REPUBLIC OF KENYA

MINISTRY OF HEALTH

DRUG-RESISTANT TB STANDARD OPERATING PROCEDURES

NATIONAL TUBERCULOSIS, LEPROSY AND LUNG DISEASE PROGRAM

DRUG-RESISTANT TB STANDARD OPERATING PROCEDURES

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List of Abrreviations

ADR	Adverse Drug Reaction
AFB	Acid Fast Bacilli
AIDS	Acquired Immunodeficiency Syndrome.
ART	Antiretroviral Therapy
CDC	Centres for Disease Control and Prevention.
CHEW	Community Health Extension Worker
CNR	Case Notification Rate
CRL	Central Reference Laboratory
CTLC	County Tuberculosis and Leprosy Coordinator
DOTS	Directly Observed Therapy Short course.
DST	Drug Susceptibility Testing
SCTLC	Sub county Tuberculosis and Leprosy Coordinator
EPTB	Extra-Pulmonary Tuberculosis
FM	Fluorescent Microscopy
FL-LPA	First Line Line Probe assay
HIV	Human Immunodeficiency Virus.
INH	Isoniazid
IPC	Infection Prevention and Control
KEMRI	Kenya Medical Research Institute.
MDR-TB	Multi- Drug Resistant Tuberculosis
MUT	Mutation
NRL	National Reference Laboratory
NSN	New Smear Negative
NSP	New Smear Positive
PTB	Pulmonary Tuberculosis
PMDT	Programmatic Management of Drug Resistant Tuberculosis
R	Rifampicin
SAE	Severe Adverse Event
SLIDs	Second line injectable drugs
SRL	Supranational Reference Laboratory
TB	Tuberculosis.
UV	Ultraviolet light
WT	Wild type

WHO	World Health Organization
XDRTB	Extensively Drug Resistant Tuberculosis
ZN	Ziehl-Neelsen
IFR	Injectable Free Regimen

CLASSIFICATION OF DRUG-RESISTANT TB

1

Classification of DRTB is as described in the tables below:

1. Classification based on the resistance patterns after drug susceptibility testing

Table 1.1: Classification based on the Resistance pattern:

Resistance pattern	Definition
Presumptive drug-resistant TB case	These are Individuals with a higher risk of getting drug resistant TB than the general population. They include: smear-positive previously treated patients such as relapse, return after default (RAD) and failure; new smear-positive pulmonary TB patients whose sputum remains smear-positive at month 2; symptomatic close contacts of the known MDR-TB patient, refugees, prisoners, health care workers with symptoms of TB, DR TB contacts.
Mono resistance	Resistance to one first-line anti-TB medicine only.
Poly-drug resistance (PDR)	Resistance to more than one first-line anti-TB medicine (other than both Isoniazid and Rifampicin)
Multi-drug resistance (MDR)	Resistance to at least both Isoniazid and Rifampicin
Rifampicin resistance(RR)	Resistance to Rifampicin detected using phenotypic or genotypic methods, with or without other anti-TB drugs. It includes any resistance to Rifampicin, whether mono resistance, multidrug resistance, Poly-drug resistance or extensive drug resistance.
Isoniazid resistance	Refers to Mycobacterium tuberculosis strains with resistance to isoniazid and susceptibility to rifampicin confirmed in vitro
Pre-XDR	Resistance to Isoniazid and Rifampicin and either a fluoroquinolone or a second-line injectable agent but not both.
Extensive drug resistance (XDR)	Resistance to any Fluoroquinolone and at least one of three second-line injectable drugs (Capreomycin, Kanamycin and Amikacin), in addition to multidrug resistance.

2. Classification based on the registration group

Table 1.2: Classification based on the registration of DR TB patients

Registration group	Definition
New (N)	Patients who have never received anti-tuberculosis treatment, or who have received anti-tuberculosis treatment for less than one month. (Note: patients who had DST at the start or within one month of a WHO regimen and are then switched to a second-line regimen because of resistance are placed in this group, even if they received more than one month of Category I treatment).
Relapse (R)	Patients previously treated for tuberculosis that has been declared cured or treatment completed and then diagnosed with MDR-TB.
Return after loss to follow up	Patients who return to treatment with confirmed MDR-TB after interruption of treatment for two months or more.
After the failure of First-Line Treatment (FFT)	Patients who return after having failed the first treatment i.e smear-positive at earliest, month 5
After the failure of Retreatment (FRT).	Patients who return after having failed the re-treatment.

3. Classification based on the anatomical pathological site of the lesion either within or outside the lung parenchyma as described in the table below.

Table 1.3: Classification based on the Anatomical site

Classification	Definition
Pulmonary Drug resistant TB	Any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree. This exclude pleural effusion - Milliary TB is classified as PTB because the lesions are in the lungs. - Tuberculous intrathoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of extra pulmonary TB. - **A patient with both pulmonary and extra pulmonary TB should be classified as a case of PTB**
Extra pulmonary Drug Resistant TB	Any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lung parenchyma, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges.

4. Classification based on the status of HIV infection:

All TB diagnosed patients should have an HIV test done and documented.

Table 1.4: Classification based on HIV status

HIV Positive TB patient	Any bacteriologically confirmed or clinically diagnosed case of TB who has a positive result from HIV testing conducted at the time of TB diagnosis or other documented evidence of enrolment in HIV care, such as enrolment in the pre-ART register or in the ART register once ART has been started
HIV negative patient	Any bacteriologically confirmed or clinically diagnosed case of TB who has a negative result from HIV testing conducted at the time of TB diagnosis. Any HIV-negative TB patient subsequently found to be HIV-positive should be re-classified accordingly
HIV status unknown TB patient	Any bacteriologically confirmed or clinically diagnosed case of TB who has no result of HIV testing and no other documented evidence of enrolment in HIV care. If the patient's HIV status is subsequently determined, he or she should be reclassified accordingly

CLASSIFICATION OF SECOND LINE ANTI-TB MEDICINES

2

The table below is a description of the most current classification of Anti TB medicines by WHO (2019). The classification is based on the efficacy of the molecules, experience of use and tolerability.

All group A drugs are considered bactericidal and should be included in all MDR /RR regimens, unless absolutely contraindicated.

Group B dugs are largely sterilizing agents and should be included in all MDR/ RR regimens, unless absolutely contraindicated.

Group C drugs are considered as ''add on'' drugs. They may be included if an effective regimen cannot be constructed with group A and B drugs or when constructing an individualized regimen for a patient. They are associated with many side effects (intolerant).

N.B: Group C drugs should be included in a regimen only after consultations with the National PMDT TWG team.

Table 1.5: Latest WHO grouping of second line Anti-TB medicines

Group	Medicine	Abbreviation
Group A Include all three medicines (Unless they cannot be used)	Fluoroquinolones *(Levofloxacin Moxifloxacin)*	Lfx Mfx
	Bedaquiline	Bdq
	Linezolid	Lzd
Group B Add both medicines (Unless they cannot be used)	Clofazimine	Cfz
	Cycloserine or Terizidone	Cs Trd

Group C Add to complete the regimen and when medicines from Group A and B cannot be used	Ethambutol	E
	Delamanid	Dlm
	Pyrazinamide	Z
	Imipenem/Cilastatin or Meropenem	Imp/Cln Mpn
	Amikacin or (Streptomycin)	Am (s)
	Ethionamide or Prothionamide	Eto Pto
	p-amino salicylic acid	PAS

NOTE

- This new classification is intended to guide the design of longer individualized regimens; however, majority of DRTB patients will be on standardized regimens.
- Medicines in Group A and C are shown in decreasing order of usual preference for use (most preferred comes first)
- Always use Carbapenems e.g. Imipenem/Cilastatin together with Clavulanate
- Group C drugs should only be added to complete the regimen and when medicines from Group A and B cannot be used.

PATIENT WORKUP

3

After the diagnosis of DRTB, pre-treatment preparation, evaluation, investigations and procedures should be done before initiating treatment. This is aimed at boosting compliance and adherence to the already complex DRTB treatment and prevent negative outcomes.

1. Pre-treatment evaluation

- Confirm diagnosis of DR TB

  Note: DR-TB is a laboratory diagnosis (except in child contacts of DR TB who are unable to expectorate) hence every effort should be made to obtain a specimen and conduct (drug susceptibility testing) DST
- Inform the patient of the diagnosis
- Educate and counsel the patient on DR TB, its treatment, need for adherence and DR TB models of care.
- Obtain a thorough history and perform a physical examination
- Obtain an informed treatment consent for treatment
- Conduct a home visit and contact screening
- Baseline ECG, Visual acuity testing, Neuropathy screening
- Baseline lab tests
- Establish a PMDT team to guide clinical management/ follow-up.

NOTE: Efforts should be geared towards meeting all the above conditions before treatment initiation. However, failure to meet the above conditions should not be a reason to delay treatment initiation.

2. History taking

What history should be taken from DR TB patients?

- Demographic Data/ Patient bio data
- TB History on: Date of previous diagnosis, type of TB start and end dates of treatment, history of HIV co-infection, Microscopy, culture and DST results, Adverse effects & complications
- Past Medical and social History with focus on: LMP & method of contraception, Prior comorbidities, history of medication, Alcohol, drug & tobacco use, drug allergies
- DR TB Contacts: Identify contacts, line list in the contact management register, screen using Chest X-ray and symptoms screening and test all presumptive DR TB using GeneXpert. Conduct home visits to screen contacts and assess TB IPC measures.

3. Physical Examination

On examination, the clinicians should elicit the following

1. Vital signs: Blood pressure, Temperature, Pulse, respiration and Oxygen Saturation (SpO_2)
2. Anthropometric measurements: BMI and Z-scores
3. General and Systemic examination
    - All body systems should be examined, not just the respiratory system
    - Visual acuity tests (Ishihara charts and Snellen's charts) and neuropathy screening should be done for all patients.
4. Review of systems for the suggestion of advanced disease
    - Fever
    - Extra pulmonary signs e.g. CNS signs, effusions
    - Respiratory distress
    - Cachexia (extreme weight loss)
5. Laboratory, radiological and clinical investigations

    A. Radiological
    - Chest X Ray (Chest CT for patients with access)
    - Any other radiological test as necessary for extra-pulmonary DR TB e.g. Head CT scan for patients with CNS signs

    B. Bacteriological Investigations
    - Sputum for Smear microscopy
    - Culture / DST and LPA for first and second Line drugs

    C Laboratory investigations Lancet request forms.pdf
    - HIV test for all patients

- Biochemistry: Urea, Creatinine, Electrolytes, ALT/AST/Bilirubin, Serum Albumin, RBS (FBS/HbA1c may be done if accessible)
- TSH
- Haemogram
- For women of childbearing age do a pregnancy test

D. ECG

E. Audiometry (hearing test) if injectable drugs are to be used.

4. Patient Education and Counselling

Counselling for DRTB patients is important. It is aimed at identifying underlying psychosocial issues that would affect treatment delivery. The table below is a detailed description of counselling sessions and the content covered in the course of treatment.

Table 3.1: DRTB counseling sessions

Phase	Session	Content
At Baseline	First contact with the patient (Provide a session at the time of giving results)	- Establish rapport and assuring confidentiality - Introduction to DR TB and clinical team - Educate patients on TB treatment and prevention; transmission, common drugs side effects - Patients assessment - social and mental (refer details in the tools) - Family planning and contraception including testing-HIV and Pregnancy. - Roles and responsibilities for the patients, family, patient supporter and health care worker - The signing of the consent form
Intensive phase	At week 2	- Adherence, supportive education - Mental health assessment - Patient Health Questionnaire 9 (PHQ 9) - Psychosocial review and support - Side effect monitoring
	If major issues are identified, intensify adherence session (every 2 weekly)	- Adherence, supportive education - Mental health assessment - Psychosocial review and support - Side effect monitoring - Flag file for clinical team awareness

Phase	Session	Content
	If NO major issue identified, see the patient on monthly basis	- Adherence, supportive education - Mental health assessment - Psychosocial review and support - Side effect monitoring
Continuation phase: follow-up	Once a month, until completion of treatment	- Adherence: support and education - Mental health assessment - Side effects monitoring - Preparation for reintegration to community - Emotional validation, reassurance about regaining functionality (at work, sexual life etc.) - Family planning and contraception

NOTE:

1. **Patients may have a positive smear with a negative culture. That may be caused by the presence of dead bacilli and hence does not necessarily indicate treatment failure.**

   Action: Discuss such cases with the Sub-county and County DR TB Clinical teams.

   - In patients with repeated negative culture and smear results with no corresponding clinical and radiological improvement.

   Action: County or Sub County clinical team to evaluate for other conditions.

   - Children with high clinical suspicion of TB should be treated for TB (empirically with the same regimen as the source contact) even if the result is negative.

THE PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

4

The PHQ-9 is a multipurpose instrument for screening, diagnosing, monitoring and measuring the severity of depression.

This easy-to-use patient questionnaire is a self-administered version of the PRIME-MD diagnostic instrument for common mental disorders.

It is not a screening tool for depression but it is used to monitor the severity of depression and response to treatment. However, it can be used to make a tentative diagnosis of depression in at-risk populations.

The PHQ-9 score is obtained by adding scores for each question (total points).
An image of the PHQ-9 form and interpretation is shown below.

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

NAME:_____ DATE:_____

Over the last *2 weeks*, how often have you been bothered by any of the following problems?
(use "✓" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3

7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite — being so figety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself	0	1	2	3

add columns ____ + ____ + ____

(Healthcare professional: For interpretation of TOTAL, please refer to accompanying scoring card). TOTAL: ____

10. If you checked off *any problems,* how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?

- Not difficult at all _____
- Somewhat difficult _____
- Very difficult _____
- Extremely difficult _____

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Interpretation of the PHQ-9 Score

Provisional Diagnosis and Proposed Treatment Actions		
PHQ-9 Score	**Depression Severity**	**Proposed Treatment Actions**
0 – 4	None-minimal	None
5 – 9	Mild	Watchful waiting; repeat PHQ-9 at follow-up
10 – 14	Moderate	Treatment plan, considering counseling, follow-up and/or pharmacotherapy
15 – 19	Moderately Severe	Active treatment with pharmacotherapy and/or psychotherapy
20 – 27	Severe	Immediate initiation of pharmacotherapy and, if severe impairment or poor response to therapy, expedited referral to a mental health specialist for psychotherapy and/or collaborative management

- Total scores of 5, 10, 15, and 20 represent cut points for mild, moderate, moderately severe and severe depression, respectively.
- **Note:** Question 9 is a single screening question on suicide risk. A patient who answers yes to question 9 needs further assessment for suicide risk by an individual who is competent to assess this risk.

TREATMENT CONSIDERATIONS 5

The following should be considered when treating DRTB patients:

1. Treatment considerations based on Mutations

Method	Expected results	Interpretation	Considerations
FL LPA (MTBDR Plus**)**	i). MTBC detected rpoB, KatG, and InhA	The bacteria is resistant to both rifampicin & Isoniazid drugs	**Rifampicin and Isoniazid (Including high dose isoniazid) should not be used**
	ii). MTBC detected rpoB (s) KatG and InhA (s)	The bacteria are susceptible to both rifampicin and isoniazid drugs	**Rifampicin and Isoniazid (Including high dose isoniazid) can be used**
	iii). MTBC detected rpoB (r) KatG and InhA (s)	The bacteria is resistant to rifampicin but susceptible to Isoniazid	**Rifampicin should not be used**
	iv). MTBC detected rpoB (s) KatG and InhA (r)	The bacteria are susceptible to rifampicin but resistant to Isoniazid	**Isoniazid should not be used (refer to the table above for Isoniazid resistance regimen)**
	v). MTBC not detected	There is NO MTBC detected	**Evaluate patient for other conditions**

Method	Expected results	Interpretation	Considerations
SL LPA (MTBDR Plus)	gyrA/gyrB (s)	The bacteria are susceptible to Levofloxacin and Moxifloxacin (fluoroquinolones)	**Fluoroquinolones can be used**
	gyrA/gyrB (r)	The bacteria is resistant to both Lfx and Mfx	**Fluoroquinolones cannot be used (refer to the table above for regimen design)**
	rrs/eis	The bacteria are resistant to Aminoglycosides (kanamycin, Amikacin, Capreomycin) The bacteria is resistant to the specific drug The bacteria is susceptible to all the drugs[I.K1]	**Avoid the use of injectable drugs in general (refer to the table above on regimen design)**

2. Treatment considerations based on resistant patterns

The Injectable free treatment regimens (IFR):

It is the recommended regimen for MDR/RR and Pre-XDR (resistant to SLIs) TB patients including adults, children and pregnant women. The Drugs used in these regimens are administered orally.

This regimen has two phases:

1. **Intensive phase:** 6 months

The end of intensive phase is defined by a negative culture at the end of the 3rd month and three consecutive negative smears taken 30 days apart after month 3. This phase may be extended in **consultation** with the National PMDT to 7 and/or 8 months in any of the following situations

a) Slow clinical response to treatment after clinical evaluation, characterized by:
   i. Ongoing /worsening TB (pulmonary) symptoms (cough, fever, drenching night sweats and weight loss/poor weight gain)
   ii. Worsening radiological features i.e. cavities, infiltrates, opacities
b) Delayed smear or culture conversion
c) Cases where baseline SL LPA results are indeterminate/FLQ susceptibility is not confirmed

A negative culture at month 4 and negative smears at the end of month 7and/or 8 month marks the END of the extended intensive phase and **should not** be extended further.

2. Continuation phase: 12 months

The continuation phase starts from month 7 as determined by culture/smear results or at the end of the extended intensive phase where applicable. The continuation phase is 12 – 14 months depending on the DST pattern. Reversion of sputum cultures (from negative to positive) indicates treatment failure. In case of reversion, a multi-disciplinary team should urgently review the patient and the national clinical team informed as soon as possible.

The following should be reported to the National Clinical Team;

- **Any person with DRTB who is not eligible for the standardized regimens due to previous history of DRTB treatment**
- **Any person with DRTB requiring modification of regimen in the continuation phase e.g. use of both Bedaquiline, Delamanid and linezolid in the continuation phase**
- **Any person with DRTB who has any contraindication or toxicity to one of the five core drugs in the intensive phase thus requiring an individualized regimen**
- **Any person with DRTB who has Hb<8g/dl, neutrophils <0.75x10^9/L or platelets <50 x10^9/L during treatment while on linezolid**

The table below describes the treatment of DRTB according to the resistant patterns

Table 5.1: Kenya DR-TB treatment regimens according to resistant patterns

Pattern of Drug Resistance	Regimen	Duration
MDR/ RR TB	**Intensive phase: 6 Bdq/Cfz/Lfx/Cs/Lzd** **Continuation phase: 12 Cfz/Lfx/Cs**	18 months
Pediatric MDR / RR TB (<6yrs and <25kg)	**Intensive phase: 6 Mfx/Cfz/Cs/Lzd** **Continuation phase: 12 Mfx/Cfz/Cs**	18 months
Pre-XDR - Injectable resistant	**Intensive phase: 6 Bdq/Cfz/Lfx/Cs/Lzd** **Continuation phase: 12 Cfz/Lfx/Cs/**	18 months
Pre-XDR - Fluoroquinolones Resistant	**Intensive phase: 6Bdq/Dlm/Lzd/Cfz/Cs/** **Continuation phase: 14 Dlm/Cfz/Cs**	20 months
Pre - XDR Pediatrics'* - Fluoro-quinolone Resistance	**Intensive Phase:** **6 Bdq**/*Dlm/Lzd/Cfz/Cs** **Continuation phase: 14 Dlm/Cfz/Cs/Z**	20 months
ISONIAZID mono resistance	**6 RZE/Lfx** **(with pyridoxine)**	6 months

Pattern of Drug Resistance	Regimen	Duration
Bedaquiline Intolerance (In cases of Severe Adverse Events or hypersensitivity)	**Intensive Phase: 6 Dlm/Lzd/Lfx/Cfz/Cs** **Continuation phase: 12 Lfx/Cfz/Cs**	18 months
Poly-drug resistance (PDR TB) (HE/HEZ +-S)	**9 RZE/Lfx** **(with pyridoxine)**	9 Months
Pyrazinamide mono-resistance(Z) Or Pyrazinamide and Ethambutol (EZ) without INH resistance Or Ethambutol Mono-resistance(E)	**2 RHZE** **4 RH** **(with pyridoxine)**	6 months
Extensively Drug-resistance (XDR)	**Individualized regimen**	18-24 months
Any case excluded from any of the regimens above	**Individualized regimen**	18-24 months

**Delamanid should only be prescribed in children under 3 years after consultation with the National Clinical team*

***Bedaquiline use in Paediatrics requires dissolution in water*

The construction of individualized regimens should be in consultation with the National clinical review team.

TREATMENT FOR DR TB IN SPECIAL SITUATIONS

6

Drug-resistant TB may coexist with a number of medical problems and thereby present clinical challenges in the management of both diseases/conditions.

TB Coordinators must be informed about these cases and further guidance sought from the National PMDT COE. Reference should be made to 2020 National PMDT Guidelines for detailed management of each case.

The table below is a summarized guide on the management of DRTB in special conditions.

Table 6.1: DRTB treatment in special situations

Special population	Comments / recommendations
HIV	- Bdq cannot be used together with EFV containing regimen (EFV reduces Bdq levels in the blood). Optimize ART regimen with Dolutegravir (DTG). - Monitor for other potential additives/overlapping toxicities for ART and Anti-TB's. - Avoid Lzd if Hb<8 /AZT - Give preference to TB treatment. Initiate ART treatment within 2-8 weeks after Ant TB initiation. - Monitor for IRIS (Immune Reconstitution Inflammatory Syndrome) and manage according to ART guidelines. - In Cryptococcal meningitis and DR TB co-infection; give preference to Cryptococcal treatment and consult National PMDT for guidance on DR TB treatment.
Children	- Moxifloxacin is preferred for use in pediatric DR TB regimens over levofloxacin because of its superior bactericidal and sterilizing activity and is well tolerated in most instances. - Children who are contacts of DR TB should be treated as the Index case (the person who is likely to have infected the child) - Treatment should be initiated even without Lab confirmation - Use of Quinolones is permitted as benefits outweigh the risks.

Special population	Comments / recommendations
Pregnancy and Lactation	- Pregnancy is not a contraindication for treatment of active drug-resistant TB - Consider drug safety profiles. Avoid class D drugs (aminoglycosides). - Lactation is permitted. However, limit time of contact with the child to prevent the spread of infection. - Nausea and vomiting may be additive, observe and monitor for severity and manage accordingly. - Linezolid, Bedaquiline, Clofazimine and Delamanid can be used safely.
Diabetes Mellitus	- Monitor blood sugars closely (glycemic controls). - Educate patients on diet, treatment compliance, and lifestyle modification. - Monitor for renal insufficiency, neuropathy and screen for visual impairment - Refer to DM care clinics.
Renal disease	- Monitor and correct electrolyte impairment (ref. to table on electrolyte replacement) - Refer for specialized care.
Liver disorders	- Monitor closely for liver function tests - Closely monitor for potential hepatotoxic drugs (pyrazinamide, isoniazid, Bedaquiline etc.) - Refer for specialized care.
Psychiatric / mental disorders	- Screen for depression and mental illness using the **PHQ9 form**. - Cycloserine deserves close monitoring as it may worsen the symptoms (use adequate effective dosages). - Refer for specialized care.
Drug and substance dependence	- Screen using CAGE 9 - May require admission and specialized inpatient care (isolation house/ward).
DR TB contacts	- Trace, screen and investigate using CXR and GXP testing for those who are symptomatic. - For those diagnosed with active disease should be treated as the index case (inform County and Sub-County clinical teams). - Offer IPC messages - Invitation and symptom screening in the course of treatment for index cases every 3 months.

The role of health care givers in the delivery of quality of care is outlined in the table below:

Table 6.2: role of HCWs in DRTB management

Cadre	Role in monitoring and recommended frequency
Clinician	- Review patients every day if hospitalized and at least every week if managed as an outpatient. - Conducts patient counseling, screening for substance abuse, ADR screening, monitor patient weight, height and BMI/ Z score at baseline and monthly thereafter until completion of treatment
DOT supporter	- Supervises daily intake of medication and signals any concerns to the clinician.
Multidisciplinary clinical review team (CRT)	- Physically reviews all DR TB patients within the sub-county at least once a month, and updates the clinical review checklist in the patient logbook - Document guidance to the clinician and DOTs provider on patient management for the next month in the patient logbook

Laboratory and other parameters monitored during DR TB treatment

Table 6.3: Lab monitoring parameters

Parameters Monitored	Frequency
Sputum smear and cultures	- Done at baseline and repeated every month until the end of treatment. - Microscopy is used for monitoring response to treatment while Culture is used to determine response and define cure.
Audiometry	- Done monthly if on an injectable drug. If any abnormality is detected, stop the injectable and refer for audio care. Repeat audiometry 3 and 6 months thereafter.
1st Line DST	- At baseline. This should also be done anytime there is a positive culture in a previously culture negative case.
2nd Line DST	- Done for all patients at baseline, month 3 and if a previously culture negative patient turns culture positive.
CXR	- At baseline and at the end of treatment
Full Hemogram	- At baseline, month 1 to 6 and monthly for every month the patient is on Linezolid
Serum Creatinine	- Done at baseline and monthly if on an injectable drug. Otherwise repeat only if the baseline creatinine was abnormal or if clinically indicated

Parameters Monitored	Frequency
Serum potassium, Magnesium	- Done at baseline and monthly if on an injectable drug. Otherwise repeat if vomiting, diarrhea, if QTcF is prolonged or if clinically indicated
TSH	- For patients on Prothionamide / PAS. Done at baseline and at month 2 if any abnormality was detected at baseline.
	- If hypothyroidism is present then monitor monthly until treatment completion.
Serum Albumin	- Done at baseline for patients on Bedaquiline & Delamanid. Repeat as necessary
LFTs (AST, ALT, Bilirubin)	- Done at baseline. Repeat if patient is vomiting, abdominal pain, jaundice or any evidence of liver injury
HIV screening	- At baseline. Repeat at month 3, 6, 12 and 18 if negative
CD4	- At baseline. Repeat at month 6 and 12 if baseline CD4 was <200
Viral Load	- Done at 6 months then yearly.
Review of Contraception	- All women of childbearing age should be encouraged to use long term contraception. This should be reviewed monthly.
Pregnancy test	- At baseline for women of child bearing age; repeat if indicated.
RBS	- At baseline, repeat if clinically indicated

Dosing schedule for DRTB treatment

The table below describes the dosing schedules for DRTB treatment in adults and adolescent patients.

Table 6.4: Adult & Adolescent dosing schedules

Drugs	Weight Class			
	Average daily dosing	33-50kg	51-70kg	>70kg
Isoniazid (H) (100,300 MG)	10-20 mg/kg daily	200 - 300 mg daily	300mg daily or	300mg
Rifampicin ® (150, 300m mg)	10-20 mg/kg daily	450-600 mg	600 mg	600 mg
Ethambutol (E) (100, 400 mg)	25 mg/kg daily	800-1200 mg	1200-1600 mg	1600-2000 mg
Pyrazinamide (Z) (500 mg)	30-40 mg/kg daily	1000-1750 mg	1750-2000 mg	2000-2500 mg
*Kanamycin Km (1G vial)	15-20mg/kg daily	500-750 mg	1000 mg	1000 mg
Amikacin (AM) (1G vial)	15-20mg/kg daily	500-750 mg	1000 mg	1000 mg

Drugs	Weight Class			
	Average daily dosing	33-50kg	51-70kg	>70kg
Capreomycin (CM) (1G vial)	15-20mg/kg daily	500-750 mg	1000 mg	1000 mg
Ofloxacin (Ofx) (200,300,400mg)	The usual adult dose for MDR-TB is 800 mg	800 mg	800 mg	800-1000 mg
Levofloxacin (LFX) (250,500 mg)	The usual adult dose for MDR-TB is 750 mg	750 mg	750 mg	750-1000 mg
**Moxifloxacin (Mfx)	The usual adult dose for MDR-TB is 400 mg	400 mg	400 mg	400 mg
Gatifloxacin (Gfx) (400 mg)	The usual adult dose for MDR-TB is 400 mg	400 mg	400 mg	400 mg
Ethionamide (Eto) (250 MG)	.15-20 mg/kg daily	500 mg	750 mg	750-1000 mg
Prothionamide (Pto) (250 MG)	15-20 mg/kg daily	500 mg	750 mg	750-1000 mg
Cycloserine (Cs) (250 MG)	15-20 mg/kg daily	500 mg	750 mg	750-1000 mg
Terizidone (Trd) (300 MG)	15-20 mg/kg daily	500 mg	750 mg	750-1000 mg
PAS 4gm sachets	150mg/kg daily	8gm	8gm	8-12gm
Clofazimine 100mg	100 mg			
Bedaquiline	400mg daily for 2 weeks followed by 200mg three times/week (Monday, Wednesday and Friday) for 22 weeks			
Delamanid	100mg twice daily for 24 weeks	100mg twice daily		
Linezolid	Reduce to 300mg if severe ADR	300mg daily	600mg daily	
Pyridoxine (50mg)	For every 250 mg of Cycloserine, give 50 mg of Pyridoxine. Maximum dose of 200 mg			

**Kanamycin may be dosed three times per week (TIW)for months 5-6 week of the shortened DRTB regimen and for the full duration of intensive phase in longer individualized DR TB regimens including Pre-XDR and XDR TB.*

***If a higher dose of Moxifloxacin 800mg is not tolerated reduce to 400mg.*

Table 6.5: Pediatric Dosing schedule

Drug name	Daily paediatric dose in mg/kg (maximum dose in mg)
Amoxicillin-Clavulanate	80 mg/kg (4000 mg amoxicillin and 500 mg Clavulanate): only to be given with Meropenem
Clofazimine	2 – 3 mg/kg
Delamanid	50 mg twice daily for 20 to 34 kg, for 6 months 100 mg twice daily for > 35 kg, for 6 months
Ethambutol	15 – 20 mg/kg (1000 mg) twice a day
Isoniazid	15 – 20 mg/kg
Levofloxacin	15 – 20 mg/kg (1000 mg)
Linezolid	10 mg/kg/dose twice daily
Meropenem	20 – 40 mg/kg (6000 mg)
Moxifloxacin	7.5 – 10 mg/kg (800 mg)
PAS	200 – 300 mg/kg
Pyrazinamide	30 – 40 mg/kg
Terizidone	10 -20 mg/kg (1000 mg) twice a day

DR TB Treatment failures

While treating MDR TB, some unfavorable outcomes are anticipated, including treatment failures and the presence of extensively drug resistant TB (XDR TB). Suspect treatment failure (except when there are Adverse drug reactions) when any of the following is present:

- Patient's clinical condition deteriorates - weight loss and respiratory insufficiency despite being on treatment.
- Persistently positive cultures or smears past 6 months of treatment
- Progressive, extensive and bilateral lung damage confirmed on X-Ray with no option for surgery.
- Reversion to culture or smear positive after they have been negative

When this happens, the following steps are recommended:

- Review the treatment card and assess adherence to determine if the patient is receiving all the right drugs and doses.
- Review all DST reports to determine the adequacy of the regimen and consider an alternative regimen where possible.
- Repeat 1st and 2nd line DST to look for resistance amplification.
- A clinical management meeting should be convened urgently to discuss the patient.

MANAGEMENT OF ADVERSE DRUG REACTIONS

7

Grading for ADRs

When reporting, ADRS should be graded as below:

Table 7.1: Grading of ADRS related to anti TB medicines

Classification	Definition
Mild	The adverse drug reaction does not interfere in a significant manner with the patient's normal functioning.
Moderate	The adverse drug reaction produces some impairment in the patient's functioning but is not hazardous to the health of the patient.
Severe:	The adverse drug reaction produces significant impairment or incapacitation of functioning.
Life-threatening:	The adverse drug reaction causes extreme impairment of functioning, requiring hospitalization and if left untreated could result in the death of the patient.

ADVERSE DRUG REACTIONS RELATED TO DR TB MEDICINES

a) Peripheral Neuropathy

Causes of neuropathy: Cs, Lzd, H,

Table 7.2: Grading peripheral neuropathy

	Grade 1: Mild	Grade 2: Moderate	Grade 3: Severe	Grade 4: Life-threatening
Neurosensory alteration (including paraesthesia and painful neuropathy)	*Asymptomatic with sensory alteration on exam or minimal paraesthesia causing no or minimal interference with usual social and functional activities*	*Sensory alteration or paraesthesia causing greater than minimal interference with usual social and functional activities*	*Sensory alteration or paraesthesia causing inability to perform usual social and functional activities*	*Disabling sensory alteration or paraesthesia causing inability to perform basic self-care functions*

Action	Monitor. If symptoms improve after 2 weeks, consider restarting these drugs. **Consider restarting Lzd at a lower dose.**	Stop Cs and Lzd (high dose H). If symptoms resolve after 2 weeks, consider restarting cycloserine. **Do not reintroduce Lzd.**	Stop Cs and Lzd. If symptoms improve after 2 weeks consider restarting cycloserine. **Do not reintroduce Lzd.**	Stop Cs and Lzd. If symptoms improve after 2 weeks consider restarting cycloserine. **Do not reintroduce Lzd.**

Symptomatic relief for peripheral neuropathy:

- **Non-steroidal anti-inflammatory drugs** or acetaminophen helps alleviate symptoms.
- **Tricyclic antidepressants** have also been used successfully. Start amitriptyline 25 mg at bedtime. The dose should be increased to a maximum of 150 mg daily for refractory symptoms.
- **Carbamazepine** is effective in relieving pain and other symptoms of peripheral neuropathy.

NOTE:

If possible, the co-administration of amitriptyline and Lzd should be avoided due to potential risk of serotonergic syndrome. Symptoms of serotonergic syndrome include high body temperature, agitation, increased reflexes, tremor, sweating, dilated pupils, and diarrhoea.

b) Myelosuppression

Possible anti-TB drug causes: Lzd, Cfz,

Table 7.3: Grading Myelosuppression

	Grade 1: Mild	Grade 2: Moderate	Grade 3: Severe	Grade 4: Life threatening
Absolute neutrophil count	*1000 – 1300/ mm³*	*750 – 999/ mm³*	*500 – 749/mm³*	*< 500/ mm³*
Haemoglobin*[1]	*10.5 - 9.5 g/dL*	*9.4 - 8.0 g/dL*	*7.9 - 6.5 g/dL*	*< 6.5 g/dl*
Platelets decreased	*100.000-124.999/mm³*	*50.000-99.999/ mm³*	*25.000-49.000/ mm³*	*<25.000/mm³*
WBC decreased	*2.000-2.500/ mm³*	*1.500-1.999/mm³*	*1.000-1.499/mm³*	*<1.000/mm³*

[1] Hemoglobin should be interoperated with baseline hemoglobin value

Action	Monitor carefully, and **consider reduction of dose of Lzd (300mg daily or 600 mg thrice weekly)**	Monitor carefully, and **consider reduction of dose of Lzd to 300mg daily**; in case of Grade 2 neutropenia, **stop Lzd immediately. Restart at reduced dose once toxicity has decreased to Grade 1.**	Stop Lzd immediately. **Restart at reduced dose once toxicity has decreased to Grade 1.**	Stop Lzd immediately. **Consider haemotransfusion or erythropoietin. Restart at reduced dose once toxicity has decreased to Grade 1.**

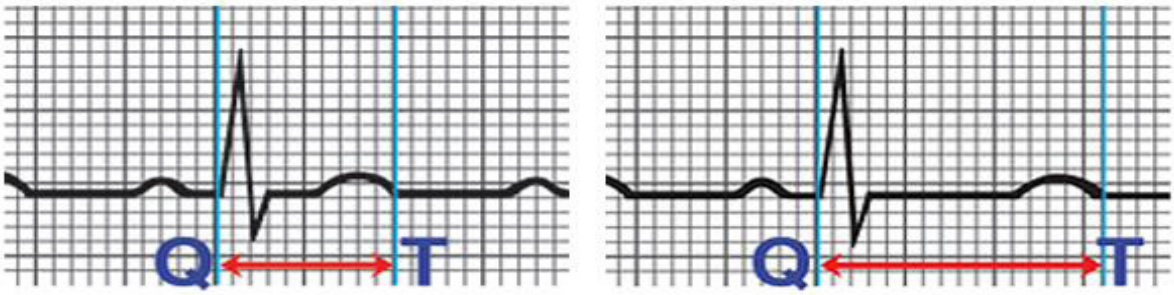
c) Prolonged QTcF Interval

Possible anti-TB drug causes: Bdq, Mfx, Lfx, Cfz

Possible other causes:

- Many other drugs can cause QT prolongation; erythromycin, clarithromycin, quinidine, ketoconazole, fluconazole, antipsychotics haloperidol, chlorpromazine, risperidone, methadone and anti-nausea drugs that include ondansetron/ granisetron, domperidone,
- Genetic causes such as long QT syndrome; hypothyroidism.

Figure 8.2: Normal vs Prolonged Q-T intervals[2]



Normal Q-T Interval *Long Q-T Interval*

Note: *The QT interval is measured from the beginning of Q-wave to the end of the T wave. Its duration varies depending on the heart rate. Its measurement must be corrected according to the heart rate. It is recommended to use the Fredericia method to calculate the QTcF (Pharmacy.umaryland.edu)*

[2] *https://my.clevelandclinic.org/health/diseases/17183-long-q-t-syndrome-lqts*

QTcF Prolongation (ms) Gender cut-offs[3]

QTc Prolongation (ms)	Normal	Borderline	Abnormal
Men	≤ 430	431- 450	>450
Women	≤ 450	451-470	>470

Table 7.4: Grading of prolonged QT interval

	Grade 1: Mild	Grade 2: Moderate	Grade 3: Severe	Grade 4: Life-threatening
Prolongation of QTcF	*Asymptomatic, QTcF 450 – 480 ms* *OR Increase interval **< 0.03** sec above baseline*	*Asymptomatic, QTcF 481 – 500 ms* *OR Increase in interval 0.03–0.05 sec above baseline*	*Asymptomatic, QTcF >= 501 ms without signs/ symptoms of serious arrhythmia* *OR Increase in interval ≥ 0.06 sec above baseline*	*QTcF >= 501ms or > 60 ms change from baseline and one of the following: Torsade de pointes or polymorphic ventricular tachycardia or signs/ symptoms of serious arrhythmia*
Action	Monitor more closely; **at least weekly ECG until QTcF has returned to grade 1 or less.**	Monitor more closely; **at least weekly ECG until QTcF has returned to grade 1 or less.**	**Stop the suspected causative drug.** Hospitalize and replete electrolytes as necessary.	**Stop the suspected causative drug**. Hospitalize and replete electrolytes as necessary.

Suggested Management strategy

Checking and replenishing serum electrolytes

- Serum potassium (K^+), ionized calcium (ionized Ca^{++}), and magnesium (Mg^{++}), should be obtained in the event a prolonged QT interval is detected.
- the cause of abnormal electrolytes should be corrected
- Whenever a low potassium is detected it should trigger urgent management with replacement and frequent repeat potassium testing (often daily or multiple times a day) to correct the levels of potassium.
- If potassium is found low, always check magnesium and ionized calcium and compensate as needed. (If unable to check, consider oral empiric replacement doses of magnesium and calcium).

[3] Cite this: QTc Prolongation and Risk of Sudden Cardiac Death: Is the Debate Over? - Medscape - Feb 03, 2006.

d) Optic Neuritis

Possible anti-TB drug causes: Lzd, E

Table 7.5: Grading of optic neuritis

	Grade 1 Mild	Grade 2 Moderate	Grade 3 severe	Grade 4 life-threatening
Visual changes (from baseline)	*Visual changes causing minimal or no interference with usual social and functional activities*	*Visual changes causing greater than minimal interference with usual social and functional activities*	*Visual changes causing inability to perform usual social and functional activities*	*Disabling visual loss*
Action	**Stop LZD** immediately if there are any suspicion of optic neuritis. **Do not restart.**	**Stop LZD** immediately if there are any suspicion of optic neuritis. **Do not restart.**	**Stop LZD** immediately if there are any suspicion of optic neuritis. **Do not restart.**	**Stop LZD** immediately if there are any suspicion of optic neuritis. **Do not restart.**

Suggested management strategy

- Do not restart the suspected causative drug (Linezolid or Ethambutol)
- Refer patients to an ophthalmologist for further evaluation and management.
- Optic neuritis generally improves following cessation of offending drug, if it can be stopped early enough.

e) Hepatitis

Possible anti-TB drug causes: H, R, Z, Bdq,

Table 7.6: Grading of Hepatitis

	Grade 1: Mild	Grade 2: Moderate	Grade 3: Severe	Grade 4: Life threatening
ALT (SGPT)	*1.25 – 2.5 x ULN*	*2.6 – 5.0 x ULN*	*5.1 – 10.0 x ULN*	*> 10.0 x ULN*
AST (SGOT)	*1.25 – 2.5 x ULN*	*2.6 – 5.0 x ULN*	*5.1 – 10.0 x ULN*	*> 10.0 x ULN*
ACTION	**Continue treatment regimen**. Patients should be followed until resolution (return to baseline) or stabilization of AST/ ALT elevation.	**Continue treatment regimen.** Patients should be followed until resolution (return to baseline) or stabilization of AST/ ALT elevation.	**Stop all drugs,** including anti-TB drugs; **measure LFTs weekly**. **Treatment may be reintroduced after toxicity is resolved.**	**Stop all drugs**, including anti-TB drugs; **measure LFTs weekly. Treatment may be reintroduced after toxicity is resolved.**

Suggested management strategy

Reintroduce anti-TB drugs once liver enzymes return to normal level. Anti-TB drugs should be reintroduced in a serial fashion by adding a new medicine every three to four days. The least hepatotoxic drugs while monitoring liver function tests after each new exposure.

Consider suspending the most likely offending drug permanently if it is not essential to the regimen. This is often the case for pyrazinamide if it is less likely to be effective by clinical history.

f) Hearing Impairment

Possible anti TB drugs causing hearing impairment: Km, Am, Cm.

Table 7.7: Grading Hearing impairment

	Grade 0: None	Grade1: Slight	Grade 2: Moderate	Grade 3: Severe	Grade 4: Profound
Decibel (dB) range	*25 dB or less*	*26-40 dB*	*Child- 31-60 *dB* *Adult- 41-60* dB*	*61-80 dB*	*>80 dB*
Severity	No/ Slight problems **Hears Whispers**	Hears/ repeats words in **normal voice** at 1 meter	Hears/ repeats words in **raised voice** at 1 meter	Hears words **shouted** into better ear	**cannot hear**/ understand shouted voice

**The grades/severity of hearing loss is also categorised differently for different age groups (see annex).*

Suggested management strategy:

Perform a monthly assessment of hearing loss and balance. Audiometry is helpful in detecting early high-frequency hearing loss that the patient may not even be aware of. If the patient is experiencing hearing loss, stop the injectable and replace it with a non-ototoxic drug. Even when non-ototoxic drugs are not available, stopping the injectable can be considered based on the patient's desire to maintain hearing. If moderate or severe vertigo, tinnitus (ringing in the ears) or vestibular disturbances arise, with or without significant hearing loss, consider decreasing frequency or stopping the injectable agent.

g) Acute Kidney Injury/Failure

Possible anti-TB drug causes: Aminoglycosides (Km, Am, Cm)

Table 7.8: Grading acute kidney injury/Failure

	Grade 1: Mild	Grade 2: Moderate	Grade 3: Severe	Grade 4: Life threatening
Acute Kidney Injury/ Chronic Kidney Disease	GFR= 60-89 mL/ min	GFR= 45-49 mL/ min	GFR= 30-44 mL/ min	GFR= 15-29 mL/ min and <15 mL/ min
Action	Consider **stopping injectable** until creatinine has returned to baseline. Consider **restarting the injectable at lower frequency** (e.g. MWF).	**Stop injectable** until creatinine has returned to baseline. Consider **restarting the injectable at lower frequency** OR **substitute** with a n**on-nephrotoxic drug**	**Stop injectable until creatinine has returned to baseline.** Consider **restarting the injectable at lower frequency** OR **substitute** with a **non-nephrotoxic drug**	**Stop injectable until creatinine has returned to baseline.** Consider **restarting the injectable at lower frequency** OR **substitute** with a n**on-nephrotoxic drug**

** The best measure of kidney function is Glomerular Filtration Rate (GFR).*

Suggested management strategy:

Monitor serum creatinine and electrolytes frequently in patients receiving injectable. Patients with pre-existing kidney disease, diabetes, or HIV are at high risk of injectable nephrotoxicity and may be monitored more frequently.

Repeat electrolytes if necessary:

Injectable nephrotoxicity may be associated with injectable-induced electrolyte wasting. For example, it is possible to see elevated creatinine and severe hypokalaemia/ hypomagnesemia at the same time. The aetiology of this phenomenon is unclear, but it may occur more often in HIV co-infected patients. Discontinue the suspected drug (usually the injectable). If the acute renal failure is severe, then stop all drugs. Follow serum creatinine and electrolytes closely until the creatinine has returned to baseline or has stabilized. Consider strict weight-based dosing of the injectable if the patient's weight is less than 50 kg. Suspend the injectable permanently if the nephrotoxicity recurs despite intermittent dosing, and add additional anti-TB drugs to reinforce the regimen.

h) Hypokalaemia

Possible anti-TB drug causes: Cm, Km, Am

Table 7.9: Normal values of potassium level and quantity of KCL required

Potassium level Normal value (3.5-5.0 Meq/L)	Quantity of KCl
3.7 or more	None
3.4-3.6	40 meq
3.0-3.3	60 meq
2.7-2.9	80 meq
2.4-2.6	80 -120 meq
2.0-2.3	60 meq IV and 80 meq PO
<2.0	60 meq IV and 100 meq PO

Table 7.10: Grading Hypokalaemia

	Grade 1: Mild	Grade 2: Moderate	Grade 3: Severe	Grade 4: Life threatening
Hypokalaemia	3.4 - 3.0mmol/L	2.9 – 2.5 mmol/L	2.4 - 2.0 mmol/L or intensive replacement therapy or hospitalization required	< 2.0 mmol/L or abnormal potassium with paresis, ileus or life-threatening arrhythmia
Action	**Continue injectable.** **Start oral potassium replacement therapy**. **Check serum magnesium and replace if necessary**	**Continue injectable**. **Start aggressive oral potassium replacement therapy.** **Replace magnesium as necessary**.	**Consider stopping the injectable temporarily**. **Start IV potassium replacement therapy in addition to oral**. **Replace magnesium and other electrolytes as necessary**.	**Stop injectable** temporarily. **Start IV potassium replacement therapy** in addition to oral. **Replace magnesium** and other electrolytes as necessary.

WHO Grouping of DRTB medicines with common adverse drug reactions

Table 7.12:

Drug	Activity against TB, Mechanism of action, and metabolism	Common Adverse Drug Reactions	Contraindications and special consideration
Group A - WHO 2018 grouping of medicines for longer MDR-TB Regimens			
Levofloxacin (Lfx)	**Bactericidal:** has strong anti-TB activity. Cross-resistance with other fluoroquinolones but may not be complete. Data suggests greater activity than ciprofloxacin or Ofloxacin. Inhibits DNA gyrase	Nausea and bloating. Headache, dizziness, insomnia or tremulousness. Rare tendon rupture, arthralgia (can usually be treated symptomatically). Moderate QTcF prolongation, hypoglycaemia	Fluoroquinolones intolerance, prolonged QTcF, pregnancy (relative contraindication).
Moxifloxacin (Mfx)	**Bactericidal:** inhibits DNA gyrase; cross-resistance with other fluoroquinolones, but may be more active based on in vitro data	Nausea and diarrhoea. Headache and dizziness. Rare tendon rupture; arthralgia. Rare hepatotoxicity. QTc Prolongation, hypo/ hyperglycaemia	Fluoroquinolones intolerance, prolonged QTc
Bedaquiline (Bdq)	**Bactericidal:** Inhibits ATP synthesis. Mainly eliminated in faeces.	Nausea, vomiting, abdominal pain, loss of appetite, joint pain, headache. QT prolongation, hyperuricemia, phospholipidosis, elevated aminotransferases.	Do not use or discontinue Bedaquiline: Clinically significant ventricular arrhythmia. A QTcF interval of >500 ms Severe liver disease. Abnormal electrolytes. Use with caution in the following situations: Use with other QT prolonging drugs (see drug interactions) A history of torsade de pointes

Drug	Activity against TB, Mechanism of action, and metabolism	Common Adverse Drug Reactions	Contraindications and special consideration
			A history of congenital long QT syndrome A history of hypothyroidism and Brady arrhythmias A history of uncompensated heart failure Serum calcium, magnesium or potassium levels below the lower limits of normal
Linezolid (Lzd)	Has in vitro **bactericidal activity** – increasing clinical experience7; inhibits protein synthesis	Myelosuppression Diarrhoea and nausea. Optic and peripheral neuropathy Lactic acidosis – patients who develop recurrent nausea or vomiting.	Hypersensitivity to Oxazolidinones Symptoms of neuropathy (pain, numbness, tingling or weakness in the extremities
Group B - WHO 2018 grouping of medicines for longer MDR-TB Regimens			
Clofazimine (Cfz)	In vitro activity against *M. tuberculosis* without much in vivo data. Generally reserved for cases with few other options. Tissue half-life estimated to be around 70 days	Discoloration of skin, conjunctiva, cornea and body fluids. Dry skin, pruritus, rash, ichthyosis, and xerosis. Gastrointestinal intolerance. Photosensitivity.	Allergy to Clofazimine Electrolytes should be monitored and replaced if vomiting is severe In the case of Gastritis, dosing on antacids should be carefully times (> 2 hours apart) so as not to interfere with the absorption of anti-TB drugs
Cycloserine (Cs)	**Bacteriostatic:** inhibits cell wall synthesis	**CNS toxicity:** including seizure, depression, psychosis and suicidal ideation Other side effects include peripheral neuropathy and skin changes.	Relative contraindications include seizure disorder, psychotic disease or alcohol abuse Initiate anticonvulsant therapy (e.g. valproic acid, phenytoin, phenobarbitone) to address the side effects associated with CNS toxicity Increase pyridoxine to 300mg daily

Drug	Activity against TB, Mechanism of action, and metabolism	Common Adverse Drug Reactions	Contraindications and special consideration
			Lower the dose of the suspected agent or discontinue or replace the suspected agent if this can be done without compromising the regimen For psychotic symptoms, initiate antipsychotic drugs and halt administration of Cs for 1-4 weeks while symptoms of psychosis are brought under control. Lower the dose if this can be done without compromising the regimen
Group C - WHO 2018 grouping of medicines for longer MDR-TB Regimens			
Imipenem-cilastatin	Given that imipenem is rapidly degraded by renal proximal tubule dipeptidases, it is used in combination with the dipeptidases inhibitor, cilastatin. (Conversely, meropenem a similar drug as imipenem is stable to renal dipeptidases and requires no cilastatin). Cilastatin is partially metabolized renally.	**Common:** Diarrhoea, nausea, or vomiting. **Less common:** Seizure (noted with CNS infection), palpitations, pseudomembranous colitis.	Carbapenems intolerance; meningitis (use meropenem rather than imipenem).
Meropenem	In vitro activity – very limited clinical experience (meropenem is stable to renal dipeptidases and requires no cilastatin).	Diarrhoea, nausea or vomiting. Seizure (noted with CNS infection), but rare compared to imipenem. Rarely elevated LFTs, hematologic toxicity, hypersensitivity	Carbapenems intolerance

Drug	Activity against TB, Mechanism of action, and metabolism	Common Adverse Drug Reactions	Contraindications and special consideration
***Delamanid (Dlm)**	Inhibition of the synthesis of the mycobacterial cell wall components, methoxy-mycolic and keto-mycolic acid. Delamanid disappears from plasma with a t1/2 of 30-38 hours. Delamanid is not excreted in urine.	Nausea, vomiting, and dizziness. QT prolongation	**Do not use or discontinue Delamanid** - Clinically significant ventricular arrhythmia. - A QTcF interval of > 500 ms (confirmed by repeat ECG). - Severe liver disease. - Serum Albumin less than 2.8. - Abnormal electrolytes. **Use with caution in the following situations (with more frequent ECG monitoring and evaluation of risk versus benefit):** - Use with other QT prolonging drugs (see drug interactions). - A history of torsade de pointes. - A history of congenital long QT syndrome. - A history of hypothyroidism and Brady arrhythmias. - A history of uncompensated heart failure. - Serum calcium, magnesium, or potassium levels below the lower limits of normal. **Use with caution in patients sensitive to lactose**

Drug	Activity against TB, Mechanism of action, and metabolism	Common Adverse Drug Reactions	Contraindications and special consideration
Ethambutol (Emb)	**Bacteriostatic:** inhibitor of cell wall synthesis; bactericidal only at the high end of the dosing range. At doses used over long periods of time, Ethambutol protects against further development of resistance	Retro bulbar neuritis (dose-related – exacerbated during renal failure).	Pre-existing optic neuritis; Visual changes on Ethambutol
Pyrazinamide (Pza)	**Bactericidal** for semi-dormant M. tuberculosis. Mechanism unclear	Gout (hyperuricemia) and arthralgia. Hepatotoxicity. Rash. Photosensitivity. Gastrointestinal upset	Allergy to pyrazinamide; severe gout
Amikacin (Am)	**Bactericidal:** Inhibits protein synthesis. Excreted primarily unchanged through the kidney.	Nephrotoxicity, Ototoxicity	Relative contraindication in pregnancy and Hypersensitivity to aminoglycosides Caution with renal, hepatic, vestibular or auditory impairment.
Prothion-amide (Pto)	**Weakly bactericidal:** blocks mycolic acid synthesis	Gastrointestinal upset and anorexia: Metallic taste. Hepatotoxicity. Endocrine effects: Gynaecomastia, hair loss, acne, impotence, menstrual irregularity, and reversible hypothyroidism	Side effects may be exaggerated in patients also taking Cycloserine For hypothyroidism, initiate L-thyroxine therapy (50-100 mcg/day). If there is no possibility of switching, monitor TSH for thyroxine.
Kanamycin (Km)	**Bactericidal:** has strong anti-TB activity. Cross-resistance with Amikacin and some data suggesting cross-resistance with Capreomycin; inhibits protein synthesis	Nephrotoxicity: Ototoxicity (hearing loss) and vestibular toxicity: Increases with advanced age and prolonged use	Pregnancy (congenital deafness seen with streptomycin and Kanamycin use in pregnancy); hypersensitivity to aminoglycosides; caution with renal, vestibular or auditory impairment; patients with intestinal obstructions.

Drug	Activity against TB, Mechanism of action, and metabolism	Common Adverse Drug Reactions	Contraindications and special consideration
Para-amino salicylic acid (PAS)	**Bacteriostatic.**	Gastrointestinal distress Rare hepatotoxicity and coagulopathy Reversible hypothyroidism	Pregnancy (relative).
Others			
Isoniazid (Inh)	**Bactericidal:** Especially for rapidly dividing cells. Affects mycolic acid (cell wall) synthesis. Inclusion of isoniazid in the regimen of patients with strain W MDR-TB was also associated with improved outcomes	**Hepatitis** (age-related). Peripheral neuropathy. Hypersensitivity reactions. Other reactions, including optic neuritis, arthralgia, CNS changes, drug-induced lupus, diarrhoea, and cramping with liquid product	**Patients with high-level isoniazid resistance** who have failed an isoniazid-containing regimen should not receive isoniazid. History of allergic reaction to isoniazid
Rifampicin (Rif)	**Bactericidal:** inhibits protein synthesis; cross-resistance with other Rifamycins	Orange staining of body fluids Rash and pruritus Gastrointestinal upsets, flu-like syndrome Hepatotoxicity. Haematological abnormalities (thrombocytopenia, haemolytic anaemia).	**Rifamycins allergy;** due to drug interactions, may be contraindicated with concurrent use of certain drugs
Rifapentine (Rpt)	**Bactericidal:** same mechanism of action as Rifampin, inhibits RNA polymerase. 100% cross-resistant with Rifampin.	Red–orange staining of body fluids Rash and pruritus Hypersensitivity reaction Hepatotoxicity Haematological abnormalities	History of hypersensitivity to any of the Rifamycins (i.e. Rifampin or Rifabutin)

NATIONAL TUBERCULOSIS, LEPROSY
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