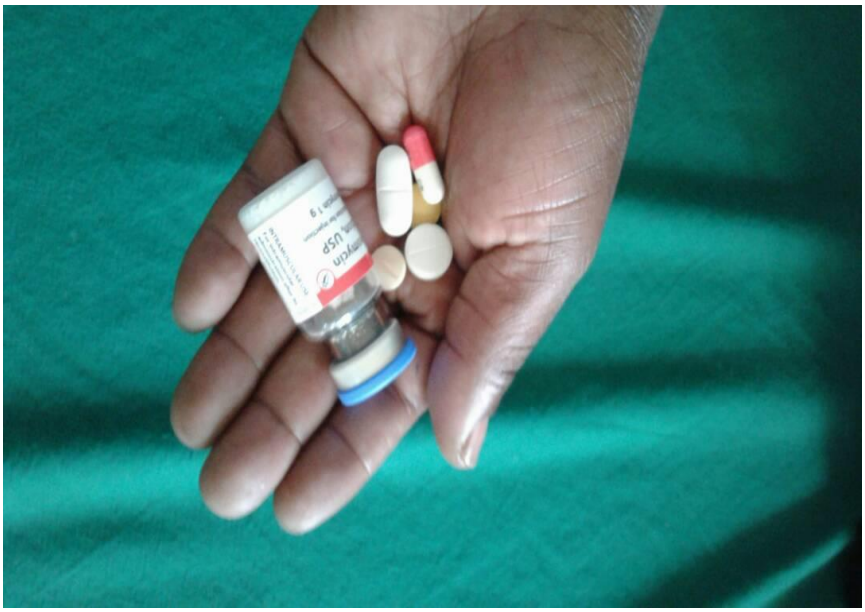
United Republic of Tanzania
Ministry of Health Community Development, Gender, Elderly and Children
National Tuberculosis and Leprosy Program



Guidelines for Management of

Multi Drug Resistant – TB in Tanzania

Second Edition

2017

National TB and Leprosy Program
Ministry of Health Community Development Gender Elderly and Children
P. O. Box 743
40478 Dodoma
Website: www.moh.go.tz/ntlp

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ABBREVIATIONS

ADR	Adverse drug reaction
aDSM	Active drug safety monitoring and management
AE	Adverse event
AFB	Acid Fast Bacilli
AIDS	Acquired Immuno-Deficiency Syndrome
ALAT	Alanine aminotransferase
ART	Anti-retroviral therapy
ASAT	Aspartate aminotransferase
BCG	Bacille Calmette-Guerin
BD	Twice A Day
BMI	Body mass index
BUN	Blood Urea Nitrogen
CHMT	Council Health Management Team
CI	Contact Investigation
CPT	Cotrimoxazole Preventive Therapy
CrCl	Creatinine Clearance
CTRL	Central Tuberculosis Reference Laboratory
CXR	Chest X-ray
dB	Decibel
DMO	District Medical Officer
DOT	Direct Observed Treatment
DOTS	Directly Observed Treatment, Short course
DRS	Drug Resistance Survey
DR-TB	Drug-Resistant TB
DST	Drug Susceptibility Testing
DTLC	District Tuberculosis and Leprosy Coordinator

ECG	Electrocardiogram
EP	Extra-pulmonary
EQA	External Quality Assurance of AFB microscopy, culture
FBP	Full Blood Picture
FDC	Full Dose Combination
FLD	First-line Drugs
GDF	Global Drug Facility
GFATM	Global Fund to Fight AIDS, Tuberculosis and Malaria
GLRA	German Leprosy and Tuberculosis Relief Association
HCW	Health Care Worker
HEPA	High Efficiency Particulate Air
HIV	Human Immunodeficiency Virus
IC	Infection Control
KNCV	KNCV Tuberculosis Foundation
LFT	Liver Function Tests
LTBI	Latent TB infection
M/XDR-TB	Multi-drug resistant TB/Extensively-drug resistant TB.
MDR-TB	Multi-drug resistant TB
MGIT	Mycobacteria Growth Indicator Tube
MIC	Minimum Inhibitory Concentration
MoHCDGEC	Ministry of HealthHealth, Community Development, Gender, Elderly and Children
MOTT	Mycobacteria Other Than Tuberculosis
MTBDRsl	Genotype Mycobacterium tuberculosis drug resistant second line assay
NDR	New drugs
NGO	Non Governmental Non-Governmental Organization
NTLP	National Tuberculosis and Leprosy Program

NTM	Non TuberculousNon-Tuberculous Mycobacteria
OD	Once Per Day
OI	Opportunistic Infection
OPD	Out Patient Department
PLHIV	People living with HIV
PMDT	Programmatic Management of Drug Resistant Tuberculosis
PTB+	Pulmonary Tuberculosis, sputum smear positive
PV	Pharmacovigilance
RFT	Renal Function Tests
rGLC	Regional Green Light Committee
RLT	Regional Laboratory Technician
RR-TB	Rifampicin resistant TB
RTLC	Regional Tuberculosis and Leprosy Coordinator
SAE	Serious Adverse events
SLD	Second-line Drugs
TB	Tuberculosis
TFDA	Tanzania Food and Drug Authority
TLCU	Tuberculosis and Leprosy Central Unit
TSH	Thyroid Stimulating Hormone
USAID	United States Agency for International Development
WHO	World Health Organisation
XDR-TB	Extensively Drug Resistant TB

ANTI-TUBERCULOSIS DRUG ABBREVIATIONS

Am	Amikacin
Amx/Clv	Amoxicillin/Clavulanate
Bdq	Bedaquilline
Cfz	Clofazimine
Cm	Capreomycin
Cs	Cycloserine
Dlm	Delamanid
E	Ethambutol
Eto	Ethionamide
HHD	High dose Isoniazid
Km	Kanamycin
Lfx	Levofloxacin
Lzd	Linezolid
Mfx	Moxifloxacin
PAS	P-aminosalicylic acid
Pto	Prothionamide
R	Rifampicin
Z	Pyrazinamide

FOREWORD

The emergence of resistance to drugs that are used to treat tuberculosis (TB), and particularly multi-drug resistant TB (MDR-TB), has become a significant public health problem in many countries, and is an obstacle to effective global TB control. In 2015, there were estimated to be about 480,000 MDR-TB cases and an additional 100,000 rifampicin resistant cases worldwide. Treatment outcomes for drug resistant TB cases are not very promising in comparison to drug susceptible TB cases with the global 2013 MDR/RR-TB cohort reporting a treatment success of 52% and 28% for MDR/RR TB and XDR-TB respectively.

In Tanzania, the Ministry of Health, Community Development, Gender, Elderly and Children (MOHCDGEC) through the National TB and Leprosy Program has taken specific measures to address the problem of Drug Resistant TB as highlighted in the National TB strategic plan 2015 – 2020. The burden of MDR TB in the country is estimated at about 1.1% among new TB cases and 3.9 % among retreatment TB cases (Drug Resistance Survey – 2006). The purpose of this document is to provide guidance on the detection of all estimated cases and facilitate early initiation of effective MDR TB treatment. Achieving this, will halt the propagation and spread of drug-resistant strains in the general population and prevent the high mortality associated with DR-TB, especially in high HIV prevalence settings.

To facilitate diagnosis of DR-TB cases, the Ministry is scaling up the use of new TB diagnostic technologies; the Xpert MTB/RIF and line probe assays for second line genotypic DST testing (SL-LPA) that will detect DR-TB including extensively drug resistant TB (XDR-TB) cases more rapidly and effectively. Furthermore, the MoHCDGEC is introducing a shorter MDR TB regimen that has an advantage over the existing regimen in reducing the treatment duration and cost to half and has better treatment outcomes. This document will provide guidance on the new interventions above and on how to conduct active drug safety, monitoring and management for new drugs such as as bedaquiline, delamanid and linezolid that will be included in the improved regimen.

The MoHCDGEC recommends an MDR-TB treatment modality whereby majority of patients will be treated on an ambulatory basis in decentralised facilities using the shorter MDR TB regimen. In some cases, patients with clinical and psychosocial indications for admission will be hospitalised in available inpatient facilities for a shorter period and be transferred to the community level using early discharge criteria.

Last but not least, second-line drugs are the last chance of curing TB in patients with MDR-TB, and to guarantee a complete cure, the treatment regimen should be strictly adhered to. Therefore, every measure should be undertaken by health workers, community based health care workers, patients and other stakeholders to ensure adherence and rational use of second-line drugs.

I hope that health workers and other stakeholders will find this document useful in guiding detection, diagnosis, treatment and support of patients with MDR-TB in Tanzania.

Dr. Mpoki. M. Ulisubisya

Permanent Secretary

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Prof. Muhammad Bakari Kambi

Chief Medical Officer

EXECUTIVE SUMMARY

Globally, Multidrug-resistant *Mycobacterium tuberculosis* (MDR-TB) is emerging at an alarming rate and presents a major challenge for the clinical management of TB. There were estimated to be about 480,000 MDR-TB cases and an additional 100,000 rifampicin resistant cases worldwide in 2015. The global 2013 MDR/RR-TB cohort reported a treatment success of 52% and 28% for XDR-TB. In Tanzania the most recent data from the National Drug Resistance Survey 2006 in Tanzania indicates that the proportion of MDR-TB among new and retreatment cases is about 1.1% and 3.9 % respectively. In 2015 there were estimated around 2600 incident MDR/RR-TB cases among which 730 MDR/RR-TB were estimated among notified pulmonary cases.The challenge in Tanzania is low case detection and enrollement whereby 178 cases were detected and 123 cases were enrolled into treatment in 2015.However the treatment outcome is high,reported as 76% treatment success in 2014.

MDR-TB is a laboratory diagnosis confirmed after culturing *Mycobacterium tuberculosis* strains and performing drug susceptibility tests (DST). Currently rapid genotypic tests such as X-pert MTB/Rif can be used in diagnosis RR-TB cases that are eligible for MDR-TB treatment.

Tanzania has a network of five zonal TB laboratories (CTRL) with capacity of performing culture of *Mycobacterium tuberculosis* and over 150 gene xpert testing sites that can be used to detect and monitor MDR-TB patient treatment.

The Tanzanian programmatic management of DR-TB (PMDT) recommends using shorter and individualised *regimen* approaches.All MDR/RR-TB patients should be access to second line drug susceptibility testing (DST) to determine the enrolment into appropriate drug resistant TB regimen which will be provided in two phases; intensive and continuation. It is important to identify MDR-TB patients as early as possible to increase the chance of successfully treating the patient and at the same time reducing the risk of transmitting MDR-TB strains to close contacts and the community at large.Some patients will have a clinical and pyscosocial indications for admission should be hospitalised in available inpatient facilities for a shorter period and be transferred to the community level using early discharge criteria.However majority of patients without admission indications should treated on ambulatory basis in decentralised facilities. Second-line drugs including new TB drugs such as bedaquiline, delamanid and linezolid are associated with many and sometimes unkown adverse events, therefore the MoHCDGEC will implement an active drug safety, monitoring and management in all MDR/RR-TB patients enrolled in shorter and individualised regimen. The serious adverse events and adverse events of special interest should be managed in line with the guidance provided henceforth in these guidelines.

The national TB and Leprosy program in collaboration with partners is transitioning from paper based recording and reporting system to a case based electronic recording and reporting system for both drug susceptible and drug resistant TB including a labortatory information module. The new system which will improve program data quality that will available in real time and inter operable with existing DHIS2 eLMIS, CTC2 and laboratory database as described in these guidelines.

THE PROGRAMMATIC MANAGEMENT OF DRUG RESISTANT TB

PREAMBLE

The diagnosis, treatment and care for a person affected with DR-TB (DR-TB) pose enormous managerial challenges in any health care system, even for those in high-income settings. The programmatic management of DR-TB (PMDT) in Tanzania aims to provide coordination of PMDT activities to achieve functions stipulated in the NTLP strategic plan V of 2015-2020.The programmatic management of drug resistsnt TB (PMDT) is defined as all functions related to orientation of systems establishment (i.e. budgetary ,infrastructure ,procurement ,communication,management) that assist and facilitate the clinical,laboratory and social support-rellated components of drug-resistsnt TB prevention,diagnosis,treatment and care.

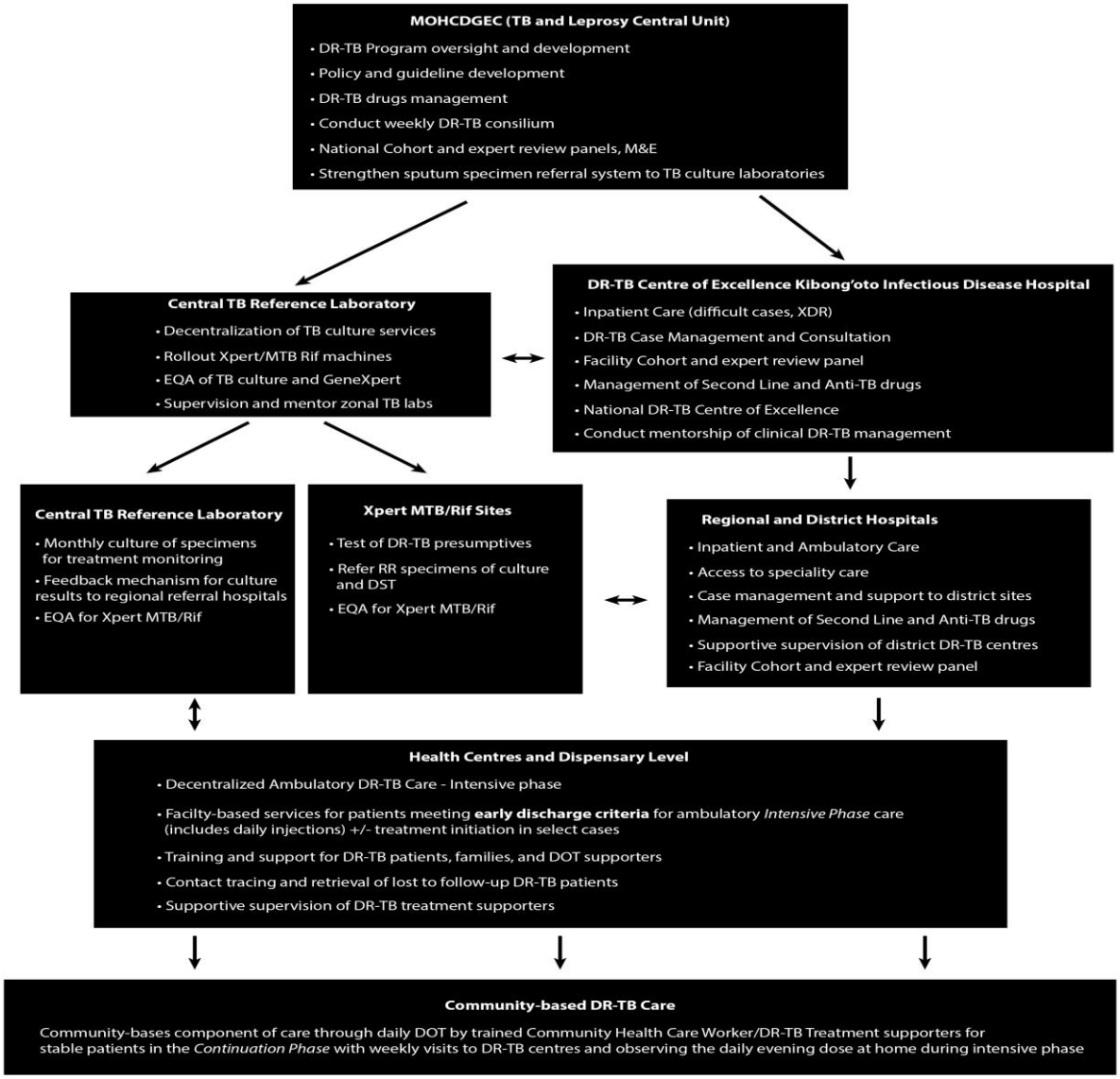
The organization of DR-TB services in Tanzania

DR-TB services are integrated within the Tanzanian national health system and they are provided and managed at various levels: national, referral/consultant, regional, district, health centre, dispensary, community and in private sectors. Figure 1 shows the different levels that have a role in DR-TB services in Tanzania and their relationship. The arrows indicate the flow of information and supervision as explained below:

- *Communities* are the grassroots level of the health care system. They provide preventive services as well as community based DR-TB care and support in the community.
- D*ispensaries, health centres, district and regional hospitals* are the entry points into the formal health care system, offering decentralised PMDT services either as treatment initiating or DOT services.
- *Referral/consultant facilities* offer the highest level of PMDT services. The MDR-TB national centre of excellence provides services for treatment of complicated DR-TB cases requiring hospitalization.
- Administratively, the *national level (MOHCDGEC-TB and Leprosy Central Unit)* is responsible for policy formulation, strategic planning, resource mobilization, standards formulation, and coordination of national health services.
- The *Regional level*, through RHMTs, is responsible for translation of policies and strategies, quality control monitoring, and evaluation, including supportive supervision of the district level.
- The *Council level*, through CHMTs**,** is responsible for provision and management of primary health care services.

- The *Private sector*, particularly not-for-profit enterprises and nongovernmental organizations (NGOs), provides a substantial amount of health services, especially to the rural population in Tanzania, whereas private-sector for-profit enterprises contribute substantially in providing health services to the urban population. The recent emphasis on public/private partnership in health, presents an opportunity for the private sector to participate in DR-TB treatment and care.

Figure 1. Organization of DR-TB services in Tanzania



Programmatic Management of Drug resistant TB (PMDT) service delivery

In line with Tanzania TB strategic plan, the MOHCDGEC has decided to decentralize DR-TB services, treating patients using mainly ambulatory care rather than through hospitalization. There are two main phases of treating patients: *Intensive and Continuation phases*. The strategic goal of the decentralizing DR-TB services is to initiate DR-TB treatment as close as possible to the patient's home to reduce treatment initiation delays, transmission, mortality, cost of referral and the negative psychosocial impact to patient and family. This strategic goal will be realized by establishing health facility ambulatory sites for management of DR-TB patients and health facility initiating sites, for initiating management of DR-TB patients and referring to ambulatory sites for continuation of treatments. Ambulatory management involves both facility and community-based MDR-TB care:

Facility based ambulatory DR-TB care

- During the *Intensive phase**:***
    - The patient will visit health facility each working day for five days (Mon-Fri) for injections and oral medications.
    - The DOT nurse will administer injections and ensure DOT at the health facility (first dose).
    - Where available, community based health care workers (CBHS) should be used to perform home visits to patients who are unable to come to the clinic for daily injection.
- During the *Continuation phase*, patients may opt to continue with daily clinic visit (facility-based DOT) or switch to weekly clinic visit (home-based DOT) under treatment supporter supervision.

Treatment initiating sites

These will be hospitals/health centres or dispensaries with TB DOT and diagnostic capacity (i.e., DOT/Diagnostic centres) depending on distance from the DR-TB patient's home.

- Baseline and follow-up laboratory investigations to be performed by initiating centres include; sputum AFB, CXR, LFTs, FBP, RFTs, Electrolytes, TSH
- Treatment initiating sites refer to nearby DOT centres after two weeks of treatment (depending on the early discharge criteria); however, they continue to review patients on monthly basis
- Initiating centres participate in regional/zonal cohorts.

Roles of DOT centres

Continue with DR-TB treatment for intensive, continuation phase; refer to initiating sites to monitoring tests on a monthly basis.

Role of Community DR-TB Services

Community TB care interventions covers a wide range of activities and services that contribute to the detection, referral, and treatment support of people with DR-TB. They are conducted outside the premises of formal health facilities in communities and community based structure for example schools, places of worship, congregate settings, markets, factories and homes. Key community stakeholders in addressing DR-TB include but are not limited to:

- DR-TB patients
- Community health workers
- Community based volunteers including Ex DR-TB patients' groups

Owned Resource Persons (CORPs) including traditional healers, traditional birth attendants, local community leaders, religious leaders, and other influential people.

Roles, tasks and responsibilities in DR-TB

DR-TB services in Tanzania are implemented at all levels, each with different roles, tasks, and responsibilities as outlined in table below.

Table1. Levels and their responsibilities.

Level	Roles, Tasks and responsibilities
TLCU	- Policy and guideline development - DR-TB drugs management - M&E; supervision, mentorship - National Cohort and expert review panels.
DR-TB National Centre of Excellence Kibong'oto Infectious Disease Hospital	- Inpatient Care (complicated cases, XDR-TB) - DR-TB supervision/mentorship to initiation and ambulatory sites - Provide mentorship on clinical management and monitoring of all DR-TB patients

	- Facility Cohort and expert review panel - Manage DR-TB commodities and supplies.
Decentralised DR-TB initiating sites	- Initiating DR-TB treatment and ambulatory careDR-TB supervision/mentorship to ambulatory sites - Facility cohort and regional expert review panel - Manage DR-TB commodities and supplies.
Decentralised DR-TB DOT centers	- Continue with ambulatory treatment for DR-TB patients discharged from DR-TB treatment initiating centres - Supervise and monitor community-based treatment supporters - Participate in cohort review organized by DR-TB initiating centres - Manage DR-TB commodities and supplies at the health centre.
Community	**Patient:** Follow treatment **DR-TB DOT treatment supporter:** - Remind and encourage the patient taking their medicines everyday - Supervise/observe the patient take their medicines every day (HB - DOT) - Mark number of daily doses on the patient's identification card after the medicines are taken on daily basis - Remind the patient on sputum collection for monitoring in case of bacteriologically confirmed cases - Inform health care provider of any problems including side effects that may be experienced by the patient - Accompany the patient to the health facility to obtain medicines (or a community health worker

	will need to visit and deliver the medicines) and whenever needed - Inform health care workers in case of travel so that the patient can select another supporter - Report to the health facility in case the patient refuse to take his/her medication for assistance and in case of any health complication **Family members** - Provide emotional, nutritional, spiritual and material support to patients during treatment. - Comfort the patient and avoid discrimination and stigmatization - Accompany patient to health facility - Encourage and motivate the patient to adhere to the medication - Report to the health facility if the patient refuses to take their medication and if there are any health complications - Advise any symptomatic family member to visit a diagnostic health facility for investigation **Roles of CHWs:** - Carry out community based DR-TB activities accordingly to National Guidelines - Empower community members on DR-TB information through effective social mobilization - Identify people with presumptive TB and refer or escort them to health facility - Ensure referral feedback of presumptive case from health facility - Ensure all TB cases are on treatment - Supervise the patient and their treatment supporter during treatment - Collect and provide data to health facilities and CSOs implementing DR-TB

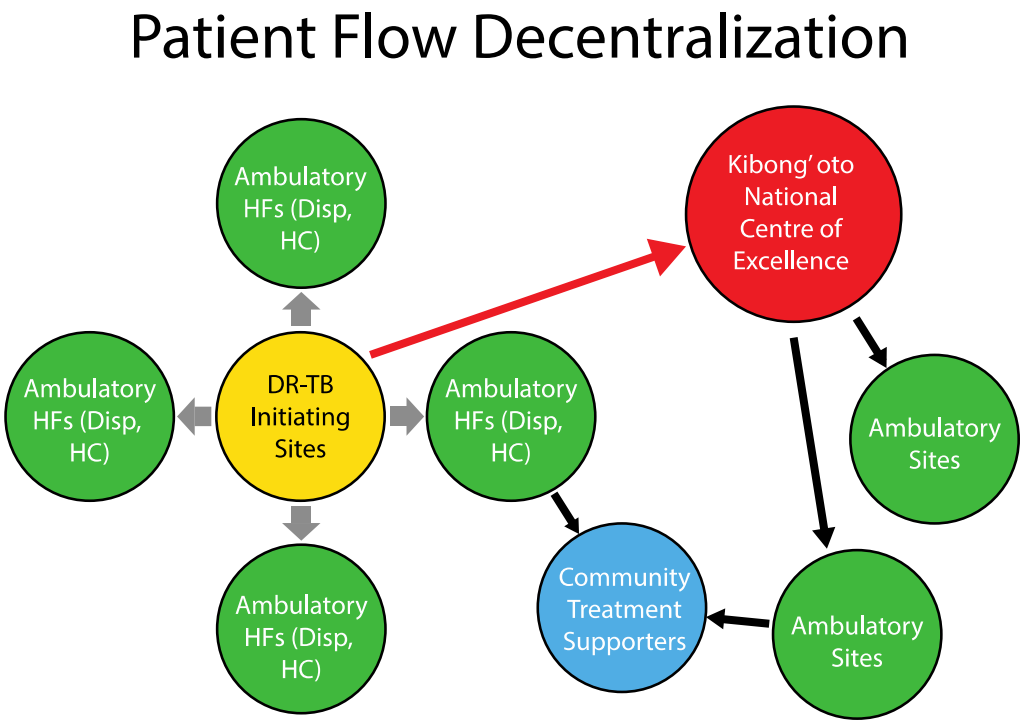
	NOTE: Household screening for DR-TB contact is a role of health care workers. **Roles of Influential People** - Provide spiritual, emotional support and counselling to patients - Sensitize communities about caring for patients at home - Strive to reduce stigma and discrimination in communities and within families **Roles of Traditional birth attendants and Traditional healers** - Be informed about DR-TB - Identify all presumptive DR-TB cases and refer them to community health care worker or health facility for investigation - Work closely with CHWs to seek and make use of updated DR-TB information - Report to CHWs for lost to follow-up patients - Support and advocate for adherence to treatment **Roles of Community groups (Ex DR-TB patients, etc.)** - Provide community with basic information on DR-TB - Sensitize the community on elimination of DR-TB related stigma and discrimination - Serve as role models/share personal experiences of dealing with DR-TB disease and its prevention (testimony) - Promote adherence to DR-TB treatment and others services - Link DR-TB patients with IGA for poverty reduction in the community - Link DR-TB patient to spiritual and psychosocial support

	- Facilitate positive behaviour change practices in the communities (Alcoholics, IDU, etc.) **Roles of CORPS within their communities on DR-TB control activities.** - Be informed about DR-TB care and preventionFind out issues and concerns the community has about DR-TB control services - Lease with other CHWs to mobilize and sensitize the community and Ex DR-TB patients to form groups in a complimentary way and not competing or conflicting with them. - Make DR-TB one of their agenda points in all their meetings/forums. - Dispels rumours and corrects misconceptions related to DR-TB - Promote DR-TB treatment and control in the community - Identify presumptive DR-TB patients and refer them to community health worker - Facilitate initiation of DR-TB treatment to all confirmed DR-TB patients and ensure completion of their treatment - Provide feedback to local authorities about what communities are saying on quality of DR-TB services at the health facility. - Correctly record information on DR-TB presumptive DR-TB cases, patients referred and patients on DR-TB treatment. **Roles of Para-social and Para-legal workers** - Be informed about DR-TB control - Work in partnership with CHWs to provide support and care to DR-TB and provide feedback to the CHWs DR-TB activities

	- Educate and counsel community members on DR-TB Facilitate steps to ensure DR-TB patients who refuse treatment are given treatment according the guidelines and Tanzania puplic health laws. **Roles of Drug Dispensers** - Identify all presumed DR-TB clients and refer them for investigations - Educating presumptive DR-TB cases on signs and symptoms, importance of early diagnosis and risks associated with not complying with the referral - Facilitate referrals of DR-TB contacts - Refer to health facility clients on DR-TB treatment who experience adverse effects - Keep records of all referrals made - Make follow-up of referred presumptive DR-TB clients **Roles of Local government executive leaders** - Provide time for CHWs to talk about DR-TB prevention, care and support during each community meeting - Mobilization of resource for community DR-TB activities - Conduct dialogue meetings with CHWs so as to identify challenges and risk behaviour for key DR-TB affected population - Incorporate community DR-TB care activities into local - plans, budgets and supervise its implementation - Facilitate multi-sectoral collaborations for implementation of community DR-TB care services **Roles of the CSOs**

	- Make DR-TB one of the agenda points in communities - Ensure DR-TB control is effectively integrated into HIV community interventions - Integrate DR-TB activities into community based framework/plans - Plan and implement community based DR-TB activities according to the national guidelines - Mobilize resources for community based DR-TB activities - Share DR-TB control information including data with District medical officer (DMO), District TB &Leprosy coordinator (DTLC) and other stakeholders - Work closely with TB coordinators in respective areas of implementation - Provide onsite mentorship and supervise CHWs - Ensure effective linkages and referrals of people suspected of DR-TB - Facilitate implementation of community DR-TB interventions through strengthening linkage between the communities, - Government and development partners

Figure 2: The flow of patient care from treatment initiation to ambulatory care



In the decentralization of DR-TB diagnosis and care, Kibong'oto remains the centre of excellence mentoring the DR-TB initiating sites. Kibong'oto also functions as a DR-TB initiation site. Patients are diagnosed and put on treatment in a DR-TB initiation site. The DR-TB initiating sites refer patients to the DR-TB ambulatory sites for treatment follow-up. The staff of DR-TB initiating sites mentor the staff at the DR-TB ambulatory sites, DR-TB community treatment supporters give DR-TB patient support at the community level, and the staff at DR-TB ambulatory sites mentor the DR-TB community treatment supporters.

EARLY DISCHARGE CRITERIA TO AMBULATORY CARE FACILITY

A patient can be cleared for early transfer to ambulatory care if the following criteria are met:

At least two consecutive sputum smear negative*

Minimum of two weeks on DR-TB regimen

Clinically stable for ambulatory care, tolerating second-line drugs

Resides within walking distance or has access to transport to a healthcare facility capable of DR-TB care for daily DOT with injections

Identified acceptable, committed and trained DR-TB DOT supporter to assist in care

Stable accommodation and has family or friends who can support.

Adequate access to nutritional support (through program or on own)

**Note: Two sputum specimens at least 8 hours apart will be obtained at baseline and at two weeks of treatment followed by one specimen per month during the Intensive Phase*

Prolonged hospitalization will be indicated if any of the above criteria are not met.

Retreatment DR-TB patients, have returned after lost to follow-up, severe disease, or pre XDR-TB and XDR-TB can be discharged only after they have two consecutive *culture negative* results.

Selected cases for initiation of treatment on ambulatory basis must agree to home isolation (except for clinic visits) and follow home infection control measures until two consecutive smear negative specimens and minimum two weeks on DR-TB regimen.

Transfer to ambulatory care facility

In transferring patients, the responsibilities of Inpatient DR-TB Team are to:

- Notify Regional TB & Leprosy coordinator (RTLC)/District TB &Leprosy ccordinator (DTLC) of potential transfer to verify readiness to accept and coordinate transfer.
- Complete DR-TB referral/transfer form (Annex 10, *Operational Guidelines*)
- Prepare a discharge package to send with patient should include copies of a transfer form, a DR-TB treatment card and a patient identity card. DR-TB drugs

must be transferred to DR-TB ambulatory care centre two weeks prior to patient discharge

- Discharge patients on Fridays (as much as possible) to optimize weekend injection holidays and visit the DR-TB ambulatory care centre on the following Monday to continue with daily injections.

At the DR-TB Ambulatory care centre, the DTLC should:

- Confirm availability of acceptable/committed DR-TB DOT Supporter
- Confirm housing availability and ability of family/friends to support care
- Notify referring hospital DR-TB team and confirm successful transfer once patient has arrived for care at district facility
- Assess second-line drug supply status and coordinate for timely stocking to avoid breaks in treatment

Transportation of patient and patient instructions, require doing the following:

- Patients will be supported with transport back to home if funding is available.
- If the patient has met discharge criteria and remains on appropriate treatment, the risk of disease transmission is low and no surgical mask or special precautions will be required for transport.
- The referring facility should make a prior communication to the receiving facility before the transfer of patient.
- Patient must report to DR-TB treatment centre within first 24 hours of arrival
- He/she must voice good understanding of importance of avoiding breaks in treatment during the transfer and should be given contact numbers to call should a delay or other problems occur while in transit back to home

Indications for re-hospitalization

Occasionally patients will need to be re-admitted to the hospital after they have started on treatment in the community. Decisions should be made on a case-by-case basis if issues are identified that interfere with successful ambulatory care. Re-admission may occur due to the following circumstances:

- Concerns for failure of SLD (new positive cultures, worsening clinical status)
- Management of clinical complications
- Poor adherence to medications

- Adverse/severe drug effects
- Vulnerable patients (e.g., disadvantaged orphans & mentally, socially, or physically handicapped individuals)

Referrals to Specialized care

Referrals for X-ray, computed tommography scans, and surgery; Ear nose & throat (ENT) and other specialty referrals or co-morbidities may be needed on a case-by-case basis. The Case Management Team and/or DR-TB Expert Panel can advise on difficult clinical management decisions where the need for specialty referral is in question.

Follow-up after completion of treatment

Follow-up after the completion of treatment is an important patient management. For one-year after treatment both cured and treatment completed patients require clinical and bacteriological (culture) 6 monthly follow-up evaluations. This is because even after being cured there is still a risk of DR-TB recurring, former DR-TB patients may have other health conditions, including treatment complications, hence:

- Proper referrals for other medical and social services should be put in place prior to discharge from treatment. Refer patients to the nearest clinic for follow-up of chronic medical problems (such as HIV or diabetes) that were managed by the DR-TB team during treatment.
- Patients should be instructed to return to the health facility for evaluation if they experience a recurrence of TB symptoms.

Coordination mechanism for DR-TB services

The NTLP will promote, implement and maintain PMDT services through the coordination of *PMDT Technical Working Group,* the National DR-TB expert review panel (National DR-TB consilium) through weekly video conference learning network (TB ECHO), the enhanced Cohort Review quarterly meetings provide a forum for different stakeholders to share experience, discuss best practice, innovations, policy, guidelines and methods and advise the national TB and Leprosy program on quality PMDT services. This is conducted in accordance with the TB National Strategic Plan V for 2015-2020, on scaling up prevention and control of drug resistant tuberculosis in the country.

CASE FINDING STRATEGIES FOR DR-TB

Preamble

This chapter describes strategies for case finding of patients with either DR-TB, Rifampicin Resistant TB (RR-TB) or XDR-TB. The appropriate strategies for testing for DR-TB in adults and children are outlined and when to use DST for first- and second-line drugs. The symptoms of DR-TB are the same as for drug susceptible TB; in particular, cough for two weeks or more, fever and night sweats, chest and/or back pain, haemoptysis (coughing up blood), weight loss and others. To address this gap, WHO's End TB strategy recommends among its top ten priority indicators for country adaptation that; 1) >90% of new and relapse TB patients get tested using a WHO-recommended rapid tests such as GeneXpert at the time of diagnosis and 2) all new and retreatment TB patients (100%) should have DST results from molecular tests (e.g. Xpert MTB/RIF) as well as conventional phenotypic DST.

These guidelines therefore recommend that there should be universal coverage of DST in health facilities with GeneXpert machines on site and targeted DST for high-risk groups in sites without GeneXpert machines on site.

Universal coverage for DST

All presumptive TB and presumptive DR-TB cases in adults and children must receive the Xpert MTB/RIF test as the initial diagnostic test in sites with GeneXpert machines to ensure universal coverage of DST.

The following diagnostic algorithm will be used:

Diagnosis of DR-TB

DR-TB is diagnosed using the susceptibility test either phenotypic or genotypic methods GeneXpert is the first-line test in the detection of DR-TB in sites with and without GeneXpert machine.

Site with access to onsite GeneXpert testing

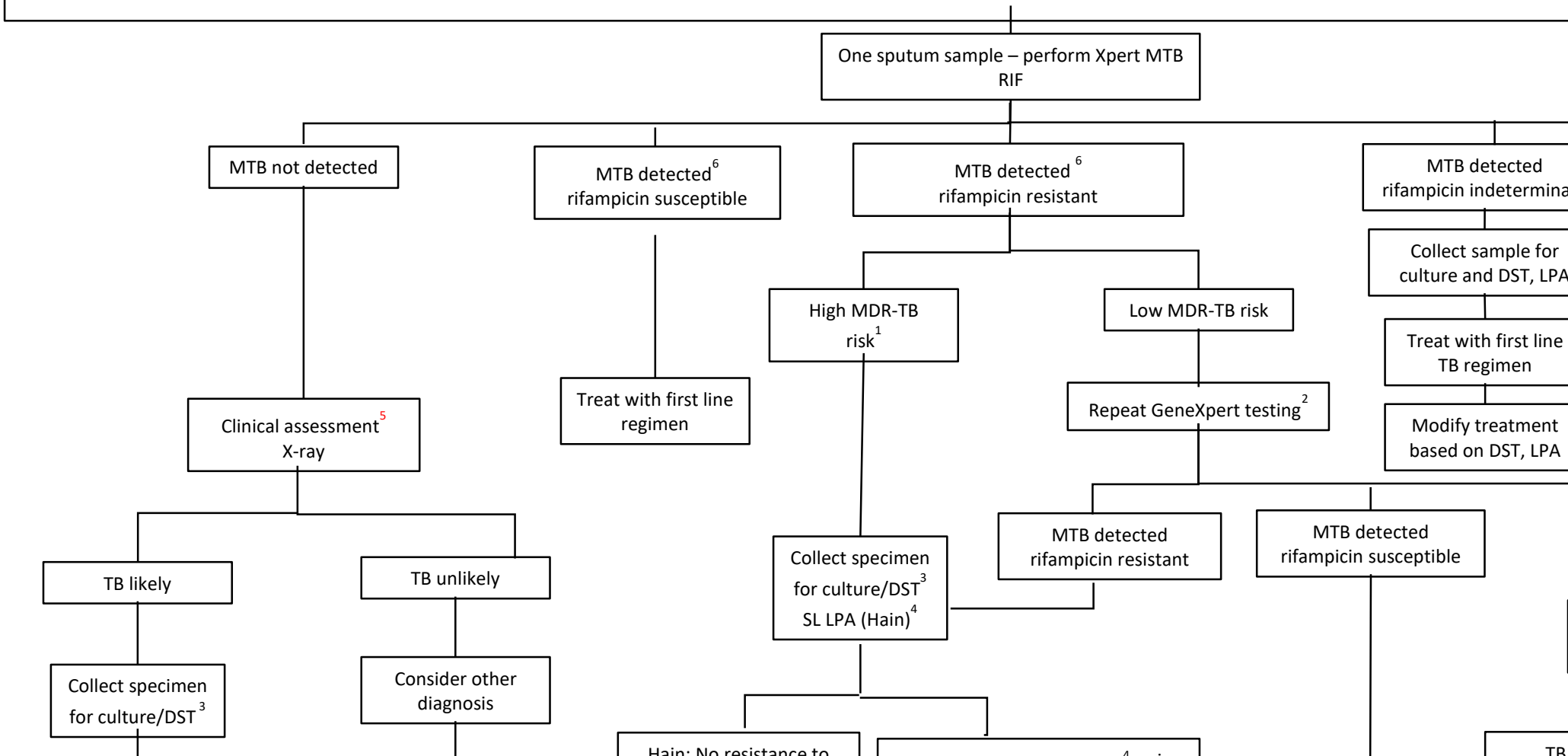
Presumptive TB cases

(All new patients with signs and symptoms suggestive of TB who are adults, children, HIV positive, HIV negative and HIV unkno

AND

Presumptive MDR-TB cases

- ((Failure of retreatment regimens with first line anti-TB drugs (SHREZ), Close contact of a known drug resistant TB case, Failure of new TB regimens (HREZ), Patients two or three of a first-line anti TB drug regimen, Relapse and return after loss to follow-up, without recent treatment failure, Vulnerable groups in congregate setti



High risk groups for targeted DST

In sites without GeneXpert machines, specimens from the following high-risk groups should be targeted for DST

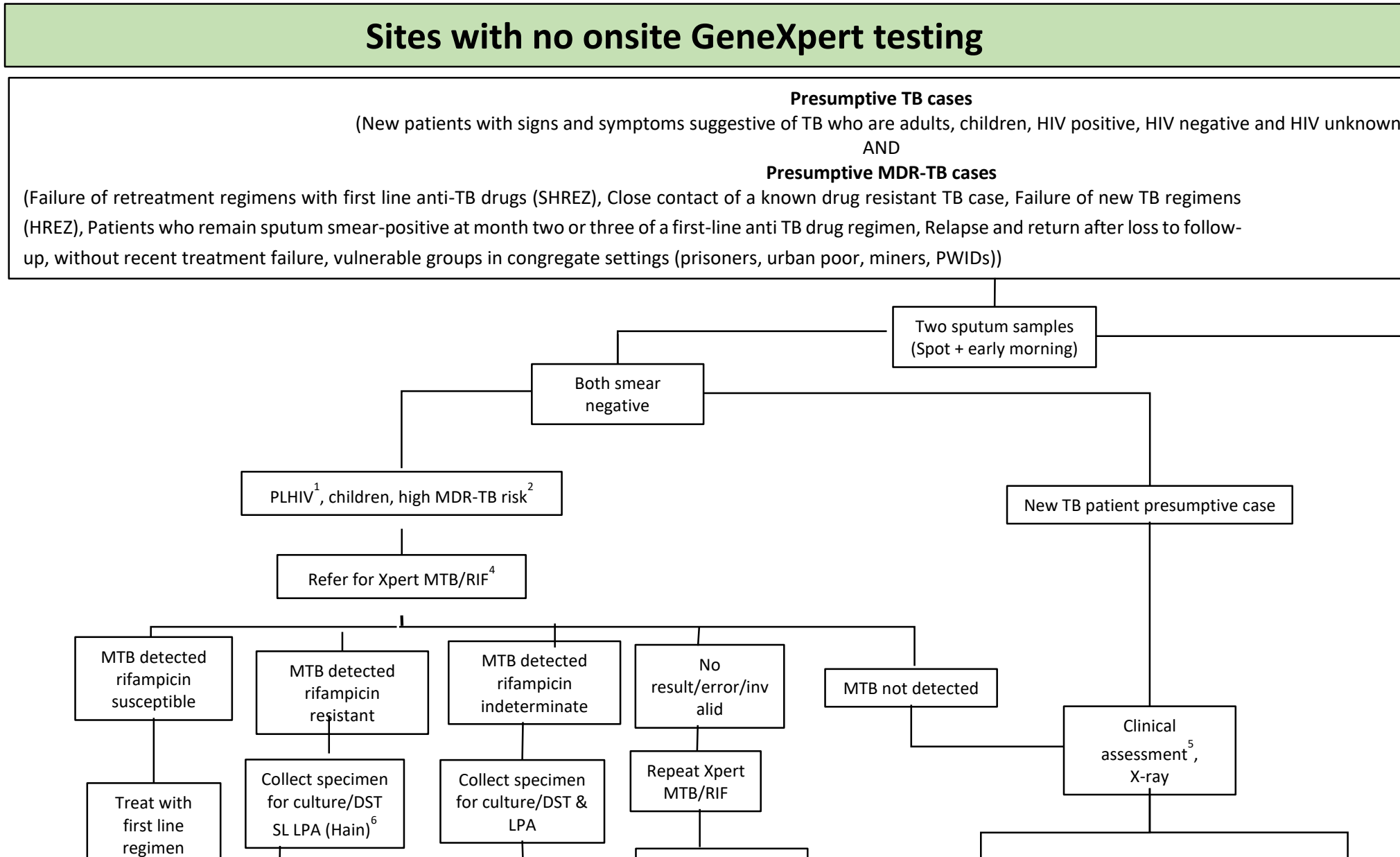
High-risk groups

- Treatment failure after using first-line anti-TB medicines
- Close contact of a known DR-TB case
- Patients who remain sputum smear-positive at month two or three of a first-line anti TB drug regimen
- Relapse and return after loss to follow-up, without recent treatment failure
- Healthcare workers presenting with TB symptoms.
- Vulnerable groups in congregate settings (prisoners, urban poor, miners,PWIDs)

Refer sputum samples from above named high-risk groups for Xpert MTB/RIF testing. The samples must be of good quality and meet the criteria for Xpert MTB/RIF testing, i.e. a sputum sample should contain no particles and be between 2-4ml to allow repeat Xpert MTB/RIF testing or referral if needed.

The following algorithm will be used in sites without GeneXpert machines

Figure 3b. Algorithm for Sites without GeneXpert



Xpert MTB/RIF only detects rifampicin resistance, START patients on DR-TB regimen BUT refer specimens with rifampicin resistance to Zonal TB Referral Laboratories for confirmation with conventional culture and DST. A list of zonal TB culture laboratories and the available testing is outlined below.

Table 2: Zonal TB laboratories and available test

Culture facility	Location	Available TB testing
Central TB Reference Laboratory	Dar es Salaam	Smear microscopy, Xpert MTB/RIF test, LPA, TB culture (solid & liquid), DST (1st & 2nd line)
Kibong'oto National MDR Laboratory	Kilimanjaro	Smear microscopy, Xpert MTB/RIF test, LPA, TB culture (solid)
Dodoma Regional Referral Laboratory	Dodoma	Smear microscopy, Xpert MTB/RIF test, TB culture (solid)
Mbeya Referral Laboratory	Mbeya	Smear microscopy, Xpert MTB/RIF test, LPA, TB culture (solid & liquid), DST (1st line)
Bugando Laboratory	Mwanza	Smear microscopy, Xpert MTB/RIF test, TB culture (solid)
Pemba Public Health Laboratory	Pemba	Smear microscopy, TB culture (solid)

Presumptive DR-TB when rapid genotypic DST is not available

When rapid DST is not available, the following selected groups of patients should be discussed in the DR-TB consilium where a presumptive diagnosis of DR-TB can be reached, and the patients can be started on an empirical DR-TB regimen.

The DR-TB regimen should be adjusted when conventional phenotypic DST results become available

The groups eligible for the presumptive diagnosis of DR-TB include:

- Failures of treatment regimens with first-line drugs (chronic excretors).
- Close contacts of DR-TB cases that are symptomatic.

Diagnosing XDR-TB

All patients diagnosed with DR-TB should be tested for XDR-TB with second-line DST every six months while on DR-TB treatment.

The high-risk factors for XDR-TB are:

1 Failure of an DR-TB treatment regimen, which contains second-line drugs including an injectable agent and a fluoroquinolone;
2 DR-TB cases who relapse or return after loss to follow-up
3 Close contact with an individual with documented XDR-TB or with an individual for whom treatment with a regimen including second-line drugs is failing or has failed.

All individuals presumed to have XDR-TB should have conventional phenotypic DST of first-line drugs isoniazid, rifampicin and second-line injectable agents (kanamycin and/or capreomycin) and a fluoroquinolone (Ofloxacin, Levofloxacin, and/or Moxifloxacin)

Case-finding in paediatric patients

Paediatric cases require additional diagnostic testing since most young children will not be able to produce adequate sputum specimens upon request.

Sputum induction with nebulised hypertonic saline may facilitate collection of tracheobronchial secretions in children who have a dry cough or no cough.

However, nebulisation may be unsuccessful in young children hence gastric aspiration
Should be used for collecting specimens for Xpert MTB/RIF or Culture/DST.

In cases where the anatomic location of disease includes sites outside the pulmonary parenchyma, fine needle aspiration or biopsy should be considered.

Multidrug-resistant tuberculosis should be suspected in the following situations:

- A child who is a close contact of an infectious MDR-TB case.
- A child who is a close contact of a TB treatment failure or someone lost to follow-up.
- A child with proven TB who is still bacteriologically positive after five months of appropriate treatment with first-line anti-TB medications. (Treatment failure).

DR-TB should be suspected under these circumstances, but confirming the diagnosis depends on Xpert MTB/RIF and Culture/DST results.

A review panel expert on DR-TB makes diagnosis of MDR-TB in children based on history, physical examination and laboratory. Symptomatic smear and culture-negative children, who are known household contacts of patients with DR-TB should be classified as ***probable*** DR-TB cases and started on DR-TB treatment regimens according to the DST results of the adult contact. Children diagnosed with DR-TB should be reported to the DTLC for record and referred to DR-TB treatment centres for further management.

DR-TB case finding among extra-pulmonary TB patients

Drug-resistant extra-pulmonary TB (EPTB) can be detected using Xpert MTB/RIF or conventional culture and DST.

These guidelines are in alignment with the 2013 WHO updated policy guidance on use of Xpert MTB/RIF, issuing the following recommendations for the use of Xpert MTB/RIF in detection of EPTB:

1 Xpert MTB/RIF should be used in preference to conventional microscopy and culture as the initial diagnostic test in testing cerebrospinal fluid specimens from patients presumed to have TB meningitis
2 Xpert MTB/RIF may be used as a replacement test for usual practice (including conventional microscopy, culture, and/or histopathology) for testing of specific non-respiratory specimens (lymph nodes and other tissues) from patients presumed to have EPTB

DR-TB case finding in HIV-infected patients

The diagnosis of TB in HIV-infected people is complex and may be confused with other pulmonary or systemic infections. PLHIV are more likely than HIV-negative persons to have smear-negative TB or EPTB.

It is recommended that Xpert MTB/RIF testing is the primary diagnostic test in the following individuals:

- All adults and children living with HIV who have signs or symptoms of TB.
- Presumptive TB cases with unknown HIV status presenting with strong clinical evidence of HIV infection.

DR-TB case finding in the Community

Currently, the health system is detecting only 36% of the estimated cases, with the remaining 64% going undiagnosed in the community. One of the challenges for TB control in the country is that a number of TB cases are not reached by the current health system and program interventions. Other challenges include inadequate community awareness on TB and its control measures, the long distances to TB diagnostic facilities, and ultimately delayed medical seeking behaviour. To address the identified challenges, the MoHCDGEC through the National TB and Leprosy Program (NTLP) adapted the ENGAGE TB approach in order to sensitize and encourage a wider range of stakeholders to involve themselves in community-based activities.

Key recommendations

Where access to Xpert MTB/RIF machine is guaranteed all presumptive TB cases should have universal DST coverage

In areas with limited access to Xpert MTB/RIF machines, high-risk patients for DR-TB should have their specimen referred for drug resistance screening.

All RIF resistance detected from rapid DST methods should have a confirmatory DST done.

Patients at increased risk of XDR-TB should be screened for resistance with conventional phenotypic DST for isoniazid, rifampicin, second-line injectable agents and a fluoroquinolone.

LABORATORY TESTING FOR DR-TB

PREAMBLE

Diagnosis of DR-TB requires that *Mycobacterium tuberculosis* be detected and resistance to anti-TB drugs determined. This can be done by:

- Isolating the bacteria by culture.
- Identifying it as belonging to the *M. tuberculosis* complex (MTBc),
- And conducting drug susceptibility testing (DST) using solid or liquid media
- By performing Xpert/MTBRIF and second-line LPA molecular test to detect TB DNA and mutations associated with resistance.

Essential laboratory services and infrastructure

Optimal management of DR-TB requires both mycobacteriology and clinical laboratory services. Culture capacity remains essential for monitoring DR-TB patients' response to therapy. The capacity to reliably identify *M. tuberculosis* and detect resistance to rifampicin and isoniazid remains a minimum requirement in any DR-TB program and along with mycobacteriological examinations; Clinical laboratory services should provide basic haematology, biochemistry, serology and urine analysis, required for adequate evaluation of patients and treatment monitoring.

In addition to diagnostic and clinical services, laboratories supporting DR-TB control program have an important role in the surveillance of drug resistance patterns, which is essential for providing information on the magnitude and trends in drug resistance, for developing appropriate treatment modalities, and for evaluating the impact of control program interventions.

Supranational Reference Laboratory (SRL) Network. A collaboration agreement with an SRL is therefore strongly recommended for DR-TB control programs also in order to establish and maintain quality-assured DST.

Organization of the TB laboratory network

The organization and operation of Level I and II laboratories are well established at peripheral and zonal TB laboratories. Different levels of biosafety precautions are needed depending on the type of procedure being performed, the risk of generating infectious aerosols, and the concentration of TB bacilli in the aerosols. Level III deals with most hazardous procedures and those related to manipulating positive cultures for isolation and identification of *Mycobacterium tuberculosis*.

Functions and responsibilities of the different levels of TB laboratory services.

Level I: The peripheral laboratory

• Receipt of specimens

• Preparation and staining of smears for Ziehl-Neelsen or LED fluorescence microscopy

• Xpert MTB/RIF for use as the initial diagnostic test in individuals presumptive of DR-TB

• Recording and reporting of results

• Maintenance of laboratory registers

• Cleaning and maintenance of equipment

• Management of reagents and laboratory supplies

• Internal quality control

• Participation in an external quality assessment program such as blinded re-checking or panel testing

Level II: The intermediate (often regional) laboratory

- All the functions of a Level I laboratory
- Line-probe assays (LPA) for direct detection of resistance mutations in acid-fast bacilli (AFB) smear-positive processed sputum samples
- Digestion and decontamination of specimens and inoculation into cultures
- Isolation by culture and identification of *M. tuberculosis*
- Training of microscopists and supervision of peripheral-level staff with respect to microscopy and Xpert MTB/RIF assay
- Preparation and distribution of reagents for microscopy to peripheral laboratories
- Proficiency testing and quality improvement of microscopy at peripheral laboratories.

Level III: The central (often national) laboratory

- All the functions of Level I and II laboratories
- Close collaboration with the central level of the national TB control program
- Provides strategic oversight for the management, quality and efficient use of the TB laboratory network balanced with all available TB diagnostics
- DST of *M. tuberculosis* isolates (first- and second-line anti-TB drugs)
- Molecular tests for TB and rifampicin resistance determination (alone or in combination with isoniazid) from positive cultures and identification of mycobacteria other than *M. tuberculosis*
- Organization of a specialist to periodically perform the technical control of and repair services for laboratory equipment
- Updating and dissemination of laboratory manuals, including guidelines on diagnostic methods, on care and maintenance of equipment, on training and supervision, and on quality assurance
- Distribution of reagents and consumables when requested by intermediate or peripheral TB laboratories (optional)
- Supervision of intermediate laboratories regarding bacteriological methods and their implementation, as well as their performance monitoring activities of the peripheral laboratories
- Quality assurance of all procedures performed at intermediate laboratories including microscopy, culture and DST
- Training of intermediate-level laboratory staff
- Organization of anti-TB drug resistance surveillance
- Operational and applied research relating to the laboratory network, coordinated with the requirements and needs of national TB control programs. Note: Xpert MTB/RIF should also be available at the central laboratory for screening of MDR-TB suspects so that the laboratory can become sufficiently competent with the technology to provide support for its use in Level I and II laboratories, and to decrease the load of full diagnostic DST needed in MDR-TB suspects.

Specimen collection and transportation

Good quality specimens are essential for proper laboratory diagnosis of TB and DR-TB. However, collecting sputum, the most frequent specimen for TB testing, represents a significant hazard as coughing produces potentially infectious aerosols.

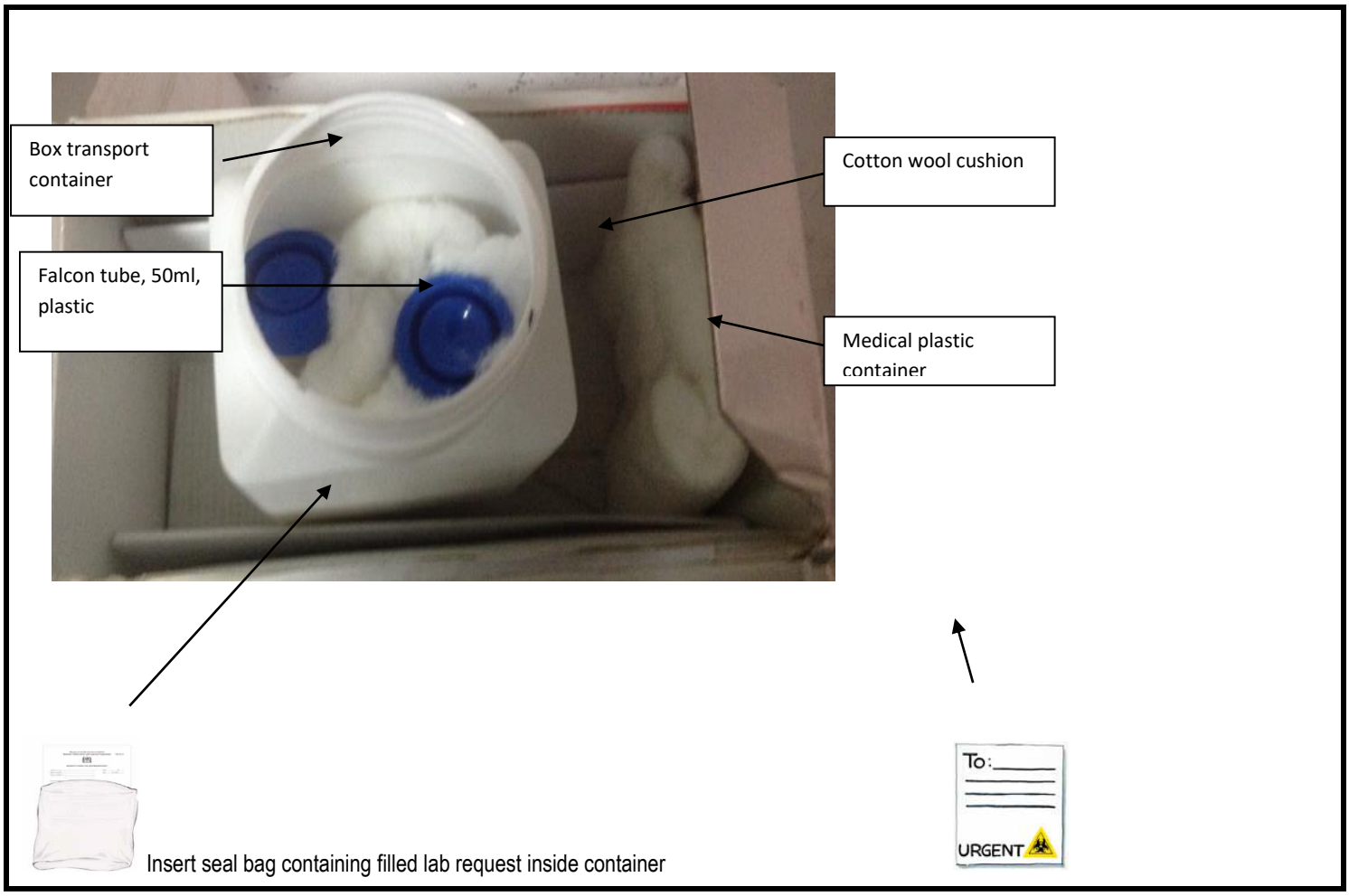
Therefore, the following specific measures must be taken to minimize exposure when sputum specimens are collected:

- Specimens should be collected in open air where infectious droplets are rapidly diluted and UV rays can rapidly inactivate TB bacilli.
- Sputum specimens should not be collected in laboratories, toilets, waiting rooms, reception rooms, or any other enclosed space not specifically conceived, organized, and equipped as a sputum collection area.

- Collecting a good specimen in a safe manner also requires that staff are trained to provide the patient with effective instructions as well as with adequate material and well-documented procedures, using wide-mouthed containers that are sterile, clear, and leak-proof (with screw caps).
- Specimen containers should be promptly transported to the laboratory using appropriate packaging for safe transport of infectious materials, i.e. surrounded by absorbent material, protected by secondary packaging and then placed in a shock-resistant outer packaging labelled according to national and international regulations for the transport of infectious materials.

Specimens should be submitted to the laboratory and processed for culture within 24 hours of collection. If transport delays are anticipated, specimens should be kept refrigerated at 4°C and transported to the laboratory in a cool box. In Tanzania the standard transit time for specimen transportation is less than 96 hours.

Figure 4. Container for collection, packing and transportation of sputum specimen for TB culture and DST



Mycobacteriology laboratory services for drug resistant TB programs

Microscopy

Smear microscopy is a low-cost and frontline tool for TB (but not DR-TB) diagnosis.

The introduction of light emitting diode (LED) fluorescence microscopy is recommended by WHO and has increased test sensitivity without increasing overall costs, in fact it has reduced the turnaround time required, allowing the screening of a larger number of slides at the peripheral level.

The main purposes of microscopy for DR-TB are:

- To assess initial bacterial load
- Specimen triage to different diagnostic algorithms.

Monitor response to therapy and to confirm the presence of AFB rather than contaminants in the culture media, before proceeding to rapid identification tests.

Microscopy for AFB cannot distinguish viable from non-viable organisms nor differentiate between drug-susceptible and drug-resistant *M. tuberculosis* bacteria, or between different species of mycobacteria. This is useful in DR-TB treatment monitoring.

Samples showing AFB by smear microscopy but negative to culture suggest that bacilli are not viable (caution is nonetheless warranted for these patients to be considered as possibly infectious).

Samples showing AFB by smear microscopy but negative by molecular tests are likely to harbour non-tuberculous mycobacteria (NTM). Among persons at risk of DR-TB, WHO recommends the use of Xpert MTB/RIF® as the initial diagnostic test rather than microscopy, culture and DST.

Xpert MTB/RIF
An automated molecular diagnostic assay that uses real-time PCR to identify *M. tuberculosis* complex DNA and the mutations associated with rifampicin resistance directly from sputum specimens, in less than two hours.

Line probe assays
Molecular LPAs allow rapid detection of resistance to rifampicin (alone or in combination with isoniazid) and were endorsed by WHO in 2008, LPA is a high through put technology, typically allowing for 12 specimens to be processed simultaneously and enabling several batches of tests to be done per day.

LPAs are suitable for use at the zonal or national reference laboratory level, with potential for decentralization to regional level if the appropriate infrastructure can be ensured (three separate rooms are required).

Culture for *M. tuberculosis*
In Tanzania sputum culture for isolation of mycobacterium performed on solid media [Lowenstein Jensen (LJ) medium] the current reference method for bacteriological confirmation of TB. However new technologies have been adopted by the country for TB case detection, including liquid culture system using Mycobacterium growth indicator tube (MGIT) which allows rapid growth and detection of *M. tuberculosis*.

Although the vast majority of mycobacterial isolates will be *M. tuberculosis*, mycobacteria other than tuberculosis (MOTT) can occur especially in patients living with HIV (PLHIV). MOTTs are inherently resistant to the commonly used first-line anti TB drugs and may clinically present as MDR-TB and may be mistakenly regarded as treatment

failure. In the laboratory, unless the species is confirmed as *M. tuberculosis*, mycobacterial isolates appearing phenotypically resistant to first-line drugs may represent infection with MOTT, not DR-TB.

Therefore, it is recommended that laboratories performing TB cultures conduct Paranitrobenzoic acid (PNB), niacin and nitrate tests (both positive in most *M. tuberculosis* strains) so as differentiate MOTTs from drug resistant MTB strains. Specimens for culture should be collected in the morning in a Falcon tube.

Identification of *M. tuberculosis.*

Laboratories supporting DR-TB control programs should be able to conduct identification tests for *M. tuberculosis* complex that follow international guidelines. There are a number of ways to identify *M. tuberculosis*: the tests can be phenotypic (the most common being the nitrate reduction and niacin tests), immune-chromatographic, or genotypic (which analyses species-specific DNA sequences).

Drug susceptibility testing

DST plays an important role in most strategies to identify and treat patients with or at high-risk of DR-TB.

Phenotypic DST (conventional DST)
Phenotypic testing determines if an isolate is resistant to an anti-TB drug by evaluating growth (or metabolic activity) in the presence of the drug.

Phenotypic methods allow the detection of drug resistance and can be performed as solid media or in liquid media. The phenotypic DST gives a wide range of drug susceptibility pattern.

Genotypic DST
Genotypic testing detects mutations in the TB genome associated with specific drug resistance. (Note: genotypic testing is also used to identify *M. tuberculosis* by detecting the presence of TB-specific mycobacterial DNA).

Molecular tests allow the detection of rifampicin resistance (alone or in combination with isoniazid) using novel technologies. LPA and the Xpert MTB/RIF are the recommended molecular tests in Tanzania.

Genotype MTBDR*s*/LPA for the detection of resistance to fluoroquinolones and second-line injectable drugs is used to detect pre-XDR and XMDR-TB for eligibility to the short DR-TB regime.

Limitations of DST
The reliability of DST (performed under optimal circumstances) varies with the drug tested.

• First-line DST

- Most reliable for rifampicin and isoniazid.
- Less reliable and reproducible for streptomycin, ethambutol and pyrazinamide (pyrazinamide testing can only be performed on liquid media after appropriate pH adjustment).

• Second-line DST

- Has good reliability and reproducibility for second-line injectable drugs (amikacin, kanamycin, and capreomycin) and fluoroquinolones.
- Data on the reproducibility and reliability of DST for the other second-line drugs are limited, and for several of them methods have not been established or standardized; in addition, data correlating DST results to the clinical outcome are still insufficient.

Testing and reporting: turnaround time

Growth detection and identification of *M. tuberculosis* (Sputum culture) may take 3–8 weeks on solid media and1-3 weeks in liquid media.

DST of a *M. tuberculosis* isolate takes an additional 2-4 weeks in solid media and 7-10 days in liquid media. Molecular test results can be available in less than two hours with Xpert MTB/RIF), and within two days with LPA. To ensure rapid diagnosis of *M. tuberculosis* and DR-TB, standard turnaround times, which should be strictly followed.

Table 3. The following turnaround times for different TB diagnostic tests available in Tanzania are recommended

Procedurals for smear, culture and DST results	Solid culture (LJ)	Liquid culture (MIGIT) MGIT	Hain test (Line Probe Assays)	Gene Xpert (Molecular technique)
Processing of collected sputum	Within 1 working day after collection	Within 1 working day after collection	Within 1 working day after collection	Within 1 working day after collection
AFB smear reports reaching clinician	Within 2 working days after specimen receipt in the laboratory	Within 2 working days after specimen receipt in the laboratory	Within 2 working days after specimen receipt in the laboratory	Within 2 working days after specimen receipt in the laboratory
Positive culture identification	Within 8 weeks of specimen collection using solid media	Within 17-21 days of specimen collection	Within 5 hours after primary isolation	Within 2 hours after primary isolation

		using broth media		
Isolate definitively identified as *M. tuberculosis* *	Within 14 weeks of specimen collection	Within 23 days of specimen collection	Within 5 hours after primary isolation	Within 2 hours after primary isolation
Drug susceptibility test results for Isoniazid, Rifampicin, Streptomycin and Ethambutol (HRSE) reported to the clinician	Within 14 weeks of specimen collection	Within 4 weeks of specimen collection	Within 48 hours of specimen collection	Within 48 hours of specimen collection

Laboratory biosafety

The relative hazards of TB as infectious microorganisms handled in the laboratory are no longer classified by WHO according to their risk of causing human disease, the potential for laboratory spread, and whether effective treatment and prevention measures are available ("risk group classification") but are now based on the assessment of the risks associated with the different technical procedures performed in the different types of TB laboratories ("risk assessment").

For laboratories conducting TB testing, the most important risk is the generation of infectious aerosols. Infection with *M. tuberculosis* occurs primarily by the inhalation of infectious aerosols (although it can also occur by direct inoculation or by ingestion).

Therefore, depending mainly on the probability of infectious aerosols being generated and on the number of bacteria in the material handled, the relative risk of laboratory-acquired TB infection varies according to the procedures performed in the laboratory, with the lowest risk being associated with direct smear and Xpert TB/RIF preparation and highest risk being associated to processing of liquid cultures and performing DST. Published guidelines for safely working with samples containing *M. tuberculosis* bacteria should be rigorously followed and expert engineering consultation sought when establishing laboratory facilities for DST.

Safety in the TB laboratory requires essential measures be in place and enforced:

- Appropriate layout of the laboratory in line with the techniques implemented: facilities (e.g. containment rooms) and engineering controls (e.g., biosafety cabinets, aerosol-containment centrifuges, ventilation systems providing directional airflow) that are well designed and functioning as designed to prevent or

contain aerosols. Effective and specific administrative controls should be enforced (e.g. standard operating procedures, waste management procedures, accident management plans, health monitoring of the staff, etc.).

- Proper practices and procedures for general laboratory safety (including physical, electrical and chemical safety) must be in place: workers should be technically proficient in good microbiological practices and in the use of safety equipment, and should be supervised by experienced laboratory professionals.

- Personal protective equipment appropriate for the techniques being performed should be used.

TB containment laboratories (high-risk TB laboratories) should have the minimum design features necessary to manipulate TB cultures safely and to perform phenotypic DST as well as LPA testing. They require the strengthening of laboratory operations and safety programs, specifically those related to laboratory design, the use of specialized equipment to prevent or contain aerosols, and health surveillance of laboratory staff.

Health and medical surveillance of laboratory personnel handling specimens or cultures containing tubercle bacilli is strongly recommended. Surveillance should include a detailed medical history, targeted baseline health assessment, monitoring of respiratory signs and symptoms, and appropriate plan for proactive medical investigations when indicated. Routine BCG vaccination is not recommended as a means of preventing DR-TB in laboratory workers. Laboratory workers who choose to disclose their status as HIV-infected, should be offered safer work responsibilities and should be discouraged from working with DR-TB specimens. Pregnant women should be reassigned until after childbirth and lactation.

Quality assurance

A diagnosis of DR-TB has profound implications for the individual patient; therefore, accuracy of the laboratory diagnosis is crucial and a comprehensive laboratory quality assurance (QA) program must be in place to ensure accuracy, reliability and reproducibility of DST results.

Internal quality control (IQC) and external quality assessment (EQA) procedures and monitoring of performance indicators should be an integral part of laboratory operations.

Recommendation: Procedures for quality assessment of microscopy, culture and DST (phenotypic and genotypic) should be developed and implemented.

To help in ensuring the quality of laboratory services and the validation of DST results, central reference laboratories supporting DR-TB programs should also establish formal links with an SRL for external quality assessment and technical assistance, which should include:

I. An initial assessment to evaluate the laboratory facilities and operations, with corrective action as required.
II. Proficiency testing with an adequate number of coded isolates.

III. Periodic visits and re-checking of isolates obtained within the DR-TB program.

Proficiency testing by the SRL involves regular distribution of panels of coded *M. tuberculosis* strains with predefined drug resistance profiles. As a minimum performance indicator, laboratories should correctly identify resistance to isoniazid and to rifampicin in more than 95% of samples, and in two out of three recent rounds of panels. Panels including isolates with second-line drug resistance are also available through the SRL Network, as well as EQA panels for molecular methods.

Infection control and biosafety in the laboratory

The relative hazards of infective microorganisms handled in the laboratory are classified by WHO according to their risk of causing human disease, the potential for laboratory spread and whether effective treatment and prevention measures are available. *M. tuberculosis* is classified by WHO as a Risk Group 3 laboratory pathogen.

Mycobacteriological culture and DST generate high-concentration aerosols requiring biosafety Level 3 containment precautions. Laboratory standards require essential measures to be in place and enforced:

- Appropriate and specific administrative controls (including good laboratory practice, standard operating procedures and accident management plans);
- Appropriate engineering controls functioning adequately as designed;
- Personal protective equipment appropriate for the tasks being performed;
- Proper waste management procedures;
- Proper procedures for general laboratory safety (including physical, electrical and chemical safety).

Guidelines on biosafety Level 3 precautions should be rigorously followed. Laboratory managers shall ensure that health and medical surveillance of laboratory personnel involved in mycobacteriological culture and DST is done. Surveillance must include a detailed medical history, targeted baseline health assessment, monitoring of respiratory signs and symptoms, and a proactive plan for appropriate medical investigations when indicated.

The use of a safety cabinet may not be necessary for laboratories that only perform direct sputum examination, e.g., most peripheral laboratories. However, for laboratories performing culture and DST the minimum level of containment requires a class II safety cabinet with a double/single filter.

N95 respirators should always be used by the laboratory technicians when handling known or suspected MDR-TB specimens.

Disinfectants
The following disinfectants are recommended for disinfection procedures in a TB laboratory:

Glutaraldehydes 2%,5% phenol,70% alcohol,Sporicidin 2%,Chlorhexidine 4%, Centrimide 5%,Hydrogen peroxide 6% and Chlorine 0.5%.

For the optimal performance of these disinfectants, users should always follow the manufacturer's instructions and ensure that the agents have not expired and are used according to the established standard operating procedures.

Laboratory waste management

In Tanzania, laboratory waste, including used sputum collection containers, cultures and devices used to transfer, inoculate and mix cultures, should be managed as follows, depending on availability: Properly handled by autoclaving at a temperature of 121^{o}C at 1 bar for at least 30 minutes; or burnt in an incinerator; or discarded in a deep pit at least 1.5 meters deep; or disinfected overnight in a solution of sodium hypochlorite in concentrated form and then discarded with hazardous health care waste; or If none of the above options can be ensured, packed in a specific bag that should be sealed and directly discarded with the hazardous health care waste.Highly infectious waste from TB isolation wards must always be incinerated on-site

TREATMENT OF DR-TB

Preamble

The treatment of DR-TB involves standardized and individualized approaches. However, as with drug-susceptible TB, treatment for DR-TB consists of two different phases, the intensive phase of treatment when a patient takes at least five effective drugs, including an injectable, and the continuation phase when the patient takes at least three effective drugs.

Once a patient has been confirmed as having DR-TB, it is important that the patient take all their medications correctly to attain the best treatment outcome and minimize the risk of relapse, failure, and death. The treatment of DR-TB in many of these patients represents the last opportunity for them to be cured.

Health care workers and treatment supporters must take an active role to ensure that every patient takes the recommended drugs, in the right combinations, on the correct schedule, for the appropriate duration using the directly observed treatment (DOT) strategy. Supervised treatment for DR-TB patients is necessary throughout the entire period of treatment.

The NTLP has designed its DR-TB treatment strategy based on DST of strain isolates from patients, or close contacts with DR-TB, previous use of the drug in the patient, and the frequency of its use or documented background data from the drug resistance surveillance survey (DRS) conducted in the country.

Baseline procedures and investigations for confirmed DR-TB case

The required baseline pre-treatment investigations and procedures of any DR-TB patient include:

- Individual patient risk assessment to determine treatment eligibility
- Informing the patient and family about the disease, counselling on the treatment options and expectations about DR-TB and its treatment
- Taking a detailed medical history
- Performing a physical examination, including weight and height measurement and document in the patient's DR-TB Treatment Card
- Conducting Provider Initiated Testing and Counselling (PITC), if the patient doesn't have a documented positive HIV test
- Educating on cough hygiene
- Performing blood test (serum creatinine, serum potassium, thyroid stimulating hormone, liver enzymes, blood sugar and a pregnancy test among women of reproductive age)
- Performing a chest radiograph
- Performing electrocardiogram (ECG)
- Audiometry
- Sputum smear, culture and second-line Line probe assay DST
- Visual acuity test and colour vision
- Giving the patient a brief orientation on the drugs that will be taken and the potential adverse reactions associated with the drugs used.

Definition of Patient's registration Group

Every confirmed DR-TB case should be grouped and recorded in the DR-TB treatment card as follows:

New: A patient who has received no or less than one month of anti-TB treatment.

Relapse: A patient who was previously treated for TB and whose most recent treatment outcome was cured or treatment completed, and who is subsequently diagnosed with are current episode of TB.

Treatment after loss to follow-up: A patient who had previously been treated for TB and was declared lost to follow-up at the end of the most recent course of treatment. (This was previously known as "Treatment after default".).

After failure of first treatment with first-line drugs: A patient who has received first-line drug treatment for TB and in whom treatment has failed.

After failure of retreatment regimen with first-line drugs: A previously treated TB patient who has received a retreatment regimen with first-line drugs and in whom the retreatment has failed.

After failure of treatment with second-line drugs: A previously treated DR-TB patient who has received treatment with second-line drugs and in whom the treatment has failed.

Other previously treated patients: A previously treated TB patient whose outcome after the most recent course of treatment is unknown or undocumented

Transfer in: DR-TB patients who have been transferred out of one facility should continue DR-TB treatment in another center. Their outcomes should be reported to the transferring unit so that it can report their outcomes in the cohort in which they originally started DR-TB treatment.

Note: Transfer in is not a patient registration group but should be documented in the DR-TB register in the remarks section.

Treatment of RR-TB/MDR-TB, RR-/MDR-TB with additional resistance to fluoroquinolones and/or second-line injectables (i.e. "pre-XDR-TB" and XDR-TB)

Overview of Second-line Drugs

The classes of anti-TB drugs have traditionally been divided into first- and second-line drugs, with isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin being the primary first-line drugs. The TB drugs used to treat DR-TB have recently been re-classified by WHO into a group system based on efficacy, which is described in Table 4.

Table 4. Grouping of anti-TB agents used to treat DR-TB [a]

Group		**Drugs**
Group A – Fluoroquinolones [b]		Levofloxacin (Lfx), Moxifloxacin (Mfx), Gatifloxacin (Gfx)*
Group B – Injectable agents		Kanamycin (Km), Amikacin (Am) *; Capreomycin (Cm), [Streptomycin (S)] [c]
Group C – Other core second-line agents [b]		Ethionamide (Eto)[d], Protionamide (Pto)[d], Cycloserine (Cs)[d], Terizidone (Trd) *, Linezolid (Lzd), Clofazimine (Cfz)
Group D - Add-on agents (not part of the core MDR-TB regimen)	D1	Pyrazinamide (Z) Ethambutol (E) High-dose isoniazid (H^h) [e]
	D2	Bedaquiline (Bdq) Delamanid (Dlm)
	D3	p-aminosalicylic acid (PAS) Imipenem-cilastatin (Ipm) * Meropenem (Mpm) * Amoxicillin-clavulanate (Amx-Cl)

		Thioacetazone (T) * (HIV status must be determined if T is considered to be used)

[a] *This regrouping is intended to guide the design of the longer individualized treatment regimens. The composition of the recommended shorter RR-/MDR-TB regimen is standardized.*

[b] *Medicines in Groups A and C are shown in decreasing order of usual preference*

[c] *Streptomycin is not usually considered as a second-line injectable drug*

[d] *These drugs in Group C may be started at a low dose and increased over two weeks; the approach of slowly escalating drug dosage is referred to as "drug ramping".*

[e] *High-dose H is defined as 10 mg/kg/day (maximum dosage 600mg per day)*

** These medicines are not used for PMDT in Tanzania*

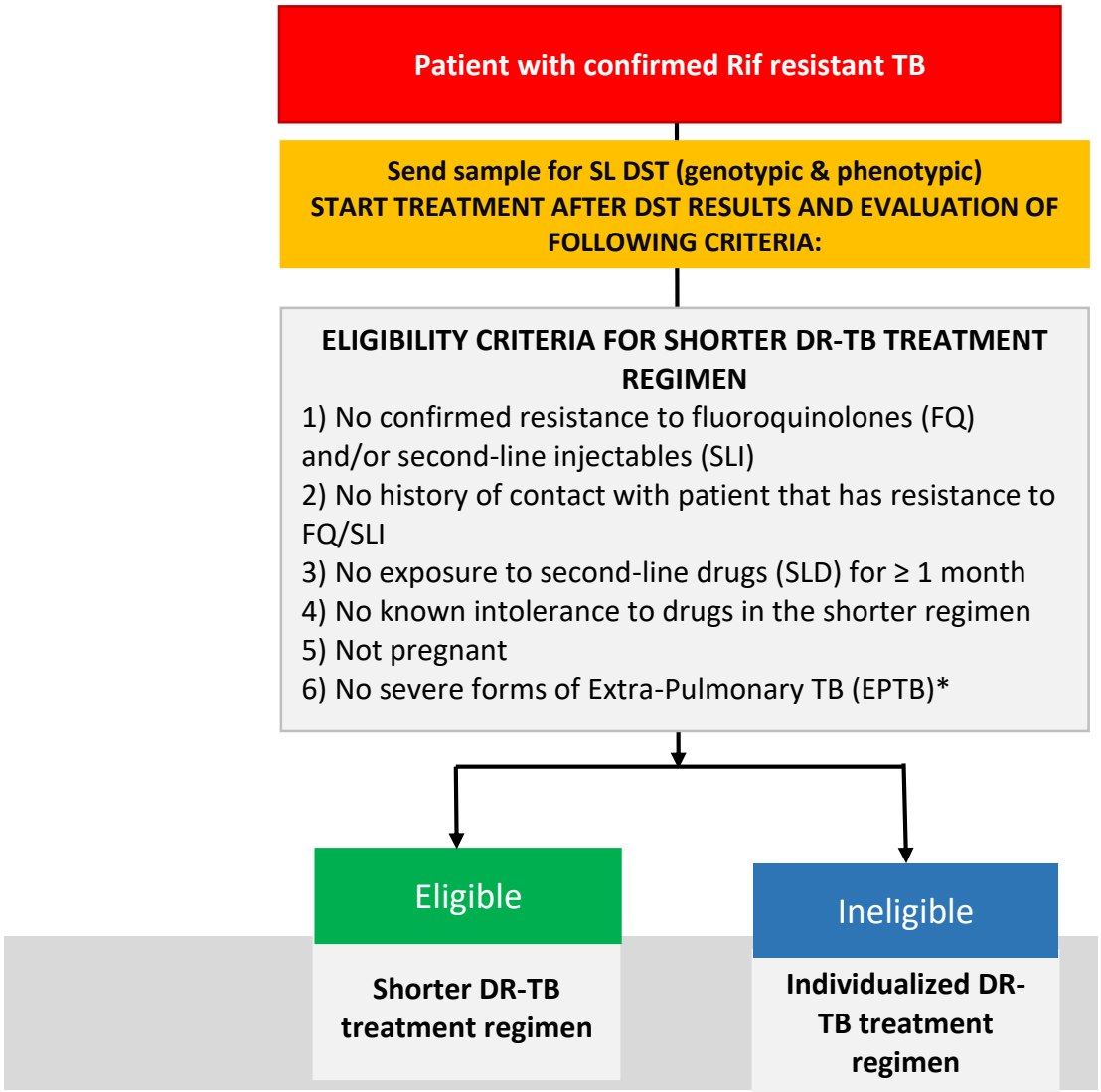
While DR-TB is generally treatable, it requires extensive chemotherapy (9 months up to 2 years of treatment) with second-line anti-TB drugs which are more costly than first-line drugs and which produce adverse drug reactions that are more severe (though manageable). Quality-assured second-line anti-TB drugs are available for use in Tanzania, through the WHO mechanism.

The Tanzanian MDR-TB program recommends using the standardised short course DR-TB regimen for eligible patients. Those patients who are not eligible DR-TB patients should be started on a longer individualized regimen, which includes a new TB drug (see Section 2). To avoid using in-appropriate drugs, every patient will be evaluated before starting treatment to determine which regimen is suitable for their treatment. This is described in Figure 5.

Treatment regimen for DR-TB in Tanzania

The treatment regimen is based on the DST results to exclude treatment of resistant cases using drugs that could be avoided. Currently there are options to treat patients with second-line drug resistance using new drugs such as bedaquiline or delamanid. Using eligibility criteria there are options to use shorter regimen (9-11 months) and individualised regimen (20 months) for MDR-TB patients and individualised regimen (24 months) for XDR-TB patients

Figure 5: Patient triage flowchart to determine regimen eligibility



* Non-severe forms of EPTB that can be eligible for the shorter regimen include TB pleural effusion (adults and children) and TB lymph node (children)

1.Standardised short regimen (SSCR) 4 (6) Km Mfx Pto Cfz E Z H(h)[1] /5 Mfx Cfz E Z

Exclusion criteria

1) Confirmed resistance to fluoroquinolone and/or second-line injectable (SLI)
2) Contact with patient that has resistance to fluoroquinolone/second-line injectable
3) Exposure to second-line drugs for ≥ 1 month
4) Known intolerance to drugs in the shorter regimen
5) Severe forms of extra-pulmonary TB such as TB meningitis, disseminated/milliary TB and TB of the bones
6) Pregnancy.

Transition from intensive to continuation phase:

- Transition from the intensive phase to the continuation phase will require that **smear results, clinical and radiological response** are taken into account. Positive smear after four months of treatment will usually indicate non-viable bacilli, but at the same time extensive disease and high bacillary load at start, are both predictors of relapse.
- Patients with a **positive smear at four months of treatment will receive an extended intensive phase** to limit the risk of relapse (and acquired resistance) while awaiting culture results. A month-by-month decision can be made up to a **maximum of six months** when they should be placed on to the continuation phase treatment.

Other considerations

- Eligible patients should be started on the shorter treatment regimen after receiving second-line DST (SL-DST) results. Ideally, the genotypic SL-DST would be available to inform the treatment decision.
- Patients who have already been started treatment on the previous standard DR-TB treatment regimen cannot be switched to the shorter DR-TB treatment regimen.
- Kanamycin should be given five days a week.
- The intensive phase may be extended to a maximum of six months until sputum smear conversion. If a sputum smear conversion is not achieved within four months Km (Am or Cm) will be given three times a week from the fourth month onwards.
- If the patient remains smear positive and/or is still culture positive at six months, the treatment will be declared a failure. Failure declaration and a switch to an individualized treatment will be considered earlier in patients with a clear lack of response (clinically, smear grading, culture).
- In case of diagnosis of any resistance to fluoroquinolone and/or SLI or AEs requiring change of two drugs, the patient will be registered as a treatment failure and an individualized regimen will be designed.

2. Individualized regimen, including Bdq and/or Dlm

Patients who are not eligible for the shorter treatment regimen should be started on a longer individualized regimen that includes repurposed and the new TB drugs - bedaquiline or delamanid. Such patients' groups include;

- RR-/MDR-TB patients with a high risk of or confirmed resistance to a second-line injectable agent and/or fluoroquinolone (i.e. "pre-XDR-TB" or XDR-TB).

- RR-/MDR-TB patients with intolerance to any of the second-line TB drugs used in Tanzania either in the shorter regimen or individualized DR-TB treatment regimen (e.g. intractable psychosis, elevated LFTs >3 times the upper limit of normal, The QT interval is the time from the start of the Q wave to the end of the T wave. The corrected QT interval (QTc) prolongation of 500 msecs, hearing loss with shift of 25Db from baseline or clinically significant ototoxicity (hearing loss) not responding after injectable dose adjustment and creatinine clearance of 30mls/min).
- RR-/MDR-TB patients with a prior history of second-line use for more than one month, or patients with a history of contact with patients who have documented "pre-XDR-TB" or XDR-TB.
- Pregnant RR-/MDR-TB patients need to be managed with an individualized regimen designed excluding either of the new TB drugs, second-line injectables, linezolid or protionamide/ethionamide due to a lack of evidence for the safety of using these drugs during pregnancy.

3. Standard Long Course MDR TB regimen (SLCR)
- Patient who cannot tolerate drugs in the short MDR TB regimen and new TB drugs; Bedaquiline and Delanamid should be started on the **standard long course MDR TB regimen**

Recommended regimens for the longer individualized regimen with repurposed and new drugs for the different patient grouping scenarios is outlined in Table 5 below:

Table 5: Proposed individualised treatment regimens for the different patient groups

SN	PATIENT GROUPS	PROPOSED REGIMENS
1	"Pre-XDR-TB" with FQ resistance	**Intensive Phase at least five effective drugs in intensive phase:** 6 Bdq/Dlm,8 Km/Cm, Cs, $Lfx_{(h)}$, Eto, Z, Lzd **Continuation Phase at least 3 effective drugs for 12 months** Cs, Eto, Z, Lzd, $Lfx_{(h}$
2	"Pre-XDR-TB" with Aminoglycoside injectable resistance	**Intensive Phase at least five effective drugs:** 6 Bdq/Dlm, 8 Cm, $Lfx_{(h)}$, Cs, Eto Z, Lzd **Continuation Phase at least 3 effective drugs for 12 months:** $Lfx_{(h)}$, Cs, Eto, Z, Lzd
3	XDR-TB	**Intensive Phase at least five effective drugs for 12 months:** 6Bdq, Dlm ,12Cm $Lfx_{(h)}$, Lzd, Cfz, PAS. Dlm may be added after consultation with the MDR-TB consilium in preference to Amox/Clv as an additional drug

		Continuation Phase at least 3-4 effective drugs for 12 months: **$Lfx_{(h)}$, Lzd, Cfz, PAS.**
4	Intolerance to SLDs used in the treatment regimen Refer to Individualized regimen, including Bdq and/or Dlm section above	Replace the offending agent with new TB drugs; bedaquiline or delamanid
5	Pregnant RR-/MDR-TB patients	During the 1st trimester, aminoglycosides, bedaquiline, delamanid, linezolid and Eto/Pto should be excluded from the treatment regimen **Proposed regimen:** Lfx/Mfx, Cs, PAS, Amox/Clv, Z Postpartum, the regimen should be strengthened by a second-line-injectable (for 3-6 months) and/or other drugs as needed.
6	Patient who cannot tolerate drugs in the short MDR TB regimen and new TB drugs; Bedaquiline and Delanamid should be started on the **standard long MDR TB regimen**	**Intensive Phase at least five effective drugs in intensive phase:** 8 Km/Cm, Cs, Lfx, Eto, Z, ± E **Continuation Phase at least 3 effective drugs for 12 months** Cs, Eto, Z, Lfx ± E

How to design individualized DR-TB regimen

The regimen design should be based on the patient's past medical history and individual DST results. The following steps outlined below and summarized in Table 6 below should be used to guide the development of a longer individualized regimen:

1) The standard duration of the intensive phase will be at least eight months, and duration of the continuation phase will be at least twelve months;
2) The duration of the injectable agent, and hence the intensive phase, may then be extended according to the patient's response to treatment and confidence in the drugs in the treatment regimen;
3) The regimen will be designed based on the patient's most recent DST results and history of previous drug use and/or exposure (see Tables 6 and 7);
4) The regimen will consist of at least five drugs with confirmed or high likelihood of effectiveness from the following list: Bdq and/or Dlm, Lfx(h)/(Mfx), Km/Cm, Pto/Eto, Lzd, Cfz, Cs, Z, E, H(h), PAS, Amx/Clv; and

5) Bdq or Dlm will be used for six months. The use of Bdq or Dlm can be extended by the MDR-TB expert committee in cases where the remaining regimen is felt to be insufficient (i.e. with less than three effective drugs) and treatment tolerability is good.

Note:

For patients enrolled on treatment regimens containing new drugs (Bdq or Dlm), as per WHO guidelines informed consent should be obtained from the patient following national policy. If indicated, Dlm or Bdq can be used also for children with the standard safety measures in place. However, for children <12 years-of-age, Dlm would be the drug of choice.

Table 6. Steps to design a longer individualized treatment regimen for DR-TB cases

STEP 1	**Choose new drug**	**Bdq or Dlm**
STEP 2	**Choose a fluoroquinolone**	**Lfx** **Mfx**
	In addition to determining strain susceptibility to ofloxacin, every attempt should be made to specifically determine susceptibility to moxifloxacin and levofloxacin through LPA • If only ofloxacin DST is known (and resistant) use levofloxacin unless thought to be compromised (previous use in failing regimen or known contact with a patient with levofloxacin resistance); • If resistance has specifically been shown to ofloxacin and/or levofloxacin, and moxifloxacin is susceptible, consider adding moxifloxacin to the regimen; • Moxifloxacin should be used only as a last resort and under carefully monitoring. In such case, the potential benefit of moxifloxacin should be weighed against the additive toxicity of prolongation of interval between Q wave and T wave in the heart's electrical cycle (QT) with bedaquiline; • If resistance shown to all FQs, exclude FQs from regimen; and • Be aware that Bdq has a long half-life and replacing Lfx with Mfx after the Bdq has stopped could still result in cardiac toxicity.	
STEP 3	**Choose an injectable[2]**	**Km** **Cm** **Am**
	• If patient's strain is still susceptible to one of the injectable drugs, include this in the regimen; and • If resistant to all injectable drugs, consider using one that the patient has never received.	

[2] Drugs are listed in order of priority until a total of at least 5 drugs deemed effective are included, including Z.

STEP 4	**Other core SL agents**	**Pto (Eto)** **Lzd** **Cfz** **Cs (Trd)**
	• Add all drugs thought to meet the criteria of an effective drug; and • If a drug is considered not to be effective or it has induced severe toxicity, do not include it in the regimen; and • If effectiveness is difficult to judge, the drug can be added to the regimen, but should not be counted as one of the effective second-line drugs.	
STEP 5	**First-line drugs**	**Z** **E** **High-dose isoniazid (H_{HD})**
	Z is routinely added in most regimens	
STEP 6	**Add on agents**	**PAS** **Amx/Clv** **Imp/Cln** **Meropenem** **Thioacetazone**
	Add one or more drugs if the regimen does not yet contain at least 5 effective drugs	

For “pre-XDR-TB” and XDR-TB cases, longer individualized regimens will be initiated based on documented resistance to FQs and SLIs from SL genotypic or phenotypic DST results. Proposed treatment regimens are given in Table 7.

Management of XDR-TB patients

The approach to designing a treatment regimen is the same as with other individualized DR-TB regimens. The steps described in Table 6 should be followed until you have at least five drugs to be used in intensive phase.

- Use of new drugs is strongly recommended
- Consider adjuvant surgery if there is localized disease
- Ensure strong infection control measures
- Provide palliative care and support for other complications as needed
- Treat HIV as outlined in these guidelines
- Provide comprehensive monitoring and full adherence support
- If the above combinations are not possible, present the case in the weekly video conference learning network (TB ECHO), for disccusion with experts.

The minimum duration of an XDR-TB regimen should be 24 months.

Weight based dosing for second line anti TB medicines

In general, anti-TB medicines should be dosed according to body weight (See Table 7&8) for weight- based dosing. Monthly monitoring of body weight is therefore important to adjust dosage as the body weight changes.

Table 7. Weight-based Dosing Chart Adults and Adolescents ≥30kg[3]

		Weight band				
MEDICATION	**DAILY DOSE**	**30 – 35 kg**	**36 – 45 kg**	**46 – 55 kg**	**56 – 70 kg**	**> 70kg**
Ethambutol (100, 400mg)	15-25mg/kg once daily	600mg	800mg	1000mg	1200mg	1200mg
Pyrazinamide (400, 500)	20-30mg/kg once daily	800mg	1000mg	1200mg	1600mg	2000mg
Levofloxacin (250mg)	750-1000mg once daily	750mg	750mg	1000mg	1000mg	1000mg
Moxifloxacin (400mg)	400mg once daily	400mg	400mg	400mg	400mg	400mg
Ethionamide (250mg)	500-750mg in 2 divided doses or once daily	500mg	500mg	750mg	750mg	1000mg
Prothionamide (250mg)	500–750 mg/day in 2 divided doses	500 mg	500 mg	750 mg	750mg	1000mg
Cycloserine (250mg)	500-750mg in 2 divided doses or once daily	500mg	500mg	500mg	750mg	750mg
p-Aminosalicylic acid (PAS) (4gm)	8g once daily in 2 divided doses	8gm	8gm	8gm	8gm	8-12gm
Bedaquiline (100mg)	400mg once daily for 2 weeks then 200mg 3 times per week					
Delamanid (50mg)	100mg twice daily					
Clofazimine (50, 100mg)	200-300mg daily first 2 months then 100mg daily					
Linezolid (600mg)	600mg OD	600mg	600mg	600mg	600mg	600mg
Amoxicillin/clavulanic acid (7/1)	80mg/kg/day in 2 divided doses	2600mg	2600mg	2600mg	2600mg	2600mg

[3] Adapted from Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. World Health Organization; 2014.

Amoxicillin/clavulanic acid (8/1)	80mg/kg/day in 2 divided doses	3000mg	3000mg	3000mg	3000mg	3000mg
High-dose isoniazid	16-20gm/kg OD	600-1000mg	1000-1500mg	1500mg	1500mg	1500mg

MEDICATION	DAILY DOSE	30-33kg	34-39kg	40-45kg	46-51kg	52-57kg	58-63kg	≥ 64kg
Kanamycin (1g/4ml)	15-20mg/kg OD	500mg (2.0cc)	600mg (2.4cc)	700mg (2.8cc)	800mg (3.2cc)	900mg (3.6cc)	950mg (3.8cc)	1000mg (4.0cc)

MEDICATION	DAILY DOSE	30-34kg	35-39kg	40-44kg	45-49kg	50-54kg	55-58kg	59-63kg	≥ 64kg
*Capreomycin (1g vial)	15-20mg/kg OD	520mg (1.4cc)	590mg (1.6cc)	665mg (1.8cc)	740mg (2.0cc)	815mg (2.2cc)	880mg (2.4cc)	960mg (2.6cc)	1000mg (2.7cc)

*__NOTE:__ When 2ml diluent is added to 1g Capreomycin dry powder, the volume increases to 2.7ml with a concentration of approximately 370mg/ml.

Kanamycin /Capreomycin dosage 10 mg/kg if 60 years or older. In impaired renal function (CrCl of < 30 or on dialysis) reduce the frequency of the dose to 2-3 times a week

Table 8 Pediatric Weight-based Dosing Chart for DR-TB Regimens

Drug	Daily dose (mg/kg)	Frequency	Maximum daily dose	Dosing for different Weight bands		
Kanamycin (Km,1g vial)	15–30	Once daily 5-7d/wk	1 g	See injectable dose calculation guidance		
Amikacin (Am, 1g vial)	15–30	Once daily 5-7d/wk	1 g			
Capreomycin (Cm,1g vial)	15–30	Once daily 5-7d/wk	1 g			
Levofloxacin (Lfx 250mg tablet [tab])	Patients < 30kg: ≤5y/o: 15-20 >5y/o: 10	See Note for dosing by age	750 mg	**NOTE: 5 years and under:** 15-20 mg/kg split into 2 doses (morning and evening) **> 5 years of age:** 10 mg/kg once daily. Child ≥ 30 kg- use adult dosing.		
				Weight: 10-15kg ≤5yrs: 1/2 tab bd	**Weight:16-23kg** ≤5yrs: 3/4 tab bd >5yrs: 1 tab od	**Weight: 24-29.9kg** ≤5yrs: 1 tab bd >5yrs: 1 1/2 tab od
Moxifloxacin (Mfx, 400mg tab)	Patients < 30kg: 7.5–10	Once daily	400 mg	**Weight: 10-17kg** Dose: 1/4 tab	**Weight: 18-29.9kg** Dose: 1/2 tab	**Weight: ≥ 30kg** Use adult dosing table
Ethionamide (Eto, 250mg tab)	Patients < 30kg: 15–20	In 2 divided doses or once daily if tolerated	1 g	**Weight: 5-10kg** Dose: 1/2 tab	**Weight:** Dose **11-18kg:** 1 tab **19-24kg:** 1 1/2 tab	**Weight:** Dose **25-29.9kg:** 2 tab **≥ 30kg:** use adult dosing
Cycloserine (Cs, 250mg) capsule [cap])	Patients < 30kg: 10–20	In 2 divided doses or once daily	1 g	**NOTE:** Dissolve one 250mg capsule in 10 ml water; **Doses reflect total daily dose**		
				Weight: Dose **5 kg** 50mg (2.0 ml) **6-12kg** 125mg (5.0 ml)	**Weight:** Dose **13-25kg:** 250mg (10ml/1cap)	**Weight:** Dose **26–29.9kg:** 500mg (20ml/2cap) **≥ 30kg:** use adult dosing
P-aminosalicylic acid (PASER®) (PAS, 4g sachets)	Patients < 30kg: 200-300	Once or daily dose divided into 2 and given twice	12 g	**NOTE:** Use PASER® dosage scoop with mg demarcations to ensure proper dose		
				Weight: Dose **5kg:** 500 mg bd **6-7kg:** 750 mg bd **8-10kg:** 1,000 mg bd	**Weight:** Dose **11-14kg:** 1,500 mg bd **15-18kg:** 2,000 mg bd **19-22kg:** 2,500 mg bd	**Weight:** Dose **23-26kg:** 3,000 mg bd **27-29.9kg:** 3,500 mg bd **≥ 30kg:** use adult dosing
Pyrazinamide (Z, **500mg tab**)	Patients < 30kg: 30–40	Once daily	2 g	**5-6kg:** 125mg (1/4 tab) **7-9kg:** 250 mg (1/2 tab) **10-11kg:** 375mg (3/4 tab)	**12-18kg:** 500mg (1 tab) **19-25kg:** 750mg (1 1/2 tab)	**26-29.9kg:** 1000mg (2 tab) **≥ 30kg:** use adult dosing
Pyrazinamide (Z, **400mg tab**)	Patients < 30kg: 30–40	Once daily	2 g	**5-7kg:** 200mg (1/2 tab) **8-9kg:** 300 mg (3/4 tab) **10-14kg:** 400mg (1 tab)	**15-20kg:** 600mg (1 1/2 tab) **21-27kg:** 800mg (2 tab)	**28-29.9kg:** 1g (21/2 tab) **≥ 30kg:** use adult dosing

All drugs should be started at full dose. However, cycloserine, ethionamide/prothionamide, and PAS, can be started at a lower dose and the dose be increased over a 2-week period ("drug ramping"). The patient is begun on a low starting dose and the dose is increased every few days until the targeted dose is reached. Vitamin B6 (pyridoxine) should be given to all patients receiving cycloserine to prevent neurological adverse effects. The recommended dose is 50 mg pyridoxine for every 250 mg of cycloserine

Corticosteroids

The use of corticosteroids in MDR-TB patients can be beneficial in cases of severe respiratory insufficiency and central nervous system involvement. Use prednisolone at a starting dose of approximately 1 mg/kg, with a gradual decrease in the daily dose by 10 mg per week when a longer course is indicated.

In patients with an exacerbation of obstructive pulmonary disease, prednisolone may be given in a short tapering course over 1–2 weeks, starting at approximately 1 mg/kg and decreasing the dose by 5–10 mg per day. Injectable corticosteroids are often used initially when an immediate response is needed.

Cross resistance among anti-TB agents

Cross-resistance is when mutations that confer resistance to one anti-TB drug also confer resistance to some or all of the members of the same drug family, and less commonly, to members of different drug families.

There is well-known cross-resistance between some of the antibiotics used in treating TB as summarized below:

- All rifamycins (rifampicin and rifabutin) have high levels of cross-resistance.
- There is high cross-resistance between isoniazid and ethionamide if the *inhA* mutation is present.
- Fluoroquinolones: In general, there is a complete class effect cross-resistance among fluoroquinolones in vitro. However, data suggest that moxifloxacin may continue to demonstrate some activity despite in vitro resistance to ofloxacin.
- Amikacin and kanamycin are considered to be very similar and have very high cross-resistance. Capreomycin and Viomycin have high cross-resistance.
- Aminoglycosides (amikacin and kanamycin) and polypeptides have variable frequency of cross-resistance.
- Thioamides (prothionamide and ethionamide) have 100% cross-resistance. Ethionamide can have cross-resistance to isoniazid if the *inhA* mutation is present (low-level isoniazid resistance).
- Bedaquiline and clofazimine cross-resistance has been reported in some studies with resistance in both directions via efflux-pump based resistance.

Treatment of mono- and poly-resistant TB other than MDR-TB

Cases with mono- or poly-resistance will be identified during the course of case finding for DR-TB. Treatment of patients infected with mono or poly-resistant strains using standardized regimens with first-line drugs has been associated with increased risk of treatment failure and further acquired resistance, including the development of DR-TB.

However, the likelihood of poor outcomes is relatively low with many types of mono- and poly-resistance and the majority of these patients will be cured with first-line drugs using regimens constructed based on the DST patterns.

Patients with mono- or poly-resistance will need to be managed in centres with experience in managing DR-TB patients. In Table 10 below are recommendations on how to treat such cases.

Table 10. Treatment regimens for the management of mono-resistant and poly-resistant TB

Pattern of drug resistance	Suggested regimen	Minimum duration Of treatment (months)	Comments
INH (± SM)	RIF, PZA, and EMB (± fluoroquinolone)	6–9 months	A fluoroquinolone may strengthen the regimen for patients with extensive disease. If the patient does not tolerate PZA, fluoroquinolone should be added. Confirm fluoroquinolone susceptibility
INH and EMB	RIF, PZA, and fluoroquinolone	6–9 months	A longer duration of treatment should be used for patients with extensive disease
INH and PZA	RIF, EMB, and fluoroquinolone	9–12 months	A longer duration of treatment should be used for patients with extensive disease.
INH, EMB, PZA (± SM)	RIF, fluoroquinolone, plus a core second-line agent, plus an injectable agent for the first 2–3 months	9–12 months	A longer course (6 months) of the injectable may strengthen the regimen for patients with extensive disease.
PZA	INH, RIF, EMB	9 months	Most commonly seen in M. bovis infections
EMB	RIF, INH, PZA,	6 to 8 months	Loss of EMB or SM from the regimen will not decrease the efficacy or change the treatment duration.

The above treatment recommendations should be considered provisional. Individual treatment plans should be decided after consultation with the DR-TB treatment review panel using the weekly video conference learning network (TB ECHO), which will review the treatment history, DST patterns and the possibility of strains of *M. tuberculosis* having acquired new resistance, and then determine the appropriate treatment regimen.

Key recommendations

−Promptly diagnose DR-TB and initiate the appropriate therapy;
−Do not use ciprofloxacin as an anti-tuberculosis agent;
−Treat for at least 9 months;
−Use adjunctive measures appropriately, including surgery and nutritional and social support;
−Aggressively treat XDR-TB whenever possible; and
−Treat adverse effects immediately and adequately
−The treatment of DR-TB in many of these patients represents the last opportunity for them to be cured

MANAGEMENT OF DR-TB IN SPECIAL SITUATIONS

Preamble

Certain associated special situations make the treatment of DR-TB more difficult. Not every patient will be able to be treated by the standardized treatment regimen because of the presence of certain medical conditions or situations. This chapter outlines the management of DR-TB in selected special conditions and situations. This chapter aims to show where the management of DR-TB differs in the presence of known or suspected co-morbid/special situation and to provide guidance on recent developments in the management approach of situation.

Contraception

All women of childbearing age who are receiving DR-TB therapy are highly recommended to use birth-control measures because of the potential risk to both the mother and foetus during pregnancy.

- All enrolled women should be counselled to use contraceptive methods during the whole duration of DR-TB treatment.
- There are no contraindications to the use of oral contraceptives with the non-rifamycin containing regimens. However, patients who vomit soon after taking an oral contraceptive have increased risk of reduced absorption of the medications, and hence reduced efficacy. These patients should be advised to take their contraceptives apart from the time that they may experience vomiting due to anti-tuberculosis medications or use other methods until medications are tolerated.
- Medroxyprogesterone intramuscular injections (Depo-provera), intrauterine contraceptive devices (IUCD) and other methods of contraception can also be considered.

- Condoms can be used when protection against sexually transmitted diseases is also needed. However, patients should be aware that condom use is not as effective especially when not used correctly. Patients should be advised on methods of contraception so they can avoid becoming pregnant during DR-TB treatment.
-

Pregnancy

All female patients of childbearing age should be pregnancy tested upon initial evaluation. Pregnancy is not a contraindication for treatment of active DR-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 severity of DR-TB. The risks and benefits of treatment should be carefully considered, with the primary goal of smear conversion to protect the health of the mother and child, both before and after birth. The following are some general principles to consider when treating pregnant women:

- Most pregnant patients should be started on treatment as soon as the diagnosis is made. However, since the majority of teratogenic effects occur in the first trimester, treatment may be delayed until the second trimester when the patient is very stable with minimum disease. Delaying treatment carries a risk as TB can advance quickly in a pregnant patient. A decision to start treatment in the first trimester or to postpone until after later should be agreed to by at least the patient and the doctor, after analysis of the risks and benefits. Other family members, especially the father-to-be, may need to be consulted depending on the relevant family, religious, cultural and social dynamics. Decision is based primarily on clinical judgment established on the basis of signs/symptoms and severity/aggressiveness of the disease.

- Treat with three or four oral second-line anti-TB drugs, which are likely to be highly effective against the infecting strain plus pyrazinamide. The regimen should be reinforced with an injectable agent and other drugs as needed immediately postpartum.

- Avoid injectable agents. Aminoglycosides can be particularly toxic to the developing foetal ear. Currently the use of Capreomycin in pregnancy has been associated with good outcome; the risks/benefits of its use should be discussed with the mother. Capreomycin may also carry a risk of ototoxicity (hearing loss) but is the injectable drug of choice if an injectable agent cannot be avoided because of an immediate life-threatening situation resulting from DR-TB. The option of using Capreomycin three times a week from the start can be considered to decrease drug exposure to the foetus.

- Avoid Ethionamide as it can increase the risk of nausea and vomiting associated with pregnancy, and teratogenic effects have been observed in animal studies.

- Consider termination of pregnancy if the mother's life is compromised. When the condition of the mother is so poor that a pregnancy would carry a significant risk to her life, a medical abortion may be indicated. The decision is based primarily on clinical judgment of the severity of the disease, the effective treatment

and care options available, and assessment of the risk/benefits with the mother. Whenever this decision is made, the TB program, in coordination with other relevant health care providers, must facilitate access to safe abortion care in the context of the existing country legislation for abortion

Newborn child of a mother with DR-TB and breastfeeding

If a child is born to a mother with DR-TB, the following should be taken into account:

- Separate the infant from the mother if the mother is untreated, or still infectious (still smear positive) despite treatment. The family should care for the infant during this separation period. If there are financial difficulties, available stakeholders may be called upon to provide assistance with the infant formula.
- No separation is required if the mother is no longer contagious, and the infant may be cared for by the mother, if she is in community care.
- Most TB drugs cross into the breast milk at low levels, however, any effects on infants due to such exposure during DR-TB treatment are not well known. Therefore, the use of infant formula should be considered, if the resources are available.

Paediatric DR-TB patients

Children (defined as aged 14 and below) with DR-TB generally have primary resistance transmitted from an index case with DR-TB. Although children often have paucibacillary TB disease and are culture negative, a strong effort should be made to confirm the diagnosis with culture and DST to avoid exposing children to toxic drugs unnecessarily.

If there are no DST results for a child with clinical evidence of active TB and who is a contact of a confirmed MDR-TB case, the regimen design for the child should be guided by DST of the presumed index case and the history of the contact's exposure to anti-TB drugs. If a child has DR-TB, the benefits of treatment far outweigh any potential risks of the anti-TB medications used for DR-TB, and the standard regimens outlined above should be used. It is of note that children typically have a lower organism load than adults and generally tolerate DR-TB medications better with fewer side effects.

Delamanid may be added to individualised regimens in children and adolescents (aged 6-17 years) with MDR/RR-TB who are not eligible for the shorter MDR-TB regimen.

In general, anti-TB drugs should be dosed according to body weight (see Table 8 for weight-based dosing). Monthly monitoring of body weight is therefore especially important in paediatric cases, with adjustment of doses as children gain weight.

In children who are not culture-positive initially, treatment failure is difficult to assess. Weight loss, failure to thrive or failure to gain weight adequately (in the presence of adequate nutritional intake), is of particular concern and often one of the first (or only) signs of treatment failure. Always monitor weight carefully in children, so doses can be adjusted as the child gains weight.

HIV Co-infection

HIV co-infection is a significant challenge for the prevention, diagnosis, and treatment of DR-TB.

In line with the national policy on TB/HIV collaborative services essential components in the management of DR-TB in HIV positive persons have the following recommendations:

- Perform provider-initiated HIV testing and counselling (PITC) in all patients with presumed or diagnosed DR-TB as it enhances earlier HIV diagnosis and paves the way for quality care
- Use Xpert MTB/RIF molecular assay in HIV-positive TB suspects as it detects TB cases twice as effectively as smear microscopy without a significant difference in performance by HIV status. It also simultaneously detects mutations associated with rifampicin resistance, thus shortening the time to diagnosis of DR-TB.
- Perform mycobacterial cultures and DST in HIV-positive DR-TB presumptive patients for prompt initiation of appropriate DR-TB treatment to reduce mortality among HIV-infected patients infected with DR-TB
- Initiate ART promptly in DR-TB HIV patients. Second-line anti-TB drugs should be initiated first, followed by ART as soon as second-line anti-TB drugs are tolerated. This should generally be within 2-4 weeks of initiating DR-TB treatment. With exception of CNS TB where initiation is delayed (within 4 to 8 weeks) to avoid life threatening IRIS.
- Provide integrated TB and HIV services as co-treatment of DR-TB and HIV is particularly difficult due to the long duration, heavy pill burden and numerous side effects. These patients should receive treatment for TB and HIV – and any other co-morbidity – at the same place and time if possible. This will improve adherence and the quality of care.
- Provide co-trimoxazole preventive therapy (CPT) for patients with active TB and HIV according to WHO recommendations
- Implement sound patient follow-up and monitoring system in order to have close monitoring of potential adverse effects including psychiatric assessments and nutritional status as well as periodic assessments of therapeutic response to both infections
- Ensure effective TB infection control to decrease the risk of DR-TB transmission and protect HIV infected patients – For further reading on infection control refer to Chapter 11.

Factors affecting DR-TB/HIV co-management

The treatment of DR-TB in patients with HIV is very similar to that in patients without HIV. A number of factors make the treatment of DR-TB in patients who are infected with HIV more complex:

- DR-TB patients may often have advanced clinical disease that puts patients at increased risk of immune reconstitution inflammatory syndrome (IRIS) in addition to frequent drug interactions and co-toxicities. New opportunistic infections or previously subclinical infections may be unmasked following immune reconstitution and cause clinical worsening. IRIS can also be confused with TB treatment failure, and co-infected patients may be demonstrating progression of TB disease due to drug resistance. Manage IRIS according to the available National TB/HIV guidelines

- For PLHIVs, Initiate treatment **"as soon as possible"** with the shorter MDR TB regimen if the patient meets eligibility criteria outlined in these guidelines. Adverse effects are more common in patients with HIV. The multiple medicines involved in DR-TB with recognized high toxicity risks, often combined with ART, results in a high incidence of adverse effects. Underlying conditions or other drugs the patient is taking may worsen drug toxicity.
- The sheer volume of medications needed for both conditions can be challenging to the patient.
- Many HIV patients will have smear-negative TB or extra-pulmonary disease complicating the diagnosis of DR-TB. The use of Xpert MTB/RIF is recommended in HIV infected patients.
- In patients who are not immune-compromised, we rely on the immune system to help control the TB. In patients with HIV disease, we must rely on the drugs alone to control and cure the DR-TB disease.
- Mal-absorption is quite common in HIV disease and may result in lower blood levels of the anti TB drugs, sometimes no longer reaching therapeutic levels needed to inhibit or kill the TB organism.
- An active drug safety monitoring (aDSM) system needs to be inplace for responses to both therapy and adverse effects. With regard to additive toxicities, the clinician should be aware of the side effects of the various agents used, and monitor more closely if two drugs are used with a similar toxicity. If serious or life-threatening adverse events occur, all medications should be suspended, and then serially re-introduced with the least suspected agents started first. Anti-TB therapy should be initiated prior to restarting ART.
- Little is known about drug-drug interactions between second-line anti-tuberculosis agents and antiretroviral therapy.
- It is recommended to give fixed dose combination of ART to DR-TB patients on treatment to decrease the burden of pills. See Table 11. Potential overlapping and additive toxicities of ART and anti-TB treatment

Table 11. Potential overlapping and additive toxicities of ART and anti-TB treatment

Toxicity	Antiretroviral Agent	Anti-TB agent	Comments
Skin rash	**ABC, NVP, EFV,** and others	**H,R,Z, PAS, Fluoro-quinolones**, and others	Do not re-challenge with ABC (can result in life-threatening anaphylaxis). Do not re-challenge with any agent that may have caused Stevens-Johnson syndrome. **Also consider co-trimoxazole as a cause of skin rash if the patient is receiving this medication.** Thioacetazone is contraindicated in HIV because of the risk of life-threatening rash.

Central nervous system (CNS) toxicity	**EFV**	**Cs,** H, Eto/Pto, FQ	EFV has a high rate of CNS side effects (dizziness, impaired concentration, depersonalization, abnormal dreams, insomnia and confusion) in the first 2–3 weeks of use, but typically resolve on their own. If these effects do not resolve, consider substitution of the agent. At present, there are limited data on the use of EFV with Cs; concurrent use is the accepted practice as long as there is frequent monitoring for central nervous system toxicity. Frank psychosis can occur with Cs but is rare with EFV alone; other causes should always be ruled out.
Depression	**EFV**	**Cs,** FQ, H, Eto/Pto	Severe depression can be seen in 2.4% of patients receiving EFV. Consider substitution of EFV if severe depression develops.
Headache	**AZT, EFV**	**Cs, Bdq**	Rule out more serious causes of headache, such as bacterial meningitis, cryptococcal meningitis, central nervous system toxoplasmosis, etc. Use of analgesics (ibuprofen, paracetamol) and good hydration may help. Headaches secondary to AZT, EFV and Cs are usually self-limited.
Nausea and vomiting	**RTV,** NVP, and most others	**Eto/Pto, PAS, H, Bdq, E, Z** and others	Persistent vomiting and abdominal pain may be a result of developing lactic acidosis (especially common with long-term d4T use) and/or hepatitis secondary to medications.
Abdominal pain	**All antiretrovirals have been associated with abdominal pain**	**Eto/Pto, PAS**	Abdominal pain is a common adverse effect and often benign; however, abdominal pain may be an early symptom of severe side effects, such as pancreatitis, hepatitis or lactic acidosis (especially common with long-term d4T use.
Diarrhoea	**All protease inhibitors, ddI (buffered formulation)**	**Eto/Pto, PAS,** FQ	Diarrhoea is a common adverse effect. Also consider opportunistic infections as a cause of diarrhoea, or *Clostridium difficile* (pseudomembranous colitis).

Hepatotoxicity	**NVP, EFV, all protease inhibitors** (RTV > others), **all NRTIs**	**H, R, E, Z, Bdq, PAS,** Eto/Pto, FQ	Also see Section on hepatotoxicity treatment related to second-line anti-TB drugs. When severe, stop both the ART and TB medications, and restart the TB medications first. Also consider co-trimoxazole as a cause of hepatotoxicity if the patient is receiving this medication. Also rule out viral aetiologies as cause of hepatitis (hepatitis A, B, C, and CMV).
Lactic acidosis	**ddI,** AZT, 3TC	Lzd	If an agent has caused hyperlactataemia (i.e. high lactate) or lactic acidosis, replace it with an agent less likely to cause lactic acidosis. Note: the goal should always be early detection and management of hyperlactataemia to prevent development of lactic acidosis.
Renal toxicity	TDF (rare)	**Amino-glycosides, Cm**	TDF may cause renal injury with the characteristic features of Fanconi syndrome, hypophosphataemia, hypouricaemia, proteinuria, normoglycaemic glycosuria and, in some cases, acute renal failure. **Avoid TDF in patients receiving aminoglycosides or Cm. If TDF is absolutely necessary, serum creatinine and electrolytes should be monitored frequently (at least every two weeks).** Even without the concurrent use of TDF, HIV-infected patients have an increased risk of renal toxicity secondary to aminoglycosides and Cm. Frequent creatinine and electrolyte monitoring is recommended. In the presence of renal insufficiency, antiretrovirals and anti-TB medications need to have their doses adjusted.

Electrolyte disturbances	TDF (rare)	**Cm, amino-glycosides**	Diarrhoea and/or vomiting can contribute to electrolyte disturbances. Even without the concurrent use of TDF, HIV-infected patients have an increased risk of both renal toxicity and electrolyte disturbances secondary to aminoglycosides and Cm.
Bone marrow suppression	AZT	**Lzd**, R, Rfb, H	Monitor blood counts regularly. Replace AZT if bone marrow suppression develops. Consider suspension of Lzd. Also consider co-trimoxazole as a cause if the patient is receiving this medication. Consider adding folinic acid supplements, especially if the patient is receiving co-trimoxazole.
Optic neuritis	ddI	**E**, Eto/Pto (rare)	Suspend agent responsible for optic neuritis permanently and replace with an agent that does not cause optic neuritis.
Dysglycaemia (disturbed blood sugar regulation)	**Protease inhibitors**	**Gfx**, Eto/Pto	Protease inhibitors tend to cause insulin resistance and hyperglycaemia. Eto/Pto tends to make insulin control in diabetics more dif cult, and can result in hypoglycaemia and poor glucose regulation.
Arthralgia	**Indinavir, other protease inhibitors**	**Z, BDQ**	Protease inhibitors can cause arthralgia and there have been case reports of more severe rheumatologic pathology. Arthralgias are very common with Z and has been reported as one of the most frequent adverse effects (>10%) in controlled clinical trials with Bdq .
QT Prolongation	ART has been associated with QTc prolongation	**Bdq, Mfx, Gfx, Cfz,** Lfx, Ofx	ARV therapy does appear to confer a significant increased risk of QTc prolongation in HIV-positive patients but data is sparse. The additive effects of combining ART with the known second-line anti-TB drugs in respect to QTc prolongation is not known.

Renal Disease

Many of the drugs used to treat DR-TB are primarily renally excreted and therefore require dose modification. It is generally the interval between doses that is lengthened, rather than decreasing the amount of drug given per dose. The dosing is based on the patient's creatinine clearance, which is an estimate of the glomerular filtration rate (eGFR) or renal function.

Creatinine clearance

Formula for calculating creatinine clearance (CrCl) using the Cockcroft-Gault Formula

$$\text{Estimated glomerular filtration rate} = \frac{\text{weight (Kg)} \times (140 - \text{age}) \times (\text{constant})}{\text{serum creatinine } (\mu\text{mol/L})}$$

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.

calculator: http://reference.medscape.com/calculator/creatinine-clearance-cockcroft-gault

For the evaluation and management of a patient with renal failure figure 7.

Consideration needs to be taken when DR-TB patients require aminoglycosides for 6 months or more. The other drugs such as ethambutol, quinolones, cycloserine, and PAS may need dose or interval adjustment in the presence of mild to moderate renal impairment. In the presence of severe renal impairment (CrCl of < 30) many other drugs may also require adjustments (as given in Table 12).

In patients with DR-TB, blood urea and serum creatinine should be monitored before the treatment initiation, monthly for 3 months after treatment initiation and then every three months while injection kanamycin is being administered. In patients with mild renal impairment, the dose of aminoglycosides may be reduced. In the presence of severe renal failure, the amino-glycoside therapy should be stopped and replaced with other potent non-nephrotoxic anti-TB drugs.

The following drugs need to have the dose adjusted in impaired renal function (CrCl of < 30 or on dialysis)

Table 12. TB drugs dose adjusted in impaired renal function

Drug	Dose	Frequency
PZA	25-35 mg/kg/dose	3 times/week (not daily)
EMB	15-25 mg/kg/dose	3 times/week (not daily)
Cycloserine	500 mg/dose	3 times/week (not daily)
Levofloxacilin	750-1000	3 times/week (not daily)
Amoxiclav	Adults: 2000 mg as amoxicillin/125 mg clavulanate twice daily. Children: 80 mg/kg/day in two divided doses.	Renal failure/dialysis: For creatinine clearance, 10-30 ml/min dose 1000 mg as amoxicillin twice daily. For creatinine clearance < 10 ml/min dose 1000 mg as amoxicillin once daily. Haemodialysis: Single dose every 24 hours and after each dialysis session
Second-line Injectables (Amikacin/capreomycin/ kanamycin)	12-15 mg/kg/dose	2-3 times/week*
Para-aminosalicylic acid	4 g/dose	Twice daily maximum dose

** Increased risk of both ototoxicity (hearing loss) and nephrotoxicity, capreomycin is the preferred injectable in renal insufficiency*

Drugs that do not require dosage adjustment in renal failure include ethionamide, moxifloxacin, isoniazid, rifampicin, bedaquiline, linezolid, delamanid, prothionamide, clofazimine, and high dose isoniazid.

While there are some recommendations for giving large doses before dialysis and supplementary doses after dialysis, the easiest and most consistent method is to give the medications immediately following haemodialysis.

Liver Disease

Patients with a history of liver disease can receive the usual DR-TB chemotherapy regimens provided there is no clinical evidence of severe chronic liver disease, 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. Refer to figure 6 on how evaluate and manage a patient with drug-induced hepatotoxicity

Pyrazinamide, ethionamide, prothionamide, moxifloxacin and para-aminosalisylic acid can all cause liver toxicity but pyrazinamide is associated with the most severe toxicity and should be avoided in patients with chronic liver disease.

If a patient has severe liver disease, consider avoiding all hepatotoxic drugs. The use of levofloxacin ethambutol, aminoglycoside, and cycloserine should be considered, if appropriate. Very rarely fluoroquinolones can be associated with hepatitis, so they should be used with caution

If the patient is resistant to ethambutol, use of ethionamide or p-aminosalisylic acid as the fourth drug is justified, and the patient should be closely followed for signs of deterioration in liver function.

A patient with TB may have concurrent acute hepatitis that is unrelated to TB or anti-TB treatment, in this case clinical judgment is necessary. In some cases, it is possible to defer anti-TB treatment until the acute hepatitis has been resolved. In other cases when it is necessary to treat DR-TB during acute hepatitis, the combination of four non- hepatotoxic drugs is the safest option.

Extra-pulmonary MDR-TB

Most forms of extra-pulmonary DR-TB can be treated with the same regimens as for pulmonary DR-TB; the exception is tuberculous meningitis. Ethambutol, para-aminosalisylic acid, and kanamycin penetrate poorly into the CSF with un-inflamed meninges, but better with inflamed meninges. Capreomycin does not penetrate the CNS at all. Pyrazinamide, ethionamide and cycloserine, have good CNS penetration. Fluoroquinolones have variable CSF penetration, with better penetration seen in the later generations i.e. moxifloxacin and levofloxacin. Linezolid is believed to penetrate the central nervous system, and has been used in meningitis treatment (Table 13).

Therefore, for patients with DR-TB meningitis, the optimum regimen will be kanamycin, moxifloxacin, pyrazinamide, ethionamide and cycloserine. Dosages should be at the higher end of the therapeutic range. Consider the use of high dose INH at 16-20 mg/kg/day because of its excellent CNS penetration and possible efficacy.

- Adjuctive-corticosteroid therapy can be given tuberculous meningitis patients in conjunction with optimal DR-TB regimen

Table 13. CNS penetration of second-line anti-tuberculosis medications

Drug	CNS penetration
Cycloserine	Extremely good penetration.
Isoniazid	Good penetration. Equal to serum.
Pyrazinamide	Good penetration.
Ethionamide	Good penetration.
Kanamycin	Penetrates inflamed meninges only.
Amikacin	Penetrates inflamed meninges only.
Capreomycin	Penetrates inflamed meninges only.
Quinolones	Fair. For ofloxacin, the penetration is 5-10% and with inflamed meninges 50-90%.
Ethambutol	Generally low. In the presence of inflammation (4–64%).
Para-Aminosalicylic Acid (PAS)	Poor.
Linezolid	CSF concentration is about 1/3 of that in serum in animal models

Diabetes mellitus (DM)

Diabetic patients on DR-TB treatment are at risk of poor outcomes if blood glucose levels are not well controlled. In addition, diabetes may potentiate adverse effects, especially renal dysfunction and peripheral neuropathy. Diabetic mellitus brings an increased risk of adverse events as many of the anti-TB drugs have side effects that put diabetic patients at special risk.

Long-standing diabetes may have underlying renal impairment that can be worsened by the second-line injectable drugs used in DR-TB.

Neuropathy is a common complication of diabetes and it can be made worse by several drugs used to treat DR-TB such as high-dose INH, cycloserine (CS), linezolid (LZD), and the fluoroquinolones.

Patients with diabetes may have decreased gastric motility (gastroparesis) and may be at increased risk of nausea and vomiting with medications like ethionamide (Eto) or other MDR-TB medications.

Therefore, the recommendations when treating diabetic patients with DR-TB include:

- Diabetics must be managed closely throughout treatment, and the health care provider should be in close communication with the patient.

- Creatinine and potassium should be monitored weekly for the first month and then at least once a month thereafter. If the creatinine level rises, a creatinine clearance should be checked and anti-TB medications should be adjusted accordingly (see renal insufficiency). Once the dose is adjusted, the creatinine should be checked weekly until it has stabilized.
- Fasting blood sugar should be monitored monthly.
- Oral hypoglycaemic agents are not contraindicated during the treatment of DR-TB, but may require the patient to increase the dosage as the use of ethionamide or prothionamide may make it more difficult to control insulin levels.

Mental illness during DR-TB chemotherapy

Due to disease chronicity, stigma and socioeconomic problems related to MDR-TB, patients have a high baseline incidence of depression and anxiety. Initial evaluation is key, and any existing psychiatric condition should be identified at the start of treatment to establish a baseline for comparison if new psychiatric symptoms develop while the patient is on treatment.

- Treatment with psychiatric medications, individual counselling, and/or group therapy may be needed to manage the patient suffering from a psychiatric condition or adverse effects. Group therapy has been very successful in providing a supportive environment for the DR-TB patient and may be helpful for patients with or without psychiatric conditions
- Cycloserine has a higher incidence of adverse effects among patients with mental illness. However, the benefits of using this drug may outweigh the potentially higher risk of adverse effects. Close monitoring is recommended if cycloserine is used in patients with psychiatric disorders.
- All health care workers treating DR-TB patients should have a system in place for monitoring psychiatric emergencies, including psychosis, suicidal indication, and any situation that involves the patient posing a danger to themselves or to others.

Substance dependence disorders during DR-TB Treatment

Patients with substance dependence disorders should be offered treatment for their addiction, although active consumption is not a contraindication for anti-TB treatment. Complete abstinence from alcohol or other substances should be strongly encouraged but should not be pursued at the expense of compromising adherence to DR-TB treatment. If the treatment is repeatedly interrupted because of the patient's dependence, therapy should be suspended until measures to ensure adherence have been established. Patient-cantered directly observed therapy (DOT) gives the patient contact with and support from health care providers, which often allows complete treatment even in patients with substance dependence.

Patients dependent on alcohol or other substances will experience the increased occurrence of adverse effects of cycloserine including higher incidence of seizures. However, cycloserine should be used if required for the therapy, and the patient should be closely monitored for any severe effects, that should then be treated adequately.

Opioid substitution therapy (using methadone) is an effective form of pharmacological treatment for opioid dependence among PWIDs with DR-TB with or without HIV co-infection. A number of drugs (e.g., efavirenz, nevirapine and rifampicin) can independently decrease methadone concentrations, which, depending on the individual, may cause withdrawal and increase the risk of relapse to opioid use. Patients receiving methadone together with efavirenz, nevirapine or rifampicin should be monitored closely, and individuals experiencing opioid withdrawal should have their methadone dose adjusted according to their needs.

Key recommendations:

- All women of child bearing age who are not pregnant should be given contraception to avoid pregnancy during DR-TB treatment
- Perform PITC in all DR-TB suspects and confirmed DR-TB patients
- Antiretroviral Therapy and cotrimoxazole preventive therapy is recommended for all patients with HIV and DR-TB. Antiretroviral therapy should be initiated as early as possible (generally within the first 2-4 weeks) following initiation of DR-TB treatment
- DOT advised for all HIV patients with DR-TB therapy throughout the DR-TB treatment course and not only in the initial phase due to the extremely serious nature of DR-TB and HIV co-infection
- In HIV infected patients, monitor for overlying toxicity with ART and DR-TB therapy
- Isoniazid, rifampicin, ethionamide, PAS, linezolid and clofazimine are not cleared by the kidney, and their dosing does not require adjustment for renal failure. Most other anti-TB drugs require dose adjustment for significant renal insufficiency
- Dosing guidelines are well established for patients with creatinine clearance less than 30mL/min or undergoing haemodialysis
- INH and PZA are the anti-TB medications most often associated with hepatotoxicity. Second-line anti-TB medications are less commonly associated with hepatotoxicity
- Close monitoring in patients with Mental illness using Cycloserine
- Substance dependence disorders – Patients receiving methadone should be monitored closely. DOT is encouraged as a means of adherence and support.

MONITORING PROGRESS OF DR-TB TREATMENT

Preamble

Patients with DR-TB will require regular monitoring throughout treatment to document sputum culture conversion and to monitor for the development of toxicities and signs of treatment failure. Early identification and management of treatment related problems should be done to ensure good treatment outcomes.

Pre-treatment screening and evaluation

The required initial pre-treatment clinical investigation includes a thorough medical history and physical examination. The initial evaluation serves to establish a baseline and may identify patients who are at an increased risk for adverse events or poor outcomes. The monitoring of treatment and the management of adverse events may have to be more intensive in patients with pre-existing conditions or conditions identified at the initial evaluation (diabetes mellitus, renal insufficiency, acute or chronic liver disease, thyroid disease, mental illness, drug or alcohol dependence, HIV co-infection, pregnancy, lactation etc.).

Monitoring progress of treatment

During monitoring, refer to the baseline and follow-up examinations for monitoring of DR-TB treatment efficacy and safety (Annex 1.) Healthcare providers monitor patients during the entire course of treatment. The basic investigations for DR-TB patients includes sputum culture collection, blood testing, radiographic imaging, audiology testing, ECG, visual acuity and physical examination such as weight and height, whereas indirect monitoring involves observation of the patient's affect, mentation, etc.

Clinical monitoring

The progress of DR-TB patients should be monitored using proper and well documented medical histories and physical examinations. The classic symptoms of TB (i.e. productive cough, weight loss, and fever) generally improve within the first few months of treatment.

Check weight (and height in children) monthly throughout the course of treatment and follow-up. When the patient has sustained substantial weight loss, or if the DR-TB patient is an infant, monitor weight on weekly basis as a measure of clinical response to therapy, and to ensure dose adjustments are made as weight increases.

Routine toxicity monitoring for patients with DR-TB should include the following:

- Obtain complete blood counts at baseline and intermittently (monthly during intensive phase and quarterly during continuation phase) or as clinically indicated.
- Obtain creatinine monthly for patients receiving aminoglycosides or capreomycin. Interpret the creatinine results carefully in patients with small body weight, for children with severe malnutrition using the RCH card (growth for health chart), for adults with a BMI < 18.5kg/m^2, adult over 50 years of age and those with diabetes (creatinine over 1.0 mg/dl is elevated in these patients). Baseline creatinine clearance

should be documented in persons with serum creatinine that is higher than expected, or if any concerns arise.

- Send baseline liver function tests (AST, ALT and total Bilirubin), and this should be repeated monthly during the intensive phase, and quarterly during continuation phase or when indicated.
- Monitor potassium levels if potassium levels are low (Reference level 3.6-5.2 mmol/L); obtain calcium and magnesium as well when injectable agents are being used.
- Lactic acid is done when indicated for work up of lactic acidosis in patients on linezolid and ART.
- Lipase/Amylase is done when indicated but special attention to patients receiving bedaquiline, linezolid, didanosine or zalcitabine and based on risk factors.
- Test for thyroid stimulating hormone (TSH) at baseline and when indicated. Refer to Annex 8.
- While most drugs can be continued safely, in general, a patient who suffers vestibular toxicity from an aminoglycoside or capreomycin may need dose adjustment. Assess the patient clinically if they are experiencing ototoxicity (hearing loss), decrease the dosing frequency of the injectables to three times a week. Consider switching to capreomycin. Assess the patient every week and if symptoms worsen despite dose adjustment, stop the injectables and add additional anti-TB drugs to reinforce the regimen.
- Perform audiogram and vestibular function monthly for patients receiving aminoglycosides or capreomycin (dizziness or ear ringing can also result from cycloserine and fluoroquinolones). Normal hearing is defined as a hearing threshold between 10 and 25 decibels. The standard threshold shift in the hearing loss is a hearing level change, relative to the baseline audiogram, of an average of 10 dB or more at 2000, 3000, and 4000 Hz in either ear. Stop the injectables if there is a shift of >25 dB relative to the baseline audiogram averaged at three contiguous test frequencies in at least one ear. Prior to stopping the injectable agents, evaluate whether other medication like cycloserine, fluoroquinolone, ethionamide, isoniazid or linezolid are causing the symptoms.
- Perform visual acuity, visual field and colour discrimination (colour blind for green) screen monthly and monitor for evidence of uveitis for patients on ethambutol, rifabutin, linezolid and clofazimine. Particular attention should be given to individuals who are on higher doses or with renal impairment.
- Perform electrocardiogram (ECG) or all patients on short regimen and is mandatory for patients receiving bedaquiline or delamanid. ECG should be performed at 2,4,8,12 and 24 weeks after starting treatment with bedaquiline or delamanid but monthly during the continuation phase.
- Perform chest radiography (CXR) for DR-TB patients, as follows. At baseline, every six months, at the end of therapy, when a surgical intervention is being considered i.e. for a pneumothorax, or when indicated. The CXR may be unchanged or show only slight improvement, especially among re-treatment patients with chronic pulmonary lesions.

Monitoring treatment efficacy and safety through laboratory tests

The most important objective evidence of improvement is conversion of the positive sputum smear and culture to negative. While sputum smear is still useful clinically because of its much shorter turnaround time, sputum culture is much more sensitive and is necessary to monitor the progress of treatment.

Persistently positive sputum smear and cultures for acid-fast bacilli should be assessed for Mycobacterium Other Than TB (MOTT) as overgrowth with MOTT in damaged lungs secondary to TB is not uncommon. In such cases, though DR-TB may be adequately treated, treatment may need to be directed towards the MOTT as well.

Culture conversion is defined as two consecutive negative cultures taken 30 days apart. The specimen date of the first negative culture is used as a date of conversion. After conversion, the minimum period recommended for bacteriological monitoring is monthly for smears and cultures.

Culture Reversion is defined as after initial conversion, two consecutive cultures taken 30 days apart are found to be positive during the continuation phase.

DR-TB treatment progress monitoring (to be determined through DR-TB Expert Panel review):

- If patient remains smear positive at six months of treatment but has good clinical response with decreased severity of symptoms, the patient can proceed to the continuation phase.
- HOWEVER - if clinical response to treatment is poor at six months of intensive phase treatment and patients remain smear positive, treatment failure and a switch to an individualized regimen should be considered.
- Failure declaration and a switch to an individualized treatment will be considered earlier in patients with clear lack of response (based on clinical status, smear grading, and culture).
- In case of diagnosis of any resistance to FQ and/or SLI or AEs requiring change of two drugs, the patient should be registered as treatment failure and an individualized regimen with new TB drugs should be designed.

Transition from shorter MDR-TB regimen to individualized regimen:

- If transition is made due to failure of the shorter MDR-TB regimen, the patient should be started back at the beginning on new individualized regimen and be re-registered and assigned a new DR-TB number.
- If switch is not due to treatment failure, the months already taken during short regimen course could be counted as part of the total treatment duration on the individualized regimen based on DR-TB Expert Panel review and decision.

Monitoring of treatment efficacy for extrapulmonary cases and smear negative cases started empirically on MDR-TB

Even though extrapulmonary TB among drug resistant TB case is uncommon, there are challenges in monitoring efficacy of treatment due to low yield of AFB smear and culture in extrapulmonary tuberculosis. Health workers should monitor therapeutic responses of patients on treatment, clinically and radiographically.

Monitoring and management of adverse events

When on DR-TB treatment many patients may experience some difficulties or drug intolerance. The timely detection and adequate management of these adverse events is vital for a successful treatment outcome. Most events occur during the first few months of treatment, some resolve spontaneously where as others need to be treated with drugs according to the symptoms experienced by the patient. In general, treat adverse reaction and encourage the patient to tolerate these effects until they resolve by themselves. Reducing the drug dose and the withdrawal of the drug or its replacement, should be done as a last resort. Adverse events are one of the main reasons for defaulting, and some patients may need additional support especially at the beginning of treatment (Annex 1).

Table 14. Monitoring and management of minor side effects

Mild Adverse Reactions Adverse Reactions	**Suspected Agents**	**Suggested Management**
Anorexia	Z, Eto/Pto, FQ	Appetite stimulant, e.g. Vitamin B complex
Arthralgias	**Z,** FQ, Bdq	Non-steroidal inflammatory drugs(NSAID), paracetamol, exercise therapy
Change in behaviour (talkativeness, irritability)	**Cs**, Ofx	Haloperidol
		Pyridoxine 50mg per 250 mg of Cs up to 200 mg/day as maximum
Cutaneous reactions	H, R, Z, E, Eto/Pto, Cs, PAS, S and other aminoglycosides	Antihistamines
		Hydrocortisone creams
Depression	**Cs**, H, FQ, Eto/Pto	Selective serotonin reuptake inhibitors (fluoxetine, sertraline), tricyclic antidepressants (amitriptyline)
Diarrhoea	PAS	Re-hydration
		Loperamide
Excessive salivation	Eto/Pto	Ice chips, metoclopromide
Flu like syndrome	R	Paracetamol
Gastritis	**PAS, Eto/Pto**	Antacids (e.g. Calcium carbonate) H2 blockers, proton pump inhibitors)
Gynecomastia	**Eto/Pto**	Reassurance, surveillance
Headaches	**Eto/Pto**	Non-steroidal inflammatory drugs(NSAID), paracetamol, exercise therapy

Insomnia	**FQ**	Antihistamine
Metallic taste	**Eto/Pto**	Reassurance
Musculoskeletal pain	No specific drug	Non-steroidal inflammatory drugs(NSAID), paracetamol
Nausea and vomiting	**Eto/Pto, PAS,** R H, Z, E, FQ	Re-hydration
		Metoclopromide
		Divide dose (AM & PM) as long as supervised
Olfactory hallucination	**Eto/Pto**	Reassurance
Peripheral Neuropathy	**INH, Cs**, S, Km, Eto/Pto, FQ	Increase pyridoxine to maximum daily dose (200 mg/day)
		Tricyclic antidepressants such as amitriptyline
Pain at injection site	S, Km, **Am**, Cm	Cold compress
Photophobia	**Eto/Pto**	Reassurance
Vertigo/dizziness	**S, Km,** Cm, Eto/Pto	Betahistine, Cinnarizine

Table 15. Moderate to Severe Adverse Reactions

Moderate – Severe Adverse Reactions	**Suspected Agents**	**Suggested Management**
Acute renal failure	**S, Km, Am,** Cm	Discontinue suspect drug
		Consider using Cm if an aminoglycoside had been the prior injectable in the regimen
		Consider dosing 2/3 times a week if drug is essential to regimen and patient can tolerate (close monitoring of creatinine)
		Adjust the dose according to creatinine clearance.
Bartter-like syndrome (decrease in serum K^+, mag^{2+} and ca^{2+})	**Cm,** Km, Am, S	Check electrolytes (K, Mg, Ca)
		Replace electrolytes as needed

Generalized hypersensitivity (Stevens-Johnson Syndrome)	Any drug	Withdrawal of the drugs and refer to specialist
Hearing loss	**S, Km, Am**, Cm, Clr	Document hearing loss and compare with baseline audiometry if available
		Change parenteral treatment to Cm if appropriate (no resistance confirmed or suspected)
		Increase frequency and/or lower dose of suspected agent if it can be done without compromising the regimen
		Discontinue suspected agent if this can be done without compromising the regimen
Hepatitis/jaundice	**Z, H, R**, Eto/Pto, PAS, E, FQ	Discontinue therapy pending resolution of hepatitis
		Eliminate other potential causes of hepatitis
		Consider suspending the most likely agent permanently. Reintroduce the remaining drugs, one at a time with the most hepatotoxic agents first, monitoring liver function
Hypothyroidism	**PAS, Eto/Pto**	Initiate thyroxine therapy
Intractable vomiting	**Eto/Pto, PAS**, H, E, Z, Bqd	Assess for dehydration, initiate rehydration if indicated
		Divide the dose (AM and PM) as long as it is supervised
		Discontinue suspected agent if this can be done without compromising the regimen
Optic neuritis	**E**	Discontinue drug and refer to an ophthalmologist
Psychosis/psychotic symptoms (violent/suicidal tendencies)	**Cs, H**	Discontinue suspected agent for a short period of time (1-4 weeks) while psychotic symptoms are brought under control.
		Antipsychotic treatment, referral to psychiatrist
		Lower the dose of suspected agent if this can be done without compromising the regimen
Seizures	**Cs,** H, FQ, Cfz	Discontinue suspected agents pending resolution of seizures
		Anticonvulsant therapy (phenytoin, valproic acid)

		Discontinue suspected agent if this can be done without compromising the regimen
Cardiac Ventricular Arrthymias; QTcF prolongation >500ms on ECG	**Mfx**, **Cfz, Bdq, Dlm,** Lfx	Confirm by repeating ECG
		Discontinue Bdq, Dlm and all QT prolonging drugs
		Schedule an emergency ad-hoc video conference learning network (TB ECHO) meeting to discuss the case

Figure 6.Management of a patient with hepatic failure

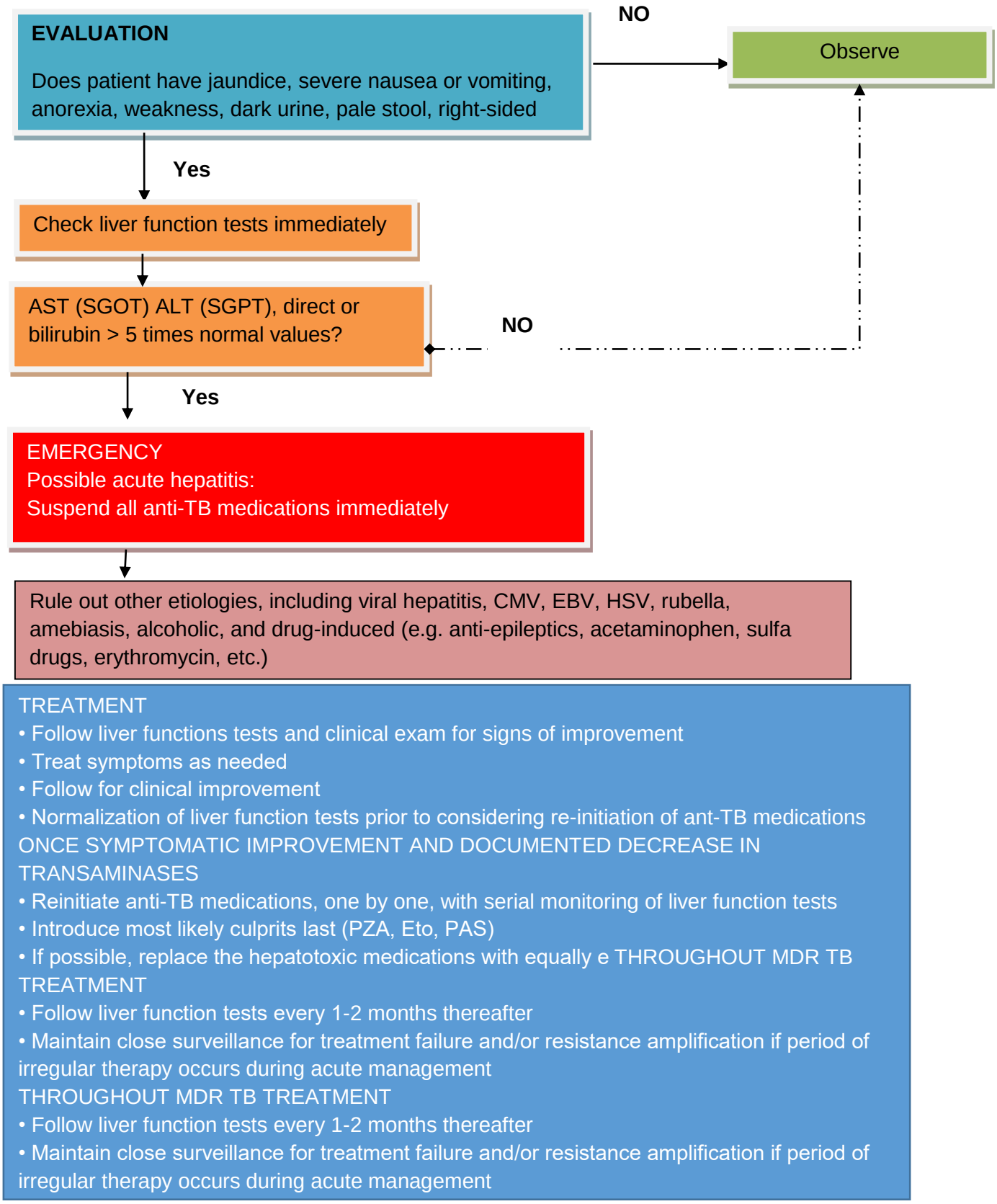


Figure 7.Management of nephrotoxicity

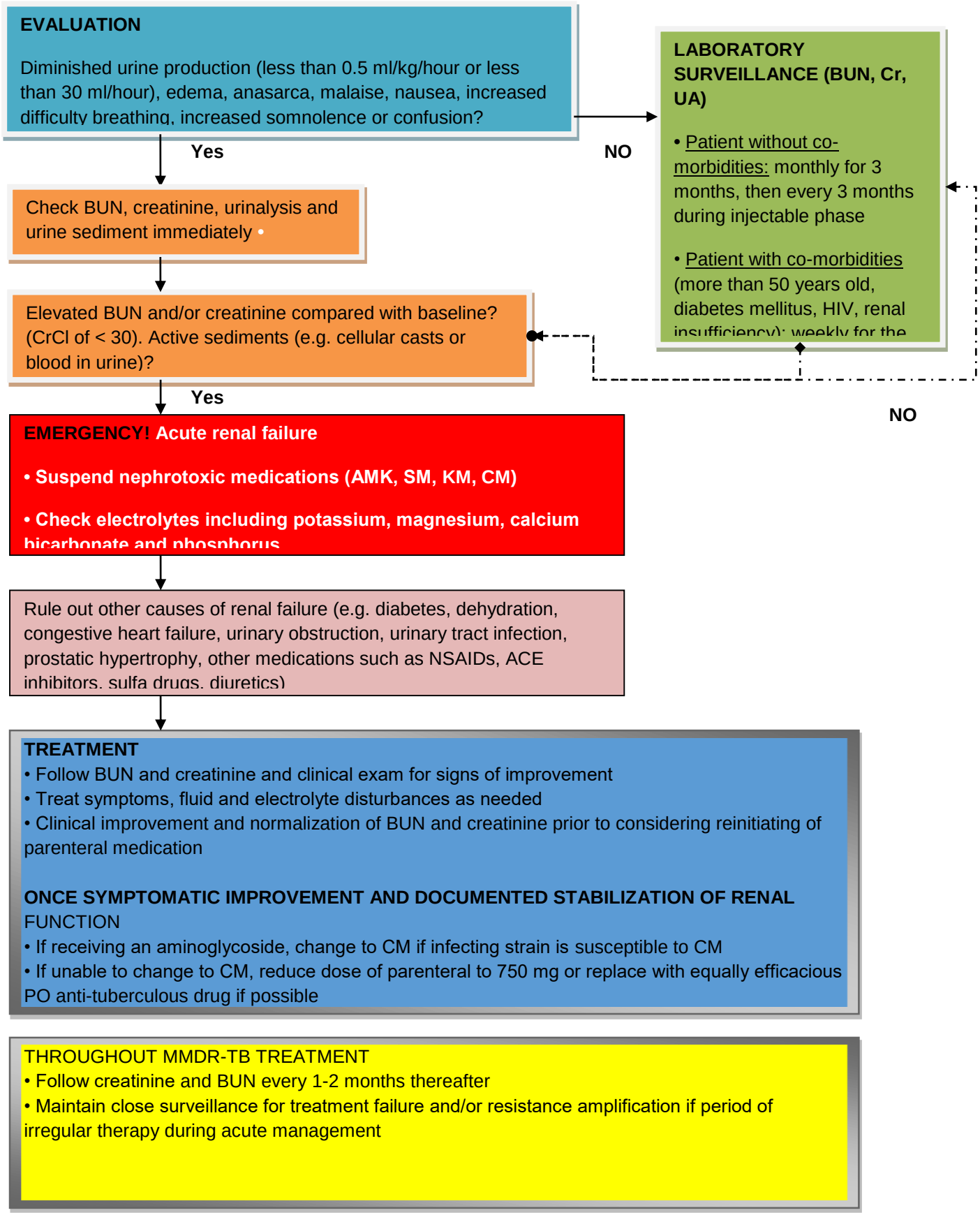
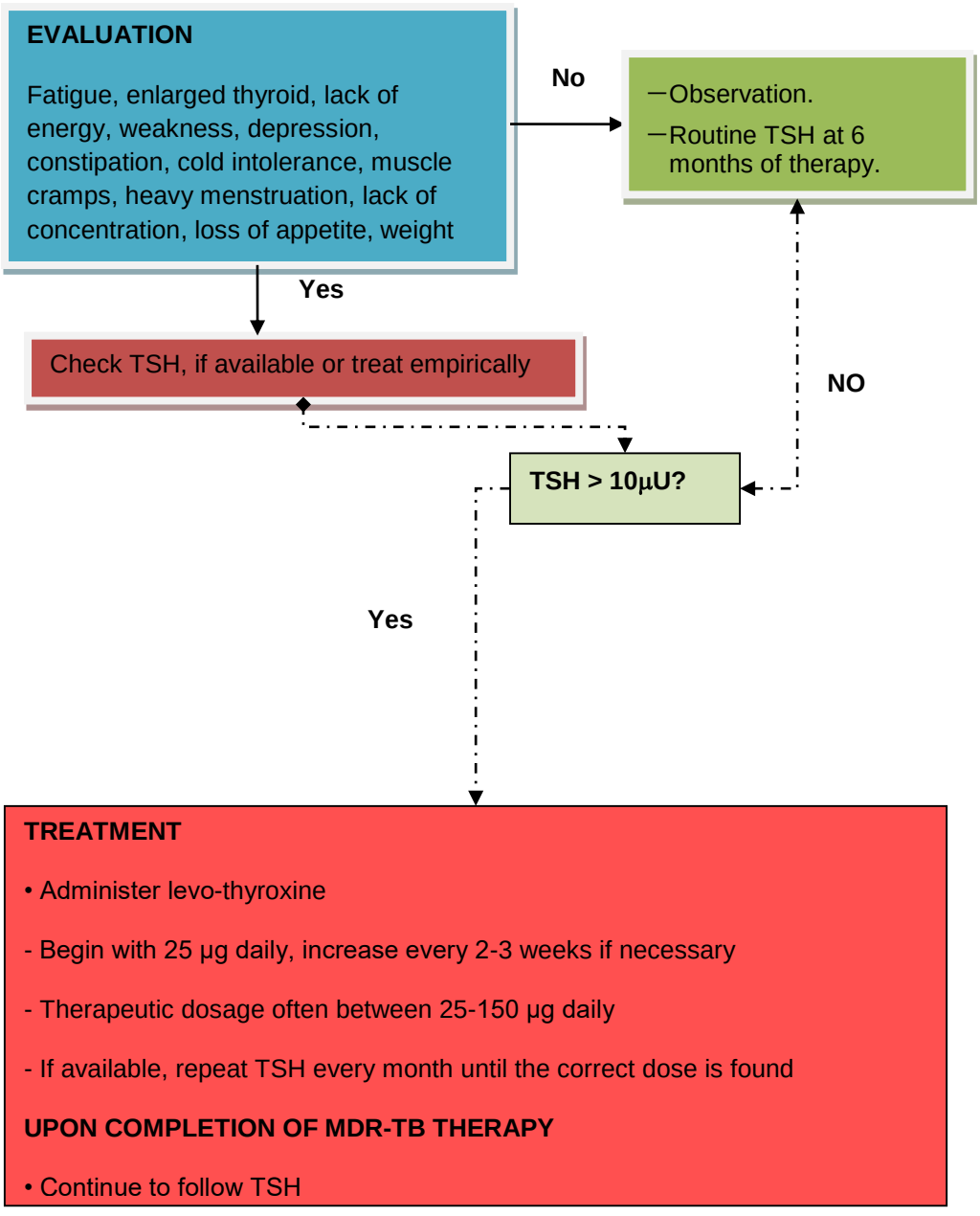


Figure 8.Management of Hypothroidism



Document all adverse events, treatment interruption, and other significant events related to the patient's treatment, actions or interventions taken in the 'comments' section of the DR-TB Treatment Card and in the side

effect monitoring form (Annex 11 and 12). Write down the type of problem the patient experienced such as an adverse reaction and the suspected drug, or absence from supervised treatment, and the action taken such as prescribing symptomatic treatment. When a patient has adverse events exhaust all options before changing the DR-TB regimen. If a patient has moderate or severe adverse events, refer to physician immediately for proper management (Annex 1).

Hypersensitivity reaction to Second-line anti-TB Drugs

When any of the severe allergic reactions are present, all anti-TB medications should be suspended. Treat allergic reactions with epinephrine, as well as corticosteroids and antihistamines. Then efforts should be undertaken to determine which drug caused the reaction. Once the patient has improved, anti-TB therapy can be reinstated as a "challenge"– a partial dose – Reintroduce one medicine after another (refer to Table 16) start with the most important medicine in the regimen first, unless there is a strong suspicion that it is the cause of the reaction. However, the challenge described should not be used for agents that may have caused an anaphylactic reaction.

Table 16. Anti-TB medication Challenge

Example of anti-TB Medication Challenge				
Drug	**Day 1 (mg)**	**Day 2 (mg)**	**Day 3 (mg)**	**Day 4**
Isoniazid	25	50	100	5 mg/kg
Rifampicin	50	100	150	10mg/Kg
Pyrazinamide	125	250	500	25-30mg/kg
Ethambutol	100	200	400	20 - 30mg/kg
Streptomycin, Kanamycin, Capreomycin, Amikacin	125	250	500	15-20mg/kg
Levofloxacin	125	250	500	750mg
Ethionamide, Prothionamide	6.25	125	250	15mg/kg
Cycloserine	62.5	125	250	15mg/kg
PAS	100am	500am	2000am	150mg/kg
	200pm	1000pm	2000pm	

Key recommendations:

- The monitoring of patients with DR-TB requires a systematic, organized approach. Elements which require monitoring include: drug administration, weight and nutrition, drug interactions, substance abuse and mental health, respiratory and systemic symptoms, symptoms of drug toxicity, blood tests, visual screens, audiology and vestibular testing, bacteriology, therapeutic drug monitoring, radiology
- Monitor both smear and culture monthly to evaluate treatment response
- Ancillary drugs for the management of adverse events should be available to the patient.

PHARMACOVIGILANCE IN PROGRAMMATIC MANAGEMENT OF DR-TB

Preamble

This chapter describes the management and monitoring of TB drug safety and framework of recording and reporting adverse events in Tanzania.

Basic Definitions Used in Pharmacovigilance

Pharmacovigilance (PV) is “the science and activities relating to the detection, assessment, understanding and prevention of adverse drug effects or any other drug-related problem”.Health programs that systematically monitor patient safety are at an advantage to prevent and manage adverse drug reactions (ADRs), as well as improve health-related quality of life and treatment outcomes. National Tuberculosis and Leprosy Program (NTLP) that actively pursue drug safety monitoring and management are also better prepared to introduce new TB drugs and novel regimens.

Active drug safety monitoring and management (aDSM) is defined as “active and systematic clinical and laboratory assessment of patients on treatment with new TB drugs, novel MDR-TB regimens or XDR-TB regimens to detect, manage and report suspected or confirmed drug toxicities.” (WHO aDSM framework 2015)

Adverse Drug Reaction (ADR)

A response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function. (WHO)

Adverse Event (AE)

Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a casual relationship with this treatment.

Adverse Event of Clinical Significance

An AE that is either (i) serious, (ii) of special interest, (iii) leads to a discontinuation or change in the treatment, or (iv) is judged as otherwise clinically significant by the clinician. The centres that offer the advanced package of aDSM will include all AEs of clinical significance in their reporting.

Adverse Event of Special Interest

An AE documented to have occurred during clinical trials and for which the monitoring program is specifically sensitized to report regardless of its seriousness, severity or causal relationship to the TB treatment. The centres that offer the intermediate and advanced packages of aDSM will include all AEs of special interest in their reporting. Suggested AEs of special interest to be reported include: CNS toxicity; hypokalemia; optic nerve

disorder; hepatotoxicity; hypothyroidism; lactic acidosis; pancreatitis; nephrotoxicity; prolonged QT interval; ototoxicity (hearing loss); myelosuppression; and peripheral neuropathy.

Serious Adverse Event (SAE)

An adverse event (AE) which either leads to death or a life-threatening experience; to hospitalization or prolongation of hospitalization; to persistent or significant disability; or to a congenital anomaly. SAEs that do not immediately result in one of these outcomes but that require an intervention to prevent it from happening are included. SAEs may require a drastic intervention, such as termination of the drug suspected of having caused the event. The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it was more severe.

Signal

Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information.

Implementating PV interventions for PMDT services in Tanzania

Many of the second-line anti-TB drugs already used by National tuberculosis and leprosy program in the treatment of DR-TB, are more prone to cause toxic reactions in patients than first-line drugs, making PV more important in the programmatic management of DR-TB. By recording the occurrence of ADRs for patients on treatment, many programs are already undertaking basic data collection inherent to PV. However, the collection of such data and the measurement of indicators on PV are not part of the standard parameters used in monitoring of DR-TB patients on treatment. Consequently, in most programs, the nature and frequency of harms caused by the drugs themselves are poorly understood, and can only be inferred indirectly from the interruption or failure of treatment.

The prospect of new anti-TB drugs and the use of novel regimens led WHO to release its first implementation manual for PV of anti-TB drugs in 2012. Later in 2012 WHO recommended the use of shorter regimens for DR-TB be accompanied by the collection of drug-safety data within a framework of observational research. In 2013 and 2014, the WHO interim policies on bedaquiline and delamanid recommended active PV as one of the five conditions to be met when using these drugs to treat MDR-TB patients. A number of programs managing MDR-TB patients have also introduced active PV to monitor drug safety and to take early action to avert treatment interruption and other unfavourable patient outcomes.

The application of pharmacovigilance methods (such as cohort event monitoring) described in the 2012 implementation manual for pharmacovigilance of anti-TB drugs in 2012 was largely based on experience with the use of drugs for malaria, HIV and non-communicable diseases. This however led to practical questions related to the implementation of drug-safety monitoring alongside other components of PMDT. The lack of familiarity of many TB practitioners with the principles of drug-safety monitoring and the limited capacity of national drug-safety authorities in some countries to provide the necessary support generated a demand for more explicit guidance. Following a meeting in July 2015, WHO issued updated guidance for NTPs on active TB drug-safety monitoring and management.

There are two main approaches to drug-safety monitoring: spontaneous and active. Spontaneous reporting is also called “passive” or “voluntary” reporting. It is the most common form of PV, and in some countries is mandatory. However reporting is entirely dependent on the initiative and motivation of the reporters. Generally, reporting rates are very low and subject to bias. There is no database of users or information on overall drug utilization available under this approach.

An active PV approach asks patients directly about ADRs and actively screens patient records. The follow-up of AE may continue after treatment ends (e.g., when medicines with long half-life are used). The most comprehensive form of active PV is cohort event monitoring. Active drug safety monitoring and management is the new approach recommended by WHO for TB drugs safety monitoring.

Why is drug safety management needed?

Adverse events (AEs) are expected in more than 80% of patients during treatment for DR-TB:

- Even mild and common events can affect treatment outcomes;
- Some AEs are life-threatening (i.e. renal failure);
- Some AEs can cause permanent disability (i.e. hearing loss)
- AEs can lead to reduced quality of life, treatment interruption, avoidable morbidity, added costs to service, etc.

Early recognition and optimal management of adverse events are key to ensuring adherence and achieving optimal treatment outcomes:

- Early detection will facilitate management of AEs and may help to prevent them from becoming more severe or serious
- May need to adjust regimen and/or provide ancillary drugs.

Why is drug safety monitoring needed?

The monitoring of patients for early detection of adverse drug reactions and their proper management have been recommended since the first PMDT guidelines, as well as the recording and reporting the occurrence of adverse drug reactions. However, most countries did not prioritize this while struggling to scale-up DR-TB treatment. With the introduction of new drugs and regimens, a renewed emphasis is being placed on its introduction. This is an opportunity to improve patient safety by obtaining better insights into the occurrence of adverse drug reactions for all DR-TB patients and acting upon them.

Why is drug safety monitoring needed for the new drugs and regimens for DR-TB patients?
With the introduction of new drugs and regimens, patient safety is of utmost importance as:

- Drugs are being used off-label and for repurposed uses (e.g., clofazimine, linezolid);
- Drugs with cardiotoxic effects are being given together (e.g., clofazimine, moxifloxacin, bedaquiline, delamanid)
- Drugs are being given in higher doses than previously recommended (e.g., moxifloxacin, isoniazid);
- New TB drugs are being used that to date have only been given to a small and selected number of patients in phase IIb trials (e.g., bedaquiline, delamanid) and hence have insufficient data to capture rare adverse events
- To date there is limited experience in programmatic use with these drugs
- Safety in specific patient populations is as yet unclear (e.g. elderly [65+], children, pregnant and lactating women, PLHIV).

There are risks for public confidence in the NTP and to the credibility of the NTP if safety signals are not detected in a timely manner. However, drug safety has previously not been one of the standard monitoring components for NTPs.

Active Drug Safety Monitoring and Management (aDSM)

aDSM is not aimed at replacing or duplicating efforts of the National Pharmacovigilance Units, but is aimed at complimenting current capacity and addressing barriers to the undertaking of active pharmacovigilance in the context of TB care. There are three essential components of aDSM activities:

1. **Clinical monitoring**
    - There is active and systematic clinical and laboratory assessment during treatment to detect drug toxicity and AEs.
2. **Management of AEs**
    - All AEs detected should be managed in a timely fashion in order to deliver the best possible patient care.
3. **Systematic and standardized recording and reporting of AEs**
    - Standardized data collection to include safety data

- At least all SAEs reported to the pharmacovigilance authority and assessed for causality
- In-country close coordination between the NTLP and pharmacovigilance centres is essential.

In the initial stages of aDSM implementation, it should cover the following groups of patients:

- RR-/MDR-TB and XDR-TB patients treated with the new drugs (i.e. bedaquiline and/or delamanid);
- RR-/MDR-TB patients enrolled on novel regimens, for example the shorter treatment regimen; and
- All other XDR-TB patients on second-line drug treatment regimens.

There are three potential levels of aDSM monitoring:

- Core Package – requiring monitoring for and reporting of all SAEs
- Intermediate Package – includes SAEs as well as AEs of special interest
- Advanced Package – includes all AEs of clinical significance.

In Tanzania, all PMDT sites with patients enrolled on new anti-TB drugs (bedaquilline and delamanid), MDR-TB shorter and XDR-TB regimens should implement the **intermediate package** for monitoring aDSM, in which SAEs as well as AEs of special interest are reported.

Based on the experience of successful implementation of other care and monitoring components of PMDT programs, WHO has identified eight key steps for programs to follow when introducing aDSM as laid down in WHO aDSM framework 2015:

1. Create a national coordinating mechanism for aDSM
2. Develop a plan for aDSM
3. Define management and supervision roles and responsibilities
4. Create standard data collection materials
5. Train staff on the collection of data
6. Define schedules and routes for data collection and reporting
7. Consolidate aDSM data electronically
8. Develop capacity for signal detection and causality assessment.

Ideally, all eight steps should be in place before patients are enrolled on treatment with new drugs, novel MDR-TB regimens or XDR-TB regimens. As this may not always be feasible, two steps: Step 4 (create standard data collection materials and step) and Step 5 (train staff for collection of data) are essential ahead of any patient enrolment. By having these minimum conditions in place there is less likelihood of data getting lost and of opportunities to manage AEs and ADRs being missed.

All AEs detected during routine clinical patient care should lead to an appropriate and timely management response in order to limit potential harms to the patient. In terms of monitoring, it is recommended that in Tanzania all SAEs and those AEs of special interest be registered and reported.

Clinical monitoring and management of adverse events

- AEs should be monitored in a systematic and timely manner. At every DOT encounter, health workers should ask the patient about clinical symptoms of common AEs including skin rashes, gastrointestinal disturbances, psychiatric disturbance (headache, anxiety, depression, irritability, behaviour change), jaundice, vestibular toxicity (nausea, vertigo, ataxia), peripheral neuropathy and symptoms of electrolyte wasting (muscle cramping, palpitations). Ototoxicity (hearing loss) needs particular attention. As moxifloxacin, clofazimine, and the new drugs, bedaquiline and delamanid, may induce QT prolongation, monitoring of ECG is essential and is required at all centres.
- There will be clinical follow-up with a doctor for all patients a minimum of two weeks after DR-TB treatment initiation and then monthly until treatment completion. At each visit, clinical assessment with evaluation of treatment efficacy and AEs will be conducted. Treatment safety will be assessed by the doctor and/or nurse with a specific data collection form.
- Providers should become familiar with potential AEs associated with the drugs used in the shorter treatment regimen. For proper management of these AEs, refer to Table 14 & 15
- Any relevant clinical event (adverse events or reactions) and any required additional diagnostic testing and/or therapy will be recorded.

Laboratory monitoring and management of adverse events

- Laboratory monitoring such as biochemistry, hormonal assays and compete blood count (outlined in Annex 1) should be performed to detect AEs.

Recording and reporting adverse events

- All AEs will be recorded in the patient treatment card and patient follow-up forms, and managed appropriately.
- All SAEs and adverse events of special interest should be reported to the zonal focal pharmacovigilance person using the aDSM report form Annex 10 and the TFDA using the yellow ADR form Annex 16, both within 24 hours.

Key recommendations

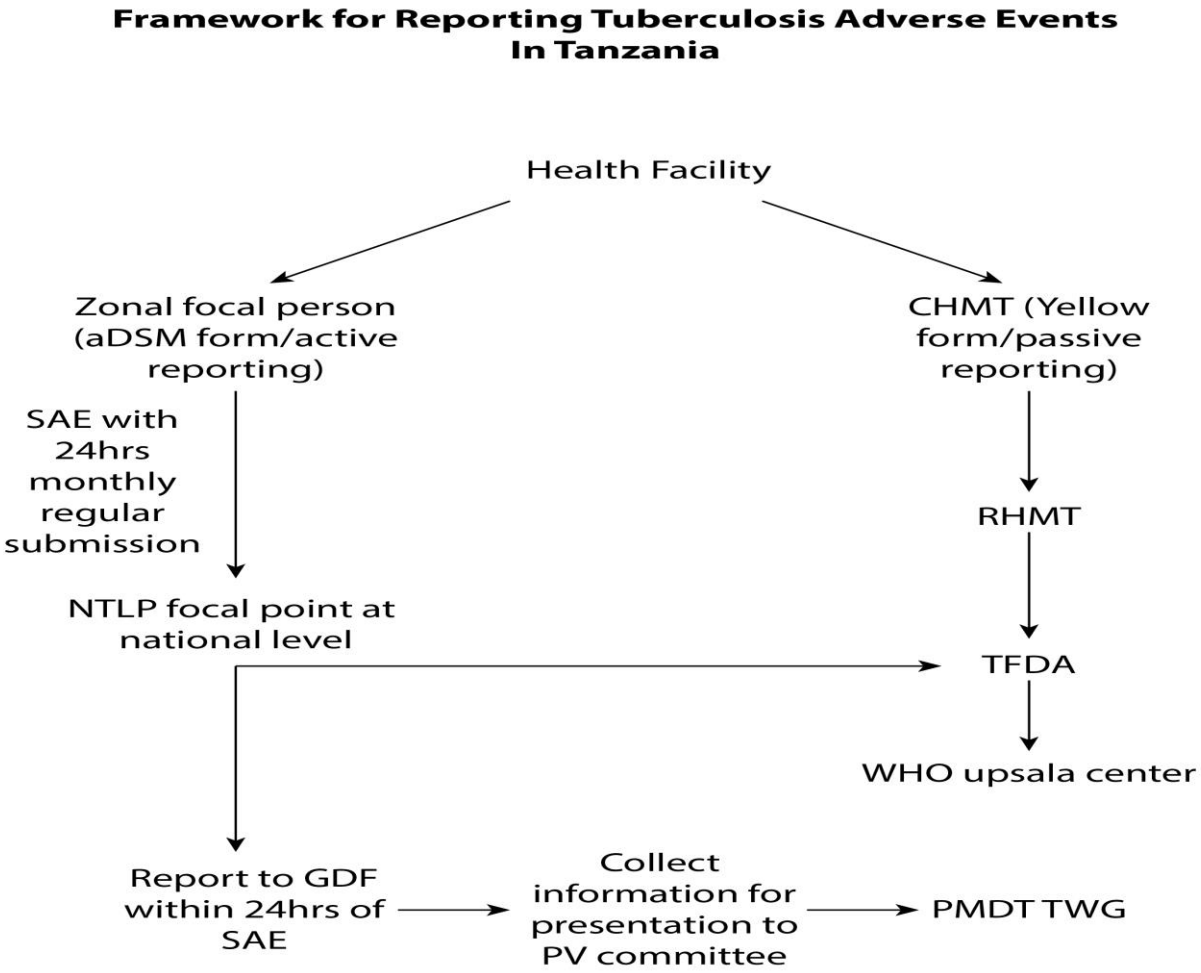
- Management of AEs should take patient safety and treatment needs into consideration. For minor AEs, re-assurance to enhance adherence is needed. For AEs that need additional evaluation and/or medical

treatment, a treatment decision structure (consultation backup for DOT provider), additional tests and ancillary medicines should be available and accessible, free of charge.

- Based on DR-TB expert panel review, offending drug(s) thought to cause the AE may need to be removed from the regimen, replacement might be required, especially in the intensive phase when the bacillary load is high. The patient can then be considered for individualized regimen. There are limited circumstances where drugs may be switched and a STR continued.

Please also refer to the NTLP's Standard Operating Procedure for "Active Drug Safety Monitoring and Management (aDSM)" (6).

Figure 9.Framework for reporting TB adverse events



TREATMENT OUTCOME DEFINITIONS FOR DR-TB PATIENTS

Preamble

This section of the guideline describes key DR-TB outcome definitions used internationally and nationally to identify, register and assign outcomes to DR-TB patients. These definitions rely on the use of laboratory smear and culture and they are recommended to be used for monitoring purpose.

Definitions of the DR-TB treatment outcomes

Cured

Patient has completed treatment of a specified regimen without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative during the continuation phase.

Treatment Completed

Patient has completed treatment of a specified regimen without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative during the continuation phase.

Treatment failed

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; or
- Evidence of additional resistance to Fluoroquinolones or second-line injectable drugs; or
- Adverse drug reactions.

Died

A patient who dies for any reason during the course of treatment.

Lost to Follow-up

A patient whose treatment was interrupted for two consecutive months or more.

Not Evaluated

A patient for whom no treatment outcome is 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.*

DR-TB CASE HOLDING

Preamble

The management of DR-TB depends on a steady supply of medicines provided to patients free of charge through a reliable network of educated providers. DR-TB treatment outcome can be successful when adequate support measures are provided to patients.

Adherence Counselling

To be eligible for the initiation of the DR-TB management, the patient has to successfully complete adherence counselling and preparation sessions. These sessions will be conducted by health facility DR-TB teams so as to ensure readiness for treatment (Annex 22 - Informed Consent).

During adherence counselling and preparation sessions, particular attention has to be given to re-treatment patients who were previously defaulters, because strict adherence to the new second-line treatment is critical.

Counselling must be done regularly, preferably on monthly basis, until the patient completes treatment. Any counselling session must cover a minimum of the following issues:

− *Nature of the disease and its infectiousness*

− *Adherence to treatment and DOT*

− *Early reporting of drugs side effects, and their effective management*

− *Drug collection, uptake and storage*

− *Follow-up examinations.*

After initiation is complete, exit adherence counselling sessions must be delivered to the patient and the family members (Annex 15). Continuum of counselling has to be provided on a monthly basis by the DOT provider or supervisor and at the patient’s request. Patients who missed-doses and those lost to follow-up must attend a counselling session once they are traced. Counselling must be done at the health facility by the counsellor or

any health care worker (HCW) who has received proper training. Patients co-infected with DR-TB and HIV should receive enhanced adherence support for both DR-TB drugs and ART.

Education of Patients

Health education should be provided by health care providers, treatment supporters, social workers, and TB outreach workers. It must be given to the patient and their family using a multimedia approach including pamphlets, posters, and videos. Health education can be delivered individually or in a group and should focus on the prevention of TB transmission, adherence to treatment, side effects, cough hygiene and DR-TB/HIV co-infection.

Treatment of DR-TB at the health facility/DOT centres

When DR-TB patients have completed the intensive phase of treatment and are potentially non- infectious, they are transferred to the nearby health facility/DOT centres for the continuation phase of treatment and follow-up. The health facility/DOT centres will be responsible for the supervision of DR-TB patient treatment five days a week. The treatment supporter will be responsible for supervising the evening dose and treatment during the weekend and on public holidays.

When a DR-TB patient comes in for treatment, DR-TB service providers must ask how the patient is progressing (and try to solve any problems identified), and record the administration of drugs. The patient must be reminded when the next dose should be taken. This daily interaction with DR-TB patients is very important as it provides constant support, and identifies potential problems and solves them before they become obstacles to treatment.

Patients who were lost to follow-up in the past, because of lack of economic resources for transportation or food, work constraints, or substance abuse should be identified and monitored closely.

There are times when a DR-TB patient will not be able to go to the health facility for supervised DR-TB treatment because of an intervening event e.g., travel or a funeral. These are counted as absences and should be avoided as much as possible while the patient is on DR-TB treatment. **Health care providers must not give drugs to DR-TB patients for self-administered treatment.** Rather, dose missed due to absence will be compensated for and treatment time will be extended.

The roles of the DTLC and the DOT provider at the nearest health facility to a DR-TB patient are:

- To supervise DR-TB treatment and document adherence, e.g. daily recording if medication is given.
- To continuously provide information and counselling to DR-TB patients and their families during treatment.
- To ensure that DR-TB patients continue taking their medications and trace DR-TB patients who do not come to receive their medications at health facility.

- To recognize promptly, document and manage minor and moderate drug reactions and refer DR-TB patients to DR-TB Referral Centres for uncontrolled or severe reactions.
- Immediately record SAE and AE of special interest and report them according to PV focal points in line with aDSM SoPs
- To ensure that DR-TB patients continue their clinical and laboratory follow-ups monthly or as scheduled.
- To manage second-line anti-TB medicines and other medical supplies.
- To mobilise resource for economic and psychosocial supports.

Management of DR-TB patients who interrupt treatment

Health care providers should call or make a home visit within 24 hours if a patient misses an appointment, using the contact information written in the DR-TB Treatment Card, and should find out the reason for the missed dose and offer a solution if this continues to pose a problem for the subsequent doses. The health care provider should remind the patient in a respectful manner to avoid missing treatment in the future as this may lead to increased drug resistance, the spread of DR-TB, and ultimately death.

Health care providers should give the daily dose of treatment to the patient as prescribed in the patient's card . For missed doses, a health care provider should not give an extra dose to compensate for the missed dose, instead the treatment period should be extended until all the drugs are taken. For patients who interrupt treatment, refer to chapter on management of loss to follow-up.

Health care providers should address treatment interruptions and document telephone calls, text messages, home visits, talks with patient and family, etc. in the patient's file .

Coordination of referrals of DR-TB patients

Referrals to specialised care

DR-TB patients may need to be referred to a specialist or to a hospital for the care of an acute or chronic problem. If this happens at the health facility, the DR-TB Centre needs to be informed of this referral within 24 hours from the time of referral to the hospital.

When a referral is necessary, health care providers should discuss it with the patient and inform the family of the need to return to the health facility to continue with DR-TB treatment after discharge from the clinician or hospital. Health care providers should ensure that the patient continues treatment for DR-TB while receiving special care outside the facility.

Referral of DR-TB patients back to DR-TB Centres

The majority of DR-TB patients who start DR-TB treatment at DR-TB centres are expected to complete it at a health facility once initiation treatment is completed. However, a DR-TB patient may be referred back by a health facility to the original DR-TB initiation centre for treatment related to complications. These complications may include:

- Frequent treatment interruptions while at the health facility

- Psycho-social constraints
- Uncontrollable drug reactions while receiving DR-TB treatment at the district health facility
- Complications after hospitalisation or treatment initiation.

Coordination of DR-TB patients' transfer between health facilities

DR-TB patients may need to be transferred to a different health facility to continue treatment. Some reasons for this may be that they are:

- Changing residence
- Having difficulty getting to their current place of treatment
- Having difficulties in transportation and access.

In all cases of transfers, the DTLC must be notified and the necessary transfer forms filled out.

Health care providers at DOT centres should coordinate the referral centres to ensure the transfer of the patient is successful.

Key recommendations

To ensure high rates of adherence, a comprehensive package of services, including health education, DOT, socioeconomic and psychological support, management of adverse effects and monitoring systems to improve adherence should be offered to all DR-TB patients.

MANAGEMENT OF LOST TO FOLLOW-UP PATIENTS WITH SECOND-LINE DR-TB TREATMENT

Preamble

As for patients on first-line TB treatment, all efforts have to be made to prevent DR-TB patients from defaulting, through the provision of attractive patient-tailored services and by ensuring that the patient and their family members fully understand the disease and its treatment.

Health care workers should ensure that patients fully understand that their DR-TB treatment should not be interrupted. The consequences of treatment interruptions puts family member and contacts at risk and may lead to poor treatment outcomes and having to receive more complicated and longer-term treatment.

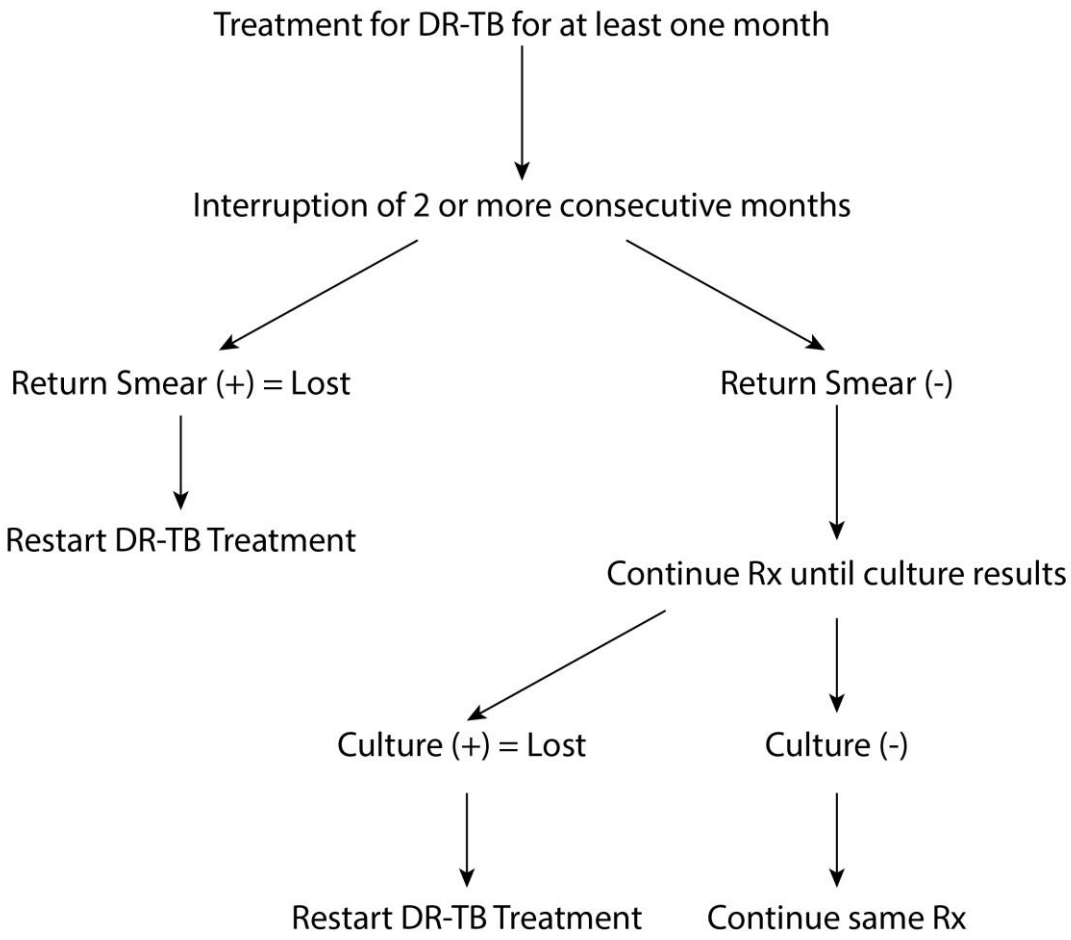
Table 17. Lost to follow-up DR-TB patient returning for second-line TB treatment

Lost to follow-up DR-TB patient	**Action to be taken**
Lost to follow-up patient: A patient who had previously been treated for TB and was declared *Lost to follow-up* at the end of the most recent course of treatment episode.	1. Collect two sputum specimens for Culture and request DST for second-line TB drugs 2. Give counselling to the patient and his family members 3. Discuss the case with a DR-TB management team, and decide social eligibility to continue second-line TB treatment 4. Re-register the patient 5. Restart original DR-TB treatment regimen from the initial phase 6. Adjust regimen when DST results are available 7. Educate patient on consequences of non-adherence to treatment.
A **Lost to follow-up DR-TB patient** after having interrupted treatment for two months or more and had more than four weeks of DR-TB treatment, and is **sputum smear-negative**	1. Collect two sputum specimens for Culture and request DST second-line TB drugs 2. Continue the previous DR-TB treatment regimen from where it was interrupted. If Culture is positive: – Restart DR-TB regimen (from the initial phase). – Give a final treatment outcome as defaulter from previous regimen – Re-register the patient with a new registration number for the new treatment episode. If Culture is negative: – Continue previous DR-TB regimen from where it was interrupted – Delete earlier “default” outcome and report – Provide final treatment outcome from current regimen.

A **Lost to follow-up DR-TB patient** after having interrupted treatment for two months or more and had less than four weeks of DR-TB treatment and is **sputum-smear positive**	Restart the DR-TB treatment regimen which the patient interrupted previously

Figure 10. Algorithm for Return after lost to follow-up

Algorithm For Return After Loss to Follow-Up



Key recommendations

- In general lost to follow-up patients with DR-TB who are sputum smear negative should continue the previous regimen and restart from the initial phase only if they had four or more weeks of DR-TB treatment and the culture result is positive
- In general lost to follow-up patients with DR-TB who are sputum smear positive should restart the DR-TB regiment from the initial phase

DR-TB INFECTION CONTROL MEASURES

Preamble

DR-TB is transmitted in the same manner as drug-susceptible TB. Well-documented outbreaks of highly drug-resistant strains of TB constitute convincing evidence that DR-TB is transmissible, especially among highly vulnerable populations (i.e. among PLHIV) and in institutional settings. Moreover, DR-TB patients respond to treatment more slowly and hence remain sputum smear positive for longer periods than other drug susceptible TB patients, they may therefore infect more contacts.

The management of DR-TB does not alter the basic TB infection control (IC) strategies in Tanzania. TB infection control has three components: administrative, environmental (engineering) measures and personal respiratory protection. The administrative controls (work practices) are the most effective and least expensive and therefore take the highest priority. Environmental controls and personal protective equipment will not work in the absence of solid administrative control measures.

TB Infection control activities for national, regional and District

1. Identify and strengthen a coordinating body for TB infection control ensuring that TB infection control is part of a general infection prevention control (IPC) program
2. Develop a comprehensive budgeted plan that includes human resource requirements for implementation of TB IPC at all levels
3. Ensure that health facility design, construction, renovation, and use are as per the prescribed criteria
4. Conduct TB disease surveillance among health workers and conduct as assessment of all health systems and congregate settings at all levels
5. Address TB IPC Advocacy Communication and Social Mobilisation (ACSM), including the engagement of civil society

TB Infection control activities for Health Facility Level

1. Develop and strengthen TB infection control (TB-IC) coordinating bodies
2. Develop a facility TB-IPC plans, policies and procedures (including human resources, policies and procedures for proper implementation)
3. Use available spaces and renovate existing facilities or construction of new ones
4. Conduct on-site surveillance of TB disease among health workers and assess facilities
5. Address ACSM for health workers, patients and visitors.
6. Monitor and evaluate the set of TB-IPC measures

7. Participate in research activities.

Administrative measures

Administrative control measures (work practices) include policies and procedures intended to reduce the amount of TB germs expelled into the air when a TB patient coughs. Their goals are:

1. To prevent TB exposure to staff and patients
2. To reduce the spread of infection by ensuring rapid and recommended diagnostic investigation and treatment for patients and staff presumed or known to have TB.

This can be accomplished through the prompt recognition, separation, provision of services, and referral of persons with potentially infectious TB disease. These are the first and most important control measures, therefore the following measures should be in place:

A written TB infection control plan should be available in all DR-TB hospitals.

- Patients with presumed DR-TB should be identified early at the health facility level by the clinician, educated on cough hygiene, and directly referred for smear, culture and DST
- The turnaround times for culture and DST should be minimized by implementing rapid diagnostic tests for drug resistance, so that DR-TB treatment can be started as soon as possible
- Confirmed DR-/XDR-TB patients should be directly referred to and hospitalized at the DR-TB hospital
- DR-TB patients should be placed in a DR-TB ward that is not overcrowded. The ward should be disinfected on daily basis. Waste (e.g., gloves, syringes, mask, needles, sputum cups etc) must be carried out in proper containers with lids and must be incinerated in the specific area of the hospital compound or burned in a pit
- DR-TB wards should be preferably fenced off from the rest of the hospital with restricted entry via a gate with a sign post
- Each DR-TB patient must receive a sputum cup with a lid to collect any expectorate. The cup should be disinfected (5% sodium hypochlorite or glutaraldehydes 2%) and waste should be incinerated on a daily basis.
- Whenever DR-TB patients have to leave the ward for any reason (e.g., investigations or recreational period) and when health personnel enter the ward, they must wear disposable N95 surgical masks
- DR/XDR-TB patients must be instructed to turn their heads and cover their mouth and nose with a handkerchief, tissues or forearm when coughing and sneezing, to dispose of waste in the trash, to wash their hands with water and soap, and to avoid indiscriminate spitting
- Nurses in charge at the DR-TB ward, under the supervision of the DR-TB clinician, are responsible for distributing cups and masks and monitoring their correct use
- Non-infectious DR-TB patients should be referred back to the community during the continuation phase of treatment
- DR/X/MDR-TB patients and their families should be counselled and educated on DR-TB and TB-IC control, and household contacts should be screened

- Training on DR-TB and TB-IC should be conducted for health workers
- Communities should be sensitized on DR-TB and TB-IC
- Infectious patients with XDR-TB, whether infected with HIV or not, should be isolated until they are no longer infectious.

Visitors' precautions

- Preventive measures directed at visitors are important for high-risk patient wards, such as DR-TB wards. Family and household members visiting TB patients should be restricted from entering DR-TB wards. Restricting visitors' access to the DR-TB isolation wards can be achieved by posting a sign that instructs family members and visitors not to enter the ward. If the need arises, family or household members who enter DR-TB ward should also wear properly fitted N95 surgical masks. DR-TB patients are recommended to meet any visitor in the outside space, and to always wear a surgical mask. Hawking and visitations by children to wards must be strongly prohibited, and signage must be put in place.

Environmental measures

Environmental measures are the second-line of defence for prevention of TB transmission to health care workers and other persons in the health care facility and aim at reducing the concentration of infectious droplet nuclei in the air in areas where contamination of air is likely.

Measures include natural and assisted ventilation. Natural ventilation is highly recommended in local settings although the instalment of filters (e.g. HEPA) and/or negative pressure rooms is desirable when feasible. Natural ventilation is controlled when windows and doors are deliberately secured open all the time (even in winter and at night) to maintain airflow and enhance cross ventilation. Air mixing increases the effectiveness of natural ventilation and therefore the use of propeller fans is also recommended.

Respiratory Personal protection

Respiratory protection aims to protect personnel who work in environments with air contaminated by TB bacilli. Health workers who enter DR-TB wards must always wear N95 respirators, which are special masks designed to protect the wearer from tiny (1–5 μm) airborne infectious droplets and hence are effective in filtering out *M. tuberculosis* bacilli. Fit testing should be conducted prior to use of the respirator and repeated annually. These respirators should fit individual wearers well. To ensure that each person receives an adequate fit while wearing a respirator, a proper seal between respirator and wearer should be enhanced by an appropriate make, model and size of respirator.

Reasons for poor fit can be weight loss/gain, facial scarring, changes in dental configuration (dentures), facial hair, cosmetic surgery, excessive make-up, the mood of workers (smiling/frowning), and body movements.

Respirators can be reused repeatedly for a week if they are not damaged and are properly stored. The main factors responsible for the deterioration of respirators are wetness, dirt, puncture, tears or any breach of the respirator, and crushing and stretching of the elastic strap. Respirators should be labelled with the wearer's name and placed on a peg in a clean dry location.

It is also recommended that health staff working with DR-TB patients receive counselling and testing for HIV. HCWs living with HIV as well as pregnant or breastfeeding HCWs who are working at the DR-TB hospital and laboratories performing culture and DST should be reassignment to an area or activity that has a low risk of exposure to *M. tuberculosis*.

HCWs working in DR-TB hospitals and laboratories performing culture and DST should undergo chest X-ray examination and sputum smear and culture on an annual basis regardless of the results of symptoms screening.

Community infection control

Community-based health workers (CHW) also have the unique opportunity to help prevent the spread of TB by teaching and monitoring proper implementation of IC measures practiced in the home during home visits. Key people involved are: CHWs, patients, and family members. Community IC can be enhanced by directly involving the respective community/political leaders on the following:

1. Offer a rapid screening referral mechanism for household members and other (close) contacts.
2. Encourage proper cough hygiene by talking with the household and people diagnosed with active TB disease about adhering to proper cough etiquette
3. Ask infectious DR-TB patients to wear surgical masks when in contact with susceptible people during intensive phase.
4. Ask the patient to not clear their throat and then spit on the ground, but spit the sputum into a tissue, cloth, covered container or toilet, in order to dispose of it
5. Environmental control measures combined with patient practices further reduce TB transmission in community. Use ventilation (either natural or mechanical) in the community and home environment.
    - Natural ventilation: Keep doors and windows open to the fullest extent possible
    - Mechanical ventilation: A fan may be used to enhance ventilation.
6. Community health care workers and household members of DR-TB patients should use N95 respirator when providing care to a DR-TB patient.

Ethical considerations for non-compliant DR-TB patients.

In general, TB treatment should be provided on a voluntary basis, with the patient's informed consent and cooperation. Engaging the patient in decisions about treatment shows respect, promotes autonomy, and improves the likelihood of adherence. Indeed, non-adherence is often the direct result of failure to engage the patient fully in the treatment process. However, in rare cases, despite all reasonable efforts, patients will not adhere to the prescribed course of treatment, or will be unwilling or unable to comply with IC measures. In this case, the interests of other members of the community may justify efforts to isolate or detain the patient involuntarily. Involuntary isolation and detention must be carefully limited and used only as a very last resort to safeguard the community and with reference to existing laws.

(Refer; Public Health Act of 2009 part II section 12 clause 1and 2, section 25 clause d, section 28 clause 2 and section 35 clause 5)

Key recommendations

- IC including administrative, engineering controls and personal protection, should be made a high priority in all DR-TB control programs.
- DR/XDR-TB patients should be placed in isolation until they are no longer infectious.

CLOSE CONTACTS OF DR-TB INDEX CASES

Preamble

Systematic investigation of contacts of known or suspected cases of DR-TB may be effective for reducing the ongoing transmission of drug-resistant strains of *M. tuberculosis* in a community. For drug susceptible TB contact investigation includes the treatment of active or latent TB. For DR-TB, however priority is on finding and treating contacts that have active TB. A list of close contacts should be made for each confirmed MDR-TB patient and these contacts should be examined for active TB.

15. 1. DEFINITIONS

Index case (index patient)

The initially identified case of new or recurrent TB in a person of any age in a specific household or other comparable setting in which others may have been exposed. An index case is the case around which a contact investigation is centered. Because the investigation generally focuses on a defined group of potentially exposed people in which other (secondary) cases may be found, the index case is generally the case identified initially, although she or he may not be the source case. Contact investigation may centre on secondary cases if the exposed group differs from that exposed to the original index case.

Contact
Any person who has been exposed to an index case (as defined above) is called a contact. Exposure may be intense or casual, easily identified or obscure. Close exposure, such as sharing a living or working space, is generally easily identified and quantified, whereas casual exposure, such as on public transport or in social situations, may be unidentifiable.

Household contact
A person who shared the same enclosed living space for one or more nights or for frequent or extended periods during the day with the index case during the three months before commencement of the current treatment episode. Definitions of 'household' vary considerably and must be adapted to the local context. Within households, there is a gradation of exposure, ranging from sharing the same bed as the index case to living in the same compound but not in the same enclosed space. Quantification of the amount of exposure, estimated as the time spent with the index case, is likely to be highly subjective. For this reason, the infectious period for the index case is set somewhat arbitrarily at three months before initiation of treatment rather than relying on recall by the index case of the time symptoms began. The three-month period is a general guideline; the actual period of infectiousness may be longer or shorter. For example, prolonged infectiousness may be associated with non-adherence (if directly observed treatment is not being used) or with unrecognized or untreated MDR-TB or XDR-TB.

Close contact
A person who is not in the household but shared an enclosed space, such as a social gathering place, workplace or facility, for extended periods during the day with the index case during the 3 months before commencement of the current treatment episode.

Out-of-household exposure is as likely to result in transmission as household exposure in many situations. Molecular epidemiological studies showed that transmission was likely to occur in social settings such as informal bars in and in facilities such as correctional institutions and hospitals Such sites (particularly social settings) are difficult to identify and require knowledge of the culture and of behavioural patterns in order to focus contact investigations.

Contact investigation
A systematic process intended to identify previously undiagnosed cases of TB among the contacts of an index case. In some settings, the goal also includes testing for LTBI to identify possible candidates for preventive treatment. Contact investigation consists of two components: identification and prioritization, and clinical evaluation. The rationale for contact investigation is that people who were recently infected with M. tuberculosis are at increased risk of developing active TB within 1-2 years after acquisition of the infection. It is assumed that people exposed to a person with infectious TB might recently have been infected and are thus at increased risk for currently having TB or for development of the disease in the near future.

Contact identification and prioritisation
A systematic process to identify contacts with or at increased risk of, developing of TB. For the purposes of these recommendations, the definition of contact identification and prioritization includes an interview with the index case to obtain the names and ages of contacts and an assessment of contacts' risk for having (generally based on the presence of symptoms compatible with TB) or developing TB, to determine those for whom clinical evaluation (defined below) is indicated. At a minimum, all index cases should be assessed with the above criteria to determine whether contact investigation should be undertaken. For example, contact investigation would not

usually be conducted for an index case with only extra pulmonary TB, except children <5 years of age, in whom investigations would be undertaken in an attempt to identify the source case.

Programmatic contact Investigation

Contact investigation should be part of routine programmatic management of DR-TB. Sometimes during contact investigation an older family member with history of chronic TB, patients with experienced failures of TB treatment, and who have lost faith in health care system are discovered to be the true index cases within the family.

The health care workers at all level should be trained to contact screening in family [household] and social contacts.

It is recommended that contact investigation be conducted for house hold and close contacts when the index case has any of the following characteristics:

- Sputum smear-positive pulmonary tuberculosis,
- MDR-TB or XDR-TB (proven or suspected),
- Is a PLHIV or other vulnerable conditions like diabetes, cancer, malnutrition.
- Is a child <5 years of age.
- Communities in congregates settings such as prisons, sober houses, mines, fishing camps, boarding schools, and military camps.

Key implementers

- Patient: Contact investigation starts with a patient education of the MDR-TB. Educated on infectiousness, risks of transmission to household and social contacts, chances of their family members being infected with MDR-TB,
- Family: one of the most important reasons to do a home visiting for every DR-TB patient, once diagnosis have been made is to do contact investigation. A community worker or HCW/Provider should educate the family and social contacts that they are likely already infected with MDR-TB and the importance of reporting when they develop symptoms of active TB.
- DR-TB management Teams: both clinical teams and DOT providers has to inquire about the health of contacts at every clinical visit. They have to use the provided contact investigation form and all presumptive DR-TB is registered in the Presumptive DR-TB Registers and the outcome known. (Refer to annexes 2 & 7)
- Community Health Workers, Ex-TB Patient Groups: In community based programs should conduct home visits to check adherence, social situation, health of family members, address fears or doubts and other barriers to treatment for DR-TB contacts.

Contact clinical evaluation

A systematic process for the diagnosis or exclusion of active TB among contacts. Clinical evaluation is undertaken if the results of contact identification and prioritization indicate a risk for having or developing TB.

For the purposes of these recommendations, the definition of contact clinical evaluation includes, at a minimum, a more extensive assessment of symptoms compatible with TB. Additional components may include:

- A more detailed medical history
- A physical examination
- Microbiological assessment of specimens from sites of suspected involvement
- Radiographic examinations
- Invasive diagnostic tests.

Implementation of these components will depend on the clinical circumstances and the available resources. In addition, depending on the epidemiological circumstances and resources, a tuberculin skin test or an interferon gamma release assay for LTBI may be part of the clinical evaluation.

The goal of contact investigation is to find previously undiagnosed cases of active TB. The goal of clinical evaluation is to diagnose or exclude TB and, in some situations, to identify and possibly treat LTBI. The approaches used depend on resources and circumstances; however, in all situations, contacts should be interviewed to determine whether they have symptoms consistent with TB, and they should be further evaluated and followed up.

Adult contact of index DR-TB case

Adult contacts of the index DR-TB patient should undergo evaluation including history and physical examination and those who are symptomatic should be investigated for AFB microscopy, GeneXpert MTB/RIF, and culture, chest X-ray and HIV testing.

If the contact is found to have active tuberculosis (bacteriological confirmed i.e., is sputum smear-positive), then two separate sputum specimens should be sent for culture and DST, one sent to a centre [or site] with GeneXpert machine or other rapid molecular DST for RR-TB Detection. If RR is not detected the patient is treated with first-line while waiting CDST results. The regimen should be adjusted as soon as DST results become available. If results are RR this is a DR-TB Patient and should be treated promptly with a standardized/individualized MDR-TB treatment regimen. Early treatment of DR-TB is cheaper and more effective compared to DR-TB that is detected late. Finally DR-TB patients are usually fewer in number than a drug susceptible TB patient meaning that the feasibility and cost of DR-TB contact investigation is realistic.

If initial investigation reveals of having EPTB bacteriological confirmation is often challenging. Sputum culture/DST should be done, since patient with EPTB often have subtle pulmonary involvement.

If the initial investigation is not suggestive of active TB but the contact remains symptomatic, physical examinations, chest X-ray, smears and cultures should be repeated monthly until there has been three months of follow-up. Antibiotics that are not active against TB should be used during this evaluation period (e.g. do not use fluoroquinolones, amikacin, or kanamycin). X-rays should be kept on file by clinical team because it is often helpful to compare subsequent radiographs for continued symptoms or development of new symptoms in future.

Close contacts without active tuberculosis should receive health education on TB, DR-TB and infection control principles while at home.

Preventive therapy with second-line anti-TB drugs **is not** recommended in Tanzania

Paediatric contact of index DR-TB case

DR-TB in children should be presumed in the following situations:

- A child who is a close contact of an infectious DR-TB case
- A child who is a close contact of a TB treatment failure or defaulter
- A child with proven TB who is still bacteriologically positive after five months of appropriate treatment with first-line anti-TB medications. (Treatment failure).

Children who live with DR-TB patients (close contacts), particularly young children, have a high risk of infection with DR-TB and the development of active DR-TB. Close contacts of DR-TB patients who develop TB disease most commonly have drug-resistant disease. All symptomatic children (age 14 years or under) who are household contacts of an infectious TB patient should be evaluated and screened for TB disease.

Screening should be conducted monthly for a period of three months and should include:

- History and physical examination
- A symptom and sign screening
- Sputum investigation for AFB smear microscopy and a rapid molecular diagnostic test such as GeneXpert MTB/Rif and culture and DST
- A chest X-ray even if asymptomatic
- HIV testing.

HIV counselling and testing should also be given to all paediatric contacts of MDR-TB cases. HIV-infected children with no evidence of TB disease should receive appropriate TB preventive therapy and/or close follow-up.

However if any of the above recommended investigations are not present or are inconclusive, the diagnosis of DR-TB can still be made clinically in a child contact by a TB team panel including paediatricians.

Since young children are often unable to produce sputum samples, gastric aspiration using a nasal gastric tube is the classic way to obtain sputum samples. Sputum induction is another method that has been shown to be safe and effective in young children.Resuscitation equipment should be available in the place where the sputum induction is undertaken and a physician should be available to supervise the procedure, which can be carried out by an experienced technician. e

NB: Empirical treatment of DR-TB contacts both in children and adults should be discussed in the weekly video teleconference network (TB ECHO) by the DR-TB expert team.

Preventive therapy in children exposed to DR and XDR-TB is not recommended in Tanzania.

Frequency

The alternative to chemoprophylaxis in DR-TB contacts (and therefore also XDR-TB contacts) is careful clinical follow-up, every 3 months for the first six months and every six months thereafter for at least two years.

If active disease develops, prompt initiation of treatment with a regimen designed to treat DR-TB and using the index case's DST pattern is recommended. If a child contact on a DR-TB patient meets the criteria for diagnosis or their clinical condition is highly suggestive of TB, or progressively deteriorates, DR-TB therapy can be started in accordance with the susceptibility pattern of the strain from the index case.

Confidentiality and consent

Maintaining confidentiality during contact investigation is a challenge because of the social connections between and among index cases and their contacts. All persons should be treated with respect, and confidentiality should be maintained.

Program guidelines on confidentiality and consent should be adhered to.

Key recommendations

- DR-TB contact investigation should be given high priority, and contact investigation of XDR-TB contacts must be conducted as soon as the index case is detected to avoid the loss of contacts.
- DR-TB patients should receive careful clinical evaluation and follow-up.
- Efforts should be made to obtain specimens from all possible sources, like gastric aspiration, sputum induction, or lymph node aspiration, for culture and DST, because MDR-TB is a microbiological diagnosis, even in children.
- It is recommended that contact investigation be conducted for household and close contacts when the index case has any of the following characteristics:
    - Sputum smear-positive pulmonary TB
    - DR-TB or XDR-TB (proven or suspected)
    - Is a PLHIV or other immunosuppressant conditions
    - Is a child below the age of 5.

MANAGEMENT OF DR-TB MEDICINES

Preamble

The management cycle of medicines comprises of six elements: drug selection, quantitative assessment of drug requirements, management of procurement, distribution, assurance of drug quality and ensuring rational use of medicines. Access to second-line medicines must be accompanied by measures to ensure rational use of medicines. Misuse of the medicines will result in loss of susceptibility to the second-line agents, producing circulating strains that will be extremely difficult to cure with currently available medicines.

Medicines Recommended for Treatment of DR-TB in Tanzania

Medicines recommended for treatment of DR-TB in Tanzania are the following:

Table 18. DR-TB Medicines

Group		**Medicines**
Group A – Fluoroquinolones [b]		Levofloxacin (Lfx); Moxifloxacin (Mfx);
Group B – Injectable agents		Kanamycin (Km); Capreomycin (Cm);
Group C – Other core second-line agents [b]		Ethionamide (Eto); Protionamide (Pto); Cycloserine (Cs); Linezolid (Lzd), Clofazimine (Cfz)
Group D - Add-on agents (not part of the core MDR-TB regimen)	D1	Pyrazinamide (Z) Ethambutol (E) High-dose isoniazid (H^h)
	D2	Bedaquiline (Bdq) Delamanid (Dlm)
	D3	p-aminosalicylic acid (PAS) Amoxicillin-clavulanate (Amx-Cl)

Commonly used ancillary medicines for the management of adverse events and how they are administered:

- Antiemetics

  Metoclopramide 10 mg PO/IM/IV three or four times a day PRN, usually given 30 minutes prior to meals or medications.

  Promethazine 12.5-25.0 mg PO/IM/PR every four to six hours.

- Medications for anticipatory vomiting

  Lorazepam 0.5-2.0 mg PO 30 to 60 minutes prior to anti-TB medicines.

  Diazepam 2.0-10 mg PO 30 to 60 minutes prior to anti-TB medicines.

- Antacids

  Aluminum hydroxide; the most common formulation is combination of magnesium and Aluminum hydroxide 1-30 ml PO three times a day PRN.

- H2 blockers

  Ranitidine 300 mg PO at night.

  Alternatives are cimetidine, famotidine, and nizatidine.

- Proton pump inhibitors

  Omeprazole 20 mg PO at night.

  Alternatives are esomeprazole, lansoprazole, pantoprazole, rabeprazole.

- Antifungal medicines

  Fluconazole 200 mg single dose, or 100 mg daily for 5 to 14 days.

  Clotrimazole 1 troche (10 mg) 5 times daily for 14 days.

  NB: HIV-negative MDR-TB patients may also have oral candidiasis.

- Antidiarrhoeals

  Loperamide 4 mg initially, then 2 mg PO after each unformed stool for a maximum of 16 mg/day.

  NB: Diarrhoea is common in patients receiving PAS.

  NB: Do not use for diarrhoea associated with fever or blood in the stool.

- Rehydration

  Oral rehydration packets as needed.

  IV fluids with electrolytes as needed.

IV hydration may be preferred if nausea and vomiting are associated with the dehydration.

- Psychiatric medicines

Tricyclic antidepressants

Amitriptyline: Start 25-100 mg PO at night; gradually increase the dose to usual effective dose 50-300 mg/day.

NB: Avoid in patients with risk of arrhythmias.

Benzodiazepines

Lorazepam 0.5-2.0 mg PO every four to six hours PRN.

Diazepam 2.0-10.0 mg PO two or three times a day PRN.

NB: Many benzodiazepines have a long half-life and should be used with caution.

Warning: Potential for addiction.

Antipsychotics

Haloperidol: Start 0.5 to 5.0 mg PO two or three times a day. Usual effective dose 2-10 mg/day for cycloserine-induced psychosis.

- Neurological medicines

Benzodiazepines

Diazepam: Active seizing: 0.2-0.4 mg/kg up to 5-30 mg IV.

NB: Diazepam may be used to control active seizures.

Anticonvulsants

Phenytoin: Load 10-20 mg/kg (1,000 mg in typical adult) IV, no faster than 50 mg/min. Oral load: 400 mg initially, then 300 mg in two hours and four hours. Maintenance 5 mg/kg or 100 mg PO three times a day.

Carbamazepine: 200-400 mg PO two or four times a day.

Valproic acid: Start 15 mg/kg PO daily or divided in two daily doses, maximum 60 mg/kg.

Phenobarbital: Load 15-20 mg/kg up to 300-800 mg IV at 25-50 mg/min. Maintenance 60 mg PO two or three times a day.

- Vitamins

  Pyridoxine: Use at least 50 mg for every 250 mg of cycloserine.

  Pyridoxine is important for the prevention of peripheral neuropathy and other neurotoxicity in patients receiving cycloserine.

  NB: Consider using high doses of 300 mg per day in patients with refractory side effects.

- Tricyclic antidepressants

  Amitriptyline: Start 25-100 mg PO at night; gradually increase the dose to usual effective dose 50-300 mg/day.

  NB: Low-dose amitriptyline is effective for the symptomatic treatment of peripheral neuropathy.

  Warning: Avoid in patients with risk of arrhythmias.

- Analgesics

  Ibuprofen 200-800 mg PO three or four times a day PRN.

  Acetaminophen 325-650 mg PO every four to six hours PRN.

  Analgesics may be helpful for headache or peripheral neuropathy.

  Alternatives include other similar non-steroidal anti-inflammatory (NSAID) medicines, paracetamol, or aspirin.

- Opioid-containing analgesics

  Codeine, often in combination with acetaminophen, for severe refractory headaches can be used: 15-60 mg every four to six hours.

  Warning: Potential for addiction.

- Medicines for cutaneous reactions

  Corticosteroid creams and ointments

  Hydrocortisone (1 percent to 2 percent): Apply to affected area two or four times a day.

- Antipruritus lotions

  Calamine, Caladryl lotions: Apply to affected area two or four times a day.

- Antihistamines

  Diphenhydramine 25-50 mg PO every four to six hours.

Chlorpheniramine 4 mg PO every four to six hours.

Dimenhydrinate 50-100 mg PO/IM/IV every four to six hours.

- Medicines for hypothyroidism
  Thyroid replacement hormone. Levothyroxine: Start 50-100 mcg per day (start 25-50 mcg in the elderly or patients with cardiac disease) and increase dose by 12.5-25 mcg every three to eight weeks.

- Medicines to manage fluids and electrolytes
  Loop diuretics

  Furosemide 20-80 mg IV/IM/PO every 6-24 hours.

- Electrolyte replacement therapy
  There are various formulations of potassium, magnesium, and calcium

Medicines for bronchospasm

Albuterol inhaler 90 mcg per spray, two puffs every four to six hours.

Beta-agonist nebulizers

Albuterol solution for nebulisation 2.5 mg (0.5 ml of 0.5 percent solution) every six hours.

- Corticosteroids

Inhaled corticosteroids

Beclomethasone, budesonide, or fluticasone HFA inhaler dosing depends on brand.

Oral corticosteroids

Prednisone 1-2 mg/kg per day; taper dose as indicated.

Injectable steroids can be used for severe cases of bronchospasm and rarely epinephrine is needed (see hypersensitivity section in this table for dosing).

Oral corticosteroids

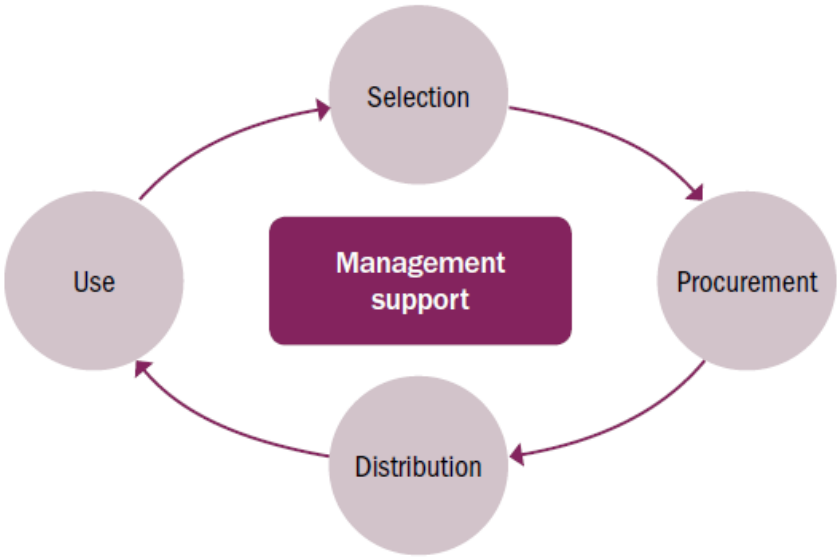
Prednisone 1-2 mg/kg per day then taper dose as indicated.

Injectable corticosteroids

Dexamethasone: Doses vary, 4 mg every 6-12 hours.

Other alternatives are prednisolone, methylprednisolone, and others.

Figure 11.Pharmaceutical management cycle



Management of DR-TB medicine will follow the management cycle indicated above, which are outlined here followed by a;

Selection:

The selection of DR-TB medicines for the programmatic management of DR-TB differs considerably from the selection of first-line treatment because a number of different regimens and medicines may be prescribed at the beginning of and within the treatment period, due to the drug-resistance patterns, availability and affordability. Currently Tanzania uses the shorter standardized regimen for 9-12 months and individualised regimen for 20-24 months.

Procurement:

The National TB and Leprosy Program (NTLP) is mandated to procure second-line anti-TB medicines from WHO-prequalified manufacturers and appropriate procurement mechanisms. Import clearance of procured products will be done by a selected clearing agent using agreeable incoterm between the supplier and the NTLP. When medicines are delivered into the country, The Tanzania Food and Drugs Authority (TFDA) takes a sample of medicines for quality analysis at the port of entry, then the consignment is transported and delivered to Medical Stores Department (MSD) Central warehouse. The quality of medicines should be maintained at all levels. To make sure the quality is maintained the NTLP should collaborate with the medicine regulatory authority to conduct a post-market surveillance of medicines stocked at MSD Zonal Office warehouse at predetermined schedule and sample size. Effective management of procurement ensures the availability of selected medicines of assured standards of quality at the right quantities, at the right time, and at affordable prices.

Forecasting:

Forecasting helps to procure appropriate quantities of DR-TB medicines. At the national level the NTLP M&E unit provides data on patients who are currently under different DR-TB treatment regimens and how many patients are expected to be enrolled on each treatment regimen during the next planned procurement period.

Forecasting at the national level is conducted annually and it utilizes a morbidity data-based approach, with projections of future needs based on records of past patients data for individual medicines. NTLP in collabolation with quantification team will quarterly review forecasting assumptions and adjust shipments accordingly. Patient information from health facility level is reported monthly to district level and districts compile data quarterly and submit to MSD through the DR-TB Report and request forms. This method assumes that the data are complete, accurate, and properly adjusted for stockouts and expected changes in demand and use. Factors to be considered in forecasting include lead times and the shelf lives of DR-TB medicines. To avoid medicines expiring, medicines with short shelf lives such as Cycloserine and Capreomycin should be delivered in staggered manner.

Distribution:

MSD zonal offices order DR-TB medicines from the MSD Central office and supply the DR-TB medicines to districts every quarter.Calculation of the amount of medicines to be orderd will depend on the number of DR-TB patients in the district.. Distribution of the medicines to facilities will be done by a recognized courier and upon delivery, the delivery note should be sent back to MSD Zonal office. The MSD Zonal office should record the batch number of medicines sent to districts/health facilities, this will facilitate tracing of medicines when batch recall is instituted.

Storage:

The entire consignment of DR-TB medicines is stored at the MSD Zonal warehouse and the consignment is issued to the districts as per the R&R quarterly form. The districts will distribute medicines to DR-TB health facilities on a monthly basis according to their request. To preserve quality, the medicines should be stored and transported using “good storage practices” and the recommendations of the manufacturer regarding temperature and humidity.

Rational use:

The rational use of DR-TB medicines should be practiced at the DR-TB Health facilities by providing comprehensive information on the medicine, the correct dosage, monitoring and management of the adverse events, contraindications, warnings and guidance on selecting the right medicines for DR-TB patients to ensure patient safety. The health worker should check that the patient knows at least the following about their treatment:

- The names of their DR-TB medicines
- The number of medicines in one dose
- The number of doses taken per day
- When to return to the DR-TB centre for more medication
- The need to report to health care provider any adverse reactions are encountered while taking second-line DR-TB medicines.

Ensuring drug supplies for the health facility

Determining the quantity of medicines needed every quarter

Two weeks before the beginning of each quarter (except for the first quarter of the year when the request is made in the first week of December to give allowance for the holidays) make an inventory of the medicines that the DR-TB patients are receiving. Each patient may have a different regimen so the quantity of each medicine must be calculated. Look at each patient's *DR-TB Treatment Card* in the section "*DR-TB Regimen*" and record the medicines that should be taken, each day row by row in a table.

Ordering at the DR-TB Health Facilities.

There are two steps in making a drug request at the DR-TB Health Facility:

Step 1: *Determining the total consumption for each drug daily, monthly and quarterly.*

a. Based on the *DR-TB Treatment Card* of the patients in the DR-TB Health Facility, record the medicines to be taken each day per patient
b. Calculate the DAILY consumption of each drug by all the patients receiving it
c. Calculate the MONTHLY consumption by multiplying the daily consumption by 30
d. Calculate the QUARTERLY consumption by multiplying the monthly consumption by three.

For example: You want to know the total consumption of Ethionamide in a DR-TB Health Facility. If you have four patients taking three tablets of 250mg Ethionamide a day, and one patient taking two tablets of the same drug per day, the next table shows that the total daily need would be 14 tablets. The monthly requirement would be 420 tablets (daily consumption multiplied by 30) and the quarterly need would be 1260 tabs (monthly consumption multiplied by 3). Repeat this procedure for all patients and medicines.

Table 19. How to calculate medicine needs

Drug	**Patient**						**Day**	**Month**	**Quarter**
	1	**2**	**3**	**4**	**5**	**6**	**Total**	**x30**	**x3**
Z 500									
E 400mg									
Amk 1gm									
Ofx 400mg									

Eto 250mg	**3**	**3**	**3**	**3**	**2**		**14**	**420**	**1260**
Cs 250mg									

Step 2: *Once the medicines required have been calculated, the DR-TB Medicines Report and Request Form (R & R) have to be filled out based on the total consumption.*

a. Write the name of the DR-TB Health Facility and the quarter the request is made for
b. Write the number of patients present
c. Write the ordering date, month and year
d. In the first column of the DR-TB *Medicines Report* and *Request Form*, write the medicines which are requested and their units of measure
e. Write the projected quarterly consumption, the one month buffer, same as quantity in the "Month" column
f. Follow the formula indicated.
g. Always double check the calculations.
h. The last two columns of the form have to be completed by the warehouse when the order is filled and sent to the requesting facility.
i. The DR-TB *Medicine Report and Request Form* should be dully signed and stamped.

Once the need for each drug for the quarter is determined, one month's supply has to be added to that sum as a buffer stock to have on hand to cater for new patient(s) and cover the period before for the next delivery (supply). After determining the total quarterly need plus one month buffer stock, the *DR-TB Medicines Requisition Form* has to be completed by subtracting the stock on hand from this number. The stock on hand is how much stock of each drug is presently in the facility at the date of placing an order.

Determine the quantity of medicines for initial patient decentralization

Every time a patient is decentralized from the DR-TB health Facility he/she is given medicines for two weeks then medicines for one quarter will be sent to the respective health facility. This first drug shipment does not require DR-TB *Medicines Report and Requisition Form* since the DR-TB Health Facility will determine the quantities to send.

The quantity of medicines to be sent to the respective health facility by the DR-TB Health Facility during this initial decentralization will depend on the timing of the decentralization. Since the decentralization of patients may not

always be on the first day of the first month of a quarter, Table 20 will serve as a guide as to the quantity to be prepared and delivered. If the decentralization happens on the first or second month of the quarter, prepare medicines for the remaining days of the quarter. Count the actual remaining doses for the month, and count 26 doses for a full month. If the decentralization happens on the third month of the quarter, send medicines for the remaining days of the quarter plus the entire coming quarter.

Table 20. Amount of Medicine to use per quater

Month of treatment	**Quantity to prepare**
First month of the quarter	Remaining days of the quarter + 1 month buffer
Second month of the quarter	Remaining days of the quarter + 1 month buffer
Third month of the quarter	Remaining days of the quarter + next quarter + 1 month buffer

Example

A local health facility receives patient X on January 15 (First month of the quarter). The MDR-TB Health Facility will need to prepare the following quantities of medicines for delivery to the specific facility:

- Actual remaining days of January (count the actual remaining doses; January 31 - 15 = 15 doses excluding Sundays)
- February and March (2 x 30 = 60) excluding Sundays = 52
- One month buffer (26)

The quantity of medicines to send to the specific facility will be for 93 days (15+52+26). The local health facility should request medicines on the second week of March for the quarter April-June.

Verifying drug supplies at the local health facility

At the local health facility, the same principles for verifying drug supplies should be applied as at the district level, although the quantities will be less and you will not order the medicines but instead verify that the medicines you receive are sufficient. Use the same table shown in the previous section to calculate the drug consumption for your DR-TB patients.

Follow these steps:

1. *List the daily number of tablets, capsules, vials or sachets per drug in the treatment regimen for every patient in the health facility*

2. *Calculate the quantity of each drug used per day, and the monthly and quarterly consumption*
3. *Complete the quarterly need with one month's buffer, and compare with the stock on hand*
4. *If the correct quantities for the quarter have not yet been received, contact the DR-TB Health Facility to correct the order.*

Always double check the calculations

Check medicines received

Upon delivery of medicines at DR-TB Health Facility, check that the correct medicines were received in the correct quantities and with expiration dates allowing full use, check if the medicines have undergone physical or chemical change. Request any missing medicines and return any which are extra, damaged or expired. If there are no discrepancies, sign the invoice receipt, indicating the correct quantities, batch numbers and expiration dates, if there are any errors fill the claim form.

At the health facilities, medicines are checked upon delivery but discrepancies are reported directly to the DR-TB Health Facility where the medicines were prepared and packed.

Important practices to be done when medicine delivery is received:

1. Sort through the drug delivery:
    a. *Inspect packages for damaged medicines, discoloured tablets, distorted boxes or canisters, etc.*
    b. *Check expiry dates*
    c. *Identify the number of tablets received and their preparations by inspecting both full and partially full containers*
    d. *Compare the quantities of each drug received with quantities delivered according to the invoice.*
2. Sign the invoice receipt
3. Note any discrepancies (e.g., insufficient quantity of a particular tablet, incorrect strength of tablet, or expired medicines). Sign any changes with your initials. Inform your pharmacist (or the contact at the DR-TB Health Facility if you work at the facility) of these changes.
4. Put the medicines in stock, placing them on the shelves behind the stock that is closer to expiration.

Only medicines that can be utilized within the expiry date should be accepted. Some of the medicines which are received might have expiry dates that are very close. This is due to the fact that the procurement process is a long one. It is normal to receive second-line anti-TB medicines with expiry dates that are close; for this reason it is important to make sure that the medicines are monitored regularly and used according to the **First Expiry, First Out (FEFO)** rule so that the medicines expiring soonest are used first. All expired medicines are

documented, stored separately from up to date (“good”) medicines and returned to the District Hospital Pharmacist of the respective district where the medicines have expired.

Monthly, check drug stock inventory

The number of DR-TB cases entering treatment each quarter or month and the quantities of medicines needed to treat them should to be counted. The district coordinator should perform a monthly stock take to ensure sufficient amounts are maintained with facility., An emergency order may be placed if the stock is not sufficient. All inventory records (including store ledgers) should be update and in place. The program monitoring staff must also perform a monthly check of drug supplies.

For health facilities, check the monthly consumption of medicines and stocks available against the medicines required until the date of the next expected quarterly supply. If there will be insufficient medicines (quarterly requirement plus one month buffer stock) or medicines in excess of two months, inform the referring DR-TB Health Facility so that the quarterly order can be adjusted.

There are a number of instances when medicines should be sent back to DR-TB Health Facility or, if you work at a DR-TB Health Facility, to the central pharmacy. Medicines will need to be retrieved when the following situations occur:

- Changes in regimen
- Patient defaults
- Patient deaths
- Patient finishes treatment
- Damaged medicines

Plan for other needed supplies

Health facilities must maintain an adequate supply of disposable needles and syringes, sterile water for injections and sufficient sputum collection containers. It should also have adequate supply of ancillary medicines that are used to counter adverse medicines reactions of patients. Adverse reactions which are not addressed may lead to patient irregular attendance and default; hence, ancillary medicines should not be prescribed for patients to buy but should be readily available for the patient at the DR-TB Health Facility. The quantities of each of these supplies must be estimated, and the quantities in the storeroom must be checked periodically. When the available supplies will not meet the needs, more must be requested according to usual procedures.

Estimate ancillary medicines

It is not easy to estimate the quantity of ancillary medicines that should be kept in a DR-TB Health facility. There are medicines that are frequently used, e.g., vitamin B6, and some that are used only as side effects are experienced. In addition a supply of co-trimoxazole may be needed if it is used for HIV-infected patients.

DR-TB Health Facilities should stock most if not all the ancillary medicines as they handle a considerable number of patients, and are where the intensive phase of treatment happens and where adverse reactions are most frequently encountered. Health facilities where there are only a few patients and where adverse reactions are more predictable and not as frequent (as patients are in the continuation phase of treatment) should not keep a stock of ancillary medicines except for vitamin B6. If/when there is a need for an ancillary medicine, the health facility can request it from the DR-TB Health Facility.

Key recommendations

- Forecasting should be a consumption-based approach
- Health facilities that will manage patients in the continuation phase will receive DR-TB medicines consignments from the MSD Zonal warehouse on quarterly basis.

MONITORING AND EVALUATION OF DR-TB SERVICES

Preamble

Monitoring and evaluation (M&E) of DR-TB is an important function of managing DR-TB services in Tanzania. Monitoring and evaluation function will enable program to collect, analyze and use information to improve DR-TB service delivery and management in Tanzania.

Types of DR-TB health information systems

Tanzania uses two sub-systems of DR-TB health information system, which are:

a) *Paper-based DR-TB health information system*: This includes various registers, cards, and forms as explained in this chapter of the guideline. This system shall be used to record and report on selected minimum indicators for the monitoring and evaluation of DR-TB services. The indicators are also explained in this chapter.
b) *Electronic-based health information system*. This captures and reports on the selected minimum indicators for the monitoring and evaluation of TB and DR-TB services at health facility, district, regional, and national levels.

Approaches of monitoring and evaluation of DR-TB services

An effective and efficient M&E system is required to inform decisions on DR-TB services. To achieve this the following approaches are used: routine monitoring, supportive supervision and mentoring, surveillance and

surveys, country situational analysis, mid-term and end-term TB and MDR-TB services review and evaluation. Overall coordination of M&E is done by the NTLP.

Routine monitoring

This involves data collected routinely for patient care and programmatic management of MDR-TB. Data are periodically compiled and analyzed to provide information on patient detection and enrolment. Likewise, retention and treatment outcomes are monitored and reported during quarterly cohort review meetings.

Supportive supervision and mentorship.

Supportive supervision and mentoring is an important element of monitoring and evaluating DR-TB services. It involves the identification and discussion of challenges and constraints encountered by staff on DR-TB services, data management, and the provision of opportunities for learning and capacity building for service provision. Supportive supervision, mentoring and coaching may be done monthly, quarterly, semi-annually or annually depending on local needs and resources. Specific tools will be designed and used during the supportive supervision, mentoring and coaching. Supportive supervision and mentoring will be planned and conducted by using competent supervisors and mentors.

Supportive supervision and mentoring to DR-TB initiating sites and ambulatory sites will be done by the national and initiating centre team respectively.

Surveillance and surveys

Routine surveillance will be used to obtain information on DR-TB burden in Tanzania. Also, special surveys will be designed and conducted to obtain information which is not captured by routine monitoring.

Country situational analysis

The country situational analysis is an important tool that brings together all the available information on disease epidemiology (including surveillance and survey data) and program structure, function, output, and impact within the context of the overall health system. The analysis will be done to identify DR-TB services strengths, weaknesses and gaps, and is often carried out as part of the planning cycle in the preparation of a multiyear national strategic plan.

DR-TB service reviews and evaluation

DR-TB services review and evaluation shall be done to cover all levels of DR-TB services and it may be done internally or externally. Programmatic DR-TB service reviews and evaluations will be organized and done as part of the mid and end term reviews of the five-year National TB strategic plans so as to inform service delivery and preparation of a multi-year national strategic plan. The evaluation of DR-TB services will be done based on an agreed frequency/timeline. It will be done by a team composed all of international and national experts, local implementation partners, ministry of health staff, civil society and donors.

DR-TB case reviews will be done by expert review panels and by cohort review teams on quarterly basis at the national, regional and district levels. DR-TB cohort reviews will systematically monitor and evaluate the interim and final outcomes of DR-TB patients at 6, 12, 24 and 36 months during and after DR-TB treatment. Ad hoc expert reviews, case management and programmatic monitoring will be facilitated by video teleconferencing facilities that will provide timely clinical review and nursing care to DR-TB patients and continued medical education through case learning.

Minimum indicators for monitoring and evaluating DR-TB services

To monitor and evaluate DR-TB services, a set of minimum indicators will be used. The indicators focus on detection, enrolment, interim results and final outcomes. Other indicators may be developed in consultation with key stakeholders to address information needs or gaps. The set of minimum indicators, sources of data, and the frequency of reporting are shown in Table 21.

Table 21. Indicators, sources of data and frequency of reporting

SN	Indicator	Numerator/Denominator	Source of data	Frequency	Remarks
DETECTION					
1	#/Proportion of TB patients with result for isoniazid and rifampicin drug susceptibility testing (DST)	Number of TB cases (in each risk category) with DST result for both isoniazid and rifampicin during the period of assessment.	Laboratory register	3 months	Require stratification by New, Retreatment and each other risk category specified in the National Policy. To be computed separately for patients detected with rifampicin resistant TB (RR-TB) alone in sites using Xpert MTB/RIF. For annual reporting to WHO (absolute numbers): DST coverage stratified by new, retreatment and previous
		Number of TB cases identified (in each risk category) during the period of assessment.	DR-TB unit register (Unit register) and treatment card. For some risk categories (e.g., contacts of MDR-TB)		
2	Number of MDR-TB cases detected among TB patients tested for susceptibility tests to	Number of confirmed MDR-TB cases in each risk category during the period of assessment.	Laboratory register DR-TB register	3 months	

SN	Indicator	Numerator/Denominator	Source of data	Frequency	Remarks
	Isoniazid and Rifampicin	Denominator: Number of TB cases (in each category risk) with DST result for both Isoniazid and Rifampicin during the period of assessment			
3	#/Proportion Confirmed MDR-TB cases tested for susceptibility to any fluoroquinolone and any second-line injectable drug	Number of confirmed MDR-TB cases tested for susceptibility to a fluoroquinolone and a second-line injectable anti-TB medication during the period of assessment.	Laboratory register	3 months	To be computed only for patients with confirmed MDR-TB. For annual reporting to WHO (absolute numbers)
		Number of confirmed MDR-TB cases during the period of assessment.	Identical to the (non-disaggregated) numerator of detection indicator 2.		
4	#/Proportion Confirmed XDR-TB cases detected among MDR-TB patients tested for susceptibility to any fluoroquinolone and any second-line injectable drug	Number of confirmed XDR-TB cases during the period of assessment.	Laboratory Register	3 months	To be computed only for patients with confirmed MDR-TB, given that the XDR-TB definition requires resistance to isoniazid as well. For annual reporting to WHO (absolute numbers).
		Denominator: number of confirmed MDR-TB cases tested for susceptibility to a fluoroquinolone and a second-line injectable anti-TB medication during the period of assessment.	Identical to the numerator of detection indicator 3.		

SN	Indicator	Numerator/Denominator	Source of data	Frequency	Remarks
ENROLMENT					
5	MDR-TB cases (presumptive or confirmed) enrolled on MDR-TB treatment. (Absolute numbers/ratio of newly enrolled to eligible). by age <15yr/15+:male /female)	Number of RR-/MDR-TB cases (presumptive or confirmed) registered and started on a prescribed MDR-TB treatment regimen during the period of assessment. Comparator: number of RR-/MDR-TB cases (presumptive or confirmed) eligible for Treatment with second-line drugs during the period of assessment.	number of cases started on treatment: second-line TB treatment register;(MDRTB Register) Number of eligible cases: basic TB register and laboratory register	3 months	Patients detected with rifampicin-resistant TB (RR-TB) in sites using xpert MTB/RIF to be included in the denominator as well as numerator. For annual reporting to WHO (absolute numbers).
6	Confirmed RR-/MDR-TB cases enrolled on MDR-TB treatment regimen. (Absolute numbers, ratio of newly enrolled to detected cases) By stratification: Cases with HIV on ART /Cases	Definition: number of confirmed RR-/MDR-TB cases registered and started on a prescribed MDR-TB treatment regimen during the period of assessment. Comparator: number of confirmed RR-/MDR-TB cases detected during the period of assessment.	Number of confirmed RR-/MDR-TB cases started on treatment: Second-line TB treatments register; Number of confirmed RR-/MDR-TB cases: laboratory register, identical to the (non-disaggregated) numerator of detection indicator 2 inclusive of any other RR-TB cases.	3 months	Patients detected with rifampicin-resistant TB (RR-TB) in sites using xpert MTB/RIF to be included in the denominator as well as numerator. For annual reporting to WHO (absolute numbers, non-disaggregated)

SN	Indicator	Numerator/Denominator	Source of data	Frequency	Remarks
	with HIV but not known to be on ART				
7	Number of confirmed XDR-TB cases enrolled on XDR-TB treatment regimen	Definition: Number of confirmed XDR-TB cases registered and started on a prescribed XDR-TB treatment regimen during the period of assessment	DR-TB Unit register	3 months	
INTERIM RESULTS					
8	#/proportion RR-/MDR-TB cases on MDR-TB treatment regimen with negative culture by six months.	Number of confirmed pulmonary RR-/MDR-TB cases registered and started on a prescribed MDR-TB treatment with negative results for culture in month 6 of their treatment. Number of confirmed RR/MDTB-cases registered and started on treatment for MDR-TB during the period of assessment.	DR-TB Unit register	6 months	Patients with rifampicin resistant -TB (RR-TB) in sites using xpert MTB/RIF who are on treatment to be included in the denominator as well as numerator. Applies only to pulmonary cases; all cases included in denominator.
9	#/Proportion RR-/MDR-TB cases on MDR-TB treatment regimen who	Number of confirmed RR-/MDR-TB cases registered and started on a prescribed MDR-TB treatment who died of any cause by the end of month 6 of their treatment	DR-TB Unit register	6 months	Patients with rifampicin resistant TB (RR-TB) in sites using xpert MTB/RIF who are on treatment to be included in the denominator as well as numerator.

SN	Indicator	Numerator/Denominator	Source of data	Frequency	Remarks
	died by six months.	Number of confirmed RR-/MDR-TB cases registered and started on treatment for, MDR-TB during the period of assessment.			
10	#/Proportion RR/MDR-TB cases on MDR-TB treatment regimen who were lost to follow-up by six months.	Number of confirmed RR-/MDR-TB cases registered and started on a prescribed MDR-TB treatment who were lost to follow-up by the end of month 6 of their treatment Number of confirmed RR-/MDR-TB cases registered and started on treatment for MDR-TB during the period of assessment	DR-TB Unit register	6 months	Patients with rifampicin resistant TB (RR-TB) in sites using xpert MTB/RIF who are on treatment to be included in the denominator as well as numerator.
11	# Patients on MDR-TB treatment regimen found not to have RR/MDR-TB.	Number of patients started on a prescribed MDR-TB treatment regimen during the period of assessment and later found not to have RR/MDR-TB	DR-TB Unit register	3 months	
12	# Patients on XDR-TB treatment regimen found not to have XDR-TB.	Number of patients started on a prescribed MDR-TB treatment regimen during the period of assessment and later found not to have RR/MDR-TB.	DR-TB Unit register	3 months	
FINAL OUTCOMES					

SN	Indicator	Numerator/Denominator	Source of data	Frequency	Remarks
13	#/Proportion RR/MDR-TB patients cured. **(XDR-TB /non-XDR-TB; HIV positive cases)**	Number of confirmed RR/MDR-TB cases started and completed treatment for a specified regimen without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative during the continuation phase.	DR-TB Unit register	24 months	Patients with rifampicin resistant TB (RR-TB) in sites using xpert MTB/RIF who are on treatment to be included in the denominator as well as numerator Applies only to pulmonary cases; all cases included in denominator for annual reporting to WHO (absolute numbers, if possible stratification of XDR-TB vs. non-XDR-TB cases)
		Number of confirmed RR/MDR-TB cases registered for treatment and starting a prescribed MDR-TB treatment regimen during the period of assessment (a calendar year).			
14	#/Proportion RR/MDR-TB patients completing treatment **(XDR-TB /non-XDR-TB;HIV positive cases)**	Number of confirmed pulmonary RR/MDR-TB cases completed treatment of a specified regimen without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative during the continuation phase.	DR-TB Unit register	24 months	Patients with rifampicin resistant TB (RR-TB) in sites using xpert MTB/RIF who are on treatment to be included in the denominator as well as numerator. For annual reporting to WHO (absolute numbers, if possible stratification of XDR-TB vs. non-XDR-TB cases)
		Number of confirmed RR/MDR-TB cases registered for treatment and starting a prescribed MDR-TB treatment regimen during the			

SN	Indicator	Numerator/Denominator	Source of data	Frequency	Remarks
		period of assessment (a calendar year).			
15	#/Proportion RR/MDR-TB patients whose treatment failed: **(XDR-TB /non-XDR-TB; HIV positive cases)**	Number of confirmed pulmonary RR/MDR-TB cases whose treatment has been terminated or need for permanent regimen change of at least two anti-TB drugs because of: 1) Lack of conversion by the end of the intensive phase; or 2) Bacteriological reversion in the continuation phase after conversion to negative; or 3) Evidence of additional resistance to Fluoroquinolones or second-line injectable drugs; or 4) Adverse drug reactions.	DR-TB Unit register	24 months	Patients with rifampicin resistant TB (RR-TB) in sites using xpert MTB/RIF who are on treatment to be included in the denominator as well as numerator. For annual reporting to WHO (absolute numbers, if possible stratification of XDR-TB vs. non-XDR-TB cases)
		Number of confirmed RR/MDR-TB cases registered for treatment and starting a prescribed MDR-TB treatment regimen during the period of assessment (a calendar year).			

SN	Indicator	Numerator/Denominator	Source of data	Frequency	Remarks
16	#/Proportion RR/MDR-TB patients who died **(XDR-TB /non-XDR-TB; HIV positive cases)**	Number of confirmed pulmonary RR/MDR-TB cases who die for any reason during the course of MDR or XDR-TB treatment. Number of confirmed RR/MDR-TB cases registered for treatment and starting a prescribed MDR-TB treatment regimen during the period of assessment (a calendar year).	DR-TB Unit register	24 months	Patients with rifampicin resistant TB (RR-TB) in sites using xpert MTB/RIF who are on treatment to be Included in the denominator as well as numerator. For annual reporting to WHO (absolute numbers, if possible stratification of XDR-TB vs. non-XDR-TB cases)
17	#/proportion RR/MDR-TB patients lost to follow-up **(XDR-TB /non-XDR-TB; HIV positive cases)**	Number of confirmed pulmonary RR/MDR-TB cases whose M/XDR-TB treatment has been interrupted for two consecutive months or more. Number of confirmed RR/MDR-TB cases registered for treatment and starting a prescribed MDR-TB treatment regimen during the period of assessment (a calendar year).	DR-TB Unit register	24 months	Patients with rifampicin resistant TB (RR-TB) in sites using xpert MTB/RIF who are on treatment to be included in the denominator as well as numerator. For annual reporting to WHO (absolute numbers, if possible stratification of XDR-TB vs. non-XDR-TB cases)

SN	Indicator	Numerator/Denominator	Source of data	Frequency	Remarks
18	#/proportion RR-/MDR-TB patients not evaluated for outcome (**XDR-TB /NON-XDR-TB; HIV** positive cases**)**	Number of confirmed pulmonary RR/MDR-TB cases whose treatment outcome is not assigned (This includes cases “transferred out” to another treatment unit and whose treatment outcome is unknown Number of confirmed RR/MDR-TB cases registered for treatment and starting a prescribed MDR-TB treatment regimen during the period of assessment (a calendar year).	DR-TB Unit register	24 months	Patients with rifampicin resistant TB (RR-TB) in sites using xpert MTB/RIF who are on treatment to be included in the denominator as well as numerator. For annual reporting to WHO (absolute numbers, if possible stratification of XDR-TB vs. non-XDR MDR-TB cases)
19	Proportion of patients started on a second-line anti-TB regimen reporting an adverse effect	Number of confirmed and presumptive RR-/MDR-/pre-XDR and XDR-TB cases registered and started on a prescribed RR-TB treatment regimen who report an adverse effect (total and for each regimen type). Number of confirmed and presumptive RR-/MDR-/pre-XDR and XDR-TB cases registered and started on second-line anti-TB treatment during the period of assessment (total and by regimen type).	DR-TB Treatment Card and the Electronic data management system for PMDT	3 months	Reported through PV reporting system

SN	Indicator	Numerator/Denominator	Source of data	Frequency	Remarks
20	Proportion of patients in each RR-TB regimen type reporting an adverse effect	Number of confirmed and presumptive RR-/MDR-/pre-XDR and XDR-TB cases for each RR-TB regimen type who report an adverse effect Number of confirmed and presumptive RR-/MDR-/pre-XDR and XDR-TB cases on each RR-TB regimen type (STR, S-MDR, I-ND, and I-O)	DR-TB Treatment Card and the electronic data management system for PMDT	3 months	
21	Proportion of relapsed by/at 12 months after successful treatment completion by RR-TB regimen type	Number of confirmed RR-/MDR-/pre-XDR and XDR-TB cases during the period of assessment who become culture positive between the time of successful treatment completion (having achieved a treatment outcome of cured or treatment completed) and 12 months post-treatment for each regimen type (STR, S-MDR, I-ND, and I-O).	DR-TB treatment cards Electronic data management system for PMDT	36 months	

SN	Indicator	Numerator/Denominator	Source of data	Frequency	Remarks
		Total number of confirmed RR-/MDR-/pre-XDR and XDR-TB cases who achieved a treatment outcome of cured or treatment completed during the period of assessment and have had sputum monitoring up to M12 post-treatment or have documented relapse within 1 year of treatment completion.			
22	Proportion of patients started on a second-line anti-TB regimen reporting an adverse effect	Number of confirmed and presumptive RR-/MDR-/pre-XDR and XDR-TB cases registered and started on a prescribed RR-TB treatment regimen who report an adverse effect (total and for each regimen type)	aDSM forms/register	6 months and at the end of treatment	
		Number of confirmed and presumptive RR-/MDR-/pre-XDR and XDR-TB cases registered and started on second-line anti-TB treatment during the period of assessment (total and by regimen type)			

SN	Indicator	Numerator/Denominator	Source of data	Frequency	Remarks
23	Proportion **of patients in each RR-TB regimen type reporting an adverse effect:**	Number of confirmed and presumptive RR-/MDR-/pre-XDR and XDR-TB cases for each RR-TB regimen type who report an adverse effect. Denominator: Number of confirmed and presumptive RR-/MDR-/pre-XDR and XDR-TB cases on each RR-TB regimen type (STR, S-MDR, I-ND, and I-O)	aDSM forms/register	6 month interim review	This safety indicator examines the proportion of patients on each of the four regimen types that report adverse effects to get a better idea of how often this occurs for patients on the different RR-TB regimens.

DR-TB recording tools

To get data for monitoring and evaluation purposes, the following DR-TB recording tools (forms card and registers) should be used:

−Presumptive DR-TB register
−MDR-TB Treatment card
−DR-TB patient identity card
−DR-TB Register
−DR-TB Contact Investigation Form
−Laboratory TB Register for culture and DST
−Drug resistance TB monthly treatment follow-up
−aDSM form
−Drug Resistant TB Referral/Transfer Form.

Presumptive DR-TB register

Each DR-TB presumptive is registered in the presumptive DR-TB register. The register is kept at the health facility and health facility staff are responsible for entering the DR-TB presumptive.

DR-TB Treatment card

Each DR-TB patient should have a DR-TB Treatment Card to monitor their intake of drugs. The card is updated daily by ticking off the supervised administration of drugs. Smear and culture results during treatment and any changes or adjustments to the regimen must be recorded in the DR-TB Treatment Card. The treatment outcome of the previous anti-TB treatment (failed, defaulted or relapse) also has to be recorded on this card. It is also important to record whether the patient ever previously received second-line drugs.

The card represents the primary source of information to complete and periodically update the DR-TB Register. The card, or a copy of the card, must always follow the patient (e.g., from an MDR-TB hospital to a district health facility where the patient will continue with the continuation phase of treatment). A copy of the card may be used as a notification form and also to report the final outcome of treatment.

DR-TB patient identity card

Each DR-TB patient has a DR-TB Patient Identity Card which is kept by the DR-TB patient for the entire period of the clinical follow-up.

DR-TB Register

Patients starting second-line TB drugs are recorded in the DR-TB register. The register is kept at the DR-TB facility. Medical officers in DR-TB facility, and district TB and leprosy coordinators are responsible for entering the confirmed DR-TB cases in the register. When a patient is starting DR-TB treatment they should be entered in the DR-TB register, the date of registration should be the day when the health staff enters the patient in the DR-TB Register. The register should be updated regularly from the DR-TB Treatment Cards and from the laboratory registers. Patients should be recorded consecutively by their date of registration. There should be a clear separation (extra line) when a new quarter is started.

Mono and poly-resistant TB patients with relatively simple resistance patterns i.e. H, HS, HE, and HZ, and whose regimens do not require or require only one second-line drug should be maintained in the regular district TB register where any adjustment of their regimen should be recorded, including any second-line agents used.

Poly-resistant TB cases involving complicated resistance patterns of HEZ requiring two or more second-line drugs should be entered into DR-TB Register at DR-TB treatment facility, but their treatment outcome will be analyzed as a separate cohort of patients from those with M/XDR-TB.

Some patients started on DR-TB regimens may be found to have drug-susceptible disease. Patients in this situation are removed from DR-TB treatment and placed on appropriate first-line therapy. Then the patient is crossed out of the DR-TB register (but the name left legible) and a comment noted in the last column that they have drug-susceptible TB. All patients who are switched should be registered in the District TB Register and reported to the NTLP on quarterly basis (see table 21 above). If they are already registered in the district register the final outcome should be documented in the original line of registration (do not create a new registration).

The DR-TB registration number is filled as follows:

0457 /KKS01 /2017 /01

0457 *refers to the region and district number for drug susceptible TB*

KKS01 *refers to the DR-TB treatment region*

2017 *refers to the year of registration*

01 *refers to the patient serial number for each district*

KKS stands for Kifua Kikuu Sugu (Swahili for MDR-TB) and 01 is the coding number assigned to the DR-TB treatment region (in this case it refers to Kibong'oto hospital); the next DR-TB centre is going to be coded as KKS02. (add table with all regions and their KKS numbers)

Serial Number	***TB Region***	***KKS number***
1.	***Kibong'oto Infectious Disease Hospital***	***KKSO1***
2.	***Ukonga Dispensary***	***KKSO2***
3.	***Kagera***	***KKSO3***
4.	***Tambukareli dispensary***	***KKSO4***
5.	***Sinza Hospital***	***KKSO5***
6.	***Rangitatu Hospital***	***KKSO6***
7.	***Geita***	***KKSO7***
8.	***Mtwara***	***KKSO8***
9.	***Mbeya***	***KKSO9***
10.	***Pwani***	***KKS10***

11.	***Amana Hospital***	***KKS11***
12.	***Morogoro***	***KKS12***
13.	***Tanga***	***KKS13***
14.	***Simiyu***	***KKS14***
15.	***Dodoma***	***KKS15***
16.	***Unguja***	***KKS16***
17.	***Tabora***	***KKS17***
18.	***Kigoma***	***KKS18***
19.	***Muhimbili***	***KKS19***
20.	***Mwanza***	***KKS20***
21.	***Mara***	***KKS21***
22.	***Arusha***	***KKS22***
23.	***Yombo Vituka Dispensary***	***KKS23***
24.	***Lindi***	***KKS24***
25.	***Kigamboni Dispensary***	***KKS25***
26.	***IDC Hospital***	***KKS26***
27.	***Magomeni Dispensary***	***KKS27***
28.	***Mwananyama Hospital***	***KKS28***
29.	***Tandale Health center***	***KKS29***
30.	***Shinyanga***	***KKS30***
31.	***Singida***	***KKS31***
32.	***Iringa***	***KKS32***
33.	***Njombe***	***KKS33***
34.	***Songwe***	***KKS34***
35.	***Rukwa***	***KKS35***
36.	***Pemba***	***KKS36***
37.	***Katavi***	***KKS37***
38.	***Ruvuma***	***KKS38***
39.	***Manyara***	***KKS39***

40.	***Buguruni Health center***	***KKS40***
41.	***Tabata Dispenary***	***KKS41***
42.	***Mnazimmoja Hospital***	***KKS42***
43.	***Mbezi dispensary***	***KKS43***
44.	***Lugalo Hospital***	***KKS44***

NB:Dar es salaam region have more sites with diferent KKS numbers due to high burden of DR-TB

Drug Resistant TB active Drug Safety Monitoring (aDSM) Form

This form is used to notify adverse effects, it is filled by the health facility DR-TB Team and it is sent to Tanzania Food and Drug Authority (TFDA).

DR-TB Referral/Transfer Form

This form is filled in by a physician when the DR-TB patient is transferred or referred to another health facility for other services and is kept in the DR-TB health facility or DTLC's office.

Drug Resistant TB Treatment Follow-Up Form

This form is filled in by a clinician and is kept in the DR-TB patient file in the DR-TB health facility.

DR-TB reporting forms

The following DR-TB reporting forms should be used to prepare reports for reporting purposes:

−Six Month Interim Outcome Assessment Form for confirmed MDR-TB cases

−Quarterly Report Form on DR-TB Detection and DR-TB Treatment Start

−Annual report Form for treatment outcome of confirmed DR-TB patients

Six Month Interim Outcome Assessment of Confirmed MDR-TB Cases

This form is filled in by a physician working at DR-TB hospital and is kept at the MDR-TB hospital. It should be used to report bacteriological status (negative, positive or no information) of those still on treatment at six months, and for those who have already defaulted, died or transferred out, this can be recorded as the final outcome. Bacteriological results are based on the smear and culture data during months five and six of treatment. Consider the six-month outcome assessment unknown for a particular patient if a culture or smear result is unknown for either month five or six.

All cases from the DR-TB Register should be included in this report. The form should be completed nine months after the closing day of the cohort. This allows culture information at month six of treatment to be included for all patients in the cohort. For instance, TB patients who started treatment during the first quarter of a year (1st January to 31st March), should have the form filled in from 1st January of the following year. Patients who do not meet the traditional definition of failure but are switched to DR-TB treatment regimens because of resistance

(DST during category I, II or III) should be included in the outcome analysis of category I, II, III – the regimen they were in initially before switching.

Quarterly Report on DR-TB Detection and DR-TB Treatment Start

This report is used to assess the number of DR-TB cases detected (distribution and trends) and the number of DR-TB cases who start treatment. The report should be made quarterly by the DR-TB hospital focal person and sent to the NTLP. A copy of the report will be kept in a reports folder at the DR-TB hospital.

The quarterly report includes:

- The number of patients, with date of result showing DR-TB during the relevant quarter taken from the Laboratory Register.
- The number of DR-TB patients started on DR-TB treatment during the quarter, taken from the DR-TB Register
- The number of DR-TB patients started on DR-TB treatment during the quarter, taken from the DR-TB Register by regimen.

If relevant, the number of XDR-TB cases registered (after cross-checking DST results with type of resistance) and the number of XDR-TB cases started on XDR-TB treatment should be added.

The patients who start treatment during the quarter may not be the same as those detected with DR-TB. This information will assist the NTLP to calculate the average delay between the detection of DR-TB and starting treatment. This report will be replaced once there is full rollout of the TB/DR-TB case based electronic TB register.

Annual report of treatment result of confirmed DR-TB patients starting DR-TB treatment (Cohort analysis report)

A DR-TB treatment cohort is defined as a group of patients who start DR-TB treatment during a defined time period. The DR-TB treatment cohort will consist of a subset of patients recorded in the DR-TB Register, i.e. those who actually started DR-TB treatment during the same quarter.

To account for the outcomes of the long and short DR-TB treatment regimens, cohort analysis should be carried out at at 12 and repeated at 15 for patients enrolled in the shorter MDR-TB regimen and 24 months and repeated at 36 months after the last patient starts treatment. The analysis is done at 24 months because most of the patients will have finished treatment, allowing the preliminary assessment of cure rates. As a few patients may be on treatment for longer than 24 months, the cohort analysis is repeated at 36 months after the last patient starts treatment. The 36-month evaluation is considered the final treatment cohort analysis result.

All patients should be assigned the first outcome they experience for recording and reporting purposes. Program may record subsequent outcomes among patients followed systematically, for example, a patient defaults on the first DR-TB treatment and then returns 14 months later to be re-registered and is cured with a second DR-TB treatment. This patient should receive a final outcome of “defaulted” in the cohort in which he or she was first registered and “cured” in the second cohort. Patients who remain on treatment at the end of a designated cohort treatment period must be identified as “still on treatment”, this is a provisional outcome until a final outcome is available.

For each cohort, an interim status should be assessed at six months after the start of treatment to monitor program progress.

Some patients may be registered twice during one cohort period (failure or default patients who are re-registered) therefore, the cohort analysis should identify the total number of treatment episodes. Stratifying cohort analysis by category of patient (e.g., new, re-treatment) will prevent the repeated inclusion of a patient in a single analysis.

All diagnosed DR-TB patients should be started on treatment. If any DR-TB patients are left untreated, the reasons for not receiving an DR-TB treatment regimen should be explicitly delineated. Some examples of reasons for exclusion from treatment include the following:
a) Died before treatment initiated; b) Patient unwilling to be treated*or treated for less than one month (four weeks)

The DR-TB management performance is eventually measured in a cohort analysis using three different registration categories.

Table 22. Reporting form of DR-TB cohort analysis

MDR-TB case categories	Treatment regimen	Total in cohort	Cured	Treatment Completed	Failed	Died	Lost to follow up	Transfer Out
Patients who are sputum smear-positive at month two **and** remain smear positive at month three of first-line regimens								
Failure of first-line regimen (patients who are sputum smear positive at five months **or** later during the course of standard new patient treatment regimen)								
Re-treatment regimen who failed								
Re-treatment regimen who relapsed								
Re-treatment regimen who returned after default								
Close contacts of a known MDR-TB case with active TB disease								

Key recommendations

−The standardized national tools for DR-TB recording and reporting should be used

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ANNEXES

Annex 1 Baseline & Follow-up examinations for monitoring of DR-TB treatment efficacy and safety

Examination	Baseline (at start of MDR/XDR-TB treatment)	Intensive phase	Continuation phase	Follow-up after treatment completion	Remarks
Clinical evaluation					
Treatment adherence and tolerance		Daily at every DOT encounter by the DOT provider			
Evaluation by clinician	√	Every day during the first weeks if hospitalized and at least every week if treated as outpatient, until the treatment is well tolerated. Once stable, the patient is seen twice a month or once a month	Monthly assessments unless there is a medical necessity to see the patient more often.	At months 6 and 12	DOT supporter sees the patient daily between consultations and signals any concerns to the clinician.
Educational, psychosocial and social consultation	√	Repeat when indicated	Repeat when indicated	Repeat when indicated	Including highlights from the informed consent, provide new information when available about medicines and regimens
Psychiatrist/HIV specialist/narcologist etc.	When indicated	When indicated	When indicated	Repeat when indicated	

Weight	√	Monthly	At least quarterly	At months 6 and 12	More frequent for children to adjust drug dosage to the bodyweight
Height	√	Monthly for children	Monthly for children		More frequent for children (to assess growth and BMI)
Neurological examination	When indicated	When indicated	When indicated	When indicated	Special attention to patients receiving Lzd
Audiometry	√	Monthly while on injectable	Monthly while on injectable	When indicated	Weekly for any patient showing an abnormality
Chest X ray	√	Every 6 months	Every 6 months	At months 6 and 12	
Electrocardiogram	Recommended for all. Mandatory for patients receiving Bdq or Dlm	At weeks 2, 4, 8, 12 and 24 after starting treatment with Bdq or Dlm. Monthly if other QT prolonging drugs other than Bdq or Dlm are used	Monthly if taking Bdq or Dlm		Special attention in patients receiving more than one QT prolonging drug (Bdq, Dlm, Mfx, Lfx, Cfz) or with low albumin (<3,4g/dl)
Visual acuity test with Snellen charts and color vision	For patients on long-term ethambutol or linezolid	When indicated	When indicated	When indicated	
Bacteriological testing					
Smear	√	Monthly	Monthly	At months 6 and 12	Programs with limited resources

Culture	√	Monthly	Monthly	At months 6 and 12	may choose to do monthly smears and cultures until conversion and then monthly smears with every other month cultures
Phenotypic DST to second-line drugs	√	When indicated: if patient remains culture-positive or reverts after month 4 of treatment	When indicated: if patient reverts after conversion	When culture-positive	Repeat DST for patients who remain culture-positive or revert after month four. This includes also DST to new drugs (Bdq and Dlm) if they are part of the regimen
Laboratory testing					
Hemoglobin and white blood count	√	Monthly	At least quarterly	When indicated	If on Lzd monitor weekly at first month, then monthly or as needed based on symptoms. For HIV-infected patients on zidovudine, monitor monthly initially and then as needed based on symptoms
Platelets	When indicated	When indicated	When indicated	When indicated	Indicated for patients using Lzd

Serum creatinine	√	Monthly while on injectable	Monthly while on injectable	When indicated	Every 1-3 weeks in HIV-infected patients, diabetics and other high-risk patients
Serum potassium	√	Monthly while on injectable	Monthly while on injectable	When indicated	Every 1-3 weeks in HIV-infected patients, diabetics and other high-risk patients
Serum magnesium and calcium	When indicated	When indicated	When indicated		Check magnesium and calcium levels whenever hypokalaemia is diagnosed. At baseline and then monthly if on Bdq or Dlm. Repeat if any ECG abnormalities develop
Liver enzymes (ALAT/SGOT, ASAT/SGPT)	√	Monthly	At least quarterly	When indicated	Periodic monitoring (every 1-3 months) for patients on prolonged Z, and patients at risk of, or with symptoms of hepatitis. Monthly if HIV-positive and if on Bdq. For patients with

					viral hepatitis monitor every 1-2 weeks for the first month, then every 1-4 weeks.
Thyroid stimulating hormone (TSH)	When indicated	When indicated	When indicated	When indicated	Close monitoring if receiving Eto /Pto and/or PAS. Every 3 months if on both drugs, every 6 months if on one of the drugs.
Serum albumin	√	Every 2 months for patients on Dlm	When indicated	When indicated	
Lipase/amylase	When indicated	When indicated	When indicated	When indicated	Special attention to patients receiving Bdq, lzd, D4T, ddI or ddc, and based on risk factors
Lactic Acid	When indicated	When indicated	When indicated	When indicated	For work up of lactic acidosis in patients on Lzd and ART
Serum glucose	√	When indicated	When indicated	When indicated	If receiving Gfx, measure fasting blood glucose at baseline and monthly
Pregnancy test	√	When indicated	When indicated	When indicated	
HIV	√	When indicated	When indicated	When indicated	Repeat if clinically indicated; should consider to test bi-yearly in high

					HIV-burden settings
Glomerular filtration	When indicated	When indicated	When indicated	When indicated	Based on risk groups (elderly, diabetes, receiving nephrotoxic drugs etc.)
Viral hepatitis serology (B and C)	When indicated	When indicated	When indicated	When indicated	Based on risk factors

Annex 2. Presumptive DR-TB Register

PRESUMPTIVE DR-TB REGISTER

Year: **Facility:**

Date	MDRTB Presumptive Number S/N	Name	DR-TB Contacts (Mark "C" and Put Index reg.Number)	Previous treated (TB Registration No	Age	Gender M/F	Complete Address and phone number	HIV Status	Date Sputum for DST Collected	Date Sputum for DST sent to Laboratory	Date Xpert results received	Results of Gene Xpert**

INSTRUCTION AT FIRST PAGE OF THE REGISTER.

Presumptive DR-TB Patient: Previous treated TB patients (relapse, failures and return after lost to follow-up), HIV positive TB patients and DR-TB contacts

Household contact

A person who shared the same enclosed living space for one or more nights or for frequent or extended periods during the day with the index case during the 3 months before commencement of the current treatment episode

Close contact

A person who is not in the household but shared an enclosed space, such as a social gathering place, workplace or facility, for extended periods during the day with the index case during the 3 months before commencement of the current treatment episode.

Register to be field after Specimen has been collected

For Contacts, use registration number of Index case

*(Pos) Positive; (Neg) Negative; (ND) Not Done/unknown. Documented evidence of HIV test performed during or before TB treatment is reported here. ** RR (MTB and RIF resistance detected); T(MTB detected RIF Resistance Not detected); TI (MTB Detected RIF resistance Indeterminate); N (MTB Not Detected); I (Invalid/Error/No Result)

Annex 3.DR-TB Treatment card.

Ministry of Health Community Development Gender Elderly and Children

DR-TB 01

National TB and Leprosy Program

Name: _____

DR-TB registration number: _____

Date of DR-TB registration: __/__/__

District TB registration number: _____

Date of district TB registration: __/__/__

Patient Address: _____

Address (Next of kin): _____

Telephone: _____

Country/District: _____

Treatment centre: _____

Sex		Age	Date of birth	
M	F			
Initial weight (kg)			**Height** (cm)	
Site (mark one):	PTB	EPTB	Both	
If EPTB, describe site:				

	Registration group	Select 1 only
1	**New**	
2	**Relapse**	
3	After **Lost to follow-up**	
4	After **failure** of first line drugs (**New patient regimen**)	
5	After **failure** of first line drugs (**Retreatment regimen**)	
6	**Transfer in** (from another 2nd-line treatment center	
7	**Other**	

Previous tuberculosis treatment episodes

No.	Start date (if unknown, put year)	Regimen (write regimen in drug abbreviations)	Outcome

Classifications of previous drug use:

Used second- line drugs previously? ❑Yes ❑No

If yes, specify: _____

_____

Drug abbreviations:

First-line drugs
H= Isoniazid
R= Rifampicin
E= Ethambutol
Z= Pyrazinamide
S= Streptomycin

Second-line drugs
Am= Amikacin
Cm= Capreomycin
Ofx= Ofloxacin
Lfx= Levofloxacin
Cs = Cycloserine
Eto= Ethionamide
PAS= p-aminosalicylic acid
BDQ=Bedaquilline
DLM=Delamanid
CfZ =Clofazimine
High-NH=HighdoseINH
Lzd =Linezolid
Km =Kanamycin
Mfx =Moxyfloxacin
Pto =Prothionamide

Treatment Review panel meetings: dates and decisions:

Date	Issue and Decision	Next date

HIV Information (Fill for all patients)
HIV status: ☐ Y ☐N ☐Unknown
Date of test: __/__/__ Results:
CD4 Cell Count: Date: __/__/__
Started on ART: ☐ Y ☐ N Date: __/__/__
Started on CPT: ☐ Y ☐ N Date: __/__/__

ART = antitretroviral therapy;

CPT = co-trimoxazole preventive therapy

Antiretroviral Flow Sheet

Regimen	Start date	Stop date	Reason for stop/change

Reasons for interruption of medications:	1 = Failure 2 = Tuberculosis/ Interaction	3 = Adverse effects 4 = Pregnancy	5 = Stock out 6 = Dose change	7 = Patient refusal 8 = PMTCT ended	9 = Other (specify)
Abbreviations:	NRTI 3TC = Lamivudine FTC=Emtricitabine AZT = ZDV= Zidovudine	NRTI ABC = Abacavir DDI = Didanosine TDF = Tenofovir	NNRTI NVP = Nevirapine EFV = Efavirenz	PI LOP/R = Lopinavir/ Ritonavir ATV/r=Atazanavir/ritonavir	PI NFV = Nelfinavir R = Ritonavir

Weight Monitoring

Month	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Date																									
Weight																									
Height																									
BMI																									

Laboratory Monitoring

Date																									
ALT/SGPT																									
AST/SGOT																									
Creatinine																									
K																									
TSH																									
Hemoglobin																									
WB count																									
CD4																									
Lipase/amylase																									
HIV test																									
Pregnancy test																									

Patient name:_____ MDR TB Registration No. _____

Drug-susceptibility testing (DST) results (notation method for DST: R = resistant, S = susceptible, C = contaminated)

Date*	INH	RMP	EMB	PZA	SM	Am	Km	Cm	Ofx	Lfx	PAS	Eto	Pto	CS	Mfx	BDQ	DLM	LZD	CFZ	Type of test (Xpert,LPA,DST)

Month	Date	Specimen Number	Smear Result	Specimen Number	Culture Result
Prior*					
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
23					
24					
25					

Chest X-ray and ECG

Date	Chest X-ray Result**	ECG result***	
At diagnosis			At diagnosis
Mo. 6			Week 2
Mo. 12			Week 4
Mo. 18			Week 8
Mo. 24			Week 12
End of Treatment			Week 24

***Report ECG and summarize as normal or abnormal

**Please note key findings of chest X-ray performed at diagnosis, during treatment, and at the end of treatment

*Refers to specimen obtained prior to MDR-TB Treatment start

Patient name:_____ MDR TB Registration No. _____

Medical Diagnosis other than tuberculosis

Date	**Type** (i.e. diabetes, hypertension, cardiomyopathy, HIV, opportunistic infections)

Adverse Effects

Date	**Type** (i.e. neuropathy, hepatitis, rash, etc.)	**Suspected drug**	**Intervention**

Vestibular, Visual and hearing Exam: (monthly while patient on injectable agent)

	DATE:															
Vestibular	Romberg															
	Heel-to-toe															
	Point-to-point															
Visual	Visual Acuity Left Eye															
	Visual Acuity Right Eye															
	Color Left Eye															
	Color Right Eye															
Audiometry	Left ear															
	Right ear															

(For audiometry exam report Hearing Loss as; N = normal, M1 = mild, M2 = moderate, S = severe, P = profound)

Patient name:_____ MDR TB Registration No. _____

Treatment Regimen (date treatment started and dosage [mg], change of dosage, and cessation of drugs

Date	H	R	Z	E	S	Km	Cm	MfxLfx	Eto/Pto	PAS	Cs	BDQ	DLM	LZD	CFZ

Administration of drugs (one line per month) INTENSIVE PHASE OF TREATMENT

Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

Mark in the boxes: X = Directly observed (in hospital or by DOT Nurse)
→ = (Draw a line) Observed by treatment supporter
N = Not supervised
∅ = Drugs not taken

Date of Discharge from inpatient care to District level care: ___/___/____

Patient name:_____ MDR TB Registration No. _____

Administration of drugs (continued) CONTINUATION PHASE OF TREATMENT

Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

Mark in the boxes: X = Directly observed (in hospital or by DOT Nurse)
→ = (Draw a line) Observed by treatment supporter
N = Not supervised
∅ = Drugs not taken

Comments:

_____
_____
_____
_____
_____
_____
_____

Treatment Outcome:

Outcome	Mark one	Date
Cured		
Completed		
Died		
Failed		
Lost to follow up		
Not evaluated		

Name of treating clinician/DTLC: _____ **Signature:** _____ **Date:** ___ / ___ / ___

Annex 4.DR-TB Patient Identity Card

Ministry of Health Community Development Gender Elderly and Children

National Tuberculosis and Leprosy Program

DR-TB 02

DR-TB PATIENT IDENTITY CARD (front side)

DR-TB Treatment Unit:	**DR-TB Reg. Number:**	**Date of registration:**		
Patient name:		**Age**	**M**	**F**
Address:	**Telephone number:**			
Place of work:	**Close relative/Treatment supporter contacts Name and Number:**	**Other Contact Name and Number:**		
Village/Street chairperson : (name and Phone number)				
Previous TB treatment history:	Number of previous treatments with first-line TB drugs (≥ 4 weeks):			
	Number of previous treatments with second-line TB drugs (≥ 4 weeks):			

Period TB drugs were taken *(start - stop date each episode)*				**Registration Group (tick)**	
Rifampicin (R)				New patient, never treated for TB, or treated for less than 4 weeks	
Isoniazid (H)					
Pyrazinamide (Z)				Previously treated with first-line drugs more than 4 weeks;H, R, Z, E only (New)	
Ethambutol (E)					
Streptomycin (S)				Previously treated with first-line drugs more than 4 weeks (Retreatment regimen)	
Fluoroquinolone (Gtx, Lfx, Mfx)					

Amikacin (Am)/Kanamycin(Km)				Previously treated with second-line drugs more than 4 weeks	
Capreomycin (Cm)					
Cycloserine (Cs)				Transfer in (from another MDR-TB treatment site)	
Clofazmine(Cfz)					
Ethionamide (Eto)/Prothionamide(Pto)					
Linezolid(Lzd)				Other (previously treated without known outcome)	
p-aminosalicylic Acid (PAS)					
Bedaquilin (BDQ)					
Delaminid(DLM)					
Other					

Pulmonary TB		**Extra-Pulmonary TB**		**Extra-Pulmonary TB Site:**	**Body weight** (kgs)

Initial sputum-smear results (neg, positive and grading, not done, no data)	**Date**	**Lab #**	**Result**	**Date**	**Lab #**	**Result**
Initial Culture results (Negative/positive *M.tb*/contaminated/not done/pending)						

Drug Sensitivity Test Results (S = sensitive; R = resistant; P = pending; ND = Not done)

Date Specimen sent for DST	**H**	**R**	**E**	**S**	**Cs**	**Am**	**Cm**	**Km**	**Ofx**	**Lfx**	**Eto**	**PAS**	**LZD**	**BDQ**	**DLM**

Contacts Tracing information:

S/No	Name of contacts	Relation to index	Screened (Tick √ appropriately)	Presumptive (Tick √ appropriately)	Confirmed (Tick √ appropriately)

(left inner side)

Medical History:

(Adverse reactions and allergies to non-TB medications; last menstrual period; method of contraception; pregnancy history)

Other complicating conditions:

(Diabetes, renal insufficiency, hepatitis, drug or alcohol abuse, psychiatric disorders, depression etc.)

Other drugs that the patient is currently taking:

Physical examination:

(General physical condition, blood pressure, length, BMI, full physical examination, urine analysis, liver /kidney function)

X-ray findings:

TREATMENT (right inner side)

Treatment Start Date:				
Second-line Regimen	**Initial phase**	**Dose**	**Continuation phase**	**Dose**
	Pyrazinamide (Z)		Pyrazinamide(Z)	
	Fluoroquinolone (Lfx, Mfx, Gtx))		Fluoroquinolone(Lfx, Mfx, Gtx)	
	Amikacin (Am)/Capreomycin(Cm)			
	Ethionamide(Eto) /Prothionamide(Pto)		Ethionamide(Eto)/Prothio namide(Pto)	
	Cycloserine(Cs)		Cycloserine(Cs)	
	Ethambutol (E)		Ethambutol(E)	
	Linezolid (Lzd)		Linezolid(Lzd)	
	Para aminosalicylic Acid (PAS)		Para aminosalicylic Acid (PAS)	
	Clofazmine(Cfz)		Clofazmine(Cfz)	
	Bedaquillin (BDQ)			
	Delaminid (DLM)			
	Isoniazid(INH hd)			
Additional treatment	Cotrimoxazole		Cotrimoxazole	
	Pyridoxine(Vit B6)		Pyridoxine(Vit B6)	
Anti-Retroviral Treatment:				
Other medicines:				

SPUTUM and WEIGHT MONITORING											
Month of DR-TB Treatment	**Sputum-smear**		**Culture** (two specimens)		**Weight** (in Kg)	Month of DR-TB Treatment	**Sputum-smear**		**Culture** (two specimens)		**Weight** (in Kg)
	1	**2**	**1**	**2**			**1**	**2**	**1**	**2**	
Initial						19					
1						20					
2						21					

3						22					
4						23					
5						24					
6						25					
7						26					
8						27					
9						28					
10						29					
11						30					
12						31					
13						32					
14						33					
15						34					
16						35					
17						36					
18						End of treatment					

INTENSIVE PHASE OF TUBERCULOSIS CHEMOTHERAPY																															
Month/ day	(X) *for date of hospital-based DOT.*																														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

CONTINUATION PHASE OF TUBERCULOSIS CHEMOTHERAPY																															
Month/ day	*For patients on health-facility DOT, put a tick (✓) on days of directly observed treatment. For patients on home - based DOT, draw a horizontal line to indicate the number of days supply given to supporter.*																														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

Treatment Outcome:

☐ Cured ☐ Completed ☐ Died ☐ Failed Lost to follow-up ☐ Not evaluated

Date: _____

Annex 5. Audio and vestibular assessment for Patient on Kanamycin or Capreomycin

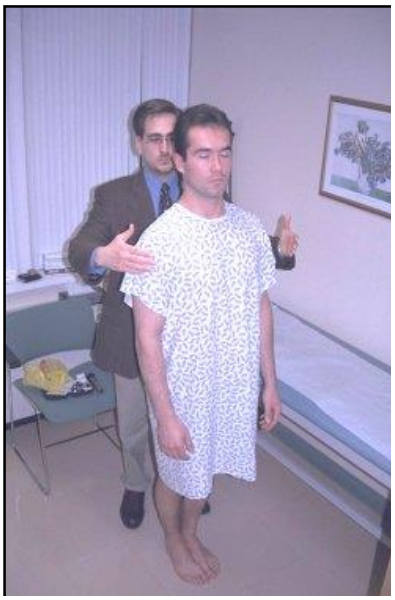
Point-to-Point Movement Evaluation

Ask the patient to extend their index finger and touch their nose, and then touch the examiner's outstretched finger with the same finger. Ask the patient to go back and forth between touching their nose and examiner's finger. Once this is done correctly a few times at a moderate cadence, ask the patient to continue with their eyes closed. Normally this movement remains accurate when the eyes are closed. Repeat and compare to the other hand.

Dysmetria is the clinical term for the inability to perform point-to-point movements due to over or under projecting ones fingers.

Rhomberg Test

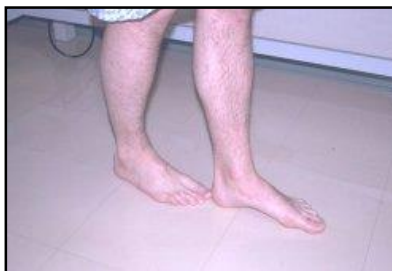
Perform the Romberg test by having the patient stand still with their heels together. Ask the patient to remain still and close their eyes. If the patient loses their balance, the test is positive.



To achieve balance, a person requires 2 out of the following 3 inputs to the cortex: 1) visual confirmation of position, 2) non-visual confirmation of position (including proprioceptive and vestibular input), and 3) a normally functioning cerebellum. Therefore, **if a patient loses their balance after standing still with their eyes closed, and is able to maintain balance with their eyes open**, then there is likely to be lesion in the cerebellum. This is a **positive Rhomberg**.

Heel to Toe

Gait is evaluated by having the patient walk across the room under observation. Gross gait abnormalities should be noted. Ask the patient to walk heel to toe across the room. Abnormalities in heel to toe walking (tandem gait) may be due to ethanol intoxication, weakness, poor position sense, vertigo and leg tremors. These causes must be excluded before the unbalance can be attributed to a cerebellar lesion. Most elderly patients have difficulty with tandem gait purportedly due to general neuronal loss impairing a combination of position sense, strength and coordination



Annex 6: MDR-TB Register

TB Treatment Registration Group	
1	**New**
2	**Relapse**
3	After **Lost to follow-up**
4	After **failure** of first line drugs (**New patient regimen**)
5	After **failure** of first line drugs (**Retreatment regimen**)
6	**Transfer in** (from another 2nd-line treatment center
7	**Other**

DST Method	
Phn	Phenotypic
LPA	Line probe assay
Gx	Gene Xpert (Xpert MTB/RIF)

Drug Abbreviations					
First-line drugs (FLDs)		Second-line drugs (SLDs)			
H	Isoniazid	Km	Kanamycin	Eto	Ethionamide
R	Rifampicin	Cm	Capreomycin	Pto	Prothionamide
E	Ethambutol	Am	Amikacin	PAS	p-aminosalycilic acid
Z	Pyrazinamide	Ofx	Ofloxacin	Cfz	Clofazimine
S	Streptomycin	Lfx	Levofloxacin	Bdq	Bedaquiline
		Mfx	Moxifloxacin	Dlm	Delamanid
		Gfx	Gatifloxacin	Lnz	Linezolid
		Cs	Cycloserine	Amx/Clv	Amoxicillin/Clavulanate
				FQ	Fluoroquinolone

MDR-TB Number*	Date of MDR-TB Treatment Start	Full Name (three names)	Sex (M/F)	Age	Address	District TB Registration number	Disease Site (P/EP/ Both)	Registration group (See above)	SLDs received previously? (y/n/unk)	Date Sample taken for DST	Date of DST Result	Result of DST (R=resistant; S=susceptible; C=contaminated; —=testing not done								
												H	R	E	S	Am/ Km	Cm	FQ —	Other —	Other —
	/ /									/ /	/ /									
						/ /				/ /	/ /									
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						/ /				/ /	/ /									

*MDR-TB Number/KKS/Year of Registration/Serial number of pt.

MDR - TB Register (Page 2)

Type of Resistance	
Gx	RR-TB by Xpert MTB/RIF
MDR	MDR by LPA or conventional DST
Poly-RR	RR+ other drug resistance (not MDR)
Mono-RR	Rifampicin mono-resistance
XDR	XDR by LPA or conventional DST
Presump	Presumptive RR-/MDR-/XDR -TB

Note: If both Gx and MDR indicate as Gx/MDR

Notation Method for Xpert MTB/RIF (Gx) Results	
T	MTB detected, rifampicin resistance not detected
RR	MTB detected, rifampicin resistance detected
TI	MTB detected, rifampicin resistance indeterminate
N	MTB not detected
I	Invalid/ no result/ error

Type of DR-TB Regimen	
SSCR	Standardized Short Course Regimen
ILCR-Bdq	Individualized Long Course Regimen + Bdq
ILCR-Dlm	Individualized Long Course Regimen +Dlm
SLCR	Standardized Long Course Regimen

Notation Method for Recording Smear Results	
No AFB	0
1-9 AFB per 100 HPF	Scanty (and report number of AFB)
10-99 AFB per 100 HPF	+
1-10 AFB per HPF	++
>10 AFB per HPF	+++

Notation Method for Recording Culture Results	
No growth reported	0
Fewer than 10 colonies	Report number of colonies
10-100 colonies	+
More than 100 colonies	++
Innumerable or confluent growth	+++

		Smear (S) and Culture (C) Results During Treatment																																															
Type of Resistance	Type of DR TB-Regimen	Baseline			Mo 1			Mo 2			Mo 3			Mo 4			Mo 5			Mo 6			Mo 7			Mo 8			Mo 9			Mo 10			Mo 11			Mo 12			Mo 13			Mo 14			Mo 15		
		S	C	Gx	S	C	BMI	S	C	BMI	S	C	BMI	S	C	BMI	S	C	BMI	S	C	BMI	S	C	BMI	S	C	BMI	S	C	BMI	S	C	BMI	S	C	BMI	S	C	BMI	S	C	BMI	S	C	BMI	S	C	BMI
		d/m/y			d/m/y			d/m/y			d/m/y			d/m/y			d/m/y			d/m/y			d/m/y			d/m/y			d/m/y			d/m/y			d/m/y			d/m/y			d/m/y			d/m/y			d/m/y		

MDR - TB Register (Page 3)

Treatment Outcomes	
C	Cure
TC	Treatment complete
F	Failed
D	Died
LTF	Lost to follow-up
NE	Not evaluated

HIV status	
Pos	Positive
Neg	Negative
Ukn	Unknown

Notation Method for Recording Smear Results	
No AFB	0
1-9 AFB per 100 HPF	Scanty (and report number of AFB)
10-99 AFB per 100 HPF	+
1-10 AFB per HPF	++
>10 AFB per HPF	+++

Notation Method for Recording Culture Results	
No growth reported	0
Fewer than 10 colonies	Report number of colonies
10-100 colonies	+
More than 100 colonies	++
Innumerable or confluent growth	+++

	Smear (S) and Culture (C) Results During Treatment																																	Treatment Outcome (see above)	Comments			
MDR - TB Number	Mo 16			Mo 17			Mo 18			Mo 19			Mo 20			Mo 21			Mo 22			Mo 23			Mo 24			Mo 25			Mo 26				HIV Status	ART (Y/N)	CPT (Y/N)	
	S	C	BMI	S	C	BMI	S	C	BMI	S	C	BMI	S	C	BMI	S	C	BMI	S	C	BMI	S	C	BMI	S	C	BMI	S	C	BMI	S	C	BMI	Date	(Circle result)	Start date	Start date	
	d/m/y			d/m/y			d/m/y			d/m/y			d/m/y			d/m/y			d/m/y			d/m/y			d/m/y			d/m/y			d/m/y							
																																		/ /	Pos; Neg; Unk	/ /	/ /	
																																		/ /	Pos; Neg; Unk	/ /	/ /	
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																																		/ /	Pos; Neg; Unk	/ /	/ /	

Annex 7.DR-TB Contact Investigation Form

DR-TB Contact Investigation Form

Name of Index Patient: ______________________________ DR-TB#: __________________

Second-line Treatment Start Date: ______________________

Index Patient Status:	On Tx	Off Tx	Died		On Tx	Off Tx	Died
Initial	☐	☐	☐	F/U 3	☐	☐	☐
F/U 1	☐	☐	☐	F/U 4	☐	☐	☐
F/U 2	☐	☐	☐	F/U 5	☐	☐	☐

Contact No.	Contact Information: Include: Name phone number(s)	Age	Sex	Rela-tion to index*	Review Period	Date of Review	TB Symptom Check: Cough?	If cough, how long?	cough-ing up blood?	Fever?	If fever, how long?	Loss of appetite or weight?	Night sweats?	Other?	If yes, specify	HIV status	TB Likely/Presumptive: Sample sent for X-pert MTB/RIF?	Referred for further eval?	Hospital findings/ further eval. results/ comment
					Initial	__/__/__	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	Y☐N☐			Y☐ N☐	Y☐ N☐	
					F/U 1	__/__/__	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	Y☐N☐			Y☐ N☐	Y☐ N☐	
					F/U 2	__/__/__	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	Y☐N☐			Y☐ N☐	Y☐ N☐	
					F/U 3	__/__/__	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	Y☐N☐			Y☐ N☐	Y☐ N☐	
					F/U 4	__/__/__	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	Y☐N☐			Y☐ N☐	Y☐ N☐	
					F/U 5	__/__/__	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	Y☐N☐			Y☐ N☐	Y☐ N☐	
					Initial	__/__/__	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	Y☐N☐			Y☐ N☐	Y☐ N☐	
					F/U 1	__/__/__	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	Y☐N☐			Y☐ N☐	Y☐ N☐	
					F/U 2	__/__/__	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	Y☐N☐			Y☐ N☐	Y☐ N☐	
					F/U 3	__/__/__	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	Y☐N☐			Y☐ N☐	Y☐ N☐	
					F/U 4	__/__/__	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	Y☐N☐			Y☐ N☐	Y☐ N☐	
					F/U 5	__/__/__	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	Y☐N☐			Y☐ N☐	Y☐ N☐	
					Initial	__/__/__	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	Y☐N☐			Y☐ N☐	Y☐ N☐	
					F/U 1	__/__/__	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	Y☐N☐			Y☐ N☐	Y☐ N☐	
					F/U 2	__/__/__	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	Y☐N☐			Y☐ N☐	Y☐ N☐	
					F/U 3	__/__/__	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	Y☐N☐			Y☐ N☐	Y☐ N☐	
					F/U 4	__/__/__	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	Y☐N☐			Y☐ N☐	Y☐ N☐	
					F/U 5	__/__/__	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	Y☐N☐			Y☐ N☐	Y☐ N☐	
					Initial	__/__/__	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	Y☐N☐			Y☐ N☐	Y☐ N☐	
					F/U 1	__/__/__	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	Y☐N☐			Y☐ N☐	Y☐ N☐	
					F/U 2	__/__/__	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	Y☐N☐			Y☐ N☐	Y☐ N☐	
					F/U 3	__/__/__	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	Y☐N☐			Y☐ N☐	Y☐ N☐	
					F/U 4	__/__/__	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	Y☐N☐			Y☐ N☐	Y☐ N☐	
					F/U 5	__/__/__	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	Y☐N☐			Y☐ N☐	Y☐ N☐	
					Initial	__/__/__	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	Y☐N☐			Y☐ N☐	Y☐ N☐	
					F/U 1	__/__/__	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	Y☐N☐			Y☐ N☐	Y☐ N☐	
					F/U 2	__/__/__	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	Y☐N☐			Y☐ N☐	Y☐ N☐	
					F/U 3	__/__/__	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	Y☐N☐			Y☐ N☐	Y☐ N☐	
					F/U 4	__/__/__	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	Y☐N☐			Y☐ N☐	Y☐ N☐	
					F/U 5	__/__/__	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	____ wks	Y☐N☐	Y☐N☐	Y☐N☐			Y☐ N☐	Y☐ N☐	

***Key for Relation to Index:** HH=household (HH1= spouse, HH2= child, HH0= other member of the household); Pr=Prison mate; Wk=coworker; (e.g., at school, shared barrack) [Sept/2016]

Annex 8: Laboratory TB Register for culture/DST-change

Part1

LABORATORY TB REGISTER FOR CULTURE AND DST								
Date received	S/N	**Patient details**				**Specimen**		
		Patient name	District TB number	Health facility	Type of Patient	Type of specimen	Dates	Transit time (TT)
							collected:	
							processed:	

Part ii

AFB-smear		Culture Laboratory serial number	**Quantified growth readings**									
Local result	Culture lab smear result		Media inoculated	Date inoculated	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8

Part iii

Culture result			
MGIT (Fill final results)	ZN smear: morphology	(Provisional) result	Date culture result reported

Part iv

DST Results for first-line					
Isoniazid	Isoniazid	Rifampicin	Streptomycin	Pyrazinamide	Ethambutol

Part v

DST batch No.	DST Result for Second-line			DST Final result (Susceptible TB)	
	Ofloxacin	Kanamycin	Others	Resistant/ Sensitive	Date reported

Part vi

DST Final result (Second-line)		Molecular results					Remarks
Resistant/ Sensitive	Date reported	LPA 1st line		LPA 2 line		Xpert (RR,T,N,I,TI)	
		R	H	FQ	SLI		

Annex 9. Drug resistance TB monthly treatment follow-up-

Ministry of Health Community Development, Gender, Elderly and Children
National Tuberculosis and Leprosy Program
DRUG RESISTANT TB MONTHLY TREATMENT FOLLOW-UP FORM

Surname: _____ First Name _____

Age _____ (years) Sex ___ (M/F) MDR-TB
Reg. No. _____Hospital File No.: _____ Location _____
Treatment Mo. _____

TB Symptoms

Improved	Not improved/worsened	
☐	☐	Cough
☐	☐	Bloody sputum (haemoptysis)
☐	☐	Fever/night sweats
☐	☐	Shortness of breath
☐	☐	Weight loss

Pregnancy	
Breastfeeding	
Liver disorders	
Renal insufficiency	
Contraception	
Psychiatric disorders/Epilepsy	
Diabetes mellitus	
Substance abuse	
Other (please indicate)	

Side Effects

☐Nausea/vomiting
☐ Fatigue
☐ Visual problems (recent change)
☐ Headache
☐ Confusion
☐ Rash
☐ Ringing in ears
☐ Deafness
☐ Joint pain
☐ Tingling in hands/legs/feet
☐ Jaundice (yellow eyes, skin)
☐ Others

Adverse Events

☐Hypokalemia
☐Psychosis
☐Depression
☐Nephrotoxicity
☐ Ototoxicity (hearing loss)
☐ Peripheral neuropathy
☐Rash
☐ Hepatotoxicity
☐ Fainting
☐Other _____

Physical Exam **Functional Status**

Wt _____ (kg) ☐ Functional

Ht/Lng ____ (cm) ☐ Ambulatory

BP ___ /____ ☐ Bedridden

Temp _____ (C) RR _____ /min

N AN

☐☐ Head, ears, eyes, nose, throat _____

☐☐ Lymph nodes _____

☐☐ Heart _____

☐☐ Lungs _____

☐☐ Abdomen _____

☐☐ Skin _____

☐☐ Urogenital _____

☐☐ Musculoskeletal _____

☐☐ Neurological _____

☐☐ Others _____

Lab results (blood tests, sputum smear /culture, etc.)

Exam or Test	**Date**
☐ Sputum smear ____/____/____	
☐ Sputum culture ____/____/____	
☐ Chest X – ray ____/____/____	
☐ DST (one/two) ____/____/____	
☐ RFT (serum creatinine) ____/____/____	
☐ LFT (ASAT, ALAT, bilirubin) ____/____/____	
☐ TSH ____/____/____	
☐ FBP ____/____/____	
☐ Serum electrolytes (Potassium, Magnesium, Calcium,Sodium) ____/	

SPECIAL CONDITIONS ORDERED THIS MONTH

HIV Information (Fill for all patients)
HIV testing done: ☐ Y ☐N ☐Unknown
Date of test: ___/___/___ Results:
CD4 Cell Count: Date: ___/___/___
Started on ART: ☐ Y ☐ N Date: ___/___/___
Started on CPT: ☐ Y ☐ N Date: ___/___/___

INVESTIGATIONS

Note details of condition in Comments section below

Annex 10.Drug Resistant TB Referral/Transfer Form-

MDR TB 06

MINISTRY OF HEALTH, COMMUNITY DEVELOPMENT, GENDER, ELDERY AND CHILDREN

National Tuberculosis and Leprosy Programme

MDR TB
REFERRAL/TRANSFER FORM

MINISTRY OF HEALTH, COMMUNITY DEVELOPMENT, GENDER, ELDERY AND CHILDREN

NATIONAL TUBERCULOSIS AND LEPROSY PROGRAMME

MDR TB REFERRAL/TRANSFER FORM

(Complete top part in triplicate)

Tick and comment to indicate the reason for this referral or transfer:

☐ Referral to register and begin MDR TB treatment ☐ Referral for _____ ☐ Transfer (registered patient is moving)

Name/address of referring/transferring facility _____

District_____ Region_____

Name/address of facility to which patient is referred/transferred _____

_____District_____Region_____

Name of the Patient (Three Names)_____ Age _____

Sex: M ☐ F ☐ Tel/Mobile No:- _____

Address (if moving, future address) _____

_____

Name and address of contact person for patient_____

Mobile No: -

Name and address of Area Leader/Village Secretary _____

_____Mob No: - _____

Diagnosis*_____

District TB No/MDR TB No: -.* _____ Date treatment started*_____

Category of treatment:* -

☐ New cases, smear & culture positive, MDRTB -positive
☐ Retreatment, MDR -TB
☐ New case, smear & culture negative, Extrapulmonary MDR-TB
☐ XDR-TB

Drug-susceptibility testing (DST) results (notation method for DST: r = resistant, s = susceptible, c = contaminated). For Xpert MTB/Rif Results, tick on appropriate box

DST Results Date	INH	RMP	EMB	SM	X-PERT MTB/Rif Results Date	MTB+ Positive	MTB/Rif Positive	MTB Negative	Invalid

Drugs patient is receiving by Names _____

Remarks (e.g. side-effects observed) _____

_____

Name _____Signature _____ Position

_____ Date of referral/transfer_____

**Complete if known. If this is a referral for diagnosis, these items may be unknown.*

For use by facility to which patient has been referred or transferred:

Name of facility _____

District _____ Date _____

Name of patient _____District TB No/MDR TB No_____

The above patient reported at this facility on _____(date)

Name_____Signature_____Position_____

Send this part back to referring/transferring facility as soon as patient has reported

NB 1st Copy: - For the Receiving facility • 2nd Copy: - For the patient • 3rd Copy: - For the Referring facility

Annex 11: aDSM – active drug safety monitoring Forms

Ministry of Health Community Development Gender Elderly and Children (MOHCGEC)
National Tuberculosis and Leprosy Programme
DRUG RESISTANT TB (DR-TB) aDSM FORM

The information collected will be kept confidential

Surname: _____Middle name_____ First Name _____

Birth Date_____ Sex ____ (M/F) DR-TB Reg. No. _____

Hospital File No.: _____ Location _____ Treatment Mo. _____

PREGNANCY ☐ YES ☐ NO ☐ N/A HEIGHT (cm)

WEIGHT (kg)

SAE or AE of special interest	☐ SAE ☐ AE of special interest

Serious adverse event(s) information		**SAE1**	**SAE2**	**SAE3**
Adverse event term				
Description of Adverse event				
Event onset date (***dd/mm/yyyy***)		_____ / _____ / _____	_____ / _____ / _____	_____ / _____ / _____
Event end date (***dd/mm/yyyy***)		_____ / _____ / _____	_____ / _____ / _____	_____ / _____ / _____
Duration if <1 day (***hrs/min***)		_____ / _____	_____ / _____	_____ / _____
If SAE, seriousness category		☐	☐	☐
	Death	*In case of death:* Death date: _____ / _____ / _____ Autopsy: Yes ☐ No ☐	*In case of death:* Death date: _____ / _____ / _____ Autopsy: Yes ☐ No ☐	*In case of death:* Death date: _____ / _____ / _____ Autopsy: Yes ☐ No ☐

	Life-threatening	☐	☐	☐
	Hospitalization required / prolonged	Required ☐ Prolonged ☐ *Hospitalization dates:* Admission: _____ / _____ / _____ Discharge: ____ / _____ / _____	Required ☐ Prolonged ☐ *Hospitalization dates:* Admission: _____ / _____ / _____ Discharge: ____ / _____ / _____	Required ☐ Prolonged ☐ *Hospitalization dates:* Admission: _____ / _____ / _____ Discharge: ____ / _____ / _____
	Persistent or significant disability / incapacity	☐	☐	☐
	Congenital anomaly / birth defect	☐	☐	☐
	Otherwise medically important	☐	☐	☐

Adverse event of Special Interest	**Adverse Events** ☐ CNS Toxicity ☐ Hypokalemia ☐ Optic nerve disorder ☐ Hepatotoxicity ☐ Hypothyroidism ☐ Lactic acidosis ☐ Pancreatitis ☐ Nephrotoxicity ☐ Prolonged QT interval ☐ Ototoxicity ☐ Myelosuppression ☐ Peripheral neuropathy ☐ Other _____

	SUSPECTED DR-TB DRUG						
Suspected drug name (Generic and Brand)	**Dose & route**	**Formulation**	**Frequency**	**Batch number and expiry date**	**Treatment start date (*dd/mm/yyyy*)**	**Treatment stop date (*dd/mm/yyyy*)**	**Continued**
					____ / _____ /	____ / _____ /	☐ Yes ☐

					_____	_____	No
					____ / _____ / _____	____ / _____ / _____	☐ Yes ☐ No
					____ / _____ / _____	____ / _____ / _____	☐ Yes ☐ No
					____ / _____ / _____	____ / _____ / _____	☐ Yes ☐ No
					____ / _____ / _____	____ / _____ / _____	☐ Yes ☐ No

CONCOMITANT MEDICATIONS

Drug name (Generic and Brand)	**Daily dose and route**	**Indication**	**Treatment start date** (*dd/mm/yyyy*)	**Treatment stop date** (*dd/mm/yyyy*)	**Continued**
			_____ / _____ / _____	____ / _____ / _____	☐ Yes ☐ No
			____ / _____ / _____	____ / _____ / _____	☐ Yes ☐ No
			____ / _____ / _____	____ / _____ / _____	☐ Yes ☐ No
			____ / _____ / _____	____ / _____ / _____	☐ Yes ☐ No
			____ / _____ / _____	____ / _____ / _____	☐ Yes ☐ No

ACTION TAKEN

☐ Medicine withdrawn
☐ Dose not changed
☐ Dose Increased
New Dose:_____ New frequency: ____ times/wk
☐ Dose reduced
New Dose:_____ New frequency: ____ times/wk
☐ Unknown

OUTCOME OF SAE

☐ Recovered / Resolved
☐ Recovering / Resolving
☐ Recovered with sequealae
☐ Not recovered / Not resolved
☐ Died
☐ Unknown

Annex 12.DR-TB Medicine Requisition Form

MINISTRY OF HEALTH, COMMUNITY DEVELOPMENT GENDER, ELDERLY AND CHILDREN

NATIONAL TB AND LEPROSY PROGRAM

DR-TB Medicine Requisition Form **FORM 20**

Region_____ Number of Patients in Intensive Phase _____

District_____ Number of Patients in Continuation Phase _____

Requesting Facility_____ Date Requested_____

Period order will cover (circle) **Q1** **Q2** **Q3** **Q4** **Year**_____

SN	**Description** (specify preparation of drug	**Unit**	**Quarterly Use**	**Buffer**	**Quantity Needed**	**Stock On-hand**	**Quantity Requested**	**Units per Pack**	**Number of Packs Sent**
			(a)	*(b)*	*(c=a+b)*	*(d)*	*(e=c-d)*		
1									
2									
3									
4									

5									
6									
7									
8									
9									
10									
11									

Prepared by;
Name_____ **Title – D.PHARMACIST**_____ **Date & Signature**_____ **Stamp**

Checked by;
Name_____ **Title – DTLC**_____ **Date & Signature**_____ **Stamp**

Approved by;
Name_____ **Title – DMO**_____ **Date & Signature**_____ **Stamp**

Annex 13.Quality Defects Reporting Form

TANZANIA FOOD AND DRUGS AUTHORITY
FORM FOR REPORTING POOR QUALITY PRODUCTS

Note: Identities of reporter(s) will remain confidential

PRODUCT IDENTITY	
Brand Name: …… Generic Name: …….. Batch/Lot Number: …….. Date of Manufacture: …… Expiry Date: …… Country of Origin: ……	Name and Address of Distributor/Supplier: …….. …… …… …… ……
PRODUCT FORMULATION (Tick appropriate box)	**COMPLAINT (Tick appropriate box(es))**
❑ Tablets/Capsules	❑ Color change
❑ Oral Suspension/Syrup	❑ Turbid Solution
❑ Injection	❑ Change of Odor
❑ Cream/Ointment/Liniment/Paste	❑ Caking
❑ Powder for reconstitution of suspension	❑ Moulding
❑ Powder for reconstitution of injection	❑ Separating
❑ Eye drops	❑ Powdering/Crumbling
❑ Ear drops	❑ Incomplete Pack
❑ Nebulizer solution	❑ Mislabeling
❑ Diluent	❑ Other, please specify:

❑ Other, please specify:			
Describe the complaint in detail:			
STORAGE CONDITIONS			
Does the product require refrigeration?	❑ Yes	❑ No	Other details (if necessary)
Was the product available at the facility?	❑ Yes	❑ No	
Was the product dispensed and returned by client?	❑ Yes	❑ No	
Was the product stored according to manufacturer's recommendations?	❑ Yes	❑ No	
Comments (if any)			
REPORTER NAME AND CONTACT ADDRESS			
Name of Reporter: Contact Phone No: _____ E-mail: (if available) _____ Date of this report: _____	Contact Address:		
Thank you for your cooperation	***Ref No. (for official use)***		

Annex 14.Adverse Drug Reaction Reporting Form for HCWs

TFDA Tanzania Food & Drugs Authority

TANZANIA FOOD AND DRUGS AUTHORITY

REPORT OF SUSPECTED ADVERSE REACTION TO MEDICINES OR VACCINES

Note: Identities of reporter, patient and institution will remain confidential

II. DETAILS OF ADVERSE REACTION	
Description of reaction: …… …… …… …… ……	Date Reaction Started →__/__/____ Date Reaction Stopped (if known) →__/__/____ Onset latency……

I. PARTICULARS OF PATIENT	
Patient Initials or Record No.: - _____ Date of Birth (dd-mm-yyyy) or age:- _____	Sex: - Male ❑ Female ❑ Weight in kg:- _____

Health related information: Medical history (e.g. hepatic, renal, HIV), allergies, pregnancy, smoking, alcohol use, etc. ***Please write any relevant medical an laboratory results including dates (if done)***……

……

III. DETAILS OF SUSPECTED MEDICINE/VACCINE USED							
Name of suspected medicine(s)/vaccine(s) (Specify brand name or manufacturer if known).	**Dosage**	**Frequency**	**Route**	**Therapy Date**		**Batch. No & Expiry date (If known)**	**Reason for use**
				Start	**Stop**		
Other medicines used at the same time and or one month before (including herbal medicines)							
1.							

2.							
3.							

IV. MANAGEMENT OF ADVERSE REACTION

Reaction subsided after stopping the suspected drug/reducing the dose:	❑ Yes ❑ No ❑Unknown
Reaction reappeared after reintroducing drug:	❑ Yes ❑ No ❑ Not applicable
Seriousness of the Reaction **(please tick all that apply):**	
❑ Discomfort but able to work	❑ Caused persistent disability or incapacity
❑ Discomfort could not work	❑ Caused a congenital anomaly
❑ Required or prolonged hospitalization	❑ Patient Died
❑ Life threatening	❑ Others, please give details……

Treatment of adverse reaction ❑ No ❑ Yes **(if yes please specify)**:……

……/……/……

……

Outcome of the reaction	Not yet recovered ❑	Recovered (Date):___ ____ ____	❑ Died (Date):___/___/___ Unknown ❑

Cause of death……

……

V. THERAPEUTIC FAILURE

PLEASE WRITE IF THE MEDICINE(S)/VACCINE(S) SHOWED LACK OF EFFICACY BELOW :

(Continue at the back)

VI. MEDICATION ERRORS AND OVERDOSAGE

PLEASE WRITE DETAILS OF MEDICATION ERRORS AND OVERDOSAGE BELOW:

PLEASE WRITE ANY OTHER RELEVANT ADDITIONAL INFORMATION BELOW :

VII. PARTICULARS OF REPORTER /HEALTH CARE PROVIDER

Name: _____ Profession: _____

Contact phone No: _____ E-mail: _____

Signature: _____ Date of this report: ____ / / ____ _____

Name and Address of the health facility:

_____

___

_____

_____

_____

❑ *Please tick if you wish to receive information about other local reports associated with the suspected drug(s)*

Thank you for your cooperation	***Submission of an ADR case report does not discredit the competence of the reporter.***	***Ref No. (for official use)***

First Fold

Guide to filling the form

How to report?

- Dully fill in the form as required
- Use a separate form for each patient
- Report direct to TFDA through the following addresses:-


Mail : Tanzania Food and Drugs Authority,
P. O. Box 77150, Dar es Salaam


Fax:: 22- 2450793


Phone: 22-2450512/2450751

An Adverse Drug Reaction (ADR) is defined as a reaction which is noxious and unintended, and which occurs at doses normally used in human for prophylaxis, diagnosis, or therapy of a disease, or for the modification of physiological function.

What to report?

Please report all undesirable patient effect suspected to be associated with drugs, cosmetics or medical devices use.

Report even if:

- You're not sure that the product caused the event
- You don't have all the details

Moisten gum and fold. For maximum adhesion, press down for few seconds

Second Fold

No postage stamp required

POSTAGE WILL BE PAID BY LICENCEE

If posted in Tanzania

BUSINESS REPLY SERVICE LICENCE No. BRS 01

TO: THE DIRECTOR GENERAL
TANZANIA FOOD AND DRUGS AUTHORIT
P. O. BOX 77150
DAR ES SALAAM

Annex16.Patient ADR Reporting Form

TANZANIA FOOD AND DRUGS AUTHORITY
ADVERSE REACTION PATIENTS' REPORTING FORM

(For reporting adverse reactions and product problems by non-health care providers)

Note: Identities of patient will remain confidential

I. PERSON REPORTING	
Patient ❑ Community health worker ❑ Mother ❑ Relative ❑ Other ❑ Specify: _____ Name of the health facility the medicine was obtained from: _____	Sex: - Male ❑ Female ❑ Age of the patient_____
II. BRIEF DESCRIPTION OF THE REACTION/EVENT	

	Date Reaction Started →___ ___ ____ Date Reaction Stopped (if known) → ___ ___ ___ Date reported……

III. DETAILS OF SUSPECTED MEDICINE USED

Name of suspected medicine(s)	Dosage	Frequency	Route	Therapy Date	
				Start	Stop
1					
2.					
3.					

IV. DESCRIPTION OF ANY HERBAL MEDICINE THE PATIENT WAS TAKING

V. SERIOUSNESS OF THE ADVERSE REACTION

❑ Discomfort but able to work	❑ Caused persistent disability or incapacity
❑ Discomfort could not work	❑ Caused a congenital anomaly
❑ Required or prolonged hospitalization	❑ Patient Died: Date of death _____
❑ Life threatening	❑ Others, please give details……

VI. SOURCE OF THE MEDICINE

❑ Hospital Pharmacy	❑ Traditional Healer
❑ Retail Pharmacy	❑ Supermarket/Open Market
❑ Wholesale Pharmacy	❑ Family/Neighbour
❑ ADDO Shop	❑ Others, please specify……

VII. REPORTER NAME AND CONTACT ADDRESS

Name: (Optional): Contact Address:

Contact Phone No: _____

E-mail: (if available) _____

Date of this report: _____

Thank you for your cooperation	*Ref No. (for official use)*

First Fold

Guide to filling the form

How to report?

- Dully fill in the form as required
- Report direct to TFDA through the following addresses:-

Mail: Tanzania Food and Drugs Authority,

P. O. Box 77150, Dar es Salaam

Fax:: 22- 2450793

Phone: 22-2450512 /2450751

An Adverse Drug Reaction (ADR) is defined as a reaction which is noxious and unintended, and which occurs at doses normally used in human for prophylaxis, diagnosis, or therapy of a disease, or for the modification of physiological function.

What to report?

Please report all undesirable effects suspected to be associated with drugs, cosmetics or medical devices use.

Moisten gum and fold. For maximum adhesion, press down for few seconds

Second Fold

POSTAGE WILL BE PAID BY LICENCEE

No postage stamp required
If posted in Tanzania

BUSINESS REPLY SERVICE LICENCE No. BRS 01

TO: THE DIRECTOR GENERAL
TANZANIA FOOD AND DRUGS AUTHORIT
P. O. BOX 77150

DAR ES SALAAM

Annex 17.Patient ADR Alert Card

TANZANIA FOOD AND DRUGS AUTHORITY *Front side*

ADVERSE DRUG REACTION ALERT CARD

PATIENT NAME:
.....
AGE: ..... GENDER:
.....
DATE ISSUED: .....ADDRESS:
.....
SUSPECTED DRUG(S):
.....
DESCRIPTION OF REACTION:
.....
Other comments (if any):
.....
.....

Please carry this card with you at all times and remember to show it to your health care provider at each time of consultation	***Tafadhali hakikisha umebeba kadi hii kila wakati na kumbuka kumwonyesha mhudumu wa afya unapo pata matibabu***

P. O. Box 77150, EPI Mabibo, Off Mandela Road, Dar es Salaam, Tel: +255-22-2450512/2450751/2452108, Fax: +255-22-2450793, Website: **www.tfda.or.tz**, Email: info@tfda.or.tz, adr@tfda.or.tz

CRITERIA FOR ISSUE OF A PATIENT ALERT CARD *Rear side*

The alert card is to be given to:

- Patients who are hypersensitive/allergic/intolerant to a particular drug,
- Patients who developed a 'near-fatal' reaction to any particular drug,
- Patients who had a drug-induced morbidity to any drug,
- Patients who had hospital admission due to an AR to any drug.

Annex 18. Quarterly report RR-TB/MDR-TB/XDR-TB Detection and Treatment start

Ministry of Health Community Development Gender Elderly and Children

National Tuberculosis and Leprosy Program

Quarterly report on RR-TB/MDR-TB/XDR-TB Detection and Treatment start

Name of unit_____

Date filled in_____

Patients identified during .Quarter_____Year_____

Date of the report_____

1. Number of patients detected with RR-TB/MDR-TB/XDR-TB in the lab (by date of result RR-TB/MDR-TB/XDR-TB in laboratory register) during the quarter.

RR-TB	MDR-TB	XDR-TB

2. Number of MDR-TB patients who started MDR-TB treatment during the quarter

Category Started on treatment	New	Relapse	Treatment after loss to follow-up	After failure of first treatment with first-line drugs	After failure of retreatment regimen with first-line drugs	After failure of treatment with second-line drugs	Other previously treated patients	Transfer in	Total
Confirmed Cases									
Presumptive cases									
Total									

Signature_____

Annex 19. Six-monthly report on detection of TB cases with rifampicin resistance (RR-TB) and multidrug resistance (MDR-TB)

Ministry of Health Community Development Gender Elderly and Children

National Tuberculosis and Leprosy Program

Six-monthly report on detection of TB cases with rifampicin resistance (RR-TB) and multidrug resistance (MDR-TB)

Name of unit_____

Date filled in_____

Quarter treatment was started_____

Date of the report_____

Category Started on treatment	Number of TB cases					
	With result for Susceptibility to Rifampicin only	Resistant to Rifampicin (RR) only	With result for Susceptibility to both Isoniazid and Rifampicin	Resistant to both Isoniazid and Rifampicin (MDR-TB)	With MDR-TB and tested for a fluoroquinolone and a 2nd line injectable	With XDR-TB
New						
Relapse						
Treatment after loss to follow-up						
After failure of first treatment with first-line drugs						
After failure of retreatment regimen with first-line drugs						
After failure of						

treatment with second-line drugs						
Other previously treated patients						
Transfer in						
Contact of a confirmed MDR-TB case						
Total						

Annex 20.Six month interim outcome assessment of confirmed MDRTB-cases

Ministry of Health Community Development Gender Elderly and Children

National Tuberculosis and Leprosy Program

Six month interim outcome assessment of confirmed MDRTB-cases

(To be filled out 9 months after treatment start)

Name of unit_____

Date filled in_____

Quarter treatment was started_____

Date of the report_____

Category Started on treatment	Bacteriological result at 5 and 6 months of treatment			No longer on treatment	
	Negative cultures during month 6 and or month 5	Positive cultures during month 6 and or month 5	Unknown culture at month 6 and or month 5 (consider unknown if culture is done done)	Died	Lost to follow-up

New					
Relapse					
Treatment after loss to follow-up					
After failure of first treatment with first-line drugs					
After failure of retreatment regimen with first-line drugs					
After failure of treatment with second-line drugs					
Other previously treated patients					
Transfer in					
Total					

Annex 21. Annual report of treatment result of confirmed MDR-TB patients staring second-line treatment

Ministry of Health Community Development Gender Elderly and Children

National Tuberculosis and Leprosy Program

Annual report of treatment result of confirmed MDR-TB patients staring second-line treatment

(To be filled in 12 and 15 for shorter regimen and 24 and 36 months for longer regimen past the closing date of year of treatment)

Name of unit_____

Date filled in_____

Year treatment was started_____

Date of the report_____

Patient Group	Cured	Treatment completed	Failed	Lost to follow-up	Died	Not evaluated	Still on treatment	Total
New								
Relapse								
Treatment after loss to follow-up								

After failure of first treatment with first-line drugs								
After failure of retreatment regimen with first-line drugs								
After failure of treatment with second-line drugs								
Other previously treated patients								
Transfer in								
Total								

Annex 22.Informed Consent Form

PATIENT INFORMATION SHEET/ENGLISH VERSION

NAME OF THE TREATMENT CENTER_____

P.O BOX_____

DISTRICT_____

REGION_____

This sheet gives information to patients who have DR-TB disease and are receiving or are about to start treatment as per National TB and Leprosy Program guideline of Tanzania. The form should be read and questions should be answered in a language in which the patient is fluent.

MULTI DRUG RESISISTANT TB MANAGEMENT INFORMATION

You are among the Multi Drug Resistant Tuberculosis (MDR-TB) patients diagnosed in this country. It is very important that you understand the following issues, which apply to all MDR-TB patients

- Treatment is very important to save your life
- Treatment is important to protect the community and your family
- After you have read the explanation, please feel free to ask any question that will allow you to understand clearly the nature of the disease.

BACKGROUND

Tuberculosis is a disease caused by bacteria and is one of the major infectious diseases in Africa including Tanzania. The treatment of Tuberculosis consist a combination of 4 to 5 drugs for a period of 9 to 11 months for shorter regimen,20 months for individualized regimen and 24 months for XDR-TB. Currently there is emergence of drug resistance and most important drug resistance is MDR-TB and XDR-TB

Multidrug-resistant tuberculosis (MDR-TB), defined as TB caused by organisms that are resistant to isoniazid and rifampicin, two potent first-line anti-TB drugs, continues to threaten the progress made in controlling the disease. The emergence of extensively DR-TB (XDR-TB), defined as MDR-TB that is resistant as well to any one of the fluoroquinolones and to at least one of three injectable second-line drugs (amikacin, capreomycin or kanamycin), has heightened this threat. Treatment outcomes are significantly worse in XDR-TB patients than in MDR-TB patients. The emergence of XDR-TB is a new threat to global public health.

Mode of transmission of tuberculosis including MDR-TB or XDR-TB is through air. If the patient has disease and cough or sneeze or speak or sing the microbes may come from the lung into the air and somebody else who is healthy may inhale the air and take the organism into his/her lungs . Then the person is infected and may develop the TB disease depending on the nature of the microbes inhaled. If microbes were MDR-TB or XDR-TB the patients get MDR-TB or XDR-TB respectively. Apart from this, MDR-TB is a man made disease that is caused by the following:

- Patient-who is suffering from TB and misused the anti TB drugs or suffer from diseases which make him/her not to absorb enough drugs e.g.diarrhoea
- Health workers who do not know appropriate regimen of ant TB for TB patient
- Drugs –if are of poor quality etc.

Patient who are at greatest risk to develop the disease after inhalation of the microbes are children, elderly, diabetic patient, HIV/AIDS patients, Miners, Alcoholics, Cigarette smokers, leukemia patient etc.

National TB and Leprosy Program which is under the Ministry of health, community development,gender,elderly and children of United Republic of Tanzania identified the problem of MDR-TB, addressed it and put strategies to mitigate its impact.

OBJECTIVE OF DR-TB MANAGEMENT

To treat MDR-TB patients with drugs and achieve cure while preventing emergence of XDR-TB and break transmission cycle of MDR-TB to the community.

WHAT DOES MANAGEMENT OF DR-TB INVOLVE

- Treatment of MDR-TB takes 9 to 11 months for shorter regimen,20 months for individualized regimen and 24 months for XDR-TB
- Wearing surgical masks during the intensive phase when you are in contact with staff and other patients, this will protect them from inhaling the microbes which will be generated from you when speaking, coughing, sneezing etc. and also avoid cross infection of microbes among patients.
- Receiving second-line ant TB drugs which are Kanamycin, ethionamide, cycloserine, pyrazinamide, Levofloxacin, capreomycin, moxyfloxacin, clofazimine, bedaquilline, delamanid,linezolid and high dose Isoniazid.
- Adhering the treatment to avoid emergence of XDR-TB
- Submitting specimen e.g. sputum, blood, for treatment monitoring
- You will get the management of other concomitant disease if you have them e.g.Diabetic,HIV,Hypertension,Flue,etc

POSSIBLE BENEFITS AND RISKS OF DR-TB TREATMENT

1. **BENEFITS**

    - You will be getting treatment for controlling the disease under close monitoring; hence attaining favorable treatment outcome (cure and treatment complete).
    - Prevent transmission of disease from you to your family and other members in the community
    - Be able to control the spread of MDR-TB in the country.

2. **RISKS**

You may get side effects from the drugs which are expected, this may cause discomfort to you. The side effects expected includes nausea, anorexia, vomiting, abdominal discomfort, decrease and/loss of hearing capacity,unsteadiness, numbness of the lower limbs, increased heartbeat, etc. but you will be managed appropriately by the physicians.

WHAT ELSE DO YOU NEED TO KNOW

- You should respect other member patients
- You should respect all staff who are taking care of your health

INFORMED CONSENT

I, _ (name), have understood patient information sheet and the rationale of getting DR-TB treatment

I do hereby agree to get treatment of MDR-TB.

Patient's name: _____

Patient's signature:_____ Date:_____

In case of illiterate patient:

Witness' name: _____

Witness' signature: _____ Date: _____

Physician's name: _____

Physician's signature:_____ Date:_____

SWAHILI VERSION

TAARIFA KUHUSU UGONJWA WA KIFUA KIKUU SUGU (MDR-TB) KWA WAGONJWA

JINA LA KITUO CHA TIBA_____

S.L.P_____

WILAYA_____

MKOA_____

Hii karatasi inatoa taarifa kwa mgonjwa aliyegundulika au aliyeanza matibabu ya kifua kikuu sugu kwa dawa mahali popote na mpango wa taifa wa kudhibiti kifua kikuu na ukoma (NTLP) Tanzania.

Hii taarifa inatakiwa kusomwa kwa makini na mgonjwa au msaidizi/msimamizi wake na maswali yote yaulizwe na kujibiwa kwa ufasaha na kwa lugha ile ambayo mgonjwa anaielewa vizuri

Ni muhimu kusoma kwa makini na kuelewa taarifa hii

TAARIFA YA MATIBABU YA UGONJWA WA KIFUA KIKUU SUGU KWA DAWA

Wewe ni miongoni mwa wagonjwa/unayetumia dawa za kifua kikuu sugu kwa dawa uliyegunduliwa katika nchi yetu ya Jamhuri ya Muungano wa Tanzania. Ni muhimu sana kwako kujua mambo yafuatayo ambayo ni muhimu sana kuyaelewa kwa mgonjwa wa kifua kikuu sugu kwa dawa. Kwamba:

1. Ugonjwa wa kifua kikuu sugu kwa dawa unatibika
2. Matibabu ya kifua kikuu sugu kwa dawa ni muhimu ili kuokoa maisha yako
3. Pia matibabu ni muhimu kwako na kwa jamii lengo likiwa ni kuzuia jamii inayokuzunguka kutokuambukizwa kifua kikuu sugu kwa dawa.

Utangulizi

Kifua kikuu (TB) ni ugonjwa wa muda mrefu unaosababishwa na vimelea (vijidudu) aina ya bacteria kwa kitaalamu huitwa *Mycobacterium tuberculosis* na kuambukiza kutoka kwa mgonjwa wa kifua kikuu cha mapafu kwenda kwa mwingine kwa njia ya hewa pale mgonjwa anapokohoa, anapopiga chafya, anapoongea na anapoimba. dalili za ugonjwa wa Kifua Kikuu ni:

- Kukohoa kwa muda usiopungua wiki mbili
- Kukohoa na kutoa makohozi wakati mwingine yaliyochanganyika na damu
- Homa hasa kipindi cha jioni
- Kutoka jasho jingi nyakati za usiku hata kama kuna baridi
- Kukosa hamu ya chakula wakati mwingine kichefuchefu
- Kupungua uzito kusiko na sababu
- Maumivu ya kifua na mwili kukosa nguvu

Kwa kawaida matibabu ya kifua kikuu huchukua miezi 9 hadi 11 kwa dawa za muda mfupi,miezi 20 kwa dawa za muda mrefu na miezi 24 kwa kifua kikuu zaidi na hutibika kwa kutumia dawa nne mpaka tano nazo ni Pyrazinamide, Ethambutol Levofloxacin, capreomycin, moxyfloxacin, clofazimine, bedaquilline, delamanid,linezolid , dosi ya juu ya Isoniazid na sindano aina ya Kanamycin na Capreomycin.

Kwa sasa duniani kumetokea mlipuko wa vimelea vya ugonjwa wa Kifua kikuu ambavyo ni sugu kwa dawa zilizotajwa hapo juu yaani Kifua kikuu sugu kwa dawa (MDR-TB) na Kifua kikuu sugu kwa dawa zaidi (XDR-TB). Tanzania ni miongoni mwa nchi duniani yenye tatizo hili kwa kiasi kidogo hivyo inaonyesha ni muhimu kiasi gani katika kuhakikisha tatizo hili halikui.

Maana ya ugonjwa wa kifua kikuu sugu kwa dawa

Ugonjwa wa kifua kikuu sugu kwa dawa (MDR-TB) ni ugonjwa wa kifua kikuu unaosababishwa na vimelea (vijidudu) ambavyo vimepata usugu kwa dawa za daraja la kwanza ambazo ni muhimili wa tiba ya kifua kikuu cha kawaida ambazo ni Rifampicin na Isoniazid hivyo kuhatarisha maendeleo ya kuzuia ugonjwa wa kifua kikuu cha kawaida. Mlipuko wa Kifua kikuu sugu kwa dawa zaidi (XDR-TB) ambacho ni kifua kikuu kinachosababishwa na vimelea (vijidudu) ambavyo vimepata usugu kwa dawa angalau moja zilizopo daraja la pili za sindano ambazo ni amikacin, kanamycin au capreomycin na dawa mojawapo zilizopo kwenye kundi la fluoroquinolones (levofloxacin, moxifloxacin

etc) umeongeza hofu kubwa katika mapambano dhidi ya kifua kikuu. Matokeo ya matibabu kwa hii aina ya kifua kikuu sugu zaidi kwa dawa (XDR-TB) si mazuri ukilinganisha na kifua kikuu sugu kwa dawa (MDR-TB), hivyo umuhimu wa kuzuia kupata XDR-TB unaonekana pale inapowezekana kwa nguvu zetu zote.

Njia za ueneaji wa MDR-TB na XDR-TB ni kwa njia ya hewa kama ilivyo kwa ugonjwa wa kifua kikuu cha kawaida. Mgonjwa aliye na vimelea anapokohoa, kupiga chafya,kuongea na kuimba bila kufunika mdomo na pua huweza kusambaza vimelea hivi hewani na kumpata mtu mwingine kwa kuvuta hewa yenye vimelea. Halafu mtu huyu huambukizwa vimelea na baadaye kupata ugonjwa ikitegemea vimelea alivyovuta kwa njia ya hewa. Kama vimelea vilikuwa ni kutoka kwa mgonjwa wa kifua kikuu sugu kwa dawa basi huyu mtu anaweza kuambukizwa vimelea vya kifua kikuu sugu kwa dawa. Zaidi ya yote, kifua kikuu sugu kwa dawa ni tatizo ambalo tunalitengeneza wenyewe kwa njia zifuatazo:

Mgonjwa anayeumwa Kifua kikuu cha kawaida asipotumia dawa za mwanzo kwa kufuata masharti ya wataalamu wa afya kama vile kutomeza dawa kwa kipindi kinachotakiwa, pamoja na mgonjwa kuwa na maradhi yanayoweza kuzuia uchukuliwaji wa dawa mwilini vizuri kama vile magonjwa ya kuharisha

Wataalamu wa afya wasipojua vizuri ni dawa gani unazotaakiwa kutumia kadiri ya uzito wako, au kutofuata masharti ya mgonjwa kunywa dawa kwa uangalizi wa mhudumu wa afya au mtu aliyeaminiwa na mgonjwa kumsimamia matibabu yake

Ubora wa dawa lakini hili kwa nchi yetu ni vigumu kutokea kwani dawa zote za ugonjwa wa kifua kikuu zinazotumika hutolewa na mpango wa taifa wa kudhibiti kifua kikuu na ukoma chini ya wizara ya afya na ustawi wa jamii.

Watu walio katika hatari ya kupata ugonjwa huu baada ya kupata vimelea hivi ni watoto chini ya umri wa miaka mitano, wazee, wagonjwa wa kisukari, watu wenye maambukizi ya virusi vya ukimwi, wachimba migodi, watumiaji pombe (walevi), wavutaji wa sigara na tumbaku, pamoja na wagonjwa wa kansa na wale wanaoumia matibabu ya kansa.

Mpango wa kudhibiti kifua kikuu na ukoma Tanzania chini ya Wizara ya afya na ustawi wa jamii uligundua tatizo hili na kuweka mikakati ya kupunguza kwa kutoa dawa ambazo ni za gharama kubwa sana kwa wagonjwa wetu.

Malengo ya matibabu ya kifua kikuu sugu

Kutibu wagonjwa wa kifua kikuu sugu kwa dawa kwa dawa za daraja la pili ili waweze kupona hivyo kuzuia mlipuko zaidi wa kifua kikuu sugu kwa dawa zaidi na kuvunja duara la maambukizi ya ugonjwa huu katika jamii.

Mambo muhimu ya kuzingatia wakati wa matibabu ya kifua kikuu sugu kwa dawa

Kabla ya kuanza matibabu ya kifua kikuu sugu kwa dawa ni muhimu ukafahamu mambo yafuatayo ambayo ni ya msingi kwa tiba yako chini ya uangalizi wa wahudumu wa afya kwamba:

1. Matibabu ya kifua kikuu sugu kwa dawa (MDR-TB) ni miezi 9 hadi 11 kwa dawa za muda mfupi,miezi 20 kwa dawa za muda mrefu na miezi 24 kwa kifua kikuu Zaidi.
2. Utapata dawa daraja la pili ambazo ni sindano aina ya Pyrazinamide, Ethambutol Levofloxacin, capreomycin, moxyfloxacin, clofazimine, bedaquilline, delamanid,linezolid , dozi ya juu ya Isoniazid na sindano aina ya Kanamycin na Capreomycin ikitegemea matokeo ya usugu wako wa dawa.
3. Utazingatia umezaji wa dawa zote zinazoshauriwa na wataalamu wa tiba
4. Utapatiwa matibabu ya magonjwa mengine kama unayo kama vile Kisukari, shinikizo la damu na Ukimwi bila malipo
5. Utaanza kufikiriwa kuruhusiwa kwenda katika wilaya yako tu mara matokeo ya vipimo vyako vya makohozi kwa kuotesha wadudu vitakapoonyesha kuwa hakuna mdudu aliyeota kwa miezi miwili mfululizo.
6. Utatakiwa kutoa vipimo kila mwezi ili kufuatilia mwenendo wa matibabu yako kama vile damu na makohozi
7. Utatakiwa kuvaa vifunika mdomo na pua (mask) wakati wote unapokuwa na wagonjwa wenzako au unapopatiwa huduma na wataalamu. Hii itasaidia kupunguza wadudu katika mazingira uliyopo unapohema, kukohoa, kupiga chafya na unapoongea. Kwa kufanya hivyo utawakinga wafanyakazi na wagonjwa wenzako kupata maambukizi.
8. Unashauriwa kuwashirikisha ndugu zako kuhusu huu ugonjwa ili kuweza kusaidiana wakati utakapokuwa umelazwa kwa matibabu huku.
9. Utatakiwa kuheshimu mgonjwa mwenzako pamoja na wafanyakazi wote wa hospitali, pale pasipoeleweka unaombwa kuuliza.

Faida na hasara wakati matibabu ya kifua kikuu sugu kwa dawa

Faida

Utapatiwa matibabu ili kuuzuia ugonjwa usiendelee chini ya uangalizi wa wataalamu hivyo kuweza kupata matokeo mazuri ya matibabu

Ukiwa kwenye matibabu ya dawa daraja la pili utazuia maambukizi ya ugonjwa huu kwenda kwa familia yako na jamii inayokuzunguka

Hatimaye utazuia kusambaa kwa ugonjwa huu katika jamii ya watu wa nchi yetu na nyingine hivyo kupunguza mzigo wa ugonjwa duniani

Hasara

Dawa hizi utakazokuwa unatumia zinaambatana na maudhi (adverse effects) ya dawa ambayo yanaweza kusababisha usipende tena kutumia dawa. Maudhi hayo ni kama vile kujisikia kichefu chefu, kupoteza hamu ya kula, kutapika, mvurugo wa tumbo, kuuma kwa chembe ya moyo (epigastric pain), kuwa na sonona, kupungua uwezo wako wa kusikia, kuwa na ganzi katika miguu na mikono na mwili kukosa nguvu.

Maudhi kama hayo yanapotokea wataalamu watayashughulikia ipasavyo chini ya uangalizi wa karibu ili kuhakikisha tiba inayotolewa haikatishwi lengo likiwa ni kuzuia usugu wa vimelea kwa dawa za daraja la pili maana hii ndiyo tiba ambayo inapatikana kwa wakati huu.

Fomu ya makubaliano ya matibabu ya mgonjwa wa kifua kikuu sugu kwa dawa (MDR-TB)

Mimi, ……..(jina kamili) nimeelewa taarifa ya matibabu ya kifua kikuu sugu na umuhimu wa kutumia dawa kwa kipindi chote nitakachotakiwa na wataalamu, ambayo nimesoma/kusomewa

Ninakubali kwa hiari yangu mwenyewe kufuata taratibu zilizowekwa ili kuweza kupata tiba ya ugonjwa wa kifua kikuu sugu kwa dawa

Jina la mgonjwa: _____

Sahihi ya mgonjwa _____

Tarehe _ _/_ _/_ _ _ _

Kama mgonjwa hawezi kusoma au kuandika sehemu hii ijazwe na shahidi:

Jina la shahidi: _____

Sahihi ya shahidi: _____

Tarehe: _ _/_ _/_ _ _ _

Jina la mtoa huduma ya afya aliyempokea: _____

Sahihi ya mtoa huduma ya afya aliyempokea:_____

Tarehe: _ _/_ _/_ _ _ _

MEDICATION GUIDE AND CONSENT FOR BEDAQUILINE

What is the most important information I should know about bedaquiline? Bedaquiline is a drug used to treat multidrug-resistant tuberculosis (MDR-TB) lungs in people with limited treatment options. MDR-TB is a serious disease that can result in death, and for which there are few treatment choices. It is important to complete the full course of treatment of bedaquiline and your other TB medicines and not skip doses. Skipping doses may decrease the effectiveness of the treatment and increase the likelihood that your TB disease will not be treatable by bedaquiline or other medicines. It is not known if bedaquiline is safe in:

 Children under 18 years

 In pregnancy

 In forms of TB that is not drug-resistant or not in the lungs.

 In patients with heart, kidney, liver or other health problems.

Before you take bedaquiline, tell your healthcare provider if:

 You have had an abnormal heart rhythm or other heart problems.

 Anyone in your family has or has had a heart problem called congenital long QT syndrome.

 You have liver or kidney problems or any other medical conditions, including HIV infection.

 You are pregnant or plan to become pregnant. It is not known if bedaquiline will harm your unborn baby.

 You are breastfeeding or plan to breastfeed. It is not known if bedaquiline passes into breast milk. You and your healthcare provider should decide if you will take bedaquiline or breastfeed.

 You are taking any prescription and nonprescription medicines, vitamins and herbal supplements. How should I take bedaquiline?

 Bedaquiline must always be taken with other medicines to treat TB. Your healthcare provider will decide which other medicines you should take with bedaquiline.

 Always take bedaquiline with a light meal (not heavy in fat).

 Swallow the tablets whole with water.

 Take bedaquiline for a total of 24 weeks (6 months). o Week 1 and Week 2: Take 400 mg (4 tablets) once a day, 7 days a week. o Week 3 to Week 24: Take 200 mg (2 tablets) thrice a week. For example, you may take bedaquiline on Monday, Wednesday and Friday of every week.

 You will need to take your other TB medicines for longer than 24 weeks, and at least for 20 months in total (the injectable drug is usually given for up to 8 months).

 Your treatment will be provided under directly observed treatment (DOT), with a patient-centred approach, which means that a healthcare provider will accompany you during the treatment.

 Do not skip bedaquiline doses. If you skip doses, or do not complete the total 24 weeks of bedaquiline your treatment may not work as well and your TB may be harder to treat.

 If for some reason you miss a dose, inform the person responsible for your treatment right away, they will tell you what to do. What should I avoid while taking bedaquiline?

 You should not drink alcohol while taking bedaquiline. What are the possible side effects of bedaquiline?

 Serious heart rhythm changes. Tell your health-care provider right away if you have a change in your heartbeat (a fast or irregular heartbeat), or if you faint. Your heart will be monitored periodically with a machine that checks that the heart rhythm is normal.

 Liver problems (hepatotoxicity). Liver toxicity can present in many ways. Tell your doctor of symptoms such as nausea or vomiting, stomach pain, fever, weakness, itching, unusual tiredness, loss of appetite, light coloured bowels, dark colored urine, yellowing of your skin or yellowing of the white of your eyes.

 Other side effects of bedaquiline include nausea, joint pain, headache, an abnormal laboratory test associated with damage to the pancreas, coughing up blood, chest pain, loss of appetite, and/or rash. It is possible that it may also cause some problems that we are not aware of. However, you will be followed closely for any unwanted effects or any problems. Other medicines to decrease the symptoms of the side effects or reactions may also be given. Always tell

your health-care provider of any side effects or problems you are having. Sometimes because of side effects bedaquiline or other drugs may need to be stopped. What monitoring tests do I need while on bedaquiline?

 You will need the same monitoring test that all patients on MDR-TB treatment need. In addition, you will need heart monitoring, extra blood tests for the liver and your electrolytes. Talk to your health-care provider on the schedule of all your monitoring tests and regular doctor visits. General information about the risks versus the benefits of taking bedaquiline

 RISK: It is possible that you will be at greater risk than you would otherwise be of certain side effects due to the drug. It is possible that a side effect could be serious and even result in death.

 BENEFIT: There is a greater chance that you will be cured of tuberculosis than if you did not take the medicine. You will possibly also become better very much sooner than if you only took the standard medicines for treatment of resistant TB. Also, it is less likely that the drugs you are taking will develop resistance if you are taking bedaquiline. Confidentiality and sharing information

 Because bedaquiline is a new drug for which we have limited experience we are collecting information on patients taking them.

 The information that we collect from you will be kept confidential and no one but the clinical staff will be able to see your medical information.

 Any information collected to help us better use the drug in patients will be unlinked to your name (made anonymous) before we share or analyse it. Right to refuse or withdraw

 You do not have to agree to take bedaquiline if you do not wish to do so, and refusing to accept the drug as part of your treatment schedule will not affect your treatment at this clinic in any way. You will still have all the benefits that you would otherwise have at this clinic.

 If you agree to take bedaquiline, you may also at any point after you start wish to stop without losing any of your rights as a patient here. Your treatment at this clinic will not be affected in any way. Contact person If you have any questions, you may contact any of the following persons: Name_____. Title_____. Phone___ _____ Name_____. Title_____. Phone_____ Name_____. Title_____. Phone_____ Name of responsible physician: _____ ___ Name of clinic/hospital/institution _____

TREATMENT CONSENT

Statement from the patient:

I have read the provided Medication Guide, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent to receive bedaquiline for treating the drug-resistant tuberculosis disease that I am suffering from.

Print Name of Patient: _____

Signature of Patient: _____

Date: _____ (Day/month/year)

If illiterate, a literate witness must sign. (If possible, this person should be selected by the participant and should have no connection to the care providers). Patients who are illiterate should include their thumbprint.

Statement from the witness:

I have witnessed the accurate reading of the consent form to the potential recipient of bedaquiline, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness: _____ AND Thumbprint of patient_____

Signature of witness: _____

Date: _____ (Day/month/year)

Statement from the person taking consent:

I confirm that the participant was given an opportunity to ask questions about the treatment, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this informed consent form has been provided to the participant.

Print name of person taking the consent: _____

Signature of person taking the consent: _____

Date: _____ (Day/month/year)

INFORMED CONSENT FOR PATIENTS USING DELAMANID

What is the most important information I should know about delamanid? Delamanid is a drug used to treat multidrug-resistant tuberculosis (MDR-TB) lungs in people with limited treatment options. MDR-TB is a serious disease that can result in death, and for which there are few treatment choices. It is important to complete the full course of treatment of delamanid and your other TB medicines and not skip doses. Skipping doses may decrease the effectiveness of the treatment and increase the likelihood that your TB disease will not be treatable by delamanid or other medicines. It is not known if delamanid is safe in:

- Children under 18 years
- In pregnancy
- In forms of TB that is not drug-resistant or not in the lungs.
- In patients with heart, kidney, liver or other health problems.

Before you take delamanid, tell your healthcare provider if:

- You have had an abnormal heart rhythm or other heart problems.
- Anyone in your family has or has had a heart problem called congenital long QT syndrome.

 You have liver or kidney problems or any other medical conditions, including HIV infection.

 You are pregnant or plan to become pregnant. It is not known if delamanid will harm your unborn baby.

 You are breastfeeding or plan to breastfeed. It is not known if delamanid passes into breast milk. You and your healthcare provider should decide if you will take delamanid or breastfeed.

 You are taking any prescription and nonprescription medicines, vitamins and herbal supplements. How should I take delamanid?

 Delamanid must always be taken with other medicines to treat TB. Your healthcare provider will decide which other medicines you should take with delamanid.

 Always take delamanid with a light meal (not heavy in fat).

 Swallow the tablets whole with water.

 Take delamanid for a total of 24 weeks (6 months). o Take 100 mg (2 tablets) early in the morning and again 100 mg (2 tablets) in the evening, every day of the week.

 You will need to take your other TB medicines for longer than 24 weeks, and at least for 20 months in total (the injectable drug is usually given for up to 8 months).

 Your treatment will be provided under directly observed treatment (DOT), with a patient-centred approach, which means that a healthcare provider will accompany you during the treatment.

 Do not skip delamanid doses. If you skip doses, or do not complete the total 24 weeks of delamanid your treatment may not work as well and your TB may be harder to treat.

 If for some reason you miss a dose, inform the person responsible for your treatment right away, they will tell you what to do. What should I avoid while taking delamanid?

 You should not drink alcohol while taking delamanid. What are the possible side effects of delamanid?

 Serious heart rhythm changes. Tell your health-care provider right away if you have a change in your heartbeat (a fast or irregular heartbeat), or if you faint. Your heart will be monitored periodically with a machine that checks that the heart rhythm is normal.

 Other side effects of delamanid include nausea, vomiting, and dizziness. Other important adverse drug reactions are anxiety, paraesthesia, and tremor. Tell your doctor of symptoms such as nausea or vomiting, dizziness, anxiety, itching, or tremor. It is possible that it may also cause some problems that we are not aware of. However, you will be followed closely for any unwanted effects or any problems. Other medicines to decrease the symptoms of the side effects or reactions may also be given. Always tell your health-care provider of any side effects or problems you are having. Sometimes because of side effects delamanid or other drugs may need to be stopped. What monitoring tests do I need while on delamanid?

 You will need the same monitoring test that all patients on MDR-TB treatment need. In addition, you will need heart monitoring, extra blood tests for the liver and your electrolytes. Talk to your health-care provider on the schedule of all your monitoring tests and regular doctor visits. General information about the risks versus the benefits of taking delamanid

 RISK: It is possible that you will be at greater risk than you would otherwise be of certain side effects due to the drug. It is possible that a side effect could be serious and even result in death.

 BENEFIT: There is a greater chance that you will be cured of tuberculosis than if you did not take the medicine. You will possibly also become better very much sooner than if you only took the standard medicines for treatment of resistant TB. Also, it is less likely that the drugs you are taking will develop resistance if you are taking delamanid. Confidentiality and sharing information

 Because delamanid is a new drug for which we have limited experience we are collecting information on patients taking them.

 The information that we collect from you will be kept confidential and no one but the clinical staff will be able to see your medical information.

 Any information collected to help us better use the drug in patients will be unlinked to your name (made anonymous) before we share or analyse it. Right to refuse or withdraw

 You do not have to agree to take delamanid if you do not wish to do so, and refusing to accept the drug as part of your treatment schedule will not affect your treatment at this clinic in any way. You will still have all the benefits that you would otherwise have at this clinic.

 If you agree to take delamanid, you may also at any point after you start wish to stop without losing any of your rights as a patient here. Your treatment at this clinic will not be affected in any way. Contact person If you have any questions, you may contact any of the following persons: Name_____. Title_____. Phone___ _____ Name_____. Title_____. Phone_____ Name_____. Title_____. Phone_____ Name of responsible physician: _____ ___ Name of clinic/hospital/institution _____

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TREATMENT CONSENT

Statement from the patient:

I have read the provided Medication Guide, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent to receive delamanid for treating the drug-resistant tuberculosis disease that I am suffering from.

Print Name of Patient: _____

Signature of Patient: _____

Date: _____ (Day/month/year)

If illiterate, a literate witness must sign. (If possible, this person should be selected by the participant and should have no connection to the care providers). Patients who are illiterate should include their thumbprint.

Statement from the witness:

I have witnessed the accurate reading of the consent form to the potential recipient of delamanid, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness: _____ AND Thumbprint of patient_____

Signature of witness: _____

Date: _____ (Day/month/year)

Statement from the person taking consent:

I confirm that the participant was given an opportunity to ask questions about the treatment, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this informed consent form has been provided to the participant.

Print name of person taking the consent: _____

Signature of person taking the consent: _____

Date: _____ (Day/month/year)