REPUBLIC OF KENYA

MINISTRY OF HEALTH

GUIDELINES ON THE PROGRAMMATIC MANAGEMENT OF DRUG RESISTANT TUBERCULOSIS

2021

NATIONAL TUBERCULOSIS, LEPROSY AND LUNG DISEASE PROGRAM

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List of abbreviations

ADR	Adverse Drug Reaction
AFB	Acid Fast Bacilli
AIDS	Acquired Immunodeficiency Syndrome.
ART	Antiretroviral Therapy
CBOs	Community Based Organizations.
CDC	Centres for Disease Control and Prevention.
CDR	Case Detection Rate
CHEW	Community Health Extension Worker
CNR	Case Notification Rate
CRL	Central Reference Laboratory
CTLC	County Tuberculosis and Leprosy Coordinator
NTLD -UNIT	National Tuberculosis, Leprosy and Lung Disease Unit
DMOH	District Medical Officer of Health
DOTS	Directly Observed Therapy Short course.
DST	Drug Susceptibility Testing
DTC	Diagnostic Testing and Counselling
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
IGRA	Interferon Gamma Release Assay
IPC	Infection Prevention and Control
KAPTLD	Kenya Association for Prevention of Tuberculosis & Lung Disease
KEMRI	Kenya Medical Research Institute.
KNH	Kenyatta National Hospital.
LF-LAM	Lateral Flow Lipoarabinomannan assay
LTBI	Latent TB infection
MDR-TB	Multi- Drug Resistant Tuberculosis
MOH	Ministry of Health
MUT	Mutation
NASCOP	National Aids & Sexually transmitted infections Coordinating Program
NGOs	Non Governmental Organizations
NRL	National Reference Laboratory

NSN	New Smear Negative
NSP	New Smear Positive
OADC	Oleic Albumin Dextrose Catalase
OPD	Out Patient Department
PANTA	Polymixin B. Amphoteric B, Nalidixic acid,Trimethoprim, Azlocillin
PPM	Private Public Mix
PTB	Pulmonary Tuberculosis
PMDT	Programmatic Management of Drug Resistant Tuberculosis
R	Rifampicin
RNA	Ribonucleic acid
SAE	Severe Adverse Event
SCC	Short Course Chemotherapy
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

Foreword

Kenya has made tremendous advancements in the Programmatic Management of Drug-resistant Tuberculosis (PMDT) despite being one of the highly burdened countries with Tuberculosis Drug-resistant TB and TB/HIV co-infection globally. Despite these advancements, Drug-resistant TB (DRTB) remains a major public health concern in Kenya.

This Programmatic DRTB guide has been developed through extensive and all-inclusive stakeholders' engagement in line with the current World Health guidelines on the management of DRTB.

Kenya started implementing the Programmatic Management of Drug resistant TB (PMDT) in 2006 and treatment has rapidly evolved ever since based on WHO guidelines. In 2018, the World Health Organization (WHO) recommended the use of injectable free regimens (IFR) for the treatment of drug-resistant TB following new evidence that the new molecules (Bedaquiline and Delamanid) and repurposed drugs (Linezolid and Clofazimine) were safer and more efficacious compared to the injectable medicines.

In December 2019 WHO issued a rapid communication on the use of all oral regimens for treatment of MDR/RR TB and Kenya transitioned on 1st January 2020 thus eliminating the need for injections with the advantages of being: Fully Oral preparations, Efficacious, Reduced risk of mortality, treatment failure and relapses. No hearing loss, Better quality of life for patients and Can be administered by non-technical HCWs sensitized on DOTS delivery strategy.

Kenya has committed to ending TB by 2030 as envisaged in the SDGs and is currently implementing the political declaration and recommendations in line with the commitment and targets set by the Head of state at the United Nations High Level Meeting (UNHLM) on TB and the END TB Strategy 2035.
These include diagnosing and treating successfully 40 million people with TB in the 5-year period 2018– 2022 including 3.5 million children, and 1.5 million people with drug-resistant TB.

The Ministry of Health is committed to optimizing the welfare and quality of care for all TB patients. I wish to draw the attention of all the healthcare providers to follow this guideline while managing drug resistant tuberculosis so that together we can achieve better treatment results and a high survival rate for our patients.

Dr. Patrick Amoth
Ag. Director General for Health

Overview of the Guidelines

Drug-resistant tuberculosis (DR TB) continues to be a major public health threat globally with about half a million new cases reported annually. In 2019, an estimated 3.3% among newly diagnosed TB cases and 18% of the previously treated TB cases had Multi-drug and Rifampicin resistant Tuberculosis (MDR /RR TB).

The 2018 WHO report estimated 558 000 new cases diagnosed with Rifampicin resistance (one among the most effective first-line drugs) of which - 82% had MDR-TB.

TB Treatment in Kenya has been decentralized across all the 47 counties. Currently, there are 4,355 TB treatment sites, 2,409 TB diagnostic sites and 226 GeneXpert testing. Phenotypic culture and Genotypic drug susceptibility testing for Ist and 2nd line drugs is performed at the National TB Reference Laboratory in Nairobi and KEMRI TB Lab at Kisian in Kisumu county.

Drug resistant TB trend in case detection and diagnosis has been increasing in the recent years (577 cases in 2017; 687 in 2018 and 689 in 2019) with a treatment success rate stagnating at an average of 72%. This Programmatic treatment guide for drug-resistant TB purposes to address the challenges affecting the quality of care and service delivery for DRTB patients in the country. These include symptom screening and DRTB presumptive case detection and diagnosis, treatment according to resistant patterns, drug safety monitoring, management and reporting and DRTB infection prevention and control measures in line with the WHO recommendations.

I wish to thank the team that put together this document and recommend for adoption by all health care providers in the country as we work towards ending TB by 2030.

Dr. Pacificah Onyancha
Ag. Director of Medical Services, Preventive / Promotive Health

Acknowledgement

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Thank you for your hard work, very much appreciated.

Dr. Waqo Ejersa
Head: Division of National TB, Leprosy and lung Disease Program

INTRODUCTION

1.

1.1 Background

Drug-resistant TB (MDR-TB) remains a public health crisis and a health security threat. The WHO estimates that there were 558 000 new cases with resistance to rifampicin – the most effective first-line drug, of which - 82% had MDR-TB. Drug-resistant TB poses a major public health problem and threatens the progress made towards TB control. Globally in 2017, there were 558,000 new cases with resistance to rifampicin (RRTB). (Global Tuberculosis report 2018).

Rifampicin the most effective first-line drugs, of which 458, 000 had multidrug-resistant TB (MDR-TB). In 2017, 161000 MDR/RR TB cases were detected where only 139000 cases were put on treatment. Global (Tuberculosis report 2018). The treatment success rate out of these cases was 55%, while 15% died, 8%failed and 21% were lost to follow up. In 2017, 8700 patients with XDR TB were enrolled on treatment of whom 34% completed treatment. (Global Tuberculosis report 2018, MDR TB update).

Kenya is one of the 22 high burden TB countries that collectively contributes to about 80% of the world's TB burden. Kenya had a population of 49 million people in 2017,and had an estimated TB prevalence of 426/100,000 population or 138,105 incident cases per year Prevalence survey 2018 report).this is much higher than the WHO estimate of 233/100,000 in 2015.

There is decentralized DS-TB and DR-TB care in Kenya's 47 counties and 300 sub-counties: Currently, there are 4500 TB treatment sites, 2409 TB diagnostic sites, 207 GeneXpert sites (and 82 audiometers distributed in all counties Culture and 1st and 2nd line DST, First and second line LPA are performed at the TB reference labs.

1.2 TB control strategy

Tuberculosis control in Kenya is based on the 6 elements of the WHO END-TB Strategy

VISION	**A WORLD FREE OF TB** — zero deaths, disease and suffering due to TB			
GOAL	**END THE GLOBAL TB EPIDEMIC**			
INDICATORS	**MILESTONES**		**TARGETS**	
	2020	2025	SDG 2030[a]	End TB 2035
Reduction in number of TB deaths compared with 2015 (%)	35%	75%	90%	95%
Reduction in TB incidence rate compared with 2015 (%)	20% (<85/100 000)	50% (<55/100 000)	80% (<20/100 000)	90% (<10/100 000)
TB-affected families facing catastrophic costs due to TB (%)	0	0	0	0

PRINCIPLES

1. Government stewardship and accountability, with monitoring and evaluation
2. Strong coalition with civil society organizations and communities
3. Protection and promotion of human rights, ethics and equity
4. Adaptation of the strategy and targets at country level, with global collaboration

PILLARS AND COMPONENTS

1. **INTEGRATED, PATIENT-CENTRED CARE AND PREVENTION**
   - A. Early diagnosis of TB including universal drug-susceptibility testing, and systematic screening of contacts and high-risk groups
   - B. Treatment of all people with TB including drug-resistant TB, and patient support
   - C. Collaborative TB/HIV activities, and management of co-morbidities
   - D. Preventive treatment of persons at high risk, and vaccination against TB
2. **BOLD POLICIES AND SUPPORTIVE SYSTEMS**
   - A. Political commitment with adequate resources for TB care and prevention
   - B. Engagement of communities, civil society organizations, and public and private care providers
   - C. Universal health coverage policy, and regulatory frameworks for case notification, vital registration, quality and rational use of medicines, and infection control
   - D. Social protection, poverty alleviation and actions on other determinants of TB
3. **INTENSIFIED RESEARCH AND INNOVATION**
   - A. Discovery, development and rapid uptake of new tools, interventions and strategies
   - B. Research to optimize implementation and impact, and promote innovations

[a] Targets linked to the Sustainable Development Goals (SDGs).

1.3 Definition of key terms

Resistance patterns

Mono-resistant TB - Resistance to only one anti-TB drug, without resistance to other drugs

Poly-drug resistant TB - Resistance to more than one anti-TB drug, other than both Isoniazid and rifampicin.

Multidrug-resistant TB (MDR-TB) - Resistance to Isoniazid and rifampicin with or without resistance to other anti-TB drugs

Rifampicin resistant TB (RR-TB) - Resistance to at least rifampicin, with or without resistance to other drugs. This category includes MDR-TB, rifampicin mono-resistant TB, pre-XDR-TB and XDR-TB.

Pre XDR-TB- MDR-TB with additional resistance to either a second-line injectable agent or a fluoroquinolone.

Extensively drug-resistant TB (XDR-TB) - MDR-TB with resistance to any fluoroquinolone as well as one or more of the three second-line injectable drugs (Capreomycin, kanamycin or amikacin).

Transmission - this is the movement of pathogens from a reservoir to a susceptible host.

Natural Resistance - resistance presented by a minimal proportion of bacilli as a consequence of random genetic mutation during successive divisions.

1.4 Basic concepts on resistance

a) Active drug-resistant TB

Drug resistance TB occurs when bacteria with naturally occurring resistant mutations are selected by inadequate therapy of a specific antibiotic. This means the bacteria with resistant mutations are not killed or inhibited by this antibiotic. This is clinically manifested by disease progression despite treatment, failure to achieve negative sputum or cultures, and/or treatment failure. There are three principal path/ways leading to the development of active drug-resistant TB:

- Natural resistance
- Primary/initial drug resistance
- Acquired (secondary) drug resistance

Natural resistance occur when all live species reach a certain number of divisions (in order to perpetuate the species), they undergo genomic mutations at random, which gives rise to organisms with certain altered functions. This is called natural resistance.

NB; Anti TB medicines do not select the resistant mutant as they do not cause mutation.

Primary resistance is an infection with a resistant strain. This refers to a patient diagnosed with resistant TB for the first time or have been on TB treatment for less than one month.

Acquired drug resistance occurs due to inadequate, incomplete or poor treatment quality that allows the selection of mutant resistant strain. Therefore, it is mostly an expression of poor treatment, i.e. Direct Monotherapy, Indirect Monotherapy (adding just one drug to a failing regimen).

b) Bacillary population

In a tuberculosis patient, the bacillary populations can be classified according to how slow or fast they multiply as follows:

a) **Rapidly multiplying bacilli**: These bacilli are usually many in number and hence have a high probability of spontaneous natural mutations. These are responsible for the following;

i) The possibility to kill the Patient,

ii) Development of symptoms to the Patients,

iii) Disease transmission

iv) Smear positivity

v) Selection of mutant strains in cases of bad therapies.

These types of bacillus require bactericidal drugs.

b) **Slowly multiplying Bacilli and intermittently growing bacilli**: These bacilli are usually few in number and they are responsible for relapses. These types of bacilli require sterilizing drugs such as Rifampicin.

c) The fall and rise mechanism: If Smear positive TB is treated with just ONE drug (H), for each million bacilli, it will kill 999,999, but it will select the resistant mutant (1 individual) that exists. If this TB has a minimum of 1,000 million (10^9) organisms, in 2-8 weeks it will have selected the 1,000 mutant bacilli (1 per million) that are resistant in this population. These 1,000 bacilli are insufficient to cause clinical symptoms or to be smear +. Good clinical progression! The problem is that these 1,000 soon will be 10^9

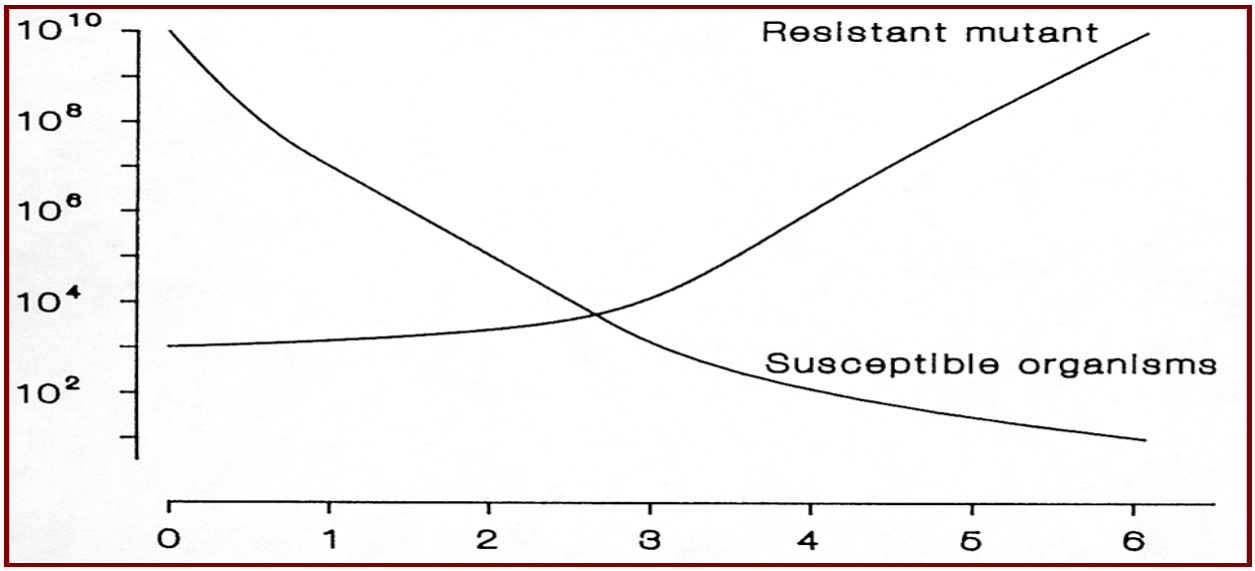


Figure 1: The fall and rise mechanism (Mitchison DA. En: Heaf F, et al. Churchill, London, 1968)

Risk factors associated with Acquired DRTB

These are classified into three:

1. Health care provider factors
2. Drugs related factors
3. Patient factors

Table 1.1: Factors associated with drug resistance TB

Health care provider factors	Drugs related factors	Patients factors
• Absence of guidelines • Non Compliance to guidelines • Inadequate training • Poor or no treatment monitoring • Poorly organized or funded TB control programs	• Inadequate supply • Poor quality • Poor storage conditions • Wrong dose or combination • Poor regulations of medicines • Unavailability of certain medicines	• Poor adherence or poor DOT • Lack of information • Lack of transportation • Adverse effects • Social barriers • Malabsorption

1.5 Classification of drug resistant TB

i. Classification based on drug resistance

Table 1.2: Classification Based on Drug Resistance

Mono resistance	Resistance to one first-line anti-TB medicine only
Poly-drug resistance (PDR TB)	Resistance to more than one first-line anti-TB medicine (other than both Isoniazid and Rifampicin)
Rifampicin resistance (RR TB)	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 (Hr-TB)	Refers to Mycobacterium tuberculosis strains with resistance to isoniazid and susceptibility to rifampicin confirmed *in vitro*
Multidrug resistance (MDR TB)	Resistance to at least both Isoniazid and Rifampicin
Pre–XDR	Resistance to Isoniazid and Rifampicin and either a fluoroquinolone or a second-line injectable agent but not both.
Extensive drug resistance (XDR TB)	Resistance to any Fluoroquinolone and at least one of three second-line injectable drugs (Capreomycin, Kanamycin and Amikacin), in addition to multidrug resistance.
Presumptive drug resistant TB cases	This is a diagnosis given to patients who have a high risk of getting MDR 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 known MDR-TB patient, refugees, prisoners, health care workers with symptoms of TB, DR TB contacts .

ii. Classification based on registration of DR TB patients

Before enrolling patients on second line drugs, one needs to establish whether she/he has previously received any anti-tuberculosis treatment, whether for drug sensitive TB or drug resistant TB, and if so, when and the treatment outcome during that illness was. The following categories are used for registration:

Table 1.3: Classification Based on Registration of DR TB patients

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 failure of First Line Treatment (FFT)	Patients who return after having failed the first treatment i.e smear positive at earliest, month 5
After failure of Retreatment (FRT).	Patients who return after having failed the re-treatment.
Transfer in (TI)	Patients who have been transferred from another register for treatment of drug-resistant TB to second line treatment. Their outcomes should be reported to the transferring unit so that it can report their outcomes in the cohort in which they originally started MDR-TB treatment.

iii. Classification based on Treatment Outcomes

Table 1.4: Classification based on Treatment Outcomes

Treatment completed	DRTB patient who has completed Treatment as recommended Without evidence of failure BUT no record that three or more Consecutive cultures taken at least 30 days apart are negative after the intensive phase.
Cured	DRTB patient who completes treatment with three or more consecutive negative cultures taken at least 30 days apart after the intensive phase.
Death	A patient who dies from any cause while on DR-TB treatment.
Loss to Follow Ups	A patient who interrupts DR-TB treatment for two or more consecutive Months.

Treatment failure:	Treatment terminated or need for permanent regimen change of at Least two anti-TB drugs because of: • Lack of conversion by the end of the intensive phase; or • Bacteriological reversion in the continuation phase after conversion to negative • Evidence of additional acquired resistance to fluoroquinolones or Second-line injectable drugs; or • Adverse drug reactions
Transfer out:	A patient who has been transferred to a reporting unit in another County and for whom the treatment outcome is unknown.
Not evaluated	A patient for whom no treatment outcome assigned. (This includes cases "transferred out" to another treatment unit and whose treatment outcome is unknown).
Treatment success	The sum of Cured and Treatment completed.
Treatment failed,	Lack of conversion by the end of the intensive phase implies that the patient does not convert within the maximum duration of the intensive phase applied by the programme. If no maximum duration is defined, an 8-month cut-off is proposed. For regimens without a clear distinction between intensive and continuation phases, a cut-off eight months after the start of treatment is suggested to determine when the criteria for Cured, Treatment completed and Treatment failed start to apply. The terms 'conversion' and 'reversion' of culture as used here are defined as follows:
Conversion (to negative)	Culture is considered to have converted to negative when two consecutive cultures, taken at least 30 days apart, are found to be negative. In such a case, the specimen collection date of the first negative Culture is used as the date of conversion. Reversion (to positive): Culture is considered to have reverted to positive when, after an initial conversion, two consecutive cultures, taken at least 30 days apart, are found to be positive. For the purpose of defining Treatment failure, reversion is considered only when it occurs in the continuation phase.

1.6 DR-TB Case Finding Strategies

This entails identifying individuals who may be at a greater risk of developing drug-resistant TB (Presumptive DR-TB) compared to the general population and evaluating them appropriately. They include the following target groups:

1. DR TB contacts with symptoms of TB. Includes children with TB symptoms who are contacts of DR TB source persons.
2. Failures on Drug susceptible TB treatment (smear positive at month 2 and 5)
3. Patients who develop TB while on IPT

4. Health care workers with TB symptoms.
5. Refugees with TB symptoms
6. Prisoners with TB symptoms
7. All previously treated patients. They include, failures, relapses, return after loss to follow ups.

DIAGNOSIS OF DRUG-RESISTANT TB

2.

The definitive diagnosis of drug-resistant TB requires the detection of Mycobacterium tubercle bacilli and determination of resistance to anti-TB drugs in the following specimens;Sputum, CSF, Gastric aspirate, Nasopharyngeal aspirate, Pleural fluid, Pericardial fluid, Ascitic fluid, FNA, Stool, skin snips, pus aspirate, bone tissue, Lymph node and tissues biopsies.

Specimen collection procedure *(Annex1)*

Currently there are a number of WHO-recommended diagnostic techniques available for detection of DR TB that are suitable for complimentary use at different levels of the tiered network of TB laboratories.

2.2.1. Microscopy:

KEY HIGHLIGHTS

Sputum smear microscopy is important largely for monthly treatment monitoring

Sputum smear examination (direct smear microscopy) is less expensive, quick, and highly specific and provides reliable evidence of Mycobacteria in the lungs. Sputum smear microscopy is important largely for treatment monitoring and for providing an indication of the degree of infectiousness of TB patients.

Sputum smear results are reported by the presence of stained bacilli (by Ziehl Neelsen or Auramine staining methods) observed.

- **Positive smear results:** A patient with at least one acid fast bacillus (AFB) in at least one sputum specimen is considered smear-positive TB.

- **Negative smear results:** A patient with two negative sputum-smear results may not have PTB, or the patient may have smear negative PTB, or EPTB.

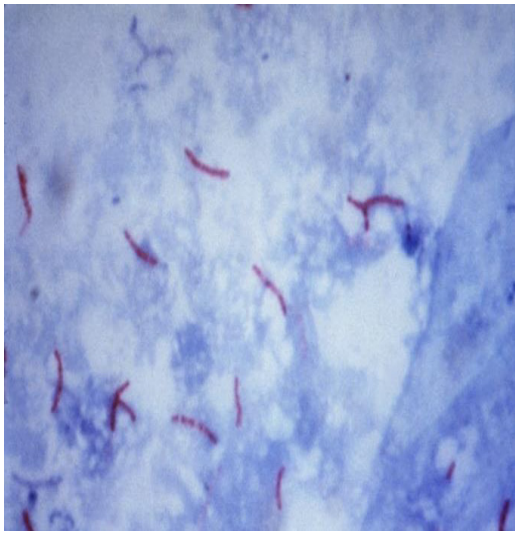


Figure 2.1: Positive Ziehl Neelsen smear

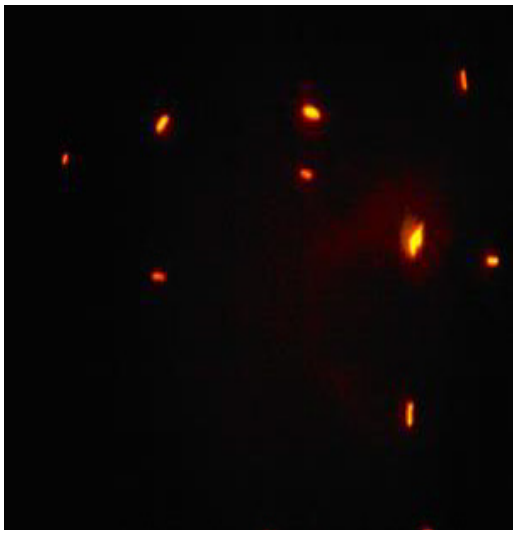


Figure 2.2: Positive fluorescent microscopy

2.2.2. Molecular and new technologies

- Xpert MTB/RIF assay should be the first diagnostic test for all presumptive cases.

KEY HIGHLIGHTS

This test is not recommended for monitoring response to TB treatment

Figure 2.3: GeneXpert machine in use

The following results may be reported after performing Xpert MTB/RIF

1. **MTB not detected:**-which should be interpreted as a negative result

2. **MTB detected rifampicin resistance not detected** *(TS)*:-which should be interpreted as rifampicin-susceptible or drug susceptible TB
3. **MTB detected rifampicin resistance detected (RR):**-which should be interpreted as rifampicin resistant TB
4. **MTB detected rifampicin resistance indeterminate (TI)**:-which is a positive result but with no conclusion on rifampicin resistance. In such cases, another specimen (2nd specimen) should be collected and tested again with Xpert MTB/RIF
5. **Insufficient specimen, error or invalid**:-Meaning a successful test could not be performed. In such cases, another specimen should be collected and tested with Xpert MTB/RIF

N.B: Xpert MTB/RIF or Ultra does not detect isoniazid resistance. Furthermore, this test does not detect mycobacteria other than tuberculosis (MOTT) and will be negative in such cases even when smear microscopy is heavily positive.

- **Line Probe Assay**

Line probe assay (LPA) detects resistance-conferring mutations in the DNA of the Mycobacteria. LPA tests are, however, complex to perform and require skilled and well-trained laboratory personnel, as well as specialised laboratory space and design to reduce the risk of false positive results.

Indications for performing LPA in Kenya are:

- **1st line LPA to confirm resistance to Isoniazid (and rifampicin):** This is for follow up specimens when there is need to establish susceptibility to Isoniazid.
- **2nd line LPA as a follow on test for Rifampicin resistance:** when Xpert MTB/RIF detects rifampicin resistance, the laboratory should forward a sputum specimen for 2nd line LPA in order to screen for resistance to fluoroquinolone and 2nd line injectable drugs.
- **LPA to detect MOTT (CM/AS):** This is useful when smear is positive but Xpert MTB/RIF is negative or to identify the species when culture grows MOTT.

NB: *MOTT is also known as Non-tuberculous mycobacteria (NTMs)*

2.2.3. Culture for detection and identification of TB

Culture is the gold standard for TB diagnosis and can detect as few as 10-100 viable bacteria/ml. We have two types of culture methods

- Liquid culture- Mycobacterium Growth Indicator Tubes (MGIT)
- Solid culture- Lowenstein-Jensen (LJ).

These are used for the detection and recovery of mycobacteria. All types of clinical specimens, pulmonary as well as extra pulmonary can be processed for primary isolation.

2.2.4. Drug susceptibility testing

A laboratory technique determines whether TB bacteria will grow in the presence of TB drugs. If bacterial growth is observed, it shows resistance, while No growth shows susceptibility to drugs used. The demand for reliable drug-susceptibility testing (**DST**) increases with the expansion of anti-tuberculosis drug-resistance surveillance, and with the need for an appropriate treatment of drug-resistant tuberculosis.

Indications for DST	
First Line DST • Previously treated patients; • Persons who develop active TB after exposure to a patient with documented DR-TB • Patients who remain smear-positive at month two and five of therapy	**Second Line DST** Patients with a DST showing resistance to at least rifampicin, isoniazid or both rifampicin and isoniazid at baseline Patients who remain culture-positive on or after Month 3 of DR TB treatment. Persons who develop active TB after exposure to a patient with documented DR-TB

Expected turnaround times (TAT) for the various laboratory techniques/assays (Annexed)

2.5. Interpretation of lab results

Table 2.1: Interpretation of laboratory results

Method	Expected results	Interpretation	Management/ Recommendation
Gene Xpert	MTB detected, -Rifampicin Resistance not detected (TS)	This shows that the patient has TB that is sensitive to Rifampicin	Collect fresh sample for Culture and DST. Initiate patient on CAT1 (2HREZ/4HR) treatment.
	MTB detected Rifampicin Resistance detected	This shows that the patient has rifampicin resistance TB	Collect fresh sample for Culture and DST 1&2 1st & 2nd Line LPA. Initiate patient on DR TB (RR / MDR) treatment.
	MTB detected Rifampicin Resistance indeterminate (TI)	Patient has TB but bacterial load is very low to determine resistance pattern.	Collect fresh samples for repeat GXP test and treat according to the second GXP results.
	MTB not detected	This shows MTB has not been detected, however it does not rule out absence of Tuberculosis,	Correlate with clinical symptomatology and other relevant history. Seek for a second opinion from SCTLC or CTLC.
NOTE: For errors and invalid Gene Expert results, collect fresh samples for repeat tests.			

Method	Expected results	Interpretation	Management/ Recommendation
FL LPA (MTBDRPlus)	MTB detected rpoB & KatG and inhA-mutation detected	The bacteria is resistant to both rifampicin (rpoB) & Isoniazid (KatG and inhA) drugs.	Start the patient on conventional injectable free treatment regimen
	MTB detected rpoB & KatG and inhA - Mutation not detected	The bacteria is susceptible to both rifampicin and isoniazid drugs.	The patient isolate is susceptible to both isoniazid and Rifampicin. Initiate CAT 1 treatment
	MTB detected rpoB - Mutation detected KatG and inhA -Mutation not detected	The bacteria is resistance to rifampicin alone	Start the patient on conventional injectable free treatment regimen
	MTB detected rpoB- Mutation not detected KatG and inhA- Mutation detected	The bacteria is resistant to isoniazid alone	Start the patient on Isoniazid mono resistant treatment regimen
	No MTB detected	MTB complex is absent	Correlate clinically Evaluate the patient for other conditions
SL LPA (MTBDRsl)	gyrA/gyrB-Mutation not detected	The bacteria is susceptible to fluoroquinolones	Fluoroquinolones can be used in the treatment regimen
	gyrA/gyrB-Mutation detected	The bacteria is resistant to fluoroquinolones	Fluoroquinolones cannot be included in the regimen Refer to the table for regimen design (*DR TB treatment according resistance pattern*)
	rrs/eis a) Mutation detected	Aminoglycosides (Capreomycin, Amikacin, Kanamycin, Viomycin) The bacteria is resistant to Aminoglycosides	Injectable drugs cannot be used
	b) Mutation not detected	The bacteria is susceptible to the Aminoglycosides	Aminoglycosides can be used. *The TB program does not recommend use of injectable agents in the treatment of DR TB under programmatic conditions*

Method	Expected results	Interpretation	Management/ Recommendation
Culture (Solid & Liquid)	Growth reported	Mycobacterium TB detected	Continue current treatment if within intensive phase of treatment
			If we have growth beyond intensive phase give an outcome of failure and consult national PMDT team for technical advice.
	Contamination reported	Sample contaminated	Continue the same treatment Obtain a fresh sample for repeat test
	No growth/Negative	Absence or non-viable mycobacteria	Continue treatment
First Line DST	Susceptible/Sensitive (RHZE)	The bacteria is sensitive to all first line drugs	CAT 1 drugs can be used in the treatment regimen (2HREZ/4HR)
	Resistance to Rifampicin and Isoniazid (RH)	The patient has MDR TB	Treat as MDR TB
	Resistance to H,Z,E and sensitive to Rifampicin	The patient has poly drug resistance	Refer to DR TB treatment guide for regimen composition
	Resistance to R ONLY (Rifampicin resistance)	The patient has resistance to Rifampicin only	Start the patient on conventional injectable free treatment regimen
	Resistance to H ONLY (Isoniazid mono resistance)	The patient has resistance to isoniazid only	Start the patient on Isoniazid mono resistant treatment regimen
Second line DST	Susceptible/Sensitive Bdq, Dlm,Lzd,Clz,Cs,Lfx/ Mfx,Cm,Amk,Kan,	The bacteria is sensitive to all second line drugs	Consider use of second line medicines in the treatment regimen
	Resistance to Aminoglycosides (Cm, Amk, Km)	The bacteria is resistant to Aminoglycosides	Injectable drugs cannot be used. Refer to DR TB treatment guide and regimen composition
	Resistance to Fluoroquinolones (Lfx, Mfx)	The bacteria is resistant to fluoroquinolones	Fluoroquinolones can not be used. Refer to DR TB treatment guide and regimen composition
	Resistance to Fluoroquinolones (Lfx, Mfx) and Aminoglycosides (Cm, Amk, Kan)	The bacteria is resistant to fluoroquinolones and Aminoglycosides	Refer to DR TB treatment guide and regimen composition
	Resistance to Bdq/ Dlm/Lzd,Clz,Cs	Resistance to specific drugs	Refer to DR TB treatment guide and regimen composition

Tabble 2.2. Interpreting Discordant results

	Test	Discordant pattern/ reports	Recommended action	Explanation
1. Smear microscopy VS GXP	Smear microscopy	Negative		
	GXP	Positive		
		RS (Rif. Sensitive)	Collect fresh sample for culture and phenotypic DST. Initiate patient on CAT1 (2HREZ/4HR) treatment.	GXP sensitivity and specificity is superior to smear microscopy.
		RR (Rif. Resistant)	Collect fresh sample for Culture and DST 1st and 2nd Line LPA 1st and 2nd line. Initiate patient on DR TB (RR / MDR) treatment	GXP superior sensitivity and specificity to smear microscopy. GeneXpert detects bacterial DNA and rpoB gene that is responsible for Rif. Resistance.
		TI (Rif. Resistant Indeterminate)	Collect fresh sample for repeat GXP test and treat according to the second GXP results.	Poor sample quality. Emphasize on good quality sample. Low bacillary load.
		I (Invalid)	Collect fresh sample for GXP test and treat according to the second GXP results	Poor sample quality. Emphasize on good quality sample.
2. Smear microscopy VS GXP	Smear microscopy	Positive	Repeat both tests on fresh samples.	Rare occurrence. Could be a lab error. Consider MOTT as well.
	GXP	Negative		

	Test	Discordant pattern/ reports	Recommended action	Explanation
3. GXP VS Culture and DST	GXP	MTBC Detected, Rif Resistance detected.	Start on RR/MDR TB treatment regimen. Adjust regimen according to SL LPA results. May obtain fresh sample for Genome sequencing.	GXP may pick silent mutations in the genome that would be missed by phenotypic testing.
	Culture and DST	MTBC Positive Rif Sensitive	Need for clinical teams decision (Sub county, County and National) attention.	
4. Xpert vs LPA RIF resistance detection	GXP	RIF resistance detected	The methods look at the same region but detect resistance using slightly different probes. Treat as Rifampicin resistant	Confirm using phenotypic methods. Xpert detects mutations in codons 531,516 and 526 which are not detected by LPA
	LPA	RIF sensitive		
	Xpert	RIF resistance not detected	The methods look at the same region but detect resistance using slightly different probes. Treat as Rifampicin resistant	Confirm using phenotypic methods
	LPA	RIF resistance detected		
5. Molecular methods (Xpert and LPA) vs Culture	Molecular methods (Xpert and LPA)	Molecular methods did not detect TB	Culture is the gold standard and has a lower limit of detection than molecular methods	Treat according to culture results
	Culture	culture positive		
	Molecular methods (Xpert and LPA)	Molecular methods did not detect TB	Non-viable cells especially if culture was delayed or if patient has been previously treated for TB as molecular tests can detect DNA from non-viable cells	Clinical decision required
	Culture	culture negative		
6. LPA Indeterminate results	This is considered as a preliminary report awaiting the final report from phenotypic culture			

NOTE

1. Culture/DST should not be used to confirm / reject GeneXpert results
2. Every diagnostic test has a risk of providing a false result
   - Factors outside laboratory testing of a sample can also cause false result
3. A laboratory test result is only part of the clinical decision making process
   - Treat the patient's worst-case scenario not the test result!

TREATMENT OF DRUG RESISTANT TUBERCULOSIS (DR TB)

3.

3.1. A brief history of DR TB treatment in Kenya

Programmatic Management of Drug Resistant TB (PMDT) in Kenya began in 2006 in a centralized model based in Nairobi. With increasing diagnostic and human resource capacity, treatment was decentralised to all 47 Counties in 2011. Currently, DRTB care and treatment can be offered at any health facility in Kenya. Prior to October 2017, all RR/MDR patients were treated using a conventional long-term DRTB regimen (LTR) with injectables and fluoroquinolones as core drugs. In 2017, Kenya rolled out the shorter-term regimen (STR) for RR/MDR patients, which reduced the treatment duration to 9 months but retained injectables and fluoroquinolones as core drugs. Additionally, new drugs were introduced to strengthen individualized regimens for Pre-XDR and XDR TB. Due to the challenges caused by use of injectable medicines, and following guidance by the WHO on management of DRTB in 2019, Kenya rolled out injectable free regimens (IFR). Below is a description of the various regimens used for DRTB treatment in Kenya.

Table 3.1: History of DR TB treatment in Kenya

Period	Resistance pattern	Intensive phase		Continuation phase	
		Duration (months))	Regimen	Duration (months)	Regimen
Before October 2017	MDR/RR TB	8-10	Km (Cm)/Lfx/Cs/ Pto/Z	12	Lfx/Cs/Pto/Z
	INH Mono TB	9	R/Z/E/Lfx		
	PDR TB	3	Km (Cm)/R/Z/Lfx	15	R/Z/Lfx
	XDR TB	Individualized regimen			

Period	Resistance pattern	Intensive phase		Continuation phase	
		Duration (months))	Regimen	Duration (months)	Regimen
Oct 2017 to Dec 2019	MDR/RR TB	4-6	Km/Mfx/Pto/Cfz/ H-Inh/Z/E (Shorter Term Regimen-STR)	5	Mfx/Cfz//Z/E
	INH Mono TB	9	R/Z/E/Lfx		
	PDR TB	3	Km (Cm)/R/Z/Lfx	15	R/Z/Lfx
	Pre XDR and XDR TB	Individualized regimen			
	Exclusion from STR	Individualised regimen			

3.2. Principles and rationale of DR TB treatment

Drugs should be used in combinations to prevent the development of resistance as it avoids the selection of naturally occurring resistant mutants

Intentional or inadvertent monotherapies should avoided as they select naturally occurring mutants to the single drugs being used.

Drug combinations should have adequate sterilizing and bactericidal effect.

Treatment should be long enough to allow drug action against all bacillary populations *(rapid, slow, and intermittently growing bacteria)*.

3.3. Objectives of DR TB treatment

1. To reduce the patient's risk of death and reduce severity of symptoms quickly
2. To cure without relapses
3. To avoid selection of resistance.
4. To reduce infectiousness quickly

3.4. Desirable characteristics of anti-TB medicines

Bactericidal activity - ability to kill the rapidly multiplying, metabolically active bacilli found in cavities and sputum of smear positive pulmonary TB patients. These drugs are responsible for reducing the risk of death, reducing the severity of symptoms, reducing infectiousness and curing the patient.

Sterilizing activity - The ability to kill the persisting, dormant or intermittently active bacilli, which are responsible for relapses. Good sterilizing effects lead to shortening of the treatment period.

Table 3.2 Desirable properties of anti-TB medicines

Properties of anti TBs				Toxicity	
Activity Level	**Prevention of Resistance**	**Bactericidal activity**	**Sterilizing activity**	**Toxicity**	**Activity Level**
High	**Rifampicin** Isoniazid Ethambutol	Isoniazid **Rifampicin** Lfx/Mfx	**Rifampicin** Pyrazinamide hMfx	Ethambutol **Rifampicin** Isoniazid Fluoroquinolone	**Low**
Moderate	Injectables Fluoroquinolones Ethionamide Cycloserine PAS Linezolid	Injectables Linezolid Bedaquiline Delamanid	LFX Linezolid Bedaquiline Delamanid Clofazimine	Injectables Pyrazinamide Linezolid Bedaquiline Delamanid	**Moderate**
Low	Pyrazinamide	Ethionamide/Pth		Rest	**High**

3.5. Drugs used in DR TB treatment

Classification of anti TB drugs used in the management of DR-TB

The drugs used in the treatment of DR TB are classified into three groups based on their efficacy and experience of use as shown in the table below:

Table 3.3 Grouping of Medicines for use in the treatment of drug-resistant TB

Group	Medicine	Abbreviation
Group A Include all three medicines (Unless they cannot be used)	Levofloxacin or 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

3.6. DR-TB treatment regimens by resistance patterns

Table 3.4 Standard DR-TB treatment regimens by Resistance pattern

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'* - Fluoroquinolone Resistance	**Intensive Phase:** **6 Bdq**/**Dlm/Lzd/Cfz/Cs** **Continuation phase: 14 Dlm/Cfz/Cs/Z**	20 months
ISONIAZID mono resistance *(Isoniazid Mono regimen)*	**6 (H)REZ/Lfx**	6 months
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/HZ/EZ)	**9 (H)REZ/Lfx** **(with pyridoxine)**	9 Months
XDR	**Individualized regimen**	18-24 months
Pyrazinamide mono-resistance	**2 RHZE** **4 RH** **(with pyridoxine)**	6 months
Ethambutol Mono-resistance	**2 RHZE** **4 RH** **(with pyridoxine)**	6 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*

3.7 Injectable free regimen for MDR/RR TB and Pre-XDR (with resistance to second line injectable)

This is a fully oral regimen. It is the recommended regimen for MDR/RR and Pre-XDR (resistant to SLIs) TB patients including adults, children and pregnant women.

Advantages

- Full y Oral
- Effective
- Lower risk of mortality, treatment failure and relapses
- No hearing loss
- Better quality of life for patients

Challenge with regimen

- Longer duration
- Requires close monitoring

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

NOTE:

- Persons with DR-TB should be screened for mental health (PHQ9) and substance abuse using form Cage8 questionnaire.
- Challenges in adhering to TB treatment or ART should be properly addressed and social support structures identified and offered
- A full blood count (FBC) should be done at baseline and then monthly. If Hb<8g/dl, neutrophils < 0.75 x109/L or platelets <50 x10 9/L, Linezolid (Lzd) should be stopped and the case referred to National PMDT Clinical Team
- Patients receiving Linezolid should be regularly assessed for peripheral neuropathy, colour blindness and visual acuity.
- ECGs should be done as per the patient monitoring schedule and corrected QT interval (QTcF) calculated and recorded. A nomogram for QTcF calculation can also be used: Any prolongation of QTcF above 450ms should be managed accordingly
- Monthly sputum smear microscopy and culture follow-up should be done and results documented in the patient logbook.
- Delayed sputum conversion or reversion (cultures turning from negative to positive) should be addressed promptly by the multidisciplinary team.

3.8. Individualized regimens for DR TB

Definition: Adaptation of a regimen based on the clinical characteristics, and DST of an individual, aiming to achieve the best possible therapeutic efficiency at the lowest risk of unwanted effects.

Each treatment regimen is designed based on

1. Previous TB treatment and drugs used,
2. DST results and,
3. Other clinical conditions

Intensive phase of 6 – 8 months with at least five effective drugs and Continuation phase at least 12 months with at least four effective drugs. The Backbone of the regimen is usually **Bedaquiline, Delamanid Linezolid and Clofazimine**

NOTE

- Never add Bedaquiline, Delamanid, Linezolid and Clofazimine as a single drug to a **failing regimen**.
- If the patient is culture negative and the newer drugs are being **SUBSTITUTED** for toxicity reasons, then a single drug substitution can be made.

This group of patients may require longer periods of follow up depending on the length of their treatment durations.

The regimen should satisfy the following principles

Table 3.5 Principles for designing Individualized DRTB regimens

	Principle
1	**Inclusion of one or more new drug** • It should contain at least drugs from one new class to which patients have not previously been exposed e.g. Bedaquiline, Delamanid • The addition of two new drug classes could increase the efficacy of the new regimen, if the agents can be safely combined.
2	**Activity against MDR and XDR strains** • It should be broadly applicable for use against MDR and XDR *Mycobacterium tuberculosis* strains • Should be based on DST results *(through culture and LPA)*
3	**Inclusion of three to five EFFECTIVE drugs** • It should contain a minimum of three effective drugs with good bactericidal and sterilizing activity. • If new drugs are developed within the same class, the drug with the better efficacy and toxicity profile should be used in the regimen.
4	**Preference of oral delivery** • Oral delivery is preferred; better tolerated and accepted by patients and for ease of administration.
5	**Simple dosing schedule** • It should have a simple dosing schedule, preferably once daily. • *Drugs requiring administration more than once daily or at specific times need to be carefully considered to ensure that their benefits outweigh the complexity of ensuring that they are properly administered*.

6	**Good side-effect profile** • It should have a good side-effect profile that allows limited monitoring. • It is essential to consider the influence of side-effects on treatment adherence and loss to follow-up • Avoid drug combinations with overlapping or additive toxicities
7	**Length of Treatment** • Long treatment duration is a major hindrance to treatment adherence • Shorter treatment courses could lead to good clinical outcomes if the right combination of drugs to which the infecting *M. tuberculosis* complex bacilli are susceptible is used.
8	**Minimal interaction with antiretroviral therapy** • Use of anti TB treatment regimen with antiretroviral agents for HIV infection should yield **MINIMAL**, if any, clinically relevant drug–drug interactions and/or overlapping toxicity.

3.9 Treatment of Isoniazid Resistance (Hr.-TB)

All patients with confirmed isoniazid-resistant and rifampicin susceptible tuberculosis (abbreviated to Hr-TB) are treated for **6 months**[1] with a regimen composed of:

1. Rifampicin (R),
2. Ethambutol (E),
4. Pyrazinamide (Z) and
5. Levofloxacin (Lfx).

It is CRITICAL to exclude rifampicin and levofloxacin resistance ahead of the start of this regimen through FLLPA and SLLPA. If Hr-TB is diagnosed during DSTB treatment, the patient should be declared a treatment failure and initiated on the regimen above

3.10. PDR treatment

PDR; defined as resistance to more than one first line anti TB drugs, except resistance to rifampicin and isoniazid together**.** Treatment is based on the specific drug resistance pattern as shown below:

Typical / Common PDR Patterns	Suggested Regimen
ISONIAZID mono resistance *(Isoniazid Mono regimen)*	**6(H)REZ/Lfx**
Poly-drug resistance (PDR TB) (HE/HEZ/HZ/EZ)	**9(H)REZ/Lfx**

3.11. Other PDR Patterns

PDR pattern	Considerations
Isoniazid and Fluoroquinolone (H/FQ)	• This will require an individualized regimen (**the national clinical team must be consulted**) • History of past anti-TB drug use is critical in determining effective drugs.(previously used medicines can be added, but are not considered effective) • Extent/disease severity must be considered as well.

Note: Use of injectable medicines for PDR treatment is no longer recommended

3.12. Extensively Drug-Resistant Tuberculosis (XDR-TB)

All XDR-TB patients should receive an individualized treatment regimen. The choice of drugs will depend on DST results in consultation with the National DR TB clinical team.

3.13. Role of surgery in DR TB treatment

There is a role for surgery in the treatment of DR TB. In patients with DR TB, elective partial lung resection (lobectomy or wedge resection) may be used alongside a recommended DR TB regimen. Decisions on surgery should be individualised based on a case to case basis in consultation with a multidisciplinary team including a surgeon.

Possible considerations for surgery include:

- A high probability of failure of medical therapy in mdr-tb patients (due to persistent cavitary disease and lung or lobar destruction) and massive haemoptysis or tension pneumothorax
- Persistent positivity of sputum-smear or sputum-culture despite adequate chemotherapy
- A high risk of relapse (based on the drug-resistance profile and radiological findings)
- Progression of tb despite adequate chemotherapy
- Repeated haemoptysis or secondary infection
- Localized disease amenable to resection
- Absence of any radiological and/or bacteriological improvements during the initial three to four months of chemotherapy;
- Allergic, toxic and mixed side-effects of drugs;
- Chronic diseases of the gastrointestinal organs hindering effective chemotherapy.

3.14. Treatment preparation and Initiation

Patient education and counselling

Adherence to DR TB treatment is essential in preventing the amplification of resistance and to increase the chance of cure. Adherence to DR TB therapy is complicated by the lengthy treatment, high pill burden, frequent and serious drug adverse reactions and high social and economic costs to patients associated with access to care. Thus, DR TB patients are at increased risk of poor adherence to treatment.

This guideline provide practical steps to be used by healthcare workers to provide patient education/counselling to patients under DR TB treatment.

Counselling explores and assesses psychological and emotional issues (mental health disturbances) that could be pre-existing, drug induced and/or emerging in the course of the treatment due to social pressures. This approach is patient-centred and geared towards helping patients find their own solutions to daily life problems that may impact negatively on adherence.

Counselling/Education will aim to achieve the following,

a) Inform and educate patients and their caregivers on DR TB

b) Increase patient understanding of DR-TB disease and treatment to enhance adherence.

c) Empower the patient to take responsibility of their treatment process.

d) Identify psychological issues arising from treatment or disease presence and provide psychological services

e) Create a harmonised patient education for enhanced holistic care.

f) Improves patient/health care worker relationship.

These rely on the quality of the therapeutic relationship established between the educator, the clinical team and the patient.

Counselling/Education before treatment initiation

DR TB patients MUST be provided with counselling/education sessions before informed consent is given and during follow-up visits. The health care workers at the DR TB treatment clinic should provide this counselling. The process of counselling/ education will follow the steps below:

i) Creating a rapport and assure confidentiality

ii) Use of simple and appropriate language that a patient can understand

iii) Listen to feedback and questions from the patient

iv) Assess the patient's TB information and treatment history

v) Clarify information and explore barriers on TB treatment and adherence

vi) Explore barriers to treatment adherence

vii) Provide information on TB treatment and adherence

viii) Provide information about treatment services, which include duration of treatment, possible side effects, importance of DOT, follow up visits and social support provided including NHIF.

ix) Roles and responsibilities for the patients, family, patient supporters and health care worker

x) Signing of the consent form in the DRTB patient log book

Counselling/Education during treatment

The session will aim to develop a DR TB treatment plan in line with patients' centred approach. The plan will include schedules of re-visits for treatment follow up and counselling/education sessions. The frequency of the visits will be every two weeks during intensive phase and monthly in the continuation phase. However, the frequency of visits for counselling/education may be increased during any phase of treatment if issues that would affect adherence are identified. The following will be conducted during the follow up counselling and education sessions

i) Adherence, supportive education

ii) Mental health assessment - Patient Health Questionnaire 9 (PHQ 9)

iii) Psychosocial review and support

iv) Side effect monitoring

Table 3.6 counselling sessions and content

Phase	Session	Content
1. Baseline	First contact with 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 • Mental health assessment - social and mental (PHQ9 Form annexed) • Family planning and contraception including testing-HIV and Pregnancy. • Roles and responsibilities for the patients, family, patient supporter and health care worker • Signing of the consent form
2. 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
	If NO major issue identified, see monthly	• Adherence, supportive education • Mental health assessment • Psychosocial review and support • Side effect monitoring

3. 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.

Patients' education sessions

During the counselling/education session, the health care worker should provide the information about TB,

1. The mode of transmission,
2. Treatment duration,
3. Importance of adherence, and
4. Infection prevention and control.

A checklist is used to ensure that all the topics are covered and level of understanding assessed. This checklist is included in the DRTB patient's logbook.

Table 3.7: Structured Health Education topics for the patients and treatment supporte

Drug resistant TB disease

- Difference between DS TB and DR-TB
- Origin: poor adherence, inappropriate regimen, primary infection
- Mode of transmission: aerosol inhalation
- Symptoms of DR-TB
- Diagnosis of DR-TB (Sputum, Genexpert/culture).

Treatment of DR-TB

- Length of therapy: drugs have many side effects, but these can be managed
- Rationale for DOTs: no fixed dose combination available, multiple side effects, complex treatment and no alternative treatment, administered by a HCW
- Different phases of treatment.

Adherence to treatment

a) **Importance of good adherence**

- Cure
- Prevent transmission
- Improve quality of life
- Prevent further resistance and relapses

b) **Consequences of bad adherence**

- You will transmit to family members, close contacts and community
- Poor quality of life
- Further resistance
- Death

Infection prevention and control

- Emphasize the importance of infection control at home, in public transport, at the clinic and any other public areas. Sensitize on public health implications.
- Contact management

Social support

- Baseline and follow up tests
- Enrolment in NHIF
- Monthly stipend

At the end of the education and counselling session, the patient will have acquired knowledge and information on how to make decisions and responses to issues during treatment. These include;

- How to deal with emotional reactions (anxiety, fear) regarding DR-TB.
- Equip patient with knowledge about TB/DR-TB and
- Understand the available social support including baseline and follow up tests, enrolment on NHIF, monthly stipend
- Need for ensuring infection prevention and control for family members, close contacts and community.

TREATMENT OF DRUG RESISTANT TUBERCULOSIS IN SPECIAL CONDITIONS

4.

Introduction.

This chapter outlines the management of drug-resistant TB in selected special populations and conditions. These include the following groups of patients whose treatment of DR TB may require special considerations:

- Children
- Pregnancy
- Breastfeeding
- HIV Co-infection
- Extra-pulmonary TB
- Diabetes Mellitus
- Renal disease
- Liver disease
- Seizure disorders
- Psychiatric disease
- Substance abuse

4.1 Drug-resistant TB in children

The burden of drug-resistant TB in children is on the rise following an increase in the number of adult cases over the years. In 2018, the Division of National Tuberculosis, Leprosy and Lung Disease (DNTLD) data reported that among all patients with drug-resistant TB, 2.8% were children compared to drug-susceptible TB at 8.4%[1]. Children are an important group for surveillance because they reflect an ongoing transmission of drug-resistant TB within the community.

4.1.1 Risk factors for drug-resistant TB in Children

Majority of the children with drug-resistant TB have primary disease transmitted from an adult index case. However, a few may still develop resistance following prior exposure to treatment. Those at high risk include:

- Contacts of known drug-resistant TB patients
- Children residing or who have resided in a high prevalence drug-resistant TB community

Further DR TB should be suspected in a child:

- Who has been in contact with an index case who is an adult or an older child with unknown susceptibility pattern including:
- A treatment failure (sputum smear positive after 5 months of treatment)
- A retreatment case
- A chronic TB case (TB despite 2 previous treatment courses)
- Recently died from TB
- Who has TB and is not responding to 1st line therapy despite good adherence
- Who was previously treated for TB and presents with a recurrent respiratory infection

4.1.2 Diagnosis of drug-resistant TB in Children

Every effort should be made to confirm the diagnosis of drug-resistant TB by culture and DST in children, particularly in older children (above age 5 years) who can be coached to produce a sputum sample for testing. However, due to the pauci-bacillary (lower bacillary load) nature of the disease and the difficulty in spontaneous expectoration of sputum in younger children, children with active TB may have smear, Xpert and culture negative results posing a diagnostic challenge.

Even with the use of other more invasive methods of acquiring a sputum sample for diagnosis, the yield is still low. Furthermore, radiological features on X-ray and clinical symptomatology do not distinguish drug-susceptible TB from drug-resistant TB.

NOTE

Children with active TB who are household contacts of a confirmed drug-resistant TB patient should be considered to have drug-resistant TB, even if smear, Xpert and culture results are negative. These children should be offered empirical treatment based on the contact's DST pattern.

Treatment of drug-resistant TB in children should be guided by DST results. In case the DST results are not available, empiric treatment of children with paediatric friendly formulations should be initiated based on the DST pattern of the index patient. Drug dosages should be based on body weight with the upper limit of the recommended range. Weight and Z-score should be measured monthly and dose adjustments made as the child's weight changes.

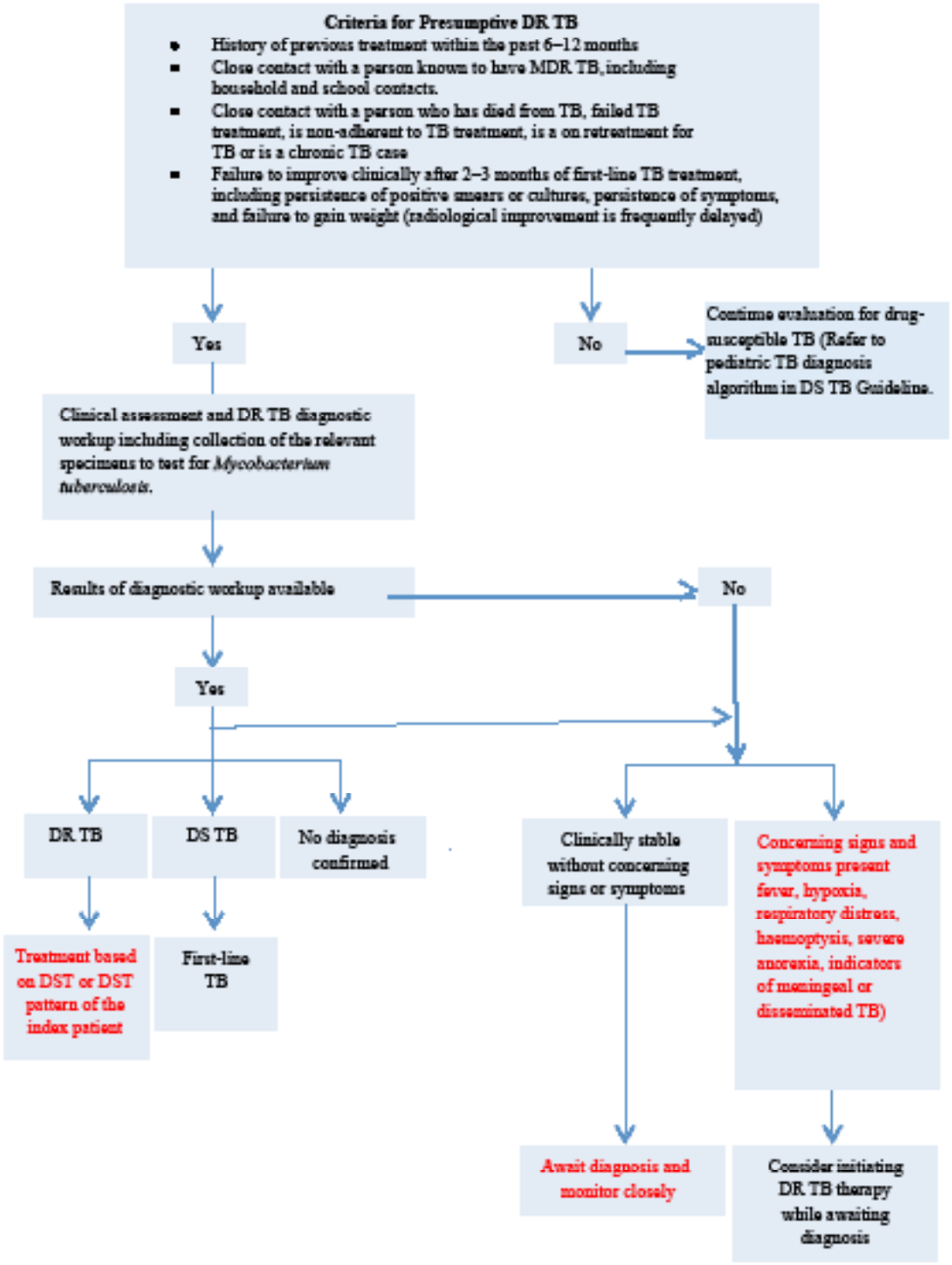


Figure 4.1 Algorithm for Managing a Child with Presumptive DRTB

Guiding Points to Choices of Drugs

The benefit of fluoroquinolones far outweighs the risk, and should be part of every drug-resistant TB regimen except if resistance is confirmed. Bedaquiline is recommended for use in children above 6 years of age. Delamanid is recommended for use above 3 years of age but it could be considered in children <3 years once safety and dosing data is available.

Bedaquiline can be dissolved in water without altering the bioavailability; which makes it easier for use in young children until the paediatric friendly formulation becomes available. Delamanid on the other hand should not be crushed or dissolved as this will alter the drug's bioavailability.

The length of use for Bedaquiline and Delamanid is six months. There are no known safety concerns with using these drugs longer than six months. Some children may benefit from using these drugs for the full duration of their therapy. Existing data suggests the combination of these two medicines does not result in any increase in adverse events[4] and should be considered on a case by case basis with careful monitoring especially in children with fluoroquinolone resistance or in whom there are limited treatment options.

A clinical criteria can be used by the drug-resistant TB clinical review teams to determine the response to therapy and the duration of the intensive and continuation phases in culture-negative children.

4.2 DR TB in pregnancy

4.2.1 General principles

All female patients of child bearing age diagnosed with drug-resistant TB should be tested for pregnancy prior to initiating treatment. Appropriate counselling and a birth control method for all non-pregnant female patients should be provided during the entire treatment duration. There is no contraindication to the use of oral contraceptives with non-Rifamycin containing drug-resistant TB regimens; however condom use is recommended for additional dual protection.

Rifampicin interacts with Combined Oral Contraceptive pills by increasing metabolism of both oestrogen and progesterone components. This results in decreased efficacy of the contraceptive and reduced protection against pregnancy. Women on rifampicin-based drug-resistant TB regimens (for treatment of mono or poly resistant TB) should use either implant or injectable forms of hormonal contraception in addition to condoms for dual protection.

Pregnancy is not a contraindication for treatment of active drug-resistant TB, but poses great risk to the lives of both the mother and foetus. Pregnant patients should be carefully evaluated, taking into consideration the gestational age and the severity of drug-resistant TB. The risks and benefits of treatment should be carefully considered and discussed with the mother, with the primary goal of smear conversion to protect the health of the mother and child, before and after birth.

4.2.2 Benefits and risks of DR TB treatment duringpPregnancy

Treatment should be started as soon as the diagnosis is made. However, since the majority of teratogenic effects occur in the first trimester, therapy may be delayed until the second trimester. Note that delaying treatment carries a risk of disease progression and transmission. The decision to postpone the initiation of treatment should be agreed upon by both the patient and Clinician after thorough analysis of the risks and benefits.

4.2.3 Ethionamide / Prothionamide us in pregnancy

Ethionamide/Prothionamide can increase the risk of nausea and vomiting associated with pregnancy, and teratogenic effects have been observed in animal studies. This group of drugs should not be used. P-amino salicylic acid (PAS) may be considered as an alternative.

4.2.4 Bedaquiline use in Pregnancy

Bedaquiline has been approved by the FDA as a pregnancy category B drug which means it may be acceptable for use in pregnancy if benefits outweigh the risks.

4.3 Drug-resistant TB in breastfeeding mothers

All lactating mothers with drug-resistant TB should receive the full course of treatment. Timely and properly administered treatment is the best way to prevent transmission to the baby. In lactating mothers on treatment, most anti-TB drugs will be found in the breast milk in concentrations that would equal only a small fraction of the therapeutic dose used in an infant. Effects on infants of such exposure during the full course of drug-resistant TB treatment have, however, not been established.

The mother and her baby should not be completely separated. However, if the mother is sputum smear positive, the care of the infant can be left to family members until she becomes sputum smear negative, if this is feasible. When the mother and infant are together, this common time should be spent in well-ventilated areas or outdoors. The mother should use a surgical mask until she becomes sputum smear negative.

NOTE

Note: There is no currently approved prophylaxis for babies born to mothers with drug-resistant TB. These babies should receive Bacillus Calmette-Guerin (BCG) vaccination at birth as per the national immunization schedule.

4.4 HIV Co-infection

4.4.1 Introduction

HIV infection is a significant risk factor for all forms of TB infections, both drug-susceptible (DS TB) and drug-resistant TB (DR TB) [3]. People Living With HIV (PLHIV) can develop drug-resistant TB due to poor adherence to prior TB treatment or infection with resistant strains from other TB patients especially in advanced HIV disease. Tuberculosis relapse is additionally a significant factor associated with Rifampicin resistant TB and Isoniazid (INH) mono-resistant TB among PLHIV.

Kenyan data shows that drug-resistant TB and HIV co-infection cases have been steadily rising over the last few years. Epidemiological data from 2018 DNTLD-P annual report also showed that the proportion of DR TB patients co-infected with HIVwas higher at 36%, while that in drug-susceptible TB was 27% and varied from one region to the other with the least from North Eastern at 0% and the highest in Nyanza North at 62%.

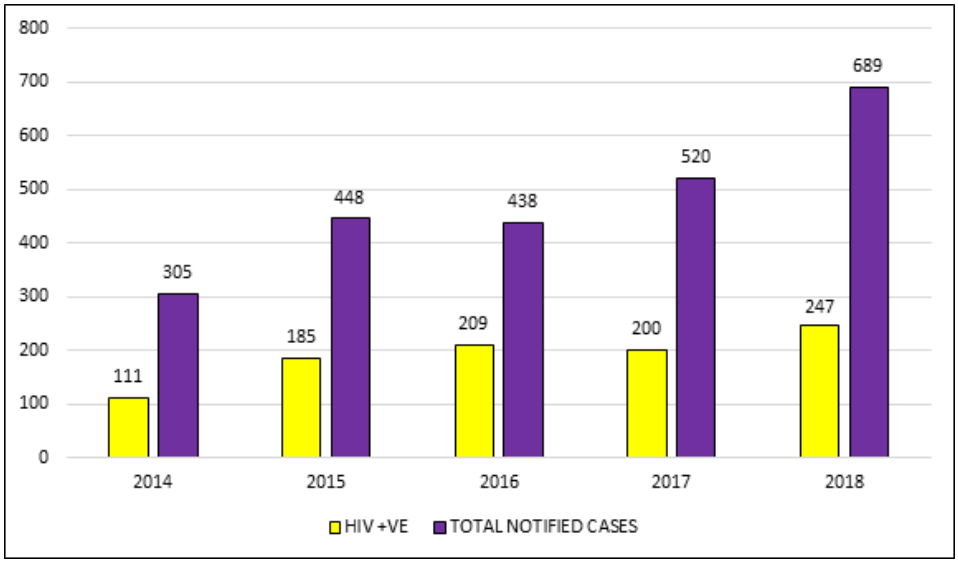


Figure 4.2 Number of drug-resistant TB patients co-infected with HIV in Kenya from 2015 – 2018

Drug-resistant TB is often associated with higher mortality rates among the PLHIV because of reasons that include the following:

1. Difficult drug management due to high pill burden
2. Drug to drug interactions and overlapping side / adverse effects.

The use of recommended TB/HIV interventions as outlined in the DNTLD-P policy documents on TB/HIV collaborative activities is important for successful treatment outcomes.

4.4.2 Drug-resistant TB and HIV collaborative activities

The following activities are applicable to drug-resistant TB/HIV co-infected patients in order to achieve early diagnosis of drug-resistant TB and HIV, prompt initiation of treatment, comprehensive patient support and strong infection control measures:

- Perform provider-initiated HIV testing and counselling (PITC) in all patients with presumed or diagnosed with DR TB as per the Kenya HIV Testing Services guidelines
- Inclusion of HIV testing in DR TB surveillance
- Use of Gene Xpert molecular assay in HIV-positive presumed DR TB cases.
- Timely initiation of appropriate antiretroviral therapy to drug-resistant TB/HIV patients
- Provision of Cotrimoxazole preventive therapy (CPT) to all PLHIV
- Implementation of comprehensive patient follow up and monitoring system for adverse effects and therapeutic response.
- Implementation of additional nutritional and socio-economic support
- Provision of integrated TB and HIV services
- Effective TB infection control
- Involvement of key stakeholders in drug-resistant TB and HIV activities

4.4.3 Screening and diagnosis of Drug-Resistant TB in PLHIV

Diagnosis of TB (including DR TB) in PLHIV is more difficult and may be mistaken for other pulmonary or systemic infections. The clinical presentation is more likely to be extra pulmonary or sputum smear- and Xpert negative than in HIV-uninfected TB patients, especially with advanced immunosuppression. This can result in misdiagnosis or delays in diagnosis, and in turn, higher morbidity and mortality in drug-resistant TB and HIV co-infected patients.

TB screening and prevention services should be offered to ALL PLHIV at every clinical visit and all household contacts of active TB patients.

Symptom-based TB screening using the Intensified Case Finding (ICF) tool MUST be performed for all PLHIV at every clinic visit to rule out active TB (Tables 5.1 and 5.2). Patients who screen positive (presumptive TB patients) must complete definitive diagnostic pathways (Figures 2.1 – reference to chapter 2).

NOTE: Gene Xpert assay is the initial diagnostic test in PLHIV suspected of having drug-resistant TB.

Table 4.1: Paediatric Intensified Case Finding Screening Tool (0-14 years of age)

Screening Questions	Y/N
1. Cough of any duration (Y/N)	
2. Fever (Y/N)	
3. Failure to thrive or poor weight gain (Y/N) (based on z-score/BMI)	
4. Lethargy, less playful than usual (Y/N)	
5. Contact with a TB case (Y/N)	
• If "Yes" to any of the above questions, suspect TB, examine the child and use the pediatric TB diagnostic algorithm to evaluate for active disease. Rule out underlying conditions, refer if necessary • If "No" to all questions, initiate workup for IPT and repeat screening on subsequent visits	

Table 4.2: Adolescent and Adult Intensified Case Finding Screening Tool (≥ 15 years of age)

Screening Questions	Y/N
1. Cough of any duration (Y/N)	
2. Fever (Y/N)	
3. Noticeable weight loss [based on BMI] (Y/N)	
4. Night sweats (Y/N)	
• If "Yes" to any question, take a detailed history, examine the patient and request for sputum sample examination if coughing (sputum for Gene Xpert and smear, Figure 2.1-TB Screening and Diagnostic algorithm), and urine TB-LAM if meets criteria. Exclude underlying illnesses • If "No" to all questions, initiate workup for IPT and repeat screening on subsequent visits **Note:** *draining lymph nodes are often due to TB*	

4.4.4 Antiretroviral therapy for DR TB/ HIV co-infection

All PLHIV who are diagnosed with TB (either DR TB or DS TB) should also be on ART and CPT as part of the comprehensive package of care for PLHIV. The multiple medicines used in DR TB treatment with recognized high toxicity risks, combined with ART often results in a high incidence of adverse effects in PLHIV.

ART improves survival of HIV-infected patients with DR TB[7]. However, DR TB patients may often have advanced clinical disease that puts them at increased risk of developing immune reconstitution inflammatory syndrome (IRIS) in addition to frequent drug interactions and co-toxicities when they are also on ART.

Due to the complexity of care for DR TB and HIV co-infected patients, particularly with regards to ART dosing, identification and management of drug-drug interactions and management of HIV care in general, all efforts must be made to ensure the involvement of an experienced HIV Clinician/specialist. This holistic management can also be made within the DR TB clinical review for DR TB drug-ART interactions

If a patient has been on ART for more than 6 months and develops TB, investigate for HIV treatment failure with viral load and CD4 count as per the Kenya ART guidelines and monitor closely for IRIS.

Drug-resistant TB with Rifampicin use (in Isoniazid mono-resistance)

In DR TB/HIV patients for whom a rifampicin based regimen is required, (in case of INH mono-resistance), refer to the Guidelines on use of antiretroviral drugs in Kenya.

For DR TB/HIV patients on 2nd line ART, subsequent regimens, or nonstandard drugs that require regimen change because of DR TB treatment, consult the Regional or National HIV Clinical TWG for further advice.

DR TB with standard injectable free RR/MDR TB regimen

DR TB patients on Standard Injectable Free RR/MDR TB regimen with HIV co-infection need special consideration due to drug interactions mainly between Bedaquiline and the Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) and Protease Inhibitor (PI) classes of ARV drugs. Considerations also depend on whether the patient is newly HIV diagnosed/ ART naive or is a known HIV patient already on ART as well as whether the patient has a detectable viral load at the time of DR TB diagnosis.

Table 4.3: Preferred ART Regimens for MDR/RR TB/HIV Co-infection for Patients Newly Initiating 1st Line ART

Age	1st Line ART if MDR/RR TB/HIV Co-infection
<4 weeks	Start anti-TB treatment immediately; start ART after 4 weeks of age, once tolerating anti-TB drugs (follow the regimen recommendations for children 4 weeks to < 3 years of age)
4 weeks - < 3 years	ABC + 3TC + RAL[1]
3 - 14 years (and < 35 kg body weight	ABC + 3TC + RAL
≥ 15 years (and ≥ 35 kg body weight)	TDF + 3TC + DTG[2]

PWID/HIV ≥ 15 years	TDF + 3TC + DTG[2]

1. When use of RAL as part of the ART regimen due to DR TB is required, consult the Regional or National HIV Clinical TWG (Uliza Toll-free Hotline 0800 72 48 48; **ulizanascop@gmail.com**)
2. DTG can be used in women and adolescent girls of child bearing age when combined with effective contraception. DTG is safe during pregnancy and breastfeeding if initiated 8 weeks after conception (although women need to be counselled on the risk of becoming pregnant while breastfeeding and provided with effective contraception)

Table 4.4: Preferred ART Regimens for Patients who Develop DR TB while Virally Suppressed on 1st Line ART

Current Regimen[3]	Age	Recommended Substitution
PI/r-based	< 3 years old	• Change LPV/r to RAL[3] • After completion of TB treatment revert to the recommended first line regimen (ABC + 3TC + LPV/r)
	3 years – 14 years (and < 35 kg body weight)	• Change LPV/r to RAL[3] • After completion of TB treatment revert to the recommended first line regimen (ABC + 3TC + LPV/r)
	≥ 15 years (and ≥ 35 kg body weight)	• Switch from PI/r to DTG[4] and continue this regimen even after completing TB treatment
EFV-based	Any age	Change EFV to RAL/DTG
NVP-based	Any age	Change NVP to RAL/DTG

1. Always assess for HIV treatment failure in patients who develop TB after being on ART for ≥ 6 months. For patients failing 1st line ART refer to the Kenya ART Guidelines 2018 for recommended 2nd line regimens.
2. For patients on 2nd line ART, subsequent regimens, or non-standard drugs who require regimen change because of TB treatment, consult the Regional or National HIV Clinical TWG (Uliza Toll-free Hotline 0800 72 48 48; *ulizanascop@gmail.com*)
3. When use of RAL as part of the ART regimen due to DR TB is required, consult the Regional or National HIV Clinical TWG (Uliza Toll-free Hotline 0800 72 48 48; *ulizanascop@gmail.com*)
4. DTG can be used in women and adolescent girls of child bearing age when combined with effective contraception. DTG is safe during pregnancy and breastfeeding if initiated 8 weeks after conception (although women need to be counselled on the risk of becoming pregnant while breastfeeding and provided with effective contraception)

NOTE: For patients failing 2nd line ART, 3rd line ART or non-standard regimens, who require regimen change because of TB treatment, consult the Regional or National HIV Clinical TWG (Uliza Toll-free Hotline 0800 72 48 48; ulizanascop@gmail.com)

4.4.5 Drug interactions in DR TB/HIV co-infection

There are several known interactions between drugs used to treat HIV and drug-resistant TB:

- **Rifampicin:** Rifampicin is used in the treatment of rifampicin-sensitive poly- and mono-resistant TB. Such patients need to be on ART regimens as outlined in the current Kenya ART Guidelines.

- **Bedaquiline (BDQ):** This drug is metabolized by the enzyme CYP3A4 and has multiple drug interactions with PIs and non-nucleoside reverse-transcriptase inhibitors (NNRTIs). Efavirenz (EFV) and BDQ are **NOT** co-administered together (EFV lowers the BDQ levels and EFV should be changed to another antiretroviral agent according to the current ART Guidelines)[8]. Ritonavir boosted Lopinavir (LPV/r) is also NOT co-administered together with BDQ because of increased risk of prolonged QT syndrome and LPV/r should be changed to another antiretroviral agent according to current ART Guidelines **(refer to Table 11 on Drug Interactions)**
- **Linezolid (Lzd), Cotrimoxazole and Zidovudine** (AZT) can cause bone marrow suppression. AZT should be changed to Tenofovir (or Abacavir in renal impairment) if Linezolid MUST be used, or use a different drug if AZT must be used. Cotrimoxazole can be changed to Dapsone if CD4 count is below 200 cells/ml.
- **Amikacin and Tenofovir** (TDF) both cause renal impairment and should NOT be co-administered.

When treating HIV infected patients for DR TB, health care workers should look out for increased drug adverse effects e.g.

- Increased risk of cutaneous hypersensitivity reactions by all the drugs
- Increased risk of neuro-psychiatric syndromes with co-administration of Efavirenz and Cycloserine
- Increased risk of renal impairment by aminoglycosides
- Increased risk of adverse gastrointestinal effects by most of the drugs

4.4.6 Monitoring of therapy in HIV co-infected patients

HIV treatment must be taken daily without exception to prevent the development of drug resistance. Since direct observation of treatment with patient-centred care is an important component of drug-resistant TB therapy, it would be advisable to explore the provision of TB medications and anti-retroviral drugs through concomitant direct observation of treatment or other methods of adherence support.

If the patient shows signs of TB treatment failure, further evaluation should be undertaken as described in the previous chapter on Monitoring.

In addition, the ART regimen should be evaluated for possible treatment failure as described in the Kenya ART Guidelines 2018 in the viral load algorithm.

4.4.7 Immune Reconstitution Inflammatory Syndrome (IRIS)

Immune Reconstitution Inflammatory Syndrome (IRIS) is a paradoxical inflammatory reaction against a foreign antigen (alive or dead) in patients who have started ART with improved functioning of their immune system.

IRIS can be classified as:

- **Unmasked IRIS:** appearance of a previously undiagnosed opportunistic infection (OI) following ART initiation (or switch of ART to a suppressive regimen)
- **Paradoxical IRIS:** worsening of a previously diagnosed disease after ART initiation (or switch of ART to a suppressive regimen)

Risk Factors for IRIS include the following:

- Advanced immunosuppression (WHO Stage 3 or 4, or CD4 count <200 cell/mm3 (or CD4% ≤ 25% for children ≤ 5 years old))
- Patients with a diagnosed opportunistic infection like TB, MAC, CMV, and PCP
- Low baseline CD4 (CD4 count ≤ 50 cell/mm3 or CD4% ≤ 10%)
- High baseline viral load
- Substantial increase in CD4 count and decrease in viral load after starting ART

IRIS is relatively common in mild to moderate forms in patients with TB started on ART (usually seen in up to one third of patients); however, it is relatively rare in its severe forms.

IRIS may present as fever, enlarging lymph nodes, worsening pulmonary infiltrates, respiratory distress, or exacerbation of inflammatory changes at other sites. It generally presents within 4 - 8 weeks of the initiation of ART (but can be months afterwards) and is more common with a low CD4 cell count (<50 cells/mm3)[11].

IRIS is a diagnosis of exclusion. Patients with advanced AIDS may show clinical deterioration for a number of other reasons. IRIS can also be mistaken for TB treatment failure, and co-infected patients may be demonstrating progression of TB disease due to drug resistance.

The management of TB IRIS is complex and depends on the clinical status of the patient and the site and extent of involvement. Various treatment modalities have been employed, including nonsteroidal anti-inflammatory drugs (NSAIDs) in mild disease and corticosteroids in moderate to severe disease. In the latter, give 1 to 2 mg/kg prednisone for 1 to 2 weeks, followed by a period of individualized tapering of the dose. Both anti-TB and antiretroviral therapy should be continued during this period.

Severe forms of IRIS may require hospitalization for individualized management and specialist review.

4.5 Extra pulmonary drug resistant TB

The Principles of managing of extra-pulmonary DR TB are the same as for pulmonary disease (except for DR TB meningitis which is discussed further below). WHO recommends the use of longer DR TB regimens in patients with extra-pulmonary disease. PLHIV are more likely than HIV-negative persons to have smear/ Xpert-negative TB or extra-pulmonary TB.

Adjustment of treatment may be required depending on the specific location of the disease in the body. Monitoring of treatment response would mostly rely on assessment of clinical parameters since bacteriological measurements may be difficult to assess. Increase in a patient's weight is also a useful indicator of improvement.

4.5.1 Drug-resistant TB Meningitis

Treatment of DR TB meningitis is best guided by drug susceptibility test (DST) of the infecting strain and by knowledge of the properties of TB medicines that cross the blood brain barrier.

The diagnostic approach should include cerebrospinal fluid (CSF) analysis and cranial imaging. Every attempt should be made to obtain CSF for Gene Xpert and phenotypic DST. Other TB diagnostic samples from other sites should also be taken for analysis if available (sputum, lymph nodes). CSF findings may be variable and difficult to distinguish between bacterial and tuberculous meningitis.

Empirical IV antibiotics may be given for bacterial meningitis and CSF Cryptococcal Antigen (CrAg) test must be done to rule out Cryptococcal meningitis in PLHIV.

In patients co-infected with HIV who are not yet on ART, ART should be initiated at least 8 weeks after DR TB treatment initiation to minimise the risk of IRIS.

DR TB treatment is recommended for a longer duration (18 - 20 months and beyond) with susceptible drugs that cross the blood brain barrier. The optimal treatment duration shall be determined mainly by the clinical response and probably CSF culture and DST results. Individualized regimens will need to be designed for DR TB meningitis.

Levofloxacin and **Moxifloxacin** penetrate the central nervous system (CNS) well, as do other drugs such as **Ethionamide/Prothionamide, Cycloserine/Terizidone, linezolid and imipenem–cilastatin**. These are illustrated in Table 4.5.

Seizures may be more common in children with meningitis treated with imipenem–cilastatin (meropenem is preferred for meningitis cases in children).

Table 4.5: CNS Penetration of Second Line TB Drugs

Drug	CNS Penetration
Bedaquiline	No data available, studies ongoing
Delamanid	Limited human data but good CSF penetration in mice
Clofazimine	Limited data available
Moxifloxacin, Levofloxacin	Variable CSF penetration with better penetration of Moxifloxacin based on animal studies
Linezolid	Good CSF penetration, excellent results in humans
Cycloserine , Terizidone	Good CSF penetration
Ethionamide/ Prothionamide	Good CSF penetration
High dose Isoniazid, Pyrazinamide	Good penetration. Can reach therapeutic levels in the CSF, useful if strains are susceptible
Meropenem	Excellent CSF penetration, preferred in children
Imipenem-cilastatin	Good CSF penetration, associated with a higher rate of seizures in children
Amikacin, Streptomycin	Penetrate CSF only in the presence of meningeal inflammation
PAS, Ethambutol	Do not pass the CNS

4.5.2 Adjuvant therapies - corticosteroids

In DR TB patients, the adjuvant use of corticosteroids does not increase mortality when the patient is on an effective regimen. Corticosteroids can be beneficial in conditions with severe central nervous system or pericardial involvement. They may also help in respiratory insufficiency and milliary TB.

Prednisone is commonly used with a tapering of dosage over 6 - 8 weeks. When a more immediate response is desired then injectable corticosteroids like dexamethasone may be used to good effect.

4.6 Drug-resistant TB in Diabetes Mellitus (DM)

The term diabetes describes a group of metabolic disorders characterized and identified by the presence of hyperglycaemia in the absence of treatment. Causes include defects in insulin secretion, insulin action, or both, and disturbances of carbohydrate, fat and protein metabolism with increased glucose production. The long-term specific effects of diabetes include retinopathy, nephropathy and neuropathy, among other complications.

Diabetes mellitus (DM) is increasing in every country in the world, with up to 95% of persons with DM having type 2 DM. In most low and middle-income countries, middle-aged or older people are at the highest risk of developing the disease although DM is starting to emerge at younger ages than previously recognized.

DM increases the risk of developing active TB by 2-3 times and patients with TB-DM have worse TB treatment outcomes compared with those who have just TB alone. Moreover, the presence of diabetes mellitus may potentiate the adverse effects of anti-TB drugs, especially renal dysfunction and peripheral neuropathy. Tuberculosis causes stress induced hyperglycaemia and this can complicate the management of DM. The use of steroids in the treatment of TB meningitis or TB pericarditis can also lead to hyperglycaemia.

4.6.1 Key risk factors for DM

Risk factors for DM can be divided into modifiable and non-modifiable factors as shown in the table below:

Table 4.6: Modifiable and Non-modifiable Risk Factor for DM

Modifiable risk factors for DM	Non- Modifiable risk factors for DM
• Overweight/obesity • Physical inactivity • High blood pressure • Dietary factors • Alcohol consumption • Prenatal/ early life influences	• Age (risk increases with older age), • Sex (risk is usually higher in men), • Family history of dm • Genetic markers • Ethnicity

4.6.2 Bi-directional screening for TB and DM

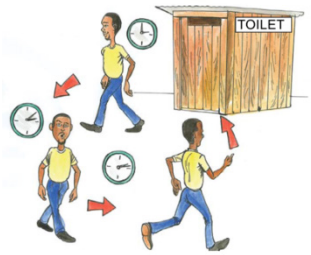
All adult TB patients should be offered screening for DM. Fasting blood glucose and, if resources are available, HbA1c are the preferred diagnostic tests for DM in patients with TB.

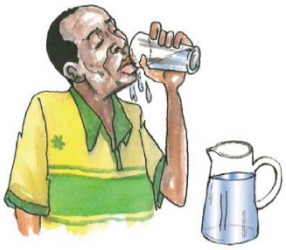
DM patients should be offered systematic screening for TB using a TB symptom screen followed by Xpert MTB/RIF if there are suggestive TB symptoms. Consider screening with a chest radiograph where available.If there are any abnormalities on chest radiography further investigation can be carried out by Gene Xpert testing.

In persons with already established DM, there should be a heightened index of suspicion of TB and health workers should have a low threshold for testing for TB if suggestive symptoms and signs are present.

4.6.3 Diagnosis of Diabetes Mellitus

DM is a progressive condition and its diagnosis is not straight forward even among people who are considered healthy. The thresholds or cut-off points for diagnosing DM on each diagnostic test are broadly based on the levels at which the risk of microvascular damage and macro vascular complications start to increase.

<table>
<tr><th colspan="2">The Classic Symptoms of DM are:</th></tr>
<tr><td> 

Polyuria – need to urinate frequently</td><td> 

Polydipsia – increased thirst and fluid intake</td></tr>
<tr><td> 

Unexpected weight loss</td><td> 

Tiredness and fatigue</td></tr>
<tr><th colspan="2">Other key symptoms of DM include:</th></tr>
<tr><td> 

Blurred vision</td><td> 

Polyphagia - Increased appetite
Extreme hunger</td></tr>
<tr><td colspan="2"> 

Slow healing of wounds</td></tr>
</table>

Figure 4.3: Classic Symptoms of Diabetes Mellitus

WHO recommends the following four tests for the diagnosis of DM:

1. Oral glucose tolerance test (OGTT)
2. Fasting blood glucose (FBG)
3. Glycosylated haemoglobin (HbA1c)
4. Random blood glucose in the presence of signs and symptoms of DM.

Table 4.7: Thresholds and cut-off points for DM and pre-DM

Blood test	Diabetes mellitus	Pre-diabetes
2-hour plasma glucose after Oral Glucose Tolerance test (OGTT)	≥-11.1 mmol/L ≥200 mg/dl	7.8-11.0 mmol/L 140-199 mg/dl
Fasting plasma glucose (FPG)	≥7.0mmol/L ≥126 mg/dl	6.1-6.9 mmol/L 110-125 mg/dl
Glycosylated haemoglobin (HbA1c)	≥6.5%	6.0-6.4%
Random blood glucose	≥11.1mmol/L ≥200 mg/dl	

Thresholds and cut-off points for DM and pre-DM. Values are given in mmol/l, mg/dl or %. Values are based on plasma glucose (venous) samples.

The diagnosis of DM is made using these thresholds and cut-off points based on whether the person investigated is *symptomatic* (for example, polyuria, polydipsia, and unexplained weight loss) or *asymptomatic* as shown below:

- If symptomatic, then a single fasting plasma glucose ≥7.0 mmol/l (≥126 mg/ dl), a post-prandial plasma glucose ≥11.1 mmol/l (≥200 mg/dl) or HbA1c ≥6.5% will be adequate for diagnosis. A random blood glucose ≥11.1 mmol/l (≥200 mg/dl) in persons with classic symptoms of DM is also diagnostic.
- If asymptomatic, then it is advisable to obtain a fasting plasma glucose ≥7.0 mmol/l (≥126 mg/dl), a post-prandial plasma glucose ≥11.1 mmol/l (≥200 mg/dl) or HbA1c ≥6.5% on two separate occasions.

4.6.4 Effects of DM on TB

Sputum bacteriological conversion:

There is some evidence that DM prolongs smear and culture positivity at 2–3 months of treatment. Poor glycaemic control may be an important factor in this delay.

Adverse drug reactions:

DM is associated with a higher risk of hepatitis and renal drug toxicity. It is also associated with gastrointestinal and other side effects that may overlap between TB drugs and glucose-lowering drugs used by persons with DM.

TB treatment outcomes

DM adversely affects TB outcomes in several ways including:

- Increases the risk of developing TB threefold.
- Increased the risk of TB treatment failure and loss to follow-up
- Increased relapse and recurrent of TB.
- Higher risk of latent TB infection
- Faster progression of TB infection to TB disease
- Altered clinical presentation of TB – more TB symptoms, poor performance status (ability to perform activities of daily living without help of others) compared to patients without diabetes
- Almost doubles the risk of mortality during TB treatment.
- Changes the sensitivity and specificity of conventional TB diagnostic algorithms.
- Accelerates the emergence of drug-resistant TB, especially multidrug-resistant TB
- Interference with the activity of certain anti-TB medications

Possible reasons for poor TB outcomes in DM include:

- Immunosuppressive effects of DM
- Drug to drug interactions
- Adverse effects from medications
- Suboptimal adherence to medication
- Reduced bioavailability of the drugs and other unlisted factors[17]

4.6.5 Effects of TB on DM

- TB prevalence and incidence are consistently higher in people with diabetes than in either the general population or in non-diabetic controls.
- TB may trigger the onset of diabetes, and worsen glycaemic control in existing diabetes.
- TB medications may interfere with the treatment of diabetes through drug interactions.

4.6.6 Management of DR TB patients with diabetes

People with both DM and DR TB should be provided holistic TB and DM management within the TB clinic. During this period, visits to the DM clinic should be avoided wherever possible to prevent the transmission of *Mycobacterium tuberculosis* to other people with Diabetes Mellitus

Management of DM in TB should be aggressive. An optimal glycaemic control results in a better patient outcome; therefore vigorous efforts should be made to achieve such control. For patients with severe, symptomatic and uncontrolled DM, specialist DM advice should be sought within the TB clinic.

Treatment for DS TB and DR TB is similar in persons with and without DM. None of the anti-TB drugs are contraindicated. Creatinine and potassium levels should be monitored more frequently, often weekly for the first month and then at least monthly thereafter, in view of the renal effects of aminoglycosides if used in the DR TB regimen.

Diabetes must be managed closely throughout the treatment of drug-resistant TB. Health workers should be vigilant about monitoring treatment response as treatment failure and recurrent TB are more common in persons with DM. Insulin is the drug of choice in treating DM in DR TB patients for better glucose control and less drug interactions.

Oral hypoglycaemic agents are not contraindicated during the treatment of MDR/RR TB. However, they present interactions with Rifampicin in INH Mono-resistant DR TB regimens. Rifampicin accelerates the metabolism of several oral hypoglycaemic agents, especially sulphonylureas and biguanides, and lowers their plasma levels. Hyperglycaemia may therefore remain uncontrolled in diabetic patients using these drugs. Oral hypoglycaemic agents are also contra-indicated in severe hepatic disease in DR TB patients. The use of Ethionamide or Prothionamide may make it more difficult to control insulin levels in RR DR TB regimens.

4.6.7 Comprehensive diabetes management

In patients with DM and TB, the aim is to treat TB while at the same time keeping blood glucose levels under control. The management of DM is aimed at reducing short-term and long-term complications such as cardiovascular disease, eye problems and foot amputations.

DM management mainly consists of:

- Counselling on appropriate lifestyle management (smoking cessation, nutritional control and physical activity).
- Treatment with oral hypoglycaemic agents.
- Measures to reduce the risk of cardiovascular disease and associated complications People with DM and a history of previous cardiovascular disease should be offered low-dose aspirin and a statin.
- Management of specific complications like diabetic feet and eye problems

4.6.8 Care of patients with diabetes after TB treatment

At the end of TB treatment patients should be counselled about:

- The need for continued DM care and monitoring.
- The increased risk and management of cardiovascular disease.
- The increased risk of TB relapse and what to do in case of renewed cough, fever, night sweats or weight loss.
- Efforts should be made for effective referral to appropriate services for continued DM care.
- Need for follow-up for any post TB lung disease for 2 years.

4.7 Renal Disease

4.7.1 General Principles

Renal insufficiency caused by long standing TB infection itself or previous use of aminoglycosides is common. Severity of aminoglycoside nephrotoxicity follows the order: Streptomycin > Kanamycin > Amikacin (least toxic). Capreomycin is a polypeptide antibiotic that should also be used with caution in renal disease.

Great care should be taken in the administration of second-line drugs in patients with renal insufficiency, and the dose and/or the interval between dosing should be adjusted accordingly

(refer to Table 4.8 below). The dosing of the second line TB drugs should be based on the patient's creatinine clearance, which is an estimate of glomerular filtration rate or renal function.

Table 4.8: Adjustment of anti-TB drugs in renal insufficiency

Drug	Recommended dosing and frequency for patients with impaired creatinine clearance (<30 ml/min or receiving haemodialysis)
Isoniazid	No adjustment necessary
Rifampicin	No adjustment necessary
Pyrazinamide	25–35 mg/kg per dose three times per week (not daily)
Ethambutol	15–25 mg/kg per dose three times per week (not daily)
Rifabutin	Normal dose can be used, if possible monitor drug concentrations to avoid toxicity
Rifapentine	No adjustment necessary
Amikacin	12–15 mg/kg per dose two or three times per week (not daily)[a]
Kanamycin	12–15 mg/kg per dose two or three times per week (not daily)[a]
Ofloxacin	600–800 mg per dose three times per week (not daily)
Levofloxacin	750–1000 mg per dose three times per week (not daily)
Moxifloxacin	No adjustment necessary
Gatifloxacin	400 mg three times a week
Cycloserine	250 mg once daily or 500 mg/dose three times per week
Prothionamide	No adjustment necessary
Ethionamide	No adjustment necessary
Para amino salicylic acid	4 g/dose, twice daily maximum dose
Bedaquiline	No dosage adjustment is required in patients with mild to moderate renal impairment (dosing not established in severe renal impairment, use with caution).
Delamanid	No dosage adjustment is required in patients with mild to moderate renal impairment (dosing not established in severe renal impairment, use with caution).
Linezolid	No adjustment necessary
Clofazimine	No adjustment necessary
Amoxicillin/Clavulanate	For creatinine clearance 10–30 ml/min dose 1000 mg as amoxicillin component twice daily; for creatinine clearance
High dose isoniazid	Recommendations not available
Clarithromycin	500mg daily

a. Caution should be taken when using injectable agents in patients with renal function impairment because of the increased risk of both ototoxicity and nephrotoxicity. If on dialysis, give dose after dialysis.

b. The appropriateness of Cycloserine 250 mg daily doses has not been established. There should be careful monitoring for evidence of neurotoxicity (if possible measure serum concentrations and adjust accordingly).

c. Sodium salt formulations of PAS may result in an excessive sodium load and should be avoided in patients with renal insufficiency. Formulations of PAS that do not use the sodium salt can be used without the hazard of sodium retention and are the preferred formulation in renal insufficiency

NOTE: *If patient is on Haemodialysis use TB medication after procedure*

Estimated glomerular filtration rate = $\frac{\text{weight (kg) x (140 – age) x (constant)}}{\text{serum creatinine (µmol/L)}}$

The creatinine is measured in the serum.

The constant in the formula is = 1.23 for men and 1.04 for women

If creatinine is reported in conventional units (mg/dl) from the laboratory, it can be converted it to a SI Unit (µmol/l) by multiplying by 88.4.

(For example, a creatinine = 1.2 mg/dl is equivalent to (88.4 x 1.2) = 106.1 µmol/l.)

Normal values for creatinine clearance are:

Men: 97 to 137 ml/min

Women: 88 to 128 ml/min

Example: If a female patient (age = 46 years, weight = 50 kg) has serum creatinine = 212 µmol/l, what is the creatinine clearance?

Calculation of creatinine clearance:

Weight (kg) x (140 – age) x (constant) / serum creatinine =

50 x (140 – 46) x (1.04 for women)/ 212 =

23.0 ml/min

The creatinine clearance is below 30; every drug in the regimen should be examined and adjusted if necessary according to Table 7.1.

Note: Creatinine clearance can also be calculated with a 24 hour urine and serum creatinine, but that is usually more cumbersome.

4.8 Liver Disease

4.8.1 General Principles

Pyrazinamide is the most hepatotoxic of the three first-line drugs while rifampicin is least likely to cause hepatocellular damage, although it is associated with cholestatic jaundice. Among the second-line drugs, Ethionamide, Prothionamide, Bedaquiline (BDQ) and PAS can also be hepatotoxic, although less so than any of the first-line drugs. Hepatitis occurs rarely with fluoroquinolones.

Patients with a history of liver disease can receive anti-TB drug regimens provided there is no clinical evidence of severe chronic liver disease, hepatitis virus carriage, and recent history of acute hepatitis or excessive alcohol consumption. However, hepatotoxic reactions to anti-TB drugs may be more common in these patients and should be anticipated. In general, DR TB patients with chronic liver disease should avoid pyrazinamide, however, all other drugs can be used with close monitoring of liver enzymes advised. If significant aggravation of liver inflammation occurs, the drugs responsible may have to be stopped.

Rarely, a patient with TB may have concurrent acute hepatitis that is unrelated to TB or anti-TB treatment; and here clinical judgment becomes necessary. In some cases, it is possible to defer anti-TB treatment until the acute hepatitis has resolved. In other cases when it is necessary to treat drug-resistant TB during acute hepatitis, the combination of four non-hepatotoxic drugs is the safest option.

4.8.2. Viral Hepatitis

There is no data on the safety or efficacy of Bedaquiline or Delamanid in this group of patients. Linezolid and Clofazimine have been used, but there can be overlapping toxicity with some of the drugs used to treat hepatitis. The new protease inhibitors for treating hepatitis C have never been used with BDQ and DLM, thus there is no information on drug to drug interactions.

Hepatitis B can be treated where applicable following a referral to a specialist with Tenofovir and Lamivudine.

If patients with hepatitis C meet the criteria for using one of the new drugs, acute hepatitis should be ruled out and the transaminases should be less than three times the upper limit of normal and total bilirubin less than 1.5 times the upper limit of normal when initiating. Frequent monitoring of liver function tests is, however, recommended. Specialist referral is needed to reduce the additive side-effects, pill burden and drug-drug interactions.

4.9 Seizure disorders

Some patients with DR TB may have a previous or current medical history of a seizure disorder. Initial evaluation should include assessment of seizure control and whether the patient is on any anticonvulsant medication. Initiation of anticonvulsants or optimization of current treatment should be done to achieve optimal control before initiation of DR TB treatment.

The cause of the seizures or any other contributing conditions must be addressed as part of the management. Patients may also develop seizures during DR TB treatment due to adverse drug effects. Review and modification of the treatment regimen should be done in these cases.

The following points should be noted about seizure disorders in DR TB patients:

- Cycloserine may be given as long as seizure disorder is controlled. Cycloserine should be avoided in patients with seizure disorders that are not well controlled on medications
- Seizures may be more common in children with meningitis treated with imipenem–cilastatin (meropenem is preferred for meningitis cases and in children)[3]
- High dose isoniazid also carries a high risk of seizures and should be avoided in patients with active seizure disorders
- Oral pyridoxine (Vitamin B6) can be used in patients with seizure disorders to protect against the neurological adverse effects of isoniazid and Cycloserine
- Drug to drug interactions should be evaluated for all drugs to be used

4.10 Psychiatric Disorders

Psychiatric assessment should be conducted prior to DR TB treatment initiation particularly in patients with existing psychiatric disorders. A simple psychiatric examination can be administered by health care workers (HCWs) at any level using the PHQ-9. Any psychiatric illness identified at the beginning of or during treatment should be fully addressed. There is a high baseline incidence of depression and anxiety in patients with drug-resistant TB, often associated with the chronicity and socioeconomic stress factors associated with the disease.

Psychiatric treatment for patients who develop psychiatric problems should be provided alongside DR TB treatment. Patients on treatment with Cycloserine who develop severe psychosis may need substitution with other second line drugs (SLDs).

All health care workers treating drug-resistant TB patients should work closely with a mental health specialist and have an organized system for managing psychiatric emergencies. Psychiatric emergencies include acute psychosis, suicidal ideations and any situation where the patient may be of danger to himself or others and in need of urgent psychiatric care.

4.11 Substance Dependence

Active substance dependence is not a contraindication to treatment with anti-TB drugs but appropriate treatment should be offered for the addiction. Complete abstinence from alcohol or other substances should be strongly encouraged. Patients with substance dependence who are at high risk of interrupting treatment should be monitored very closely with strict DOTs (Directly Observed Treatment) applied. If the treatment is repeatedly interrupted because of the patient's dependence, therapy should be suspended until measures to ensure adherence have been established.

Health care workers should be aware that Cycloserine side effects may be more common in patients dependent on alcohol and other substances, including a higher incidence of seizures; the drug is contraindicated in severe central nervous system disease.

Patients with opioid use disorder who are on oral methadone for opioid substitution treatment (OST) may develop poly-resistant or mono-resistant TB and will have drug interactions between rifampicin and methadone. Rifampicin lowers the serum concentration of methadone by 33% to 66%. Administration of rifampicin to patients on methadone has led to opioid withdrawal in patients on methadone replacement therapy. Clinics need to increase methadone dose and monitor carefully to prevent withdrawal with co-administration of rifampicin and methadone.

DR TB TREATMENT MONITORING AND QUALITY OF CARE

5.

Introduction

Treatment monitoring refers to a systematic process of tracking patients through the whole continuum of care. It aims at improving treatment outcomes by ensuring adherence to treatment and management of adverse events.

Quality of care is a construct framework based on interactions among different actors involved in different levels of care with an overarching aim of ensuring patient safety and wellbeing as standard deliverable outcome (Mitchell H,P.defining patient safety and quality care-NCBI).

Treatment monitoring and ensuring the delivery of quality healthcare is critical in DR TB management given the many associated challenges.

5.1 Monitoring and follow up while on DR TB treatment

Monitoring and treatment follow up is done through history taking, physical examination, laboratory investigation, chest radiography/ CT scanning and other specialized tests such as audiometry, visual acuity tests, and electrocardiography (ECG).

Using smear microscopy and culture to assess conversion of bacteriological status is an important means of monitoring response to treatment. Most patients convert to smear and culture negative status within the first few months of starting treatment (WHO Consolidated PMDT guideline, 2019).

The table below summarizes the roles and responsibilities of HCWs in monitoring of DR TB treatment.

Table 5.1: summary of the roles and responsibilities of HCWs in monitoring of DR TB treatment.

Cadre	Role in monitoring and recommended frequency
Clinician	• Reviews patients at baseline/treatment initiation, every 2 weeks in the 1st month and thereafter monthly until completion. Clinical review/assessment includes patient counselling, screening for substance abuse, ADR screening, monitoring of weight, height and BMI/ Z score.

Cadre	Role in monitoring and recommended frequency
	• Documents clinical notes in the patients' treatment logbook and ensures laboratory requests are filled and results well documented. Supports monthly reporting.
DOT supporter	• The DOTs supporter supervises and observes daily medication, and reports any concerns to the clinician.
Multi-disciplinary clinical review team (CRT)	• Physically reviews all DR TB patients managed within the sub county at least once a month, and updates the review checklist in patients' log book. The team documents guidance to the clinician and DOTs provider on patient management for the next month in the DRTB patient log book.
CTLC	Has the overall responsibility for DRTB care in the County. • Convene and chairs County DRTB meetings. • Participates in sub-county clinical review meetings monthly.
SCTLC	Has the overall responsibility for DRTB care in the County. • Chairs the sub-county clinical review meetings monthly • Participates in the County clinical review meetings monthly • Oversees the implementation of clinical guidance by the Multi-disciplinary team.

Table 5.2: Laboratory and other parameters monitored during DR TB treatment

Parameters Monitored	Rationale and Frequency of measurement
Sputum smear microscopy	Microscopy is used for monitoring of response to treatment and guides the decision to switch to the continuation phase . • Done at baseline and repeated every month until the end of treatment. Persistent smear positivity beyond the intensive phase of treatment is an indication of treatment failure, a trigger for a repeat drug-susceptibility testing and clinical review.
Sputum Culture	Culture is used to determine conversion/ reversion and to determine cure at the end of treatment. • Done at baseline and repeated every month until the end of treatment. Persistent culture positivity beyond the intensive phase of treatment is an indication of treatment failure, a trigger for a repeat drug-susceptibility testing and clinical review
Audiometry	It is done to assess for ototoxicity leading to hearing loss. • Done at baseline and repeated monthly if the patient is on an injectable drug. If any abnormality is detected, the injectable should be stopped immediately and NOT reintroduced. The clinical team is then consulted on management.

1st Line DST	• Done at baseline. • Should also be done at month 3 ,if a patient is still smear positive and if a previously culture negative patient turns culture positive. The purpose of 1st line DST is exclude resistance to 1st line anti TB drugs(HREZ)
2nd Line DST	• 2nd line DST should be done for all patients at baseline, month 3 (if smear positive) and if a previously culture negative patient turns culture positive The purpose of 2nd line DST is to exclude resistance to second line drugs e.g quinolones
Chest X-ray / Chest CT scan	• A chest x-ray should be done at baseline, at the end of intensive phase and at the end of treatment. Where a CT scan is available and accessible, it is preferred, since it gives additional clinical information. Chest X-ray/ CT scan is useful in assessing the severity of lung disease and post TB disease complications
Full Haemogram +differential count	• Should be done at baseline and monthly during the intensive phase. For patients on a linezolid-based regimen, it will be done monthly for every month the patient is still on. The purpose of this test is to evaluate the patient's haematological status and assess for bone marrow suppression.
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. The purpose is to evaluate renal function and assess for nephrotoxicity.
Serum potassium, Magnesium	• Done at baseline then monthly if on an injectable drug. Otherwise repeat if the patient has vomiting and diarrhoea, if QTcF is prolonged or if clinically indicated. The purpose is to evaluate for electrolyte imbalance.
TSH	• Done at baseline and at month 2 if any abnormality is detected at baseline. It is done to evaluate thyroid function. If abnormality is present, the clinical team should be consulted.
Serum Albumin	• Done at baseline and repeat as indicated. The purpose is to rule out low albumin levels, which is associated with increased risk of toxicity.
LFTs (AST, ALT, Bilirubin)	• Done at baseline. Repeat if abnormal or if patient is vomiting, has abdominal pain and or jaundice with any other evidence of liver injury. The purpose is to evaluate liver function and any hepatotoxicity
HIV screening/ testing	• As per the HTS guidelines. This is done to screen for HIV co-infection.
CD4 count	• As per ART guidelines The purpose is to evaluate the patients immunologic status
Viral Load	• As per the ART guidelines. The purpose is to evaluate for viral suppression

Review of Contraception	• This should be reviewed monthly All women of childbearing age should be encouraged to use dual contraception..
Pregnancy test	• Should be done at baseline for women of child bearing age. Repeat if indicated. The purpose is to exclude pregnancy and if positive to guide the choice of regimen and follow up.
RBS	• Should be done at baseline, and repeated if clinically indicated. The purpose is to screen all DRTB patients for diabetes mellitus
Visual Acuity and Colour blindness screen	• Done at baseline (Using a Snellen chart and Ishihara charts) and monthly while the patient is on linezolid. The purpose is to screen for optic neuritis due to linezolid.
ECG monitoring	• Done at baseline, every 2 weeks in month 1, then monthly thereafter in the intensive phase. • In the continuation phase it should be done every 3 months while the patient is on Clofazimine until the completion of treatment. It is done to evaluate the patients QT interval (QTcF)

Monitoring schedule for patients on injectable free regimen

Month	Baseline	1	2	3	4	5	6	7	8	9	10	11	12	15	18
Patient Counselling	X	X	X	X	X										
Screening for substance abuse	X				X										
Review by a Clinician	X	Every 2 weeks	Monthly until treatment completion												
ADR screening	X	Monthly until treatment completion													
Weight/ BMI/ Z-Score	X	Monthly until treatment completion													
Smear microscopy	X	Monthly until treatment completion													
Culture	X	Monthly until treatment completion													
1st line DST	X			X (If still smear positive)		X (If any reversion to positive culture in the continuation phase)									
2nd line DST	X			X (If still smear positive)		X (If any reversion to positive culture in the continuation phase)									
ALT/ AST/ Bilirubin	X	Repeat if patient is vomiting, has abdominal pain, jaundice or any evidence of liver injury													
Serum Albumin	X														
Creatinine	X	Do monthly if on an injectable drug. Otherwise repeat only if the baseline creatinine was abnormal or if clinically indicated.													
Potassium, Magnesium	X	Do monthly if on an injectable drug. Otherwise repeat if vomiting, diarrhoea, if QTcF is prolonged or if clinically indicated.													
Full Hemogram	X	X	X	X	X	X	X	Monthly if on Linezolid							
HIV Test	X	As per HTS guidelines													
CD4	X*	As per ART guidelines													
Viral Load	X*	As per ART guidelines													
RBS	X														X
Review Contraception	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test	X														
CXR	X														X
TSH	X		X												
Audiometry‡	X														
ECG (QTcF monitoring)††	X	Every 2 weeks	X	X	X	X	X			X			X	X	X
Visual test (Ishihara & Snellen)	X	X	X	X	X	X	X	Test monthly each month that the patient is on LZD							

†If baseline CD4 <200
* If not done in the last 3 months. Otherwise, use the most recent Viral load
††At baseline and monthly in the intensive phase. Continue monthly if on Bedaquilline or Delamanid. Otherwise, ECG should be done every 3 months while on CFZ.
‡ Audiometry monthly if on an injectable drug. If any abnormality is detected, stop the injectable and consult the clinical team

Figure 5.1: Monitoring schedule.

Models of DRTB Care

There are three models of DRTB care in Kenya i.e.:

- Community based care
- Facility based (Ambulatory) care
- Facility based (Isolation) care

Criteria for selecting the model of care for DR TB treatment

Isolation	Facility based (Ambulatory)	Community based
Preferred for • Severely ill patients • Patients with poor adherence • Refugees, street families and the homeless • Mobile populations / Nomadic • Patients with Total Drug Resistance • Patients with mental illness without social support	Preferred when • The patient chooses to receive care in the health facility • There is ease of access to a health facility with adequate transport availability • The general condition of the patient is stable	Preferred when • The patient chooses to receive care while in the community • There is a confirmed treatment supporter • There is a challenge in accessing health facility or when there are transport challenges • The general condition of the patient is stable

Isolation Care

The use of isolation should be strictly limited to the infectious period; once patients are on effective treatment and are no longer infectious, there is no need for further isolation.

NB: Before isolation is sought, all other means including community based interventions should be explored.

Criteria for involuntary isolation care

The following groups of patients may be isolated involuntarily:

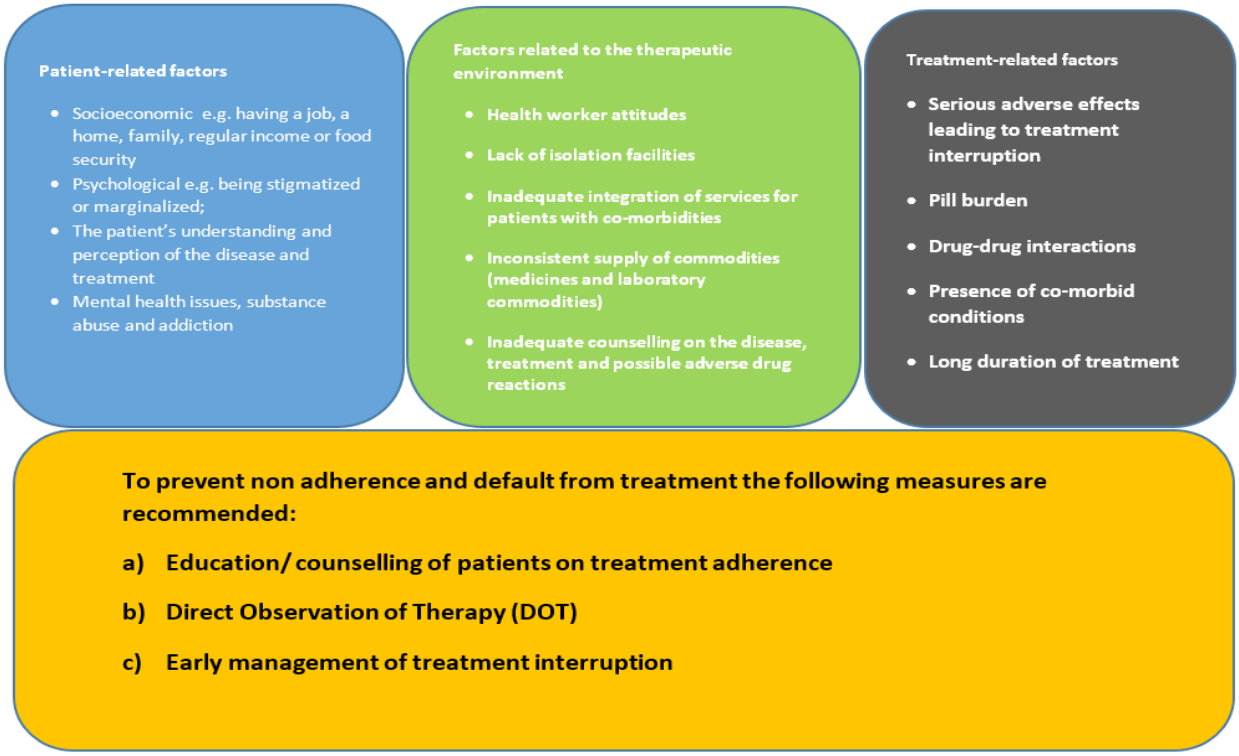
1. Non-adherent patients despite counselling intervention
2. Patients with uncontrolled mental illness without family or social support
3. Patients who decline to take medications despite adequate education and counselling

Criteria for voluntary Isolation care

1. Patients with multiple co-morbidities who require specialized inpatient care
2. Patient with serious adverse drug reaction from TB treatment who require specialized care
3. Patients without social support including the homeless (Street populations)
4. Patients with Total drug resistance

Adherence

Factors that influence adherence to DR TB Treatment



Ensuring Quality in Patient follow-up and Care

a) **DR TB Clinical review teams**

A clinical team must review all DRTB patients monthly and the reviews documented in the DRTB logbook. This team is composed of the County TB coordinator, Sub county TB coordinator, Clinician, Nurse, Pharmacist, DOT observer, Social worker, Psychologist/ counsellor, Public health officer, Laboratory technologist, Nutritionist and Community Health Extension Worker.

Roles & Responsibilities of the clinical review team (CRT)

- Coordinate, support and streamline clinical management of each DR TB patient**.** The team **physically reviews** all DR TB patients within the sub county **at least once a month,** and updates the CRT checklist in patient log book
- Monitoring the follow up of DR TB patients on treatment and reviewing all laboratory results.
- Reviewing complex cases as need arises e.g. patients with serious adverse drug reactions, co-morbidities and recommending appropriate interventions.
- Document guidance to DOTs provider on patient management for the next month in DRTB patient log-book
- Support clinical and programmatic management concerns should they arrive mid-month including
    - Clinical management-adjustment of dosages, ADR monitoring and reporting
    - Nutritional support

- Psycho social support
- Public health support
- Laboratory support

Post DRTB treatment follow-up

DRTB patients will be followed up for a period of 2 years after treatment completion to assess for any relapses/ re-infections and post TB treatment complications that may arise. These include pulmonary fibrosis, chronic obstructive pulmonary disease (COPD), aspergillosis, bronchiectasis, and possibly carcinoma.

At the end of the follow up period, all patients should be given a case summary indicating the patient biodata, DRTB registration number, results of all investigations, the initial resistance pattern, treatment history including the date treatment regimen started and ended, any ADRs and medication administered, co-morbidity, current clinical condition and treatment outcome. All previous chest radiographs provided to the patient for future reference.

Patients with post TB disease complications should be referred and linked to an appropriate specialist for review and management.

Scheduled plan for post-DRTB treatment follow up.

Scheduled appointments should be given at month 3, 6, 12, 18 and 24 after completion of treatment. Symptom screening for TB should be done at each visit and those symptomatic investigated as follows:

- Send a sputum sample to the laboratory for GeneXpert, Culture and DST.
- Do a chest X-ray (CT scan if available) as clinically indicated

At each visit, screen for post-TB disease complications and evaluate for other conditions, including regular assessment of lung function by spirometry. Prompt referral for specialist review and management as clinically indicated

Month (after treatment completion)	3	6	12	18	24
Screening for substance abuse	X	X	X	X	X
Review by a Clinician	X	X	X	X	X
Weight/ BMI	Done at each follow up visit				
GeneXpert (for presumptive DRTB)	X	X	X	X	X
Culture (For presumptive DR TB)	X	X	X	X	X
1st line DST	Done for any culture positive patient on follow up				
2nd line DST	Done for any culture positive patient on follow up				
CXR/ Chest CT scan	Done for any presumptive DRTB patient on follow up				
Spirometry	Done as clinically indicated (when there is impairment of lung function)				

Figure 5.2: Post treatment follow up

PATIENT SUPPORT AND NUTRITION

6.

Introduction

Pillar one of the End TB Strategy explicitly adopts a patient-centred approach, which puts patients at the heart of service delivery. A patient-centred approach recognizes that the direct beneficiary of TB care is the individual who is sick, and that strategies must therefore be designed with this individual's rights and welfare in mind. The National Strategic Plan for TB, Leprosy and Lung Disease (2019-2023) advocates for a more patient-centred focus. DR-TB patients' needs should be attended to from diagnosis to treatment initiation and follow up.

Patient support and treatment involves more than routine medical diagnosis, hospitalized care or even the prescription of drugs. When confronted by illness, patients seek professional help and advice from their doctors, and also rely on support from family members, peers and fellow patients *(https://www.who.int/genomics/public/patientsupport/en/)*.

DR TB patient support can be categorized into three areas:

- Support from the community and family members
- Support from the health care workers
- Support from the health care system through information, referral linkages, supplies of patient commodities (nutritional commodities, medicines and equipment)

Patients incur catastrophic costs while seeking care and adherence to treatment, adverse drug reactions and the stigma attached to the disease and subsequent discrimination, aggravates the quality of life and financial situation for DR TB patients. Specific interventions from diagnosis, enrolment on treatment, maintaining the patient on treatment, psychosocial support and nutritional support are key in improving treatment outcomes.

6.1 DR TB patient social support requirements

DR TB patient social support is determined by access to the following four resources:

(i) Informational support - Any useful information that helps a person to solve problems and address sources of stress e.g. training, education. IEC materials specific for DR TB patients should be shared through the patient's most preferred medium. *(Refer to DR TB Information pack)*

(ii) Emotional support: expressions of care that contribute to strengthen self-esteem through empathy, trust, encouragement and care, among others.

- It helps to deal with the psychological challenges in life.
- It involves listening to the patient's concerns and encouraging them to gain trust in the healthcare worker and health care system.

(iii) Companionship support: It is the help that makes a person feel that he or she belongs to the social network, and that he or she can rely on it for certain needs.

(iv) Material support: All commodities e.g. financial support that a person receives through the social network as assistance to deal with daily essential needs.

Social support as the person's perception and confirmation that he/she is part of a social network that cares for him/her (WHO, 2014).

To aid the patient to adhere to DR TB treatment, depending on their specific needs, all DR TB patients should be linked to the following social support services at initiation of treatment:

- Existing health insurance schemes e.g. National Health Insurance Fund (NHIF) to cater for any additional medical costs
- Nutritional support programs
- Existing cash transfer programs for TB or DR TB patients
- Patient support groups
- Other existing social safety nets such as community DOT, referral to the social worker for linkage to disability allowances, isolation packages e.g. TB Manyatta, food basket rations programmes, transport reimbursements, the religious social missions, etc.

6.2 Challenges with DR TB treatment

1. **Diagnostic delays:**

Inadequate surveillance-Inability to identify the most at risk and intensify diagnostic work-ups for increased case findings.

HCW knowledge gap- When HCWs have not been sensitized enough to understand the implications of DRTB, treatment challenges and public health ramifications

Poor index of suspicion-Where patients with DRTB visit health facilities without clinicians raising eyebrows on the possibility of TB infection. The monitoring gaps especially failure to do sputum follow-ups allows treatment failures among non converters to to go undetected.

2. **Treatment Delays:**

Delays initiating treatment-Allows infectious patients to continue transmitting TB in the community.

Loss within Health system -Frequent transfers from one health facility to another causes treatment interruption and inability to track patients who have defaulted on treatment. It also leads to failure to allocate treatment outcomes which somehow reduces treatment success rate.

3. **Management challenges:**

Pill burden-Taking too many pills daily causes fatigue and the associated side effects lead to non-adherence.

Long duration of treatment-DRTB treatment is associated with prolonged treatments. This brings issues of attrition from treatment and stigma associated with DRTB treatment.

Adverse Drug Reactions-If not well addressed through appropriate counselling before treatment initiation, adverse drug events can cause discontinuation of therapy.

4. **Provider issues:**

HCW attitude-Instances have been reported where HCWs refer patients with DRTB away from their facilities. Some of these episodes cause patients to discontinue treatment as they face discrimination from both the community and the supposed care givers.

5. **Patient issues:**

Psycho social issues-Disease stigma causes social isolation, low self esteem, self pity, depression and loss of self confidence and emancipation.

Loss of income-Long treatments and follow up of appointments means that patients cannot be involved in gainful employment. This is worsened by stigma where employers keep them away for fear of infecting the workplace.

6. **Adherence issues**

Prolonged treatment and adverse drug events cause attrition from care. Loss of relationship-DRTB being a stigmatizing disease causes social isolation with loss of intimacy and social capital.

6.3 Focused interventions towards DR TB patient support

In DR TB management during and post treatment, the patient's education, emotional and social needs require a concerted effort. It takes the approach focusing on the patient as an individual and the community. These interventions include;

a) Community engagement:

Support for the DR TB patient should involve the community structures. The following are the activities that can be carried out by community health extension workers and community health volunteers:

i) Create awareness

ii) Systematic identification of community members with signs and symptoms of TB and refer them to health facilities for evaluation and diagnosis.

iii) Contact tracing and identification

iv) Link clients who are initially lost to follow up to facilities for care and treatment and ensure they reach the facility

v) Treatment adherence support system throughout the treatment period including tracing patients who miss appointments or are lost to follow up

vi) Accurate and orderly record keeping of community tools.

vii) Establish support groups in the community and link patients

Community Health extension workers and community health volunteers must ensure confidentiality as they carry out the above activities.

b) Counselling and psychosocial support

Continuous health education and counselling should be provided to DR TB patients before, during and after treatment. Persons involved in conducting the counselling may need resources like Job Aids, session guide and supervisors, DR TB flip chart, role players and training tool kits. Support supervision for healthcare workers and counsellors should be ongoing to promote quality of care.

c) Human rights, informed consent & ethical issues.

Patient-centred approach:

A patient-centred care approach which ensures that treatment is accessible, acceptable, affordable and appropriate for the patient should be adopted. Ethical principles and human rights are supported under WHO guidelines, the Public Health Act Cap 242 and Isolation Policy, 2017 and Constitution of Kenya, 2010.

i. Ethical principles

- *Harm Principle* - DR TB patients are free to act as they choose as long as they don't harm another non-consenting person. If a DR TB patient requires isolation, this principle applies.
- *Respect and dignity* - DR TB patients should not be subject to prejudice, discrimination and stigma on the basis of their beliefs or life choices or circumstances such as disease status, religion, race, gender or sexual orientation.
- *Autonomy* - DR TB patients are guaranteed the right to make decisions regarding their health. This includes the choice of model of care, timing of DOT and DOT provider.

ii. Human Rights

The Patients' Charter for Tuberculosis Care outlines the rights and responsibilities of people with TB. Patients should be provided with a copy of the Patients' Charter in the local language. Its distribution will assist the provider in educating the patient on the disease and treatment. Health care providers should also understand the Patients' Charter.

All DR TB patients have the rights to:

Care

- The right to free and equitable access to tuberculosis care, from diagnosis through treatment completion, regardless of resources, race, gender, age, language, legal status, religious beliefs, sexual orientation, culture, or having another illness
- The right to receive medical advice and treatment which fully meets the new International Standards for Tuberculosis Care, centering on patient needs, including those with multidrug-resistant tuberculosis (MDR-TB) or tuberculosis-human immunodeficiency virus (HIV) coinfections and preventative treatment for young children and others considered to be at high risk
- The right to benefit from proactive health sector community outreach, education, and prevention campaigns as part of comprehensive care programs.

Dignity

- The right to be treated with respect and dignity, including the delivery of services without stigma, prejudice, or discrimination by health providers and authorities
- The right to quality healthcare in a dignified environment, with moral support from family, friends, and the community.

Information

- The right to information about what healthcare services are available for tuberculosis and what responsibilities, engagements, and direct or indirect costs are involved
- The right to receive a timely, concise, and clear description of the medical condition, with diagnosis, prognosis (an opinion as to the likely future course of the illness), and treatment proposed, with communication of common risks and appropriate alternatives
- The right to know the names and dosages of any medication or intervention to be prescribed, its normal actions and potential side-effects, and its possible impact on other conditions or treatments
- The right of access to medical information which relates to the patient's condition and treatment and to a copy of the medical record if requested by the patient or a person authorized by the patient
- The right to meet and share experiences with peers and other patients and to voluntary counselling at any time from diagnosis through treatment completion.

Choice

- The right to a second medical opinion, with access to previous medical records
- The right to accept or refuse surgical interventions if chemotherapy is possible and to be informed of the likely medical and statutory consequences within the context of a communicable disease
- The right to choose whether or not to take part in research programs without compromising care.

Confidence

- The right to have personal privacy, dignity, religious beliefs, and culture respected
- The right to have information relating to the medical condition kept confidential and released to other authorities contingent upon the patient's consent.

Justice

- The right to make a complaint through channels provided for this purpose by the health authority and to have any complaint dealt with promptly and fairly
- The right to appeal to a higher authority if the above is not respected and to be informed in writing of the outcome.

Organization

- The right to join, or to establish, organizations of people with or affected by tuberculosis and to seek support for the development of these clubs and community-based associations through the health providers, authorities, and civil society
- The right to participate as "stakeholders" in the development, implementation, monitoring, and evaluation of tuberculosis policies and programs with local, national, and international health authorities.

Security

- The right to job security after diagnosis or appropriate rehabilitation upon completion of treatment.

6.4 DR TB patients' responsibilities

The following are the responsibilities of a DR TB patient.

1. **Share Information**

- The responsibility to provide the healthcare giver as much information as possible about present health, past illnesses, any allergies, and any other relevant details
- The responsibility to provide information to the health provider about contacts with immediate family, friends, and others who may be vulnerable to tuberculosis or may have been infected by contact.

2. **Follow Treatment**

- The responsibility to follow the prescribed and agreed treatment plan and to conscientiously comply with the instructions given to protect the patient's health, and that of others
- The responsibility to inform the health provider of any difficulties or problems with following treatment or if any part of the treatment is not clearly understood.

3. **Contribute to Community Health**

- The responsibility to contribute to community well-being by encouraging others to seek medical advice if they exhibit the symptoms of tuberculosis

The responsibility to show consideration for the rights of other patients and healthcare providers, understanding that this is the dignified basis and respectful foundation of the tuberculosis community.

4. Show Solidarity

- The moral responsibility of showing solidarity with other patients, marching together towards cure
- The moral responsibility to share information and knowledge gained during treatment and to pass this expertise to others in the community, making empowerment contagious
- The moral responsibility to join in efforts to make the community tuberculosis free

6.5 Health Care Workers Approach

i. Ethical principles

- Privacy and confidentiality: It is important to keep all private information of persons with, or being investigated for DR TB confidential, in keeping with the guidelines and policies provided.
- Duty to care: All healthcare workers have a duty to care for persons with TB, as well as to care for the well-being of the patient's family through contact management, infection prevention and control and linkage to social support systems.
    - Health care workers should have a safe working environment, receive adequate training and support, have adequately equipped facilities and access to quality and regular supplies and legal protection.
    - Health care workers should regularly be screened for TB as stipulated in the guidelines *(Refer to Ch. 4 above)*
    - Health care workers should always uphold DR TB patients' rights.

ii. Disclosure of DR TB diagnosis to contacts

Health care workers should inform and counsel patients about the process of identification of contacts for the corresponding follow up, without exposing the patient to stigma or discrimination in the community or workplaces.

Declined consent to disclose TB diagnosis: Ethical dilemma may be presented by unwillingness of a DR TB patient to cooperate in the process of contact investigation consistent with the laws and policies of the country. The balance to prevent harm can only be determined in the context of an actual scenario. A multi-disciplinary approach should be applied.

6.6 Community Approach

i. Ethical principles

- *Common good:* DR TB not only threatens the health of an affected individual, but of the whole population. The removal or reduction of the threat of DR TB from a society is therefore something from which the whole community benefits.

- *Solidarity:* It is about standing together as a group or community, either nationally or internationally, particularly for DR TB patients and affected persons. Strong community ties should result in cooperative action to implement the End TB Strategy and address TB social determinants.
- *Equity:* All DR TB patients should have equal protections of their rights, interests and welfare. The resources necessary to tackle DR TB should be distributed on the basis of need and with the goal of addressing the disease and underlying social and economic factors.
- *Participation and community engagement:* Mobilization and utilisation of local resources should be done with sensitivity to local customs and norms of communities in order to foster trust. All players should prioritize engagement with communities and those suffering from DR TB in all processes.

ii. Education

The community has a right to access and understand information about DR TB, its causes, its implications on their health, and the internationally recommended standards and policies for prevention, diagnosis and treatment. People should participate actively in decisions related to what is being done to their bodies and to the samples obtained from their bodies, and why it is being done. This may help to instil trust in the health system.

6.7 Patient education and informed consent

All DR TB patients and their primary caretaker(s) should receive health education about DR TB and its treatment and the need for adherence to therapy. Adjustments in the attitudes and language used by health care providers while delivering key information about the disease should be applied.

- Information and education interventions should commence as soon as diagnosis is made and continue throughout the course of treatment.
- Education can be provided by: physicians, nurses, community health workers and other health care providers.
- Materials should be appropriate to the literacy levels of the patient and should be gender, age and culturally sensitive.
- All health care providers should adopt methods of 'communicating with' (and not 'talking at') patients and their caretakers
- For patients with literacy limitations, efforts should be undertaken to use e-health tools based on audio or visual support.
- Patient education should be continuous in the course of treatment.

***Avoid words that demean or blame the patient such as 'defaulter', 'suspect' and 'control', 'patient failed treatment' as they contribute to disempowering DR TB patients.*

B. Informed consent

- A person diagnosed with DR TB should be counselled and given health education in a language they best understand, to make informed decisions and give consent to initiate treatment. *(Refer to details under Treatment of DR TB guidelines above)*

- In the event that the patient is a child or adolescent (0-<18 years), they should be accompanied by the identified caregivers who should sign the consent form on their behalf.
- Non-consensual disclosure of a patient's DR TB status should be made only to close contacts who would be at a significantly higher risk of having acquired infection or of developing disease, and only when all reasonable efforts to engage the patient's cooperation have failed.
- A person with DR TB should be notified when all options are exhausted and a non-consensual disclosure has to be carried out. *Where and when appropriate, it may be important to activate social or community support systems to mitigate any potential fallout for the patient, such as stigma and discrimination, while deploying mechanisms to prevent loss to follow up.*

Patients who refuse to consent to DR TB treatment, should be counselled about the risks to both themselves and the community and factors leading to non-consent discussed and addressed. Patients should be informed of subsequent action such as involuntary isolation

6.8 Nutrition support in DR TB

Nutrition Assessment, Counselling and Support for DR TB Patients

Evidence has shown important links between improved treatment outcomes and good nutrition. Adequate nutrition is necessary to maintain the immune system and optimize response to medical treatment and sustain healthy levels of physical activity. Good nutrition also supports optimal quality of life for people with TB. Nutrition interventions also help to optimize the benefits of anti TB medicines as well as increase compliance with treatment regimens, both of which are essential for curing and preventing transmission of TB. (Castle man, T. et al, 2004) ;(World Bank, 2007).

NTLD-P annual report 2019, 29% DR TB patients were malnourished at the time of diagnosis

Definitions

Nutrition	Refers to the sum of all processes involved in taking of nutrients and their assimilation and use for proper body functioning and maintenance of health. The successive stages include; ingestion, digestion, absorption, assimilation and excretion.
Nutrients	These are chemical substances obtained from food and used in the body to provide energy, structural materials and regulating agents to support growth, maintenance and repair of the boy's tissues. Nutrients are categorized into two; macronutrients and micronutrients
Macronutrients	This refers to a nutrient that is required in large amounts for the normal growth and development. Protein, fat and carbohydrates are macronutrients that make up the bulk of a diet and supply the body's energy.
Micronutrients	This refers to essential dietary elements that are needed only in very small quantities for normal body function. Micronutrients are divided into two classes as Type I, which includes iodine, iron, Vitamins A and C. Type II include; magnesium, sulphur, nitrogen, essential amino- acids, phosphorus, zinc, potassium, sodium and chloride.
Malnutrition	It refers to deficiencies, excesses or imbalances in a person's intake of energy and nutrients. It is grouped in 2 broad categories;

Over nutrition	It Is a condition of excess nutrient and energy intake over time, it may lead to morbid obesity which is an abnormal accumulation of body fat, usually 20% or more above an individual's ideal body weight
Under-nutrition	This refers to a state when the nutritional status of the person is sub-optimal and thereby health and growth may be limited. It may be due to illness that impairs nutrient intake and metabolism or result from inadequate intake of macronutrients, micronutrients or both.
Micronutrient deficiencies	This is a form of malnutrition often referred to as hidden hunger. It is caused by inadequate intake of vitamins, minerals and trace elements.

Composition of Food

Different foods provide various nutrients that have different functions in the body

Nutrient	Function	Food sources
Protein	- Body-building - Aiding in immune function Controlling foods biochemical reactions	Animal foods: Meat, fish, milk & dairy products, eggs Plant foods: Legumes (beans, lentils),nuts (groundnuts, peanuts) , soybean products (meat, bean, milk)
Carbohydrates	- Source of energy	Cereal grains and their products: maize, millet, wheat, sorghum, rice, Roots and Tubers: Potatoes, cassava, yam, sweet potatoes, plantain (cooking bananas)
Lipids (Fats/oils)	- Energy reserve - Protection of vital organs - Thermal insulation	Visible fats (solid at room temperature) Visible oils (liquids at room temperatures) Invisible fats/oils: nuts, animal foods, avocado
Vitamins	- Reducing infection by supporting in the immune system -Aiding in metabolism	Fruits: mango, oranges, pawpaw, pineapple, passion, melon Vegetables: kales, cabbages, spinach, lettuce, carrots, broccoli
Minerals	- responsible for building structures like bones and teeth - Support various chemical reactions	Vegetables, meats and meat products, milk and milk products
Fibre	Regulate digestion -Reduction of cholesterol levels (soluble fibre)	Soluble: Legumes, apples, carrots, beans, cucumber, oranges Insoluble: Whole grains, fruits, vegetables
Water	-Transportation of nutrients -Transportation of waste material -Normal body functioning	Drinking water, Juices, soups

Components of a Healthy Diet

When planning a meal, it is important to consider the following basic principles. The food guide pyramid below will help you explain how to achieve good feeding practices.

Food Pyramid

Source: Diabetes Educator, 2010

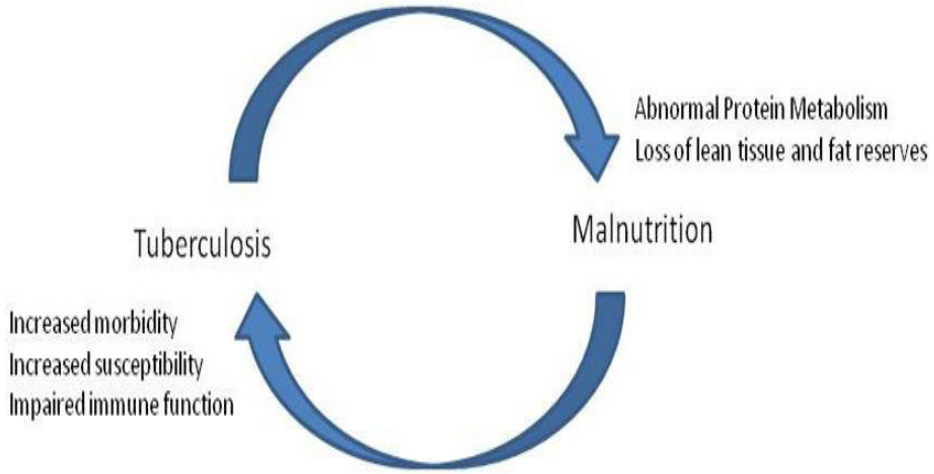
Additional Nutrient requirements for DR TB patients

Nutrient	Normal Kcals or grams	Additional for TB patient	Food examples
Energy	2100Kcal	300-500Kcals	1 to 2 cups of enriched porridge
Protein	0.8 g/ kg	0.4- 0. 7g/kg	Milk, egg, nuts, pulses and meat
Carbohydrates	55-60% of total Kcals	10-15% of total Kcals	enriched porridge, *nduma*, bread, sweet potatoes
Fats	25 – 30% of total Kcals	Nil	Margarine, butter, vegetable oil

Nutritional status is one of the most important determinants of resistance to infection. It is well known that there is a close association between TB and malnutrition as malnutrition increases the risk of developing TB and the vice versa.

DR TB and Malnutrition

TB affects the metabolism of important nutrients such as protein and some micronutrients. Malnutrition on the other hand limits cell-mediated immunity and increases susceptibility to infections. Nutritional deficiencies are associated with impaired immune functions; This affects cell mediated immunity by reducing the expression of gamma interferon, tumor necrosis alpha and other myco-bactericidal substances that are important for containing and restricting TB. This leads to nutritional stress and weight loss, thus weakening immune system causing body's inability to fight infections.



Source: TB Nutrition guidelines, 2012

Malnutrition markedly increases mortality among DRTB patients and should be addressed concurrently. Active TB often leads to malnutrition. TB patients frequently suffer from a loss of weight and appetite, consequently present a low body mass index, and skin fold thickness. Nutritional derangements include:;

- A 13% increase in basal metabolic rate (BMR) change with every 1 degree Celsius rise in body temperature
- The adipose and glycogen stores normally decrease due to increase in energy expenditure.
- Loss of body fluids - sweating and urination during the acute phase hence electrolyte loss.
- Loss of body weight due to increased catabolism
- Reduced appetite and ability to take food (anorexia, Cachexia and generalized weakness).
- Reduced ability of body to absorb nutrients
- Increased nutritional needs through metabolic changes
- Micronutrient deficiencies like Zinc, Vitamins A, C and D and Iron.

Consequences of malnutrition

- Reduced access to food due to morbidity/low productivity
- Less activity, less lung function and less heart function
- Serum protein levels can affect airway function and diffusing capacity of lungs

- Cachexia also affects lung function
- Decreased cough and inability to mobilize secretions
- Increased risk of mortality
- Diminished effectiveness of anti-TB drugs /Regimen
- Impair the protective efficacy of Bacillus Calmette-Guerin (BCG)
- Progressed disabilities
- Delayed and prolonged healing

Role of nutrition

Optimal Nutrition combined with medical treatment is an important component in treatment and care. Good nutrition enhances:

- Growth, development, replacement and repair of cells and tissues.
- Helps chemical processes such as digestion, metabolism, assimilation and excretion
- Restores and protects the integrity of the immune system.
- Prevent wasting and other forms of malnutrition micronutrient included.
- Improve drug efficacy
- Optimize cellular activity and tissue/organ function by providing sufficient amounts that meets daily body requirement

Nutrition Assessment Counselling and Support

Nutrition assessment counselling and support (NACS) aims to establish routine nutrition assessment as an integral component of facility- and community-based health care providers to deliver nutrition-specific services. It links clients to nutrition-sensitive interventions provided by the health, agriculture, food security, social protection, education and rural development sectors.

i. Methods of Nutrition Assessment

a. Anthropometric assessment

Anthropometric screening is carried out through serial measurements of weight, height, mid upper arm circumference (MUAC) and skin fold thickness (SFT). The values obtained are used to show changes body mass and dimensions.

b. Biochemical

These are chemical assays/ Lab assessments/analysis in most cases done on body fluids and have nutrition implications e.g. Haemoglobin, sugar levels, Liver function, CD4, Thyroid function, calcium levels, creatinine, kidney functions.

c. Clinical assessment;

This involves physical observation/ judgement Signs of nutrient deficiencies like visible wasting, hair changes, oedema, skin changes.

d. Dietary assessment

24 hour recall, food diary, food frequency and diet history

e. Environmental and psychosocial assessment

Includes the assessment of food security, source of income, number of household members and social support

f. Functional assessment

Functionality of body parts assess the energy levels- (ability to prepare or consume meals and mobility) lethargy and disability.

KEY HIGHLIGHTS

All DRTB patients should receive nutritional assessment, counselling and support at baseline and monthly tailored to individual needs

Nutrition Diagnostic Statement

A nutrition diagnostic statement is written in a PES format that states the Problem (P), the Aetiology (E), and the Signs & Symptoms (S). However, if the problem is either a risk (potential) or wellness problem, the nutrition diagnostic statement may have only two elements, Problem (P), and the aetiology (E), since Signs & Symptoms (S) will not yet be exhibited in the patient.

Classification of Nutritional Status and Management - Image not clear

CHILDREN 6-59 MONTHS		
WEIGTH/HEIGHT LEVEL	**CLASSIFICATION**	**MANAGEMENT**
80% or >-1z score or MUAC >=12.5	Normal	i. Nutrition counselling on weight maintenance ii. Vitamin A supplementation as per WHO recommendation iii. Monthly nutrition assessments
<80% or <-2z score or MUAC <12.5CM	Moderate acute malnutrition	i. Nutrition counselling on weight increase ii. Monthly nutrition assessments iii. Nutrition supplementation(Vitamin A, Fortified blended foods like fast food, Ready To Use Supplementary Food-RUSF)
<70% 0R -3 Z score or MUAC <11.5	Sever acute malnutrition without medical complication (passes appetite test, alertness, care giver willing to manage SAM at home	i. Nutrition counselling on weight increase ii. Weekly nutrition assessment iii. Therapeutic feeds(Ready To Use Therapeutic Foods – RUTF- either bar or Paste)
<70% or -3 z score with oedema +++ or MUAC <11.5	Severe acute malnutrition with medical complication(fail appetite test, intractable vomiting, anorexia,high fever, convulsions, no alertness, lethargy, lower RTI, severe anemia or dehydration, hypoglycaemia and hypothermia)	Manage in inpatient set up as per IMAM guidelines

BMI FOR AGE CHILDREN 5-17 YEARS, CLASSIFICATION AND MANAGEMENT

BMI FOR AGE	CLASSIFICATION	MANAGEMENT
80% or >-1z score or MUAC 5-9years >=14.5cm 10-14years >=18.5 15-17years >=19.5	Normal	• Nutrition counselling on weight maintenance • Vitamin A supplementation as per WHO recommendations • Monthly nutrition assessments
<80% or <-2z score or MUAC 5-9years>=13.5 to <14.5cm 10-14years>=16 to< 18.5cm 15-17years>=17.5 to <19.5	Moderate acute malnutrition	• Nutrition counselling on weight increase • Monthly nutrition assessments • Nutrition supplementation (Vitamin A, Fortified blended foods like foundation plus, Ready To Use Supplementary Food
<70% 0R -3 Z score or MUAC 5-9years>=13.5cm 10-14years<16cm 15-17years17.5cm	Sever acute malnutrition without medical complication (passes appetite test, alertness, care giver willing to manage SAM at home	• Nutrition counselling on weight increase • Weekly nutrition assessment • Therapeutic feeds(Ready To Use Therapeutic Foods either bar or Paste) • Hydrolysed feeds
<70% or -3 z score with oedema +++ or MUAC 5-9years<13.5cm 10-14years<16cm 15-17years17.5cm	Severe acute malnutrition with medical complication Fail appetite test(fail appetite test, intractable vomiting, anorexia,high fever, convulsions, no alertness, lethargy, lower RTI, severe anemia or dehydration, hypoglycaemia and hypothermia)	• Manage in inpatient set up as per IMAM guidelines

BMI for adults, classification and management

BMI	CLASSIFICATION	MANAGEMENT
BMI >30	Obese	• Nutrition counselling on weight reduction • Vitamin A and Pyridoxine supplementation • Monthly nutrition assessment
BMI>25cm-29.9	Overweight	• Nutrition counselling on weight reduction • Vitamin A and Pyridoxine supplementation • Monthly nutrition assessment
BMI >18.5-24.9 or Pregnant and postpartum up to 6months MUAC= >23CM	Normal	• Nutrition counselling on weight maintenance • Vitamin A and Pyridoxine supplementation as per WHO recommendation • Monthly nutrition assessments
BMI<18.5 or MUAC <23cm	Moderate acute malnutrition	• Nutrition counselling on weight increase • Monthly nutrition assessments • Nutrition supplementation(Vitamin A, Pyridoxine, Fortified blended foods like foundation plus, Read To Use Supplementary Food
BMI<16.0 CM or MUAC <19CM	Severe acute malnutrition without medical complications	• Nutrition counselling on weight increase • Vitamin A and Pyridoxine supplementation • Weekly nutrition assessment • Therapeutic feeds(Ready To Use Therapeutic Foods either bar or Paste) Hydrolysed feeds
BMI < 16.0CM with bilateral pitting oedema +++ or MUAC <16CM	Severe acute malnutrition with medical complications(fail appetite test, intractable vomiting, anorexia,high fever, convulsions, no alertness, lethargy, lower RTI, severe anemia or dehydration, hypoglycaemia and hypothermia)	• Manage in inpatient set up as per IMAM guidelines

For pregnant and postpartum mother	MUAC	>23	<23	<19	CLASS	Normal	MAM	SAM

DRTB INFECTION PREVENTION AND CONTROL

7.

Introduction

Infection prevention and control refers to all measures taken to prevent the spread of DR TB. It involves the adoption of several elements that need to be integrated to ensure TB infection prevention between the patient, the health care worker and other persons in contact with an index case.

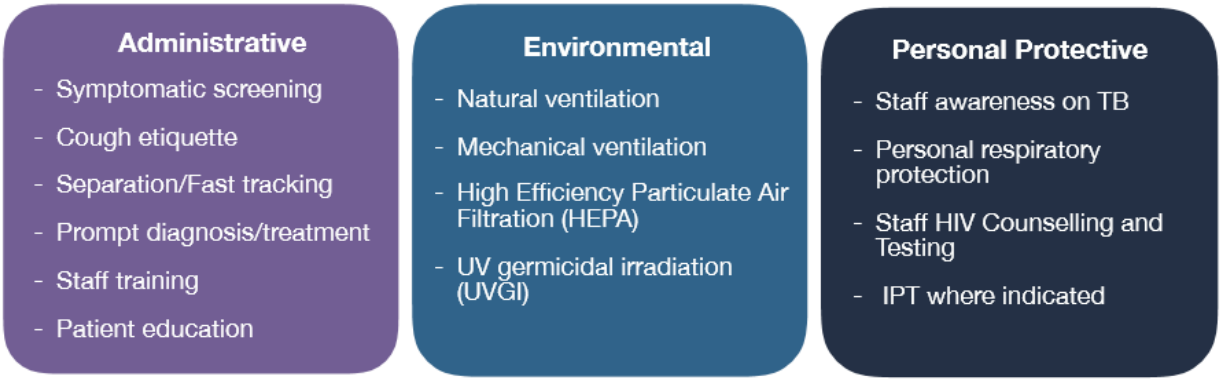
It is important that TB patients take all of their medications exactly as prescribed by their health care worker and ideally through a high quality DOTS program. Additionally, health care workers can help prevent DR TB by increasing index of suspicion of TB for early diagnosis, following recommended treatment guidelines, monitoring patients' response to treatment, and making sure the full course of treatment is completed.

To achieve IPC in health facilities, several key steps need to be followed:

1. Identification of a focal person for IPC among health workers who should have the support and authority to conduct, apply and evaluate TB IPC policies.
2. Creation/Formation of an infection prevention and control committee which should be multi-disciplinary and may include doctors, nurses, laboratory technicians, logisticians and administration staff (as applicable).
3. Conduct a facility IPC risk assessment using a standardized risk assessment tool
4. Development of a health facility IPC plan based on the findings of the facility risk assessment exercise. This written IPC plan should be updated annually and displayed in the facility. It must be accessible to all healthcare workers, including staff not directly involved in TB patients' management, such as cleaners, kitchen staff, etc.

7.1 TB and DRTB infection control in the health facility

There are three levels of controls in TB IPC, which include



7.1.1. Administrative controls

Administrative control measures have the greatest impact on preventing TB transmission and serve as the first line of defence for preventing the spread of TB in health-care settings. These controls aim at, preventing DRTB exposure of staff and patients and reducing the spread of infection by ensuring rapid and recommended diagnostic investigation and treatment for patients and staff suspected or known to have DRTB.

They include:

- **Patient triage**

Triage of people with TB signs and symptoms, or with DRTB disease, is recommended to reduce transmission to health workers, persons attending health care facilities or other persons in settings with a high risk of transmission. Upon entry into the health facility, a member of the medical staff should identify patients with a cough as soon as possible.

Respiratory hygiene (including cough etiquette)

Respiratory hygiene (including cough etiquette) s recommended in people with presumed or confirmed DRTB to reduce transmission to health workers, persons attending health care facilities or other persons in settings with a high risk of transmission

- **Controlled flow of movement within the facility**

Circulation of patients and attendants is controlled in health facilities to reduce infection transmission. For TB IPC, the following measures should be put in place:

- Encourage patients/attendants to spend as much time as possible outdoors if weather permits or in areas that are open on three or four sides.
- Limit visitation duration, particularly for contagious patients.
- Have visiting areas well identified with signage.
- Restrict entry for persons most at risk in catching/getting infection including young children, the elderly and the immunocompromised.

- **Segregation of hospitalized patients**

Respiratory separation / isolation of people with presumed or demonstrated infectious TB is recommended to reduce TB and DRTB transmission to health workers or other persons attending health care facilities

TB care is primarily ambulatory and patients should be treated as outpatients. Hospitalisation should be limited to severely ill patients.

TB wards must be separated from the other wards in the health facility. Ideally, within the TB department, patients should be placed in single rooms. If this is not possible, cohort isolation must be implemented and different sections should be labelled according to the degree of contagiousness (smear/culture status) and risk of resistance.

Where health facilities with admission wards do not have isolation rooms that can be used for DRTB care, it should be a high priority to establish at least 1 isolation room.

NB: Presumptive TB cases should not be hospitalized for TB diagnosis unless hospitalization is necessary. Any such patients need to be managed in isolation rooms.

- **Prompt initiation of effective treatment**

Prompt initiation of effective treatment of people with TB disease is recommended to reduce TB transmission to health workers, persons attending health care settings or other persons in settings with a high risk of transmission

- **DRTB infection prevention control training**

All healthcare personnel should receive initial training on TB transmission, information on high-risk areas in the facility and on protective measures. Continuing education should be offered annually.

The training should also include how staff can teach patients, visitors and attendants about the risk of DRTB transmission and how to avoid it (cough etiquette, use of masks and respirators).

- **Health Worker Screening for TB and DRTB**

All health workers (including support staff and administrative staff working in health facilities) should be screened for TB every 6 months using the symptoms screening approach. The adult TB ICF tool may be used to screen health workers. Any health worker found to presumptive for TB should be tested for DRTB using Gene Xpert **and** culture.

7.1.2. Environmental controls

Environmental measures aim at reducing the concentration of infectious droplet nuclei in the air and ensure sufficient air exchange and control airflow direction to reduce the risk of TB and DRTB exposure.

Ventilation

Ventilation refers to the replacement of inside air with outside air. It is the most effective means for reducing the concentration of M. tuberculosis in the air, and as a result, lowering the risk of transmission.

There are 2 main ways of achieving effective ventilation:

- **Natural ventilation**

Natural ventilation, especially cross-ventilation (windows/doors in opposite sides of the room), has the best cost-effective ratio. It should be done with the windows and outside doors open (as much as weather conditions permit). Create shady open spaces so that patients, attendants and visitors can stay outside during the day.

Wind-driven roof turbines or chimneys can also be used to improve natural ventilation, in that they can keep the principle of directing room air towards the exterior. In addition, extractor fans can be used when the natural ventilation flow rate is too low i.e assisted natural ventilation.

- **Mechanical ventilation**

This involves use of mechanical equipment to maintain an air pressure difference in order to draw air into a room and vent it outside. It requires continuous and meticulous maintenance, which renders it costly and difficult to implement and operate. It is only preferred when resource constraints are not an issue

Key considerations to adequate ventilation

1. Position windows and doors in opposite walls of wards and rooms. Keep windows and doors open to maximize cross ventilation.
2. Maintain openings in or above entrance doors to improve cross ventilation where doors cannot be left open
3. Designate responsible staff members to check ventilation equipment and open windows/doors according to a daily time schedule. Report and repair deficiencies immediately. Keep a log of both your daily ventilation checks and a log for equipment repairs
4. Incorporate preventive maintenance procedures into existing facility maintenance programs
5. Consider closed mechanical ventilation systems only in well-established settings with a constant power supply, where trained maintenance staff are guaranteed and there is easy access to parts

7.1.3. Respiratory controls (Personal Protective Equipment)

The respiratory controls (also known as personal protective equipment) are intended to provide additional protection in high-risk circumstances. The administrative and environmental controls are however far more effective in reducing TB transmission risk. Respiratory protection (if used correctly) can give additional benefit, especially for exposures to drug-resistant TB

Surgical masks are effective in containing respiratory droplets, its filter efficiency is however poor and short-lived. For this reason, surgical masks are not recommended for respiratory protection of healthcare workers.

N95 respirators should be worn when in contact with a person with confirmed infectious DRTB. These respirators have very high filtering efficiency, preventing inhalation of over 95% of particulate aerosols. Particles from 0.1–10 microns in size are filtered out, including TB droplet nuclei which are about 2–5 microns in size.

Fig 7.1 : Surgical and Respirator Masks

N95 respirators should be worn by health care workers in close contact with DRTB patients

7.2 DRTB infection prevention and control at home

Reduction of transmission of DR-TB in households is necessary because the household members are at high risk of becoming infected and consequently developing DRTB.

Patients with DR-TB convert later than those with drug-susceptible TB. This may prolong the risk of transmission in the household. DR-TB increases the risk of morbidity and mortality, particularly in people living with HIV. Infection control measures therefore should be implemented for the management of DR-TB patients at home.

Key considerations for DRTB infection control during home visits

Systematic DRTB infection control evaluations on patients' homes are recommended as part of DR TB patient management.

Key activities to be conducted during home visits include:

- **Assessing the risk of TB transmission:**

Gather information on the number of people that live in the house, number of rooms, advise on sleeping/ living arrangements to reduce transmission, ventilation and natural lighting in the home should also be assessed.

- **Screening of contacts for TB.**

Regular screening of DR TB contacts should be conducted. All contacts should be referred to a health facility for screening.

At baseline	In addition to symptomatic screening, a Chest X-ray and Gene Xpert should be done for all symptomatic contacts.
At month 3, 6 and 9 of treatment	Symptom screening should be done for all contacts. The contacts should be educated on the schedule for screening to ensure compliance with screening appointments. Screening of contacts should be suspended 3 months after the index case converts or after month 9 (whichever comes first)

For under 5 contacts of DR TB, the index case should use a surgical mask while taking care of the child until he/ she becomes culture negative. Outdoor visitation should also be encouraged.

Offer education on DRTB transmission, clinical symptoms of DRTB and infection prevention precautions at home (cough etiquette, ventilation and use of surgical masks)

The following are key considerations for infection prevention at home

1. Adequate ventilation of rooms, particularly rooms where people with DRTB spend considerable time (natural ventilation may be sufficient to provide adequate ventilation).
2. Those who cough should be educated on cough etiquette and should follow such practices at all times.
3. Ideally, TB patients should spend as much time as possible outdoors, sleep alone in a separate, adequately ventilated room and spend as little time as possible in public places or in public transport.
4. MDR-TB patients who cough should always practice cough etiquette (including use of face masks) when in contact with people. Ideally, health service providers should wear respirators when attending patients in enclosed spaces.
5. Family members living with HIV, or family members with strong clinical evidence of HIV infection, should not provide care for infectious MDR-TB patients. If there is no alternative, HIV positive family members should wear respirators.
6. Children below five years of age should spend as little time as possible in the same living spaces as culture-positive MDR-TB patients. Such children should be followed up regularly with TB screening and, if positive, drug-susceptibility testing.
7. When conditions do not exist to minimize risk of TB infection in a household, XDR-TB patients should be admitted to a specialized healthcare facility.
8. Household members of any TB patients should be encouraged to get screened for HIV and TB and be given appropriate (preventive) therapy. If possible, HIV-positive family members, or family members with a strong clinical evidence of HIV infection, should not share a household with culture positive XDR-TB patients.

7.3 DRTB infection control in congregate setting

DRTB infection control measures should be assessed and implemented in prisons and other settings where people have a higher risk of TB transmission due to a confined setting. TB is spread more readily in congregate settings than in healthcare facilities because of the longer duration of potential exposure, crowded environment, poor ventilation, and limited access to healthcare services and so is DRTB.

The measures for DRTB infection prevention should include the following,

1. **Preventing the spread of infection from community to prison**.
    - Using intensified DRTB screening for new or transferred prisoners.
    - Preparing adaptation blocks or rooms (to be used for two to four weeks) for new or transferred prisoners.
2. **Preventing TB infection among prisoners (from one TB prisoner to other prisoners) or to prison's staff.**
    - Conducting a contact investigation for DRTB suspects and cases.
    - Improving infection control (i.e. implementing managerial, administrative, and environmental interventions) in prisons.
3. **Preventing infection of family members and the community by released prisoners or prison staff.**
    - Examining prisoners before they are released.
    - Examining prison staff regularly

7.4 Infection Prevention and Control in the COVID-19 setting

Counties should ensure that adequate measures are put in place to limit transmission of TB and COVID-19 in congregate settings and health care facilities. Although modes of transmission of the two diseases are slightly different, administrative, environmental and personal protection measures apply to both (e.g. basic infection prevention and control, cough etiquette, patient triage). Provision of TB preventive treatment should be maintained as much as possible to reduce the number of TB/ COVID-19 co-infected.

ADVERSE DRUG REACTIONS AND THEIR MANAGEMENT

8.

Introduction

TB program systematically monitor patient safety to prevent and manage adverse drug reactions (ADRs), as well as improve health-related quality of life and treatment outcomes for patients who have TB. National tuberculosis programmes is actively pursuing drug safety monitoring and management to better preparedness to introduce new tuberculosis (TB) drugs and novel regimens.

8.1 Pharmacovigilance definition

The science and activities related to detection, assessment, understanding and prevention of adverse effects or any other possible medicine related problems. The Pharmacovigilance of importance in PMDT is active Drug safety monitoring for serious adverse drugs reactions.

8.2 Active TB Drug Safety Monitoring and Management (aDSM)

8.2.1: Introduction

Active TB drug safety monitoring and management (aDSM) is defined as an active and systematic clinical and laboratory assessment of patients while on treatment (ref). aDSM applies to patients on treatment with: (i) new anti-TB drugs; (ii) novel MDR-TB regimens; or (iii) extensively drug-resistant TB (XDR-TB) regimens, in order to detect, manage and report suspected or confirmed drug toxicities. The recording and reporting of aDSM primarily targets common side effects and adverse drug reactions (ADRs) as a core requirement. Core components of aDSM include clinical monitoring, clinical management, recording and reporting.

8.2.2: Components of active Drug safety Monitoring

The major components are;

- Data collection (passive, active or mandatory)
- Data analysis
- Reporting

8.2.3: Objectives of aDSM

The overall objectives of aDSM is to reduce risks from drug-related harms in patients on treatment for drug-resistant TB and to generate standardized aDSM data to inform future policy updates on the use of TB medicines for treatment of patients with DR TB. This include monitoring of AEs of clinical significance, including:

Serious Adverse Events (SAEs) defined as any untoward medical occurrence that, at any dose: Results in death, hospitalization, significant disability/incapacity, life threatening; congenital anomaly or a birth defect.

AEs of interest, defined as all AEs regardless of their seriousness, severity or causal relationship to the MDR TB treatment, pertaining to the following medical conditions: Peripheral neuropathy, Myelosuppression, Prolonged QT interval, Optic nerve disorder (optic neuritis), Hepatitis, Hearing impaired, Acute kidney injury, Hypokalemia and Hypothyroidism.

8.2.4: Rationale

In the current National Strategic Plan, (2019-2023) aDSM has been identified as a key focus area to improve patient safety and treatment success rate. Monitoring ADRs with the introduction of relatively new DRTB medicines that include Bedaquiline, Delamanid, and Pretomanid and repurposed is paramount due to low clinical experience for new molecules and long-term use of repurposed drugs. ADRs can lead to increased mortality, permanent disability/morbidity, non-adherence and modification of regimen leading to lower efficacy and subsequent treatment failure. Deliberate effort and actionable guidance is therefore necessary to provide health care workers with the tools and skills to optimize early detection and management of ADRs.

8.3 Detection of ADRs and Adverse events

ADRs and adverse events can affect both physiological and pathological pathways making them difficult to distinguish. The step-wise approach below is recommended for assessing ADRs;

a) Ensure the correct medication and dosing is prescribed to the patient

b) Verify that the onset of the suspected ADR was after the drug was taken, not before and discuss carefully the observation made by the patient;

c) Determine the time interval between the beginning of drug treatment and the onset of the event;

d) Evaluate the suspected ADR after discontinuing the drugs or reducing the dose and monitor the patient's status. If appropriate, restart the drug treatment and monitor recurrence of any adverse events.

e) Analyse the alternative causes (other than the drug) that could on their own have caused the reaction;

f) Report any suspected ADR to the person nominated for ADR reporting in the hospital or directly to the National PV Centre (PPB).

8.3.1: Laboratory Monitoring to support Identification of ADRs Early

Regular laboratory tests for patient taking DR TB treatment is recommend in detecting and averting ADRS before clinical presentation. Detecting abnormalities in select clinical surrogate markers in a timely manner is an important step in identifying potential drug safety issues with the patient.

Refer to **Table 8.1** *(annexed) on a schedule of lab tests required for D TB patients*

8.3.2: Risk Factors for ADRs

When evaluating and determining the ADR it is important to consider some Risk factors that could be associated with the patient.

- Advanced age
- Malnutrition
- Pregnancy and lactation
- Alcoholism
- Liver failure
- Chronic renal failure
- HIV infection
- Disseminated and advanced TB
- Allergy/Atopy
- Anaemia
- Diabetes mellitus
- Family history adverse drug reactions
- Patient receiving intermittent treatment
- Patients receiving medication for other disorders, in addition to anti-tuberculosis drugs

8.3.3: Management of Adverse drug reactions

Management of ADRs include reassuring the patient, drug removal or replacement, dose adjustment, symptomatic management and in some cases discontinuation of treatment depending on clinical presentation and the severity of the ADR. Proper management of ADRs is important as it may affect DR patient's adherence to their medicines, which in turn affects resistance. Hence, designing DRTB regimens should consider adverse reactions and the possibility of defaulting.

Principles in the Management of Adverse drug Reactions

- Early identification and treat immediately & adequately
- Rule out other causes
- Consider additive or potentiating SE with concomitant therapy

- Consider drug-drug interaction
- For minor and moderate reactions: Symptomatic management (recommended algorithms, OTCs and ancillary medications)
- For moderately severe reactions: Reduce dosage/ frequency of the suspected drug.
- Severe reactions: Patient hospitalized and managed. If a reduced dose does not help to resolve stop and replace or immediate stoppage of all treatment or removal of a drug from the regime

8.3.4: Recording and reporting of ADRs and Adverse events

All ADRs, adverse event and side effect need to be reported. DRTB side effects, adverse events and ADRs should be recorded in the primary source of data, which is the DRTB patient logbook. The main source of ADR data at the facility is patient logbook.

ADR reporting tools include aDSM/ADR reporting tool and PPB ADR reporting form (yellow form) (annexed table 8.2).

8.3.5: Grading for ADRs

Table 8.2: Grading ADRS

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.

8.4. Commonly used terms in aDSM

They include the following;

Adverse Drug Reactions: are defined as a response to a medicine which is noxious and unintended and which occurs at a dose normally used in humans for prophylaxis, diagnosis or therapy of disease or for modification of physiological function.
Adverse Event: Any untoward medical occurrence that may be present during treatment of product but which does not necessarily have a causal relationship with the treatment.
Side Effect: is defined as any unintended effect of a medicine occurring at dose used in humans which is related to pharmacological properties of the medicine

8.5. Adverse drug reaction related to DR TB drugs

8.5.1. Peripheral Neuropathy

Possible anti-TB drug that causes neuropathy: Cs, Lzd, H,

Table 8.2: 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.

8.5.2. Myelosuppression

Possible anti-TB drug causes: Lzd, Cfz,

Table 8.3: Grading Myelosuppression

	Grade 1: Mild	Grade 2: Moderate	Grade 3: Severe	Grade 4: Life threatening
Absolute neutrophil count	*1000 – 1300/ mm^3*	*750 – 999/ mm^3*	*500 – 749/mm^3*	*< 500/ mm^3*
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/mm^3*	*50.000-99.999/mm^3*	*25.000-49.000/ mm^3*	*<25.000/mm^3*
WBC decreased	*2.000-2.500/ mm^3*	*1.500-1.999/mm^3*	*1.000-1.499/mm^3*	*<1.000/mm^3*
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.**

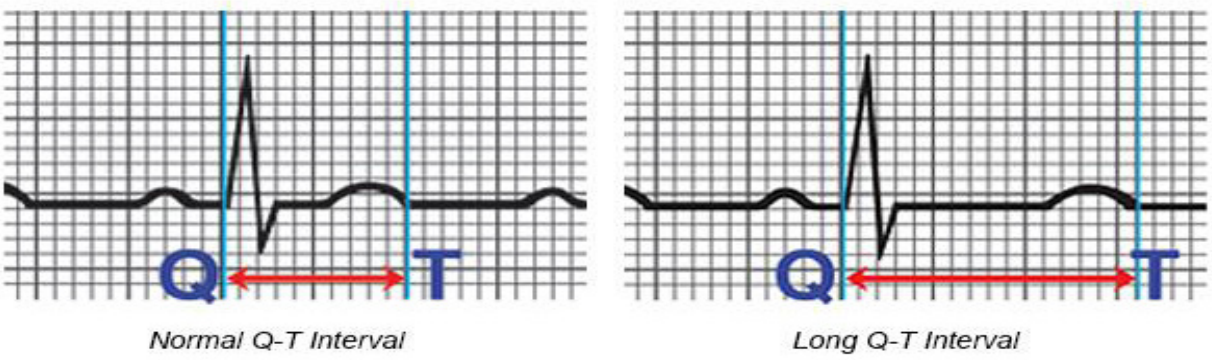
8.5.3.Prolonged QTcF Interval

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[4]



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)*

Table 8.4: QTcF Prolongation (ms) Gender cut-offs[5]

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

Table 8.5: 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.

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

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

Suggested Management strategy

Checking and eplenishing 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).

8.5.4. Optic Neuritis

Possible anti-TB drug causes: Lzd, E

Table 8.6: 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.

8.5.5. Hepatitis

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

Table 8.7: 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.

8.5.6 Hearing Impairment

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

Table 8.8: Grading Hearing impairment[6]

	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).*

[6] (https://www.mtaa.org.au/hearing-background)

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.

8.5.7 Acute Kidney Injury/ Failure

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

Table 8.9: 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 **non-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 **non-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.

8.5.8 Hypokalemia

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

Table 8.10: 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 8.11: 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.

8.6. WHO Grouping of DRTB medicines with common adverse drug reactions

Group A - WHO 2018 grouping of medicines for longer MDR-TB Regimens			
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 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 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
***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**
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.
Prothionamide (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.
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)

8.7 Drugs interaction (ref: SA AIDS conference June 2017)

Drug to drug interactions (DDIs) has recently received concern and increasingly reported attention. With new interventions, large number of drugs are manufactured and introduced into the market space every year, new interactions between medications needs to be monitored and reported. Precipitant drugs modify the object drug's absorption, distribution, metabolism, excretion, or actual clinical effect. Therefore, it's the role of the physician, pharmacists to report and inform possible drug interaction following patient history and inform the patient of the side effects pertaining to a drug administered. Patients also need to discuss any drugs they are taking as majority are prescribed over the counter to avoid any complication that may arise after initiation to certain regimen. Some common drugs have specific drug-drug interactions that may require dose adjustment or substitution of the ARV or the other interacting drugs

Table 8.12: An overview of selected serious drug interactions is given in Table below

Antiretroviral	Bedaquiline	Delamanid
Efavirenz	Do not co-administer Reduces BDQ by 50%	No interaction
Nevirapine	No dose adjustment. No dose adjustment	Not expected
Rilpivirine	Not expected	Not expected
Lopinavir/Ritonavir	Increase BDQ exposure: may lead to toxicity?	Increase DLM exposure: clinical relevance
Atazanavir/ritonavirRaltegravir & Dolutegravir Darunavir/ritonavir	No interaction expected	Not studied, no interaction expected
Raltegravir Dolutegravir	No interaction expected	Not studied, no interaction expected

8.8 Anti TB drugs and dietary relations

Drug Name	Dietary Restriction	Possible side effect
Rifampicin	To be taken 1 hr before or 2 hrs after food. 1 hr before Antacids. Avoid Alcohol	Nausea, Vomiting, Appetite loss
Isoniazid	Taken 1 hr before or 2 hrs after food. Give 50mg of Pyridoxine daily. Avoid alcohol	Hepatotoxicity, Cutaneous hypersensitivity, Peripheral Neuropathy
Ethambutol	May be taken with food. Avoid Alcohol	Anthralgia,Retrobulbar neuritis.
Pyrazinamide	May be taken with food	Hepatotoxicity, arthralgia, nausea, Vomiting
Prothionamide	Take with or after meals (Supplement with Vit. B6). Avoid Alcohol	Abdominal discomfort, Nausea, Vomiting

Bedaquiline	Absorption increases after a standard meal. Avoid alcohol	Prolonged QT, Hepatotoxicity, Nausea, vomiting, arthralgia, headache, itchiness,
Linezolid	Avoid foods rich in tyramine (fermented meat product, pickles) avoid alcohol	Myelosuppression, Lactic acidosis, optic and peripheral neuropathy, skin reaction
Delamanid	Absorption increased after a standard meal	Serious Heart rhythm changes Nausea, Vomiting, Dizziness, Insomnia, Upper abdominal pain Anxiety, paraesthesia Itchiness

8.9 Roles and responsibilities of HWC in Pharmacovigilance / aDSM

The entire system of pharmacovigilance works with the support of each healthcare provider, the regulatory bodies, the pharmaceutical industry, other stakeholders and the public at large. Hence, each of these have an important role to play and responsibility to bear:

Patient / Public

Patients to report any unacceptable, unexpected or suspected adverse effect of medicine dispensed to them.

Health Care Worker

Patient awareness of possible serious reactions, and development of a culture to report reactions to clinics, will be essential for any pharmacovigilance system. Health facility staff provides an essential link in the detection of ADRs at the periphery of the health care system. The healthcare worker's roles in the PV system are:

- Patient education
- Detection and appropriate clinical management
- Reporting
- Documentation- to maintain accurate documents
- Investigation, where necessary
- Patient feedback

Sub County Pharmacist

- Receive reports from health centres and send ADR reports from district to PPB on a monthly / weekly basis or on an ad hoc basis in an emergency.
- Facilitate investigations initiated by PPB, where necessary.
- Training of healthcare staff in facilities

County Pharmacist

The two most important roles of the county pharmacist are:

- Coordinate all activities of pharmacovigilance in the county
- Training of healthcare staff in the county.

Clinical Review Team

The clinical review team plays a central role in monitoring DR TB patients for ADRs. The team ideally will comprise of clinicians, pharmacists, nutritionist as well as the head nurse or matron of the facility. Detailed follow-up of suspected drug reactions would be used to define causality. The clinician who sees the patient reports any suspected ADRs to the PPB, and contributes to public education on drug safety.

Pharmacy & Poisons Board (PPB)

The PPB will take responsibility for any regulatory action with respect to the implicated medicinal product/s. These actions will be officially communicated to the drug manufacturers, who have liability for the drug. The PPB will:

- Receive reports from health workers and other sources
- Develop and maintain ADR database
- Detect ADR signals and take necessary action on received reports
- Support the clinical review team to investigate relevant ADR reports
- Send ADR reports to Uppsala Monitoring Centre
- Provide feedback to the users on reported ADRs through quarterly newsletters
- Establish and provide secretariat for the Expert Safety Review Panel
- Advocacy, Training and Education
- Provide support to whole system
- Communication / IEC
- Implement appropriate regulatory framework.

References

1. WHO consolidated guidelines on drug resistant tuberculosis treatment
2. WHO companion handbook to the guidelines on the management of DR TB
3. Guidelines on use of antiretroviral drugs in Kenya:
    - *For the preferred ART options for TB/HIV Co-infection for patients newly initiating 1st line ART,*
    - *Preferred ART Regimens for Patients who Develop TB while Virally Suppressed on 1st Line ART*
    - *Recommended ART Regimens for Patients who Develop TB while Failing 1st Line ART respectively*.
4. WHO Patients' Charter for Tuberculosis Care

ANNEXES

ANNEX 1: SPUTUM COLLECTION PROCEDURE

Why is a sputum test necessary?

Your doctor wants to collect some of the sputum ("phlegm") that you cough up from your lungs. The laboratory will test the sputum for tuberculosis (TB) germs.

Checking your sputum is the best way to find out if you have TB disease. If you are already taking medicine for TB, checking your sputum is the best way to tell if the medicine is working.

To be sure the test is accurate, you must cough up sputum from deep inside your lungs. Sputum from your lungs is usually thick and sticky. Saliva comes from your mouth and is watery and thin. Do not collect saliva.

TIP:

If you cannot cough up sputum, try breathing steam from a hot shower or a pan of boiling water.

How to collect a sputum sample

Your doctor or nurse will give you a special plastic cup for collecting your sputum. Follow these steps carefully:

1. The cup is very clean. Don't open it until you are ready to use it.
2. As soon as you wake up in the morning (before you eat or drink anything), brush your teeth and rinse your mouth with water. Do not use mouthwash.
3. If possible, go outside or open a window before collecting the sputum sample. This helps protect other people from TB germs when you cough.
4. Take a very deep breath and hold the air for 5 seconds. Slowly breathe out. Take another deep breath and cough hard until some sputum comes up into your mouth.
5. Spit the sputum into the plastic cup.
6. Keep doing this until the sputum reaches the 5 ml line (or more) on the plastic cup. This is about 1 teaspoon of sputum.
7. Screw the cap on the cup tightly so it doesn't leak.
8. Wash and dry the outside of the cup.
9. Write on the cup the date you collected the sputum.
10. Put the cup into the box or bag the nurse gave you.
11. Give the cup to your clinic or nurse. You can store the cup in the refrigerator overnight if necessary. Do not put it in the freezer or leave it at room temperature.

ANNEX 2: EXPECTED TURNAROUND TIMES (TAT) FOR THE VARIOUS LABORATORY TECHNIQUES/ASSAYS

Test menu	Lab TAT	Comments
AFB Microscopy	24hrs	All specimens (sputum & SOTS)
Genexpert	48hrs	All specimens except blood
TB culture- **Solid culture**	8 weeks 2-8weeks	Culture Negative Culture Positives
TB culture- **Liquid Culture**	6weeks 5-28days	Culture Negative Culture Positives
TB drug susceptibility testing - RHE **- PZA**	 7-14 days 7- 21 days	 MGIT DST
Molecular DST –FL-LPA **Molecular DST-SL-LPA** **MTB speciation**	7 working days 7 working days 7 working days	Smear Positives All samples All samples
Gene sequencing **(batched)**	2-14 days	All samples

ANNEX 3: DR-TB CASE SUMMARY TOOL

Bio-Data	**Name**		
	Age		
	Gender		
	Occupation		
	NHIF No.		
	Physical Address (Including County and Sub-county)		
	Name of Facility		
Anthropometric measurements	**Weight**		
	Height		
	BMI/BMI for Age/ Z-Score		
Vitals	**BP**		
	HR		
	RR		
	Saturation (SPO2)		
HIV status			
Date of test			
Initiation on ART		**Date of ART initiation**	
Date of initiation			
Initiation on CPT			
Type of TB			
Registration group			
Model of care			
Does the patient receive monthly social support?			
Patient's last review date with a clinical review team			
Presenting complaints and duration:			
History of presenting illness:			
Past medical History:			
Past Treatment History:			

Current treatment history: (Include all the treatment remedies/regimens the patient is currently on)				
Family and social History: (Include contacts history)				
Comorbidities:				
Physical Examination: (Include details on all systems)				
Investigations (Customize accordingly where appropriate- Include the dates)				
Date done	**Smear Microcopy**	**Culture**	**1st Line LPA**	**2nd Line LPA**
	Month 0			
	Month 1			
	Month 2			
	Month 3			
	Month 4			
	Month 5			
	Month 6			
Hematological and Biochemistry Investigations (Include all that have been undertaken with dates of each investigation- Each investigation should be captured on its own row)				
Imaging modalities (Audiometry, CXR, ECG , ECHO, CT SCAN)				
PATIENT CARE & SUPPORTIVE MANAGEMENT				
SPECIFIC THERAPUTIC MANANGEMENT (For the current illness)				
Other important notes:				

ANNEX 4: PATIENT EXPERIENCES

Below is a living account from cured patients who were put on DR TB treatment in 2008/2012 and are now engaged fully in DR TB advocacy in Kenya. Their experiences have contributed to the development of DR TB patient support guidelines.

Former DR TB Patient Experience 1

"My nightmare started in 1992, coughing without stopping for a long duration of time, visiting private clinics in south coast of Kenya where the doctors treated for pneumonia without proper examinations and putting me on antibiotics for eight years without improvement. Some of my friends directed me to the witch doctors thinking that I was bewitched some directing me to the herbal clinics where I spent a lot of money weekly and still the cough never ended instead it became worse.

In 1998, it got worse and along the way, someone directed me to Port Ritz hospital in Mombasa island the only facility by then which treated TB cases. In this facility, I was examined and tested for TB through CXR (chest x-ray) and the results showed TB infection in my lungs and that's when I started knowing about TB. Life at work even became more difficult. I was put on first line TB treatment for eight months a combination of sixty (60) injections and oral TB drugs for two months then the continuation phase of oral TB drugs for six months. After completing my eight months of treatment, the cough never ended instead it became worse and the doctors started suspecting I could have developed resistance, it took me about a year to get diagnosed and this was in 2004. As at that time, Kenya did not have a TB confirmatory test and the confirmatory test used to be done in Australia, a process that would take anything from six months to one year.

By those times, I had to meet several conditions before being 'qualified' for DR TB treatment. Some of the conditions included; a bank deposit of about USD 1500 to show that I could sustain myself on treatment in Nairobi the only city which had a DR TB treatment site, a letter from the local administrative authorities as show of residence and a committed treatment supporter among others.

In 2008, the country had just started the DR TB treatment and I happened to be among the first seven patients to be put on treatment. I was put on treatment in December 2nd 2008 on second line treatment for Drug Resistance TB. I had to buy some drugs as a monthly dose which was costly something I continued to do till I completed treatment. I received injections for eleven months (380 injections) and up to the day I completed my treatment I had done twenty nine months of treatment. In seeking this treatment, I had to walk twenty three kilometres from where I lived to the DRTB clinic and back home and sometime spent some nights at the emergency wing at the hospital because my legs could not move because not all the times I could afford paying transport and strikes by public transport vehicles.

In this journey I also lost so much weight from 75kgs to 37kgs I was very weak couldn't walk to and from. Despite all these during my times on treatment, I sacrificed my life for others looking beyond my disability going out creating awareness and pushing for the rights of TB patients. I led the other six patients to fight for our rights on 2009 asking for sustained supply of DR TB drugs, ensuring all confirmed cases were initiated on treatment unconditionally, demanding that the country improved her MDR TB treatment and management capacity to take in all patients, that the patients were given social support and nutrition to support their treatment because we really had rough times. We also asked for decentralization of MDR TB treatment. I led other patients approached both the Ministers for public health and medical services demonstrating

for these rights but when nobody responded, we staged a sit-in outside the Ministers office and did the same at the office of the Head of the TB program. We then walked to the office of the Human Rights Commission and this is where our grievances were heard and considered.

A letter was written to the National TB Program asking the program to consider the patients ask and this is when the ministry ensured there were enough drugs and no patient was put on a waiting list. Most of the transformation in the management of DR-TB patients was through the advocacy efforts I started. All these results have been possible because i have put on the garment of hope beyond death in particular love to people suffering not only on TB other chronic diseases too.

I got cured on 7th April 2011 but DR TB is a horrible illness as unfortunately I lost my left lung after it collapsed and the second one only about 46% functional as an effect of DR TB. I survive on an Oxygen concentrator machine donated to me through Stop TB Kenya by Amref Health Africa in Kenya and this is a fact as the journey to fight DR TB is a real experience and at this moment I am using my reason to manipulate reality."

Former DR TB Patient Experience 2

"I experienced chest pains for some time forcing me to visit different private facilities where doctors treated Asthma through injections but I was also receiving herbal treatment. After battling for long, I visited a public facility in Kongowea where I did a sputum test which showed no TB active bacteria. I was then advised to go for x-ray which indicated effusion on the left side of my lung and I was put on the DS TB treatment for 6 months . The more I took the drugs, the weaker I became and I started coughing. After six months I did a culture test and when the results came out, it was revealed that I was resistant to first line TB treatment. At this point, I was put on DR TB treatment for eighteen (18) months (8 months daily injections and 1year on oral drugs) and completed treatment in 2013. During the treatment phase, I was being supported nutritionally through health education and was given food supplements."

The two cured patients are among other DR TB champions who are involved in giving hope and strength to other people who have completed the treatment journey and those are still undergoing DS TB and DR TB treatment countrywide.

ANNEX 5:

Table 8.1: Schedule of lab tests required for DR TB patients

	TIME IN TREATMENT										
	Baseline	**Week 2**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**	**If Patient on Injection**	**Till end**	**End of treatement**
Lab tests											
ECG	X	X	X	X	X	X	X	X			X
CBC	X	X	X	X					Monthly		X
Urea&Cr	X		X	X	X	X	X	X	Monthly		X
K^+,Mg^+,Ca^+	X		X	X	X	X	X	X	Monthly		X
AST,ALT	X		X	X	X	X	X	X	Monthly		X
TSH	X				X			X	Every 3 months		
FT4/FT3											
Sr Albumin	X										
HBV&HCV	X										
BS/HBA1C	X										
Pregnancy	X										
HIV	X										
CD4,/VL if HIV^+	X										
CXR	X							X			X

ANNEX 6: ADULT & ADOLESCENT DOSAGES FOR SECOND LINE ANTI TB MEDICINES

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
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**

ANNEX 7: PAEDIATRIC DOSAGES FOR SECOND LINE ANTI TB MEDICINES

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

ANNEX 8: PMDT DRAFT 2020, REVIEW TEAM

Topic	Name	Organization / Affiliation
Introduction/Background(DS/DRTB)	Samuel Misoi Dr. Stephen Macharia	DNTLD DNTLD
TB Diagnostics and Lab reporting	Nelly Mukiri Kennedy Muimi George Kamau Zipporah mwongera Nicholas Ezati Albert Okumu	NTRL USAID TB ARC 11(CHS) NTRL NTRL DNTLD CDC
Treatment	George Oballa Dr. Irungu Karugah Timothy Malika Dr.Herman Weyenga	DNTLD MOH MOH CDC
Treatment Monitoring/Quality of Care/Post treatment follow up	Dr.Simon Wachira Hussein Kerrow Dr. Boru Okotu Judi Lisike	USAID TB ARC 11(CHS) MSF DNTLD CHAI
Prevention	Wesley Tomno Dr. Handson Bota Wendi Nkirote	DNTLD DNTLD DNTLD
DR TB in Special Populations	Dr. James Wagude Dr. Andrew Owuor Dr. Lorraine Mugambi Dr. Saumu Wayuwa Rhoda Pola Dr.Elizabeth Onyango Dr.Philip Owiti Prof.Lameck Diero Evelyne Kimani	MOH KNH USAID TB ARC 11(CHS) MOH DNTLD DNLTD DNTLD MTRH/Moi University USAID TB ARC 11(CHS)
ADR's and Commodity section	Dr. Kiogora Gatimbu Dr. Asmahani Ndaisi Philip Kimani Najma salim Dr.Kituzi Evans Dr.Maurice Maina	MOH MOH CHAI CHAI DNTLD USAID
Patient Support, human rights, Nutrition and communication	Jacqueline Limo Ann Munene Lucy Ghatti Rose Wandia Felix Mbetera Ramadhan wangatia John Mungai Diana Kagwiria Mary Nyagah	DNTLD AMREF KELIN USAID TB ARC 11(CHS) DNTLD CHAI Amref Kenya USAID TB ARC 11(CHS) DNTLD

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