under 10kg	100mg	1 tab 24–hourly	
10–13.9kg	150mg	1 ½ tabs 24–hourly	½ tab 24 hourly
14–19.9kg	200mg	2 tabs 24–hourly	
20–24.9kg	250mg	2 ½ tabs 24–hourly	
25kg or above	300mg	3 tabs 24–hourly	

Tuberculosis is treated with multiple drugs in the form of Fixed Dose Combinations, single tablets, and streptomycin for injection. The dosages are calculated based on weight. These are indicated in the tables 4–7:

Table 4: Dosages for Treatment of Susceptible Tuberculosis in Adults

ADULTS		
Body weight in kg	Initial phase 2 months [RHZE] [R150/H75/Z400/E275]	Continuation phase 4 months [RH] [R150/H75]
30–37	2	2
38–54	3	3
55–74	4	4
75 and over	5	5

Table 5: Dosages for Treatment of Susceptible Tuberculosis in Children

CHILDREN			
Body weight in kg	Initial phase 2 months [RHZ] (R60/H30/Z150) Number of tablets	 E100 Number of tablets	Continuation phase 4 months [RH] (R60/H30) Number of tablets
< 7	1	1	1
8–9	1.5	1.5	1.5
10–14	2	2	2
15–19	3	3	3
20–24	4	4	4
25–29	5	5	5

The following dosages of anti-TB medicines should be given daily for the treatment of TB in children:

isoniazid (H) 10mg/kg (range 7–15mg/kg); maximum dose 300mg day

rifampicin (R) 15mg/kg (range 10–20mg/kg); maximum dose 600mg/day

pyrazinamide (Z) 35mg/kg (range 30–40mg/kg)

ethambutol (E) 20mg/kg (range 15–25mg/kg)

Table 6: Dosages for Treatment of TB Meningitis

TB MENINGITIS TREATMENT FOR ADULTS & CHILDREN					
Body weight in kg	Initial phase 2 months (SRHZE)				Continuation phase 7 months (RH)
	S	RH	Z	E	
< 5kg	15mg/kg	0.25	0.25	0.25	0.25
5–8kg	15mg/kg	0.5	0.5	0.5	0.5
9–14kg	15mg/kg	1	1	1	1
15–19kg	15mg/kg	1.5	1.5	1.5	1.5
20–24kg	15mg/kg	1.5	1.5	1.5	1.5
25–39kg	0.5g	2	2	2	2
40–55kg	0.75g	3	3	3	3
> 55 kg	1g	4	4	4	4

Table 7: Retreatment Regimen with First Line Drugs for Patients Previously Treated for Tuberculosis with Low-Risk for MDR-TB

Intensive Phase	Continuation Phase
SRHZE daily for 2 months, then RHZE for 1 month	RHE daily for 5 months

Note: All medicines should be given under direct observed treatment (DOT) throughout the entire course of treatment.

SECOND LINE ANTI-TB MEDICINES

CAPREOMYCIN (CM)

An aminoglycoside-related polypeptide antibiotic, produced by Streptomyces capreolus, which is active against human strains of Mycobacterium tuberculosis.

Indications:

Used in combination with other drugs in the treatment of tuberculosis resistant to first line drugs.

Cautions:

- Pregnancy;
- Renal impairment;
- Neonates, infants, and elderly;
- Avoid prolonged use; and
- Obesity.

Contraindications:

- Hypersensitivity to capreomycin and
- Myasthenia gravis.

Side effects:

- Hypersensitivity reactions, including urticarial and rashes;
- Leucoytosis or leucopenia, rarely thrombocytopenia;
- Changes in liver function tests;
- Nephrotoxicity, electrolyte disturbances;
- Hearing loss with tinnitus and vertigo;
- Neuromuscular block after large doses; and
- Pain and induration at injection site.

For the management of side effects, see appendix A.

Dosage and administration: See table 8.

ETHIONAMIDE (ET)

Ethionamide is chemically related to isoniazid. It is poorly water-soluble and available only in oral form. It is metabolized by the liver.

Indications:

It is used in combination with other drugs in the second line treatment of tuberculosis.

Cautions:

- Hepatic impairment;
- Alcohol dependence;
- Poor vision;
- Diabetes mellitus;
- Hypothyroidism; and
- Vitamin B12 deficiency, folic acid deficiency, megaloblastic anaemia, sideroblastic anaemia.

Contraindications:

Severe hepatic impairment.

Side effects:

- Nausea, vomiting, diarrhoea, abdominal pain, excessive salivation, metallic taste, stomatitis, anorexia, and weight loss.
- Psychotic disturbances, mental depression, drowsiness, dizziness, restlessness, headache, peripheral neuritis, and a pellagra-like syndrome;
- Optic neuritis, diplopia, and blurred vision;

- Transient increases in serum bilirubin, SGOT, SGPT, and hepatitis, with or without jaundice;
- Rash, photosensitivity, thrombocytopenia, and purpura;
- Hypoglycemia and hypothyroidism;
- Gynecomastia and impotence;
- Thrombocytopenia and purpura; and
- Postural hypotension.

For the management of side effects, see appendix A.

Dosage and administration: See table 8.

CYCLOSERINE (CS)

Cycloserine, a broad-spectrum antibiotic, which may be bactericidal or bacteriostatic, and is produced by Streptomyces garyphalus. It is active against some resistant strains of Mycobacterium tuberculosis.

Indications:

It is used in combination with other drugs in the second line treatment of tuberculosis.

Cautions:

- Renal impairment;
- Hepatic impairment; and
- Pregnancy and breastfeeding.

Interactions:

For interactions, see appendix E.

Contraindications:

Severe renal impairment, epilepsy, depression, severe anxiety, psychotic states, alcohol dependence, and acute porphyria.

Side effects:

Mainly neurological, including—

- Headache, dizziness, vertigo, drowsiness, tremor, convulsions, confusion, psychosis, depression;

- Rashes, allergic dermatitis;
- Megaloblastic anaemia;
- Changes in liver function tests; and
- Heart failure at high doses reported.
- For the management of side effects, see appendix A.

Dosage and administration: See table 8.

LEVOFLOXACIN (LFX)

Levofloxacin is a synthetic broad-spectrum antibacterial agent which belongs to the fluoroquinolone class. It is active against some resistant strains of Mycobacterium tuberculosis.

Indications:

It is used in combination with other drugs in the second line treatment of tuberculosis.

Cautions:

- Patients with a history of epilepsy or conditions that predispose to seizures;
- G6PD deficiency;
- Myasthenia gravis (risk of exacerbation);
- Renal impairment;
- Pregnancy and breast-feeding;
- Children or adolescents; and
- Patients with or without a history of convulsions; taking nonsteroidal anti-inflammatory drugs (NSAID) at the same time, may also induce them.

Note: Exposure to excessive sunlight should be avoided (discontinue if photosensitivity occurs).

Contraindications:

- Quinolone hypersensitivity; and
- History of tendon disorders related to quinolone use.

Side effects:

- Nausea, vomiting, dyspepsia, abdominal pain, diarrhoea, headache, dizziness, rash;
- Less frequent side effects include anorexia, sleep disturbances, asthenia, confusion, anxiety, depression, hallucinations, tremor, blood disorders (including eosinophilia, leucopenia, thrombocytopenia), arthralgia, myalgia, disturbances in vision and taste; and
- Also, tachycardia; very rarely pneumonitis, hypoglycaemia, and rhabdomyolysis.

For the management of side effects, see appendix A.

Dosage and administration: See table 8.

DOSAGE AND ADMINISTRATION OF SECOND LINE DRUGS

Table 8: Dosages for Treatment of Multi-Drug Resistant Tuberculosis

ADULTS		
Body Weight in kg	Initial Phase 6 Months Dosage (mg)	Continuation Phase 18 Months Dosage (mg)
<50Kg	Capreomycin (Cm) 1g Ethionamide (Et) 500mg Pyrazinamide (Z) 1000mg Levofloxacin (Lfx) 750mg Cycloserine (Cs) 500mg	Ethionamide 500mg Levofloxacin 750mg Cycloserine 500mg
50–65Kg	Capreomycin 1g Ethionamide 750mg Pyrazinamide 1500mg Levofloxacin 750mg Cycloserine 750mg	Ethionamide 750mg Levofloxacin 750mg Cycloserine 750mg
>65Kg	Capreomycin 1g Ethionamide 750mg Pyrazinamide 2000mg Levofloxacin 750mg Cycloserine 750mg	Ethionamide 750mg Levofloxacin 750mg Cycloserine 750mg

CORTICOSTEROIDS AND TUBERCULOSIS

- Corticosteroids, in conjunction with anti-TB medicines, reduce the risk of death in TB meningitis and TB pericarditis.
- Patients with TB meningitis or TB pericarditis should be given corticosteroids for an initial period of 21 days, followed by tapering off by 25% per week, over four weeks.
- Either prednisolone or dexamethasone can be used.

Table 9: Corticosteriod Dosing in TB Meningitis

Patient category	Corticosteriod	Initial Phase Dose	Initial Phase Duration
Children	Prednisolone	2mg/kg (max 40mg)	21 days
Adults	Dexamethasone	12mg per day	21 days
	Prednisolone	60mg per day	21 days

Table 10: Prednisolone Dosing in Tuberculous Pericarditis

Patient Category	Days 0–28	Days 29–56	Days 57–70	Days 71–77
Adults	60mg	30mg	15mg	5mg
Children	1mg/kg	0.5mg/kg	0.25mg/kg	0.1mg/kg

CORTICOSTEROIDS IN CUTANEOUS AND GENERALISED HYPERSENSITIVITY REACTION SKIN ERUPTIONS

If a patient complains of itching, but without a rash, give antihistamines. If a rash develops, all treatment should be stopped because of the risk of precipitating a severe reaction. If the rash is severe, or there is evidence of mucosal involvement or hypotension, corticosteroid treatment (1 mg/kg prednisolone) should be instituted. The amount of prednisolone is gradually reduced in the following days, based on the patient's response. In patients with severe reactions, sometimes anti-TB treatment must be stopped for 3–4 weeks.

REINTRODUCTION OF ANTI-TB MEDICINES

After the reaction has subsided, anti-TB medicines are reintroduced sequentially according to Girling's standard guidelines, using increasing challenge doses (see table 11). First, determine if the patient can tolerate a full dose of isoniazid before adding rifampicin; then, evaluate if the patient can tolerate a full dose of rifampicin before introducing pyrazinamide, and so on.

Table 11: Challenge Doses

Drug	Day	Dose 1	Dose 2	Dose 3
Isoniazid (H)	1	50mg		
	2		300mg	
	3			300mg
Rifampicin (R)	4	75mg		
	5		300mg	
	6			Full dose
Pyrazinamide (Z)	7	200mg		
	8		800mg	
	9			Full dose
Ethambutol (E)	10	100mg		
	11		400mg	
	12			Full dose
Streptomycin (S)	13	125mg		
	14		500mg	
	15			Full dose

The drugs at the top of the table are the least likely to cause a reaction and should be reintroduced first. Drugs at the bottom of the table are most likely to cause a reaction. If the initial cutaneous reaction was severe, smaller initial challenge doses should be given, approximately 1/10 of the doses shown for day 1. If a patient is recommenced on an adequate anti-tuberculosis treatment regimen (e.g., isoniazid, rifampicin, and pyrazinamide), then rechallenging with the implicated drug (e.g., streptomycin) is not advisable.

REFERENCES

BMJ Group. (2008). ***British National Formulary (BNF) 56th edition.*** London: RPS Publishing.

Katzung, B. (2006). ***Basic and Clinical Pharmacology*** (10th ed.). Columbus, OH: McGraw Hill.

Ministry of Health, Malawi. (2012). ***National Tuberculosis Control Programme Manual 7th Edition.*** Lilongwe: Ministry of Health, Malawi.

Ministry of Health, Malawi. (2014). ***2014 Clinical Management of HIV in Children and Adults.*** Lilongwe: Ministry of Health, Malawi.

Ministry of Health, Malawi. (2014). ***Malawi Standard Treatment Guidelines (MSTG) 5th Edition 2014: Incorporating Malawi Essential Medicines List (MEML) 2014.*** Lilongwe: Government of Malawi.

Ministry of Health, Malawi. (2015). ***National Tuberculosis Control Programme National Strategic Plan 2015 to 2020.*** Lilongwe: Ministry of Health, Malawi.

Partners In Health. (2013). ***The PIH Guide to the Medical Management of Multidrug-Resistant Tuberculosis*** (2nd ed.). Boston, USA.: USAID TB CARE II.

Rang, H., Dale, M., Ritter, J., & Flower, R. (2007). ***Rang and Dale's Pharmacology*** (6th ed.). Churchill Livingstone.

APPENDIX A

Management of Side Effects of Anti-TB Medicines

Side Effect	Suspected Agent(S)	Suggested Management Strategies	Comments
Seizures	Cs H, Fluoroquinolone	Suspend suspected agent pending resolution of seizures. Initiate anticonvulsant therapy (e.g., phenytoin, valproic acid). Increase pyridoxine to maximum daily dose (200mg per day). Restart suspected agent or reinitiate suspected agent at lower dose, if essential to the regimen. Discontinue suspected agent if this can be done without compromising regimen.	Anticonvulsant is generally continued until MDR-TB treatment is completed or the suspended agent is discontinued. History of previous seizure disorder is not a contraindication to the use of agents listed here, if a patient's seizures are well controlled and/ or the patient is receiving anticonvulsant therapy. Patients with history of previous seizures may be at increased risk for developing seizures during MDR-TB therapy.

Side Effect	Suspected Agent(S)	Suggested Management Strategies	Comments
Peripheral neuropathy	Cs, H S, Kanamycin (Km), Amikacin (Am), Cm, Et/ Prothionamide (Pto), fluoro-quinolones	Increase pyridoxine to maximum daily dose (200mg per day). Change injectable to capreomycin if patient has documented susceptibility to capreomycin. Initiate therapy with tricyclic antidepressants, such as amitriptyline. Non-steroidal anti-inflammatory drugs or acetaminophen may help alleviate symptoms. Lower dose of suspected agent, if this can be done without compromising regimen. Discontinue suspected agent, if this can be done without compromising regimen.	Patients with co-morbid disease (e.g., diabetes, HIV, alcohol dependence) may be more likely to develop peripheral neuropathy, but these conditions are not contraindications to use of the agents listed here. Neuropathy may be irreversible; however, some patients may experience improvement when offending agents are suspended.

Side Effect	Suspected Agent(S)	Suggested Management Strategies	Comments
Hearing loss	S, Km, Am, Cm, Clarithromycin (Clr)	Document hearing loss and compare with base line eudiometry, if available. Change parental treatment to capreomycin if patient has documented susceptibility to capreomycin. Increase frequency and/or lower dose of suspected agent, if this can be done without compromising the regimen (consider administration three times a week). Discontinue suspected agent if this can be done without compromising the regimen.	Patients with previous exposure to aminoglycocides s may have baseline hearing loss. In such patients, audiometry may be helpful at the start of MDR-TB therapy. Hearing loss is generally not reversible. The risk of further hearing loss must be weighed against the risks of stopping the injectable in the treatment regimen.
Psychotic symptoms	Cs, H, fluoro-quinolones, Et/Pto	Stop suspected agent for a short period of time (1–4 weeks) while psychotic symptoms are being brought under control. Initiate antipsychotic therapy. Lower dose of suspected agent if this can be done without compromising the regimen. Discontinue suspected agent if this can be done without compromising the regimen.	Some patients will need to continue antipsychotic treatment throughout MDR-TB therapy. Previous history of psychiatric disease is not a contraindication to the use of agents listed here, but may increase the likelihood of psychotic symptoms developing during treatment. Psychotic symptoms are generally reversible upon completion of MDR-TB treatment or cessation of the offending agent.

Side Effect	Suspected Agent(S)	Suggested Management Strategies	Comments
Depression	Socio-economic circumstances, chronic disease, Cs, Fluoroquinolone, H, Et/Pto	Improve socioeconomic conditions. Group or individual counselling. Initiate antidepressants therapy. Lower dose of suspected agent, if this can be done without compromising the regimen. Discontinue suspected agent, if this can be done without compromising the regimen.	Socioeconomic conditions and chronic illnesses should not be underestimated as contributing factors to depression. Depressive symptoms may fluctuate during therapy and may improve as illness is successfully treated. History of previous depression is not contraindication to the use of the agents listed, but may increase the likelihood of depression developing during treatment.
Hypo-thyroidism	Para-aminosalicylic acid (PAS), Et/Pto	Initiate thyroxine therapy. Follow thyroid stimulating hormone (TSH) levels and adjust thyroxine periodically.	Completely reversible upon discontinuation of PAS or ethionamide/protionamide. The combination of ethionamide/protionamide with PAS is more frequently associated with hypothyroidism than the individual use of the drug.

Side Effect	Suspected Agent(S)	Suggested Management Strategies	Comments
Nausea and vomiting	Et/Pto, PAS, H, E, Z	Assess for dehydration; initiate hydration, if indicated. Initiate antiemetic therapy. Lower dose of suspected agent, if this can be done without compromising regimen. Discontinue suspected agent, if this can be done without compromising regimen—rarely necessary.	Nausea and vomiting universal in early weeks of therapy and usually abate with time on treatment and adjunctive therapy. Electrolytes should be monitored and replete if vomiting is severe. Reversible upon discontinuation of suspected agent. Severe abdominal distress and acute abdomen have been reported with the use of clofazimine. Although these reports are rare, if this effect occurs, clofazimine should be suspended.
Gastritis	PAS, Et/Pto	H2 blockers, proton pump inhibitors, or antacids. Stop suspected agent(s) for short periods of time (e.g., 1–7 days). Lower dose of suspected agent, if this can be done without compromising regimen. Discontinue suspected agent, if this can be done without compromising regimen.	Severe gastritis, as manifested by haematemesis, melaena, or haematecheza is rare. Dosing of antacids should be carefully timed so as not to interfere with the absorption of anti-tuberculosis drugs (take 2 hours before or 3 hours after anti-tuberculosis medications). Reversible upon discontinuation of suspected agent(s).

Side Effect	Suspected Agent(S)	Suggested Management Strategies	Comments
Hepatitis	Z,H, R, Et/Pto, PAS,E, fluoro-quinolones	Stop all therapy pending resolution of hepatitis. Eliminate other potential causes of hepatitis. Consider suspending most likely agent permanently and reintroduce remaining drugs; one at a time, with the most hepatotoxic agents first, while monitoring liver function.	History of previous hepatitis should be carefully analyzed to determine most likely causative agent(s); these should be avoided in future regimens. Generally reversible upon discontinuation of suspected agent.
Renal toxicity	S, Km, Am, Cm	Discontinue suspected agent. Consider using capreomycin if an aminoglycoside had been the prior injectable in regime. Consider dosing 2–3 times a week, if drug is essential to the regimen and patient can tolerate (close monitoring of creatinine). Adjust all TB medications according to the creatinine clearance.	History of diabetes or renal disease is not a contraindication to the use of the agents listed here, although patients with these co-morbidities may be at increased risk of developing renal failure. Renal impairment may be permanent.
Electrolyte disturbances (hypokalae-mia and hypomagn-esaemia	Cm, Km, Am, S	Check potassium If potassium is low also check magnesium (And calcium, if hypocalcaemia is suspected). Replace electrolytes, as needed.	If severe hypocalcaemia is present, consider hospitalization. Amiloride 5–10mg or spironolactone 25mg may decrease potassium and magnesium wasting and is useful in refractory cases.

Side Effect	Suspected Agent(S)	Suggested Management Strategies	Comments
Optic neuritis	E	Stop E. Refer patient to an ophthalmologist.	Usually reverses with cessation of E. Rare case reports of optic neuritis have been attributed to streptomycin.
Arthralgias	Z, fluoroquinolone	Initiate therapy with non-steroidal anti-inflammatory drugs. Lower dose of suspected agent, if this can be done without compromising regimen. Discontinue suspected agent, if this can be done without compromising regimen.	Symptoms of arthralgia generally diminish over time, even without intervention. Uric acid levels may be elevated in patients on pyrazinamide. Allopurinol does not appear to correct uric acid levels in such cases.

Note: Take note of the following when dealing with drugs considered hepatotoxic:

- Isoniazid, rifampicin, and pyrazinamide are recognised as being hepatotoxic.
- TB patients with active liver disease (i.e., those with jaundice or ascites) should not receive pyrazinamide or rifampicin.
- They should be given 2 months of streptomycin, isoniazid, and ethambutol during the intensive phase of treatment; followed by 10 months of isoniazid and ethambutol.
- If the jaundice is acute and severe, then treat initially with only streptomycin and ethambutol.

APPENDIX B

Ancillary Medicines for the Management of Side Effects and Complications

Drug Class	Medicine and Dosage	Notes
Gastrointestinal drugs		
Antiemetics	Metoclopramide: 10mg PO/IM/IV three or four times a day PRN, usually given 30 minutes prior to meals or medications.	Many of these drugs have side effects, including extrapyramidal reactions, drowsiness, sedation, etc.
	Dimenhydrinate: 50–100mg PO/IM/IV every four to six hours.	Stop if tardive dyskinesia develops.
	Prochlorperazine: 5–10 mg PO/IM/PR three or four times a day.	
	Promethazine: 12.5–25.0mg PO/IM/PR every four to six hours.	
	Ondansetron: 4–8mg PO 30 minutes before anti-TB medicines, repeated every eight hours.	
Medications for anticipatory vomiting	Lorazepam 0.5-2.0mg PO 30 to 60 minutes prior to anti-TB medicines.	Because of its shorter half-life, lorazepam is preferable over diazepam.
	Diazepam: 2.0–10mg PO 30 to 60 minutes prior to anti-TB medicines.	Warning: Potential for addiction.

Drug Class	Medicine and Dosage	Notes
Antacids	CaHCO3, MgSO4, aluminum hydroxide: the most common formulation is combination of magnesium and aluminum hydroxide 1–30mL PO three times a day PRN.	Must be taken three hours before or two hours after taking anti-TB medications. Magnesium-containing antacids can cause diarrhoea, and aluminum-containing antacids can cause constipation.
H2 blockers	Ranitidine: 300mg PO at night.	Alternatives are cimetidine, famotidine, and nizatidine.
Proton pump inhibitors	Omeprazole: 20mg PO at night.	Alternatives are esomeprazole, lansoprazole, pantoprazole, and rabeprazole.
Gastrointestinal drugs		
Antifungal drugs	Fluconazole: 200mg single dose, or 100mg daily for 5 to 14 days. Clotrimazole: 1 troche (10mg) 5 times daily for 14 days.	HIV-negative MDR-TB patients may also have oral candidiasis. These drugs have significant interactions with rifampicin, oral hypoglycemics, phenytoin, theophylline, and other medications.
Antidiarrheals	Loperamide: 4mg initially, then 2mg PO after each unformed stool, for a maximum of 16mg/day.	Diarrhea is common in patients receiving PAS. Do not use for diarrhea associated with fever or blood in the stool. Rehydration: Oral rehydration packets, as needed. IV fluids with electrolytes, as needed. IV hydration may be preferred if nausea and vomiting are associated with the dehydration.
Psychiatric drugs		

Drug Class	Medicine and Dosage	Notes
Tricyclic antidepressants	Amitriptyline: Start 25–100mg PO at night; gradually increase the dose to usual effective dose 50–300mg/day.	Avoid in patients with risk of arrhythmias.
Selective serotonin reuptake inhibitors	Fluoxetine: Start 20mg PO daily, usual effective dose 20–40 mg/day, maximum dose 80mg/day. Sertraline: Start 25–50mg PO daily; usual effective dose 50–200mg/day, maximum dose 200mg/day.	Other alternatives include citalopram, fluvoxamine, and paroxetine.
Benzodiazepines	Lorazepam 0.5–2.0mg: PO every four to six hours PRN. Diazepam 2.0–10.0mg: PO two or three times a day PRN. Clonazepam: Start 0.25–0.50mg: PO three times a day; maximum 20mg/day (often doses much less than this are effective).	Many benzodiazepines have a long half-life and should be used with caution. Warning: Potential for addiction.
Antipsychotics	Haloperidol: Start 0.5–5.0mg PO two or three times a day. Usual effective dose 2–10mg/day for cycloserine-induced psychosis. Risperidone: Start 0.5–5.0mg PO two or three times a day. Usual effective dose 2–10mg/day for cycloserine-induced psychosis.	Risperidone is more expensive, but has fewer side effects. Benztropine 1–4mg PO QD/BID or biperiden 2mg QD/BID may be used to treat extrapyramidal side effects.
Neurological drugs		
Benzodiazepines	Diazepam: Active seizing: 0.2–0.4mg/kg up to 5–30mg IV.	Diazepam may be used to control active seizures.

Drug Class	Medicine and Dosage	Notes
Anticonvulsants	Phenytoin: Load 10–20mg/kg (1,000mg in typical adult) IV, no faster than 50mg/min. Oral load: 400mg initially, then 300mg in two hours and four hours. Maintenance 5mg/kg or 100mg PO three times a day. Carbamazepine: 200–400mg PO two or four times a day. Valproic acid: Start 15mg/kg PO daily or divided in two daily doses, maximum 60mg/kg. Phenobarbital: Load 15–20mg / kg up to 300-800mg IV at 25–50mg/min. Maintenance 60mg PO two or three times a day.	
Vitamins	Pyridoxine: Use at least 50 mg for every 250mg of cycloserine.	Pyridoxine is important for the prevention of peripheral neuropathy and other neurotoxicity in patients receiving cycloserine. Consider using high doses of 300mg per day in patients with refractory side effects.
Tricyclic antidepressants	Amitriptyline: Start 25–100mg PO at night; gradually increase the dose to usual effective dose 50–300mg/day.	Low-dose amitriptyline is effective for the symptomatic treatment of peripheral neuropathy. Avoid in patients with risk of arrhythmias.
Antihistamines	Meclizine 25mg: PO every six hours.	May be effective in patients with vestibular symptoms.

Drug Class	Medicine and Dosage	Notes
Analgesics	Ibuprofen 200–800mg: PO three or four times a day PRN. Acetaminophen 325–650mg: PO every four to six hours PRN.	Analgesics may be helpful for headache or peripheral neuropathy. Alternatives include other similar NSAID drugs, paracetamol, or aspirin.
Opioid-containing analgesics	Codeine, often in combination with acetaminophen, for severe refractory headaches can be used: 15–60 mg every four to six hours.	Warning: Potential for addiction.
Drugs for cutaneous reactions		
Corticosteroid creams and ointments	Hydrocortisone (1 percent to 2 percent): Apply to affected area two or four times a day.	
Antipruritus lotions	Calamine, Caladryl lotions: Apply to affected area two or four times a day.	
Antihistamines	Diphenhydramine 25–50mg: PO every four to six hours. Chlorpheniramine 4mg: PO every four to six hours. Dimenhydrinate 50–100mg: PO/IM/IV every four to six hours.	
Corticosteroids	See sections below on drugs for systemic hypersensitivity reactions.	

Drug Class	Medicine and Dosage	Notes
Drugs for arthralgias, non-gouty arthritis		
Analgesics	Ibuprofen 200–800mg: PO three or four times a day PRN. Acetaminophen 325–650mg: PO every four to six hours PRN.	Can also use similar NSAID drug or aspirin.
Drugs for hypothyroidism		
Thyroid replacement hormone	Levothyroxine: Start 50–100mcg per day (start 25–50mcg in the elderly or patients with cardiac disease) and increase dose by 12.5–25mcg every three to eight weeks.	Usual maintenance dose is 100–200mcg/day.
Drugs to manage fluids and electrolytes		
Loop diuretics	Furosemide 20–80mg: IV/IM/PO every 6–24 hours.	Added ototoxicity when used with an aminoglycoside.
Potassium-sparing diuretics	Amiloride 5mg: PO daily, maximum dose 20mg/day.	Used for uncontrolled potassium wasting.
Electrolyte replacement therapy	There are various formulations of potassium, magnesium, and calcium replacement therapy.	
Drugs for bronchospasm		
Beta-agonist inhalers	Albuterol inhaler 90mcg per spray, two puffs every four to six hours.	For acute bronchospasm, use 400–500mcg (four to five puffs).
Beta-agonist nebulizers	Albuterol solution for nebulization 2.5mg (0.5mL of 0.5 percent solution) every six hours.	
Inhaled corticosteroids	Beclomethasone, budesonide, or fluticasone HFA inhaler; dosing depends on brand.	

Drug Class	Medicine and Dosage	Notes
Oral corticosteroids	Prednisone 1–2mg/kg per day; taper dose, as indicated.	Injectable steroids can be used for severe cases of bronchospasm and epinephrine is rarely needed (see hypersensitivity section in this table for dosing).
Drugs for systemic hypersensitivity reactions		
Antihistamines	Diphenhydramine 25–50mg PO/IM/IV every four to six hours.	
Oral corticosteroids	Prednisone 1–2mg/kg per day, then taper dose as indicated.	
Injectable corticosteroids	Dexamethasone: Doses vary, 4mg every 6–12 hours.	Other alternatives are prednisolone, methylprednisolone, and others.
Other drugs	Epinephrine 0.1–0.5mg SC (1:1,000 solution).	May repeat after 20 minutes.

APPENDIX C

Use of Anti-TB Medicines in Pregnancy

CONSIDERATIONS

- Pregnancy should be avoided while undergoing treatment for MDR-TB, because some of the second-line anti-TB medicines may cause birth defects.
- Determination of the degree of TB disease severity in the pregnant woman is critical:
  - Severity of symptoms of active TB.
  - Degree of weight loss and ability to do normal daily activities.
  - Extent of disease on chest x-ray.
  - Bacteriological evaluation (e.g., sputum smear and culture).
- The decision to postpone the start of treatment should be agreed upon by the patient and doctor after discussing the risks of untreated TB versus the benefits of delaying exposure of the foetus to teratogens.
  - Untreated MDR-TB in pregnant women carries similar risks of morbidity and mortality compared to non-pregnant women.
  - The foetus can develop congenital TB or, more commonly, can be infected in the postnatal period and progress rapidly to disease.
  - The safety of many second line anti-TB medicines is uncertain.

MANAGEMENT

- The risk of birth defects in MDR-TB treatment is highest in the first trimester of pregnancy. The gestational age of the foetus should be determined, either through calculation based on the last menstrual period or by dating using ultrasound.

- The benefit of treating MDR-TB in pregnancy, in most circumstances, outweighs the risks.
  - Most patients should start treatment as soon as the diagnosis is made.
  - Treatment can be deferred until the second trimester only if the patient is clinically stable, with minimal disease.
- Avoid aminoglycosides during pregnancy due to the risk of toxicity to the developing foetal ear. Capreomycin may carry a lower risk of ototoxicity and is the drug of choice if an injectable cannot be avoided.
- Avoid ethionamide due to the increased risk of nausea and vomiting, as well as its potential teratogenicity.
- Levofloxacin, cycloserine, and PAS have limited data on safety and long-term use in pregnancy but are considered the drugs of choice for MDR-TB treatment in pregnancy.
- The regimen may be reinforced with an injectable and other drugs immediately postpartum.
- Total treatment duration is the same as in non-pregnant patients.

Safety of Anti-TB Medicines in Pregnancy

Medication	Comments
First-line anti-TB medicines	
Isoniazid (H)	Experience in gravid patients suggests safety. Pyridoxine (vitamin B6) should be used during pregnancy.
Rifampin (R)	Experience in gravid patients suggests safety.
Ethambutol (E)	Experience in gravid patients suggests safety.
Pyrazinamide (Z)	Experience in gravid patients suggests safety; however, there is less data than other first-line anti-TB medicines. WHO recommends its routine use.
Streptomycin (S)	Documented toxicity to developing foetal ear. Risks and benefits must be carefully considered. Avoid use when possible.
Second-line anti-TB medicines	
Kanamycin (Km) Amikacin (Am)	Documented toxicity to developing foetal ear. Risks and benefits must be carefully considered. Avoid use when possible.
Capreomycin (Cm)	Avoidance strongly recommended. Less ototoxicity reported in adults with capreomycin than with aminoglycosides; unknown if these data can be extrapolated to the developing foetal ear. Generally, injectables are avoided in the gravid patient, but in life-threatening situations when an injectable is needed, capreomycin could be considered.

Medication	Comments
Fluoroquinolones	Use with caution when essential. No teratogenic effects seen in humans when used for short periods of time (two–four weeks). Long-term use in gravid patients is limited, but given bactericidal activity, benefits may outweigh risks.
Ethionamide (Et)	Avoid, if possible. Teratogenic effects observed in animal studies; significantly worsens nausea associated with pregnancy.
Cycloserine (Cs)	No significant experience in gravid patients; animal studies have not documented toxicity.
PAS	Use with caution when essential. Not considered to be teratogenic.
Bedaquiline (Bdq)	Not recommended due to limited data. This drug should only be used in pregnancy when there are clearly no other options.
Linezolid (Lzd)	Not recommended due to limited data.
Clofazimine (Cfz)	Use with caution when essential; drug appears to be safe during pregnancy when used at lower doses for leprosy, but experience is limited.
Clarithromycin (Clr)	Avoid if possible. May be teratogenic
Rifabutin (Rfb	Experience in gravid patients suggests safety.
Amoxicillin/ Clavulanic acid (Amx/Clv)	Experience in gravid patients suggests safety.

APPENDIX D

Dosing of Anti-TB Medicines in Patients with Renal Insufficiency

CONSIDERATIONS

- Chronic kidney disease is common in MDR-TB patients. Etiologies include renal TB disease, damage due to previous injectable toxicity, diabetes mellitus, and HIV-associated nephropathy.
- Anti-TB medicines that are excreted by the kidney can accumulate to toxic levels in patients with renal dysfunction.

MANAGEMENT

- Renal function should be estimated by calculating the creatinine clearance in all patients receiving MDR-TB treatment.
- Anti-TB therapy should be adjusted in patients with decreased creatinine clearance.

Drug (s)	Dose and Frequency if Creatinine Clearance < 30 mL
Isoniazid (H)	No change
Rifampicin (R)	No change
Pyrazinamide (Z)	25–35mg/kg three times per week (not daily)
Ethambutol (E)	15–25mg/kg three times per week (not daily)
Rifabutin (Rfb)	2.5–5.0mg/kg per day
Streptomycin (S)	12–15mg/kg two or three times per week (not daily)
Kanamycin (Km)	Dose and frequency if creatinine clearance < 30 mL 12–15mg/kg two or three times per week (not daily)

Drug (s)	Dose and Frequency if Creatinine Clearance < 30 mL
Amikacin (Am)	12–15mg/kg two or three times per week (not daily)
Capreomycin (Cm)	12–15mg/kg two or three times per week (not daily)
Levofloxacin (Lfx)	750–1,000mg three times per week (not daily)
Moxifloxacin (Mfx)	No change
Ofloxacin (Ofx)	600–800mg three times per week (not daily)
Ethionamide (Et)	250–500mg daily
Prothionamide (Pto)	250–500mg daily
Cycloserine (Cs)	250mg once daily or 500mg three times per week
PAS	8g/day in two divided doses
Bedaquiline (Bdq)	No change in mild to moderate renal impairment (dosing not established in severe renal impairment, use with caution)
Linezolid (Lzd)	No change
Clofazimine (Cfz)	No change
Amoxicillin/clavulanic acid (Amx/Clv)	1,000/250mg once daily for creatinine clearance < 10 mL/min
Imipenem/cilastatin (Imp/Cln)	750mg every 12 hours for creatinine clearance 20–40mL/min 500mg every 12 hours for creatinine clearance < 20mL/min
Meropenem (Mpm)	750 mg every 12 hours for creatinine clearance 20–40mL/min 500mg every 12 hours for creatinine clearance < 20mL/min

APPENDIX E

Drug-Drug Interactions between Anti-TB Medicines and Antiretroviral Therapy

- Certain combinations of anti-TB medicines and ARVs increase the risk of side effects or reduce each other's effectiveness (due to faster excretion).
- The following table shows the relevant interactions:
  - **Green:** The combination has no problems.
  - **Yellow:** The combination usually causes no problems, but monitoring is required for increased side effects. Dose adjustment may be required.
  - **Red:** Do not combine the drugs without specialist advice.

	Isoniazid	Rifampicin	Streptomycin	Ethambutol	Pyrazinamide
TDF	OK	OK	renal toxicity	OK	OK
AZT	OK	OK	OK	OK	OK
3TC	OK	OK	OK	OK	OK
d4T	neuropathy	OK	OK	OK	OK
EFV	OK	OK	skin rash	OK	hepatitis
NVP	skin rash	start NVP full dose, hepatitis	skin rash	OK	hepatitis
ABC	OK	OK	OK	OK	OK
ATV/r	OK	no experience (don't combine)	OK	OK	OK
LPV/r	OK	major dose adjustment	OK	OK	OK

APPENDIX F

Recommended ART Regimens for Children in Need of TB Treatment

SUMMARY OF RECOMMENDED ART REGIMENS[A] FOR CHILDREN IN NEED OF TB TREATMENT

Recommended Regimen for Children and Infants Starting ART While on TB[b] Treatment[c]		
Younger than 3 years		2 NRTIs + NVP ensuring that dose is 200mg/m^2 or Triple NRTI (AZT + 3TC + ABC)[d]
3 years and older		2 NRTIs + EFV or Triple NRTI (AZT + 3TC + ABC)[d]
Recommended Regimen for Children and Infants Starting TB Treatment[b] While on ART		
Child on standard NNRTI-based regimen (2NRTIs + EFV or NVP)	Younger than 3 years	Continue NVP, ensuring that dose is 200mg/m^2 or Triple NRTI (AZT + 3TC + ABC)[d]
	3 years and older	If on EFV, continue same regimen If on NVP, change to EFV or Triple NRTI (AZT + 3TC + ABC)[d]

Child on standard PI-based regimen (2 NRTIs + LPV/r)	Younger than 3 years	Triple NRTI (AZT + 3TC + ABC)[d] or Change to NVP ensuring that dose is 200mg/m^2 or Continue LPV/r and consider adding RTV to achieve full therapeutic dose[e]
	3 years and older	*If no history of NNRTI-based regimen failure:* Change to EFV[f] or Triple NRTI (AZT + 3TC + ABC)[d] or Continue LPV/r and consider adding RTV to achieve full therapeutic dose[e] *If history of NNRTI-based regimen failure:* Triple NRTI (AZT + 3TC + ABC)[d] or Continue LPV/r and consider adding RTV to achieve full therapeutic dose[e] Consider consultation with experts for construction of second-line regimen.

a Abbreviations used: ABC (abacavir); AZT (zidovudine); EFV (efavirenz); LPV/r (lopinavir/ritonavir); NNRTI (non-nucleoside reverse transcriptase inhibitor); NRTI (nucleoside reverse transcriptase inhibitor); RTV (ritonavir); 3TC (lamivudine).

b Ensure optimised dosing of rifampicin, based on new dosing guidelines.

c Switch to age-appropriate ART regimen, based on national first-line ART at termination of TB treatment.

d Triple NRTI treatment is recommended only for the duration of TB treatment: an age-appropriate PI- or NNRTI-based regimen should be restarted at termination of rifampicin-based therapy. Based on findings from the ARROW trial, this regimen should be considered as the preferred option for children less than 3 years on LPV/r regimen when starting TB treatment. It should also be considered as the preferred regimen for children older than 3 years with a history of NNRTI failure.

e Increase RTV until same dose as LPV in mg in a ratio of 1:1.

f Change to EFV should be considered as the preferred option and EFV could be maintained after termination of TB treatment to allow simplification and harmonisation with ARVs regimen in use in older children.

NOTES