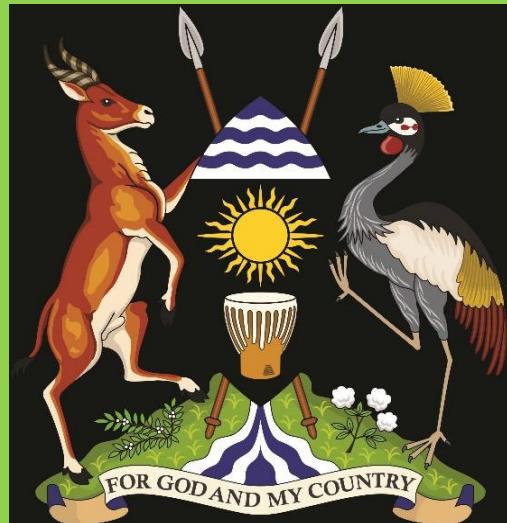


National Tuberculosis and Leprosy Program



Ministry of Health

Uganda National Guidelines for the Programmatic
Management of Drug-Resistant Tuberculosis

Third Edition, 2024

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REPUBLIC OF UGANDA

NATIONAL GUIDELINES FOR THE PROGRAMMATIC MANAGEMENT OF DRUG-RESISTANT TUBERCULOSIS

**MINISTRY OF HEALTH
THE NATIONAL TUBERCULOSIS AND LEPROSY PROGRAM**

THIRD EDITION, 2024

Foreword

Uganda remains a high-burden tuberculosis (TB) country, ranking 18th globally, with an estimated 1,506 drug-resistant TB (DR-TB) cases annually. In 2020, only 470 of the targeted 745 DR-TB cases were notified, leaving almost a quarter (37%) of rifampicin-resistant/multidrug-resistant (RR/MDR) TB cases missed. Of the diagnosed cases, 88% were treated, achieving a treatment success rate (TSR) of 87%, which remained steady at 89% in 2021, though the mortality rate is concerning at 8%.

In 2022, only 74% of new TB cases were tested for rifampicin resistance using GeneXpert, revealing a 26% gap in utilization. Despite efforts to expand DR-TB care, gaps in case detection and mortality persist. To address this, interventions like the (Community Awareness, Screening, Testing, Prevention, and Treatment) CAST TB campaign and mortality audits have been implemented.

This 2024 national DR-TB treatment guideline updates the 2015 second edition, 2019 addendum and integrates WHO's 2022 guidelines /2024 rapid communication recommendations and local innovations. Key changes include introducing shorter 6-month all-oral regimens (**6BPaLM/BPaL, 6BDLLfxC**) and updated 9-month regimens, (**BLMZ, BLLfxCZ, and BDLLfxZ**) treatment modalities and post-treatment follow-up; accessing the baseline single test Xpert MTB/XDR assay, adopting digital adherence monitoring technologies and implementing the new Levofloxacin recommendation for TB preventive therapy.

Patients currently on treatment using the existing 9-month modified shorter treatment regimen (mSTR) and longer 18-20-month regimens will continue their treatment until completion. As of 2024/2025, Uganda will have RR/MDR TB patients on three regimens: 6 months, 9 months, and 18-20 months regimens. All new patients will enroll on the new regimens. Although 6-month regimens aim to reduce loss to follow-up, there is potential for higher relapse rates, necessitating strengthened post-treatment follow-up.

This third edition of the National Programmatic Management of Drug-Resistant TB guidelines was developed through a consultative process involving key stakeholders, implementing partners, and international experts. These updated guidelines will support the introduction and implementation of the shorter 6-month regimens—BPaLM/BPaL and BDLLfxC—and updated 9-months regimens in Uganda. Healthcare workers and partners are encouraged to utilize these guidelines to enhance programmatic management of drug-resistant tuberculosis in Uganda.



Dr. Charles Olaro
Acting Director General of Health Services
Ministry of Health

Introduction

The third edition of the drug-resistant TB guidelines provides information on the programmatic management of drug-resistant TB (PMDT) including Rifampicin resistant or multi-drug-resistant TB (RR/MDR) and confirmed Rifampicin-susceptible Isoniazid resistant TB (Hr-TB).

This guideline emphasizes the importance of using effective, all-oral treatment regimens for patients with multidrug-resistant or rifampicin-resistant TB (MDR/RR-TB), including those with additional fluoroquinolone resistance.

A key development in the WHO May 2022 guidelines is the prioritisation of the 6-month BPaLM regimen, which combines bedaquiline, pretomanid, linezolid, and moxifloxacin, offering a shorter treatment option for in patients (aged ≥ 14 years) with MDR/RR-TB who have not had previous exposure to bedaquiline, pretomanid and linezolid (defined as >1 -month exposure). This regimen may be used without moxifloxacin (BPaL) in the case of documented resistance to fluoroquinolones (in patients with pre-XDR-TB).

In June 2024, the WHO released a rapid communication introducing the new BDLLfxC regimen which expands the use of the 6-month regimens to additional patient groups, like children, adolescents, and pregnant women, who could not benefit from the currently recommended BPaLM regimen (due to the absence of safety and dosing data for pretomanid). Rapid drug susceptibility testing (DST) for fluoroquinolones is encouraged but should not delay treatment initiation with regimens that are also effective in patients with pre-XDR-TB.

The use of the modified 9-month, all-oral regimens (BLMZ, BLLfxCZ and BDLLfxZ) is preferred over currently recommended longer (18-month) regimens in patients with MDR/RR-TB who have not had previous exposure to bedaquiline, delamanid and linezolid (defined as >1 -month exposure) and in whom resistance to fluoroquinolones has been excluded(using BLMZ is suggested over BLLfxCZ, and BLLfxCZ is suggested over BDLLfxZ).Access to rapid DST for ruling out fluoroquinolone resistance is required before starting a patient on one of these

Patients with extensive forms of DR-TB (e.g., XDR-TB) or those who are not eligible for or have failed shorter treatment regimens will benefit from individualized longer (≥ 18 months) regimens designed using the priority grouping of medicines recommended in current WHO guidelines

All TB treatments should follow WHO-recommended standards, which emphasize patient-centered care, obtaining informed consent, adhering to good clinical practices, actively monitoring drug safety, and regularly evaluating treatment effectiveness and resistance to assess regimen effectiveness.

1.1. Summary table of major guidelines changes

Diagnosis

The Line Probe assay will be phased out and the GeneXpert XDR (Xpert MTB/XDR) cartridge will be used to detect fluoroquinolone and INH resistance. This test also detects resistance to Ethionamide and the second line injectables (amikacin, kanamycin and capreomycin) in a single test.

Phenotypic testing for Linezolid and Bedaquiline will be rolled out nationally for all patients who have RR-TB. This test can also be done at the clinician's request. Pretomanid testing is not currently available in Uganda, but procurement processes are in place to ensure accessibility by early 2025.

Stool testing using GeneXpert to diagnose MTB/Rifampicin resistance in children

Definitions of died (including a patient who died before starting treatment), loss to follow up (including a patient who did not start treatment) pre-XDR and XDR-TB have been updated in line with latest WHO guidance.

Treatment

All persons with RR-TB will either be treated with standardised 6 months or 9 months or individualized longer (≥ 18 months) regimens

6-month BPaLM regimen:

Combines bedaquiline, pretomanid, linezolid, and moxifloxacin.

For patients aged 14+ with MDR/RR-TB without prior exposure to these drugs (>1-month exposure).

Can be modified to BPaL (without moxifloxacin) for patients with documented fluoroquinolone resistance (pre-XDR-TB)

6-month BDLLfxC regimen:

Expands 6-month treatment to children, adolescents, and pregnant women who cannot use BPaLM (due to lack of pretomanid safety data).

Can be used in Fluoroquinolone resistance by dropping Lfx and using BDLC

Rapid drug susceptibility testing (DST) is encouraged for fluoroquinolones but should not delay treatment initiation.

Modified 9-month, all-oral regimens (BLMZ, BLLfxCZ, BDLLfxZ):

Preferred over longer (18-month) regimens for patients without prior exposure to bedaquiline, delamanid, and linezolid.

Used in patients without fluoroquinolone resistance.

BLMZ is preferred over BLLfxCZ, and BLLfxCZ is preferred over BDLLfxZ.

Requires rapid DST to confirm fluoroquinolone susceptibility before starting.

Patients with extensive drug-resistant TB (XDR-TB) or those who failed shorter regimens require individualized longer regimens (≥ 18 months) based on WHO-recommended priority medicines.

Treatment monitoring

Follow up facilities will be gradually phased out, with Directly Observed Therapy (DOT) being monitored through Digital Adherence Technologies (DAT). These electronic monitoring devices track each time a medication cap is opened, assuming that the medication has been taken.

All persons who are not responding to therapy will be identified early, based in part on month 3 culture status assessed during the month 5 visit

Post TB Treatment monitoring

Monitoring patients for at least 12 months after TB treatment completion

Recording and Reporting

Electronic case-based surveillance systems eCBSS-to capture individual detailed data of each DR-TB case.

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Source documents

Primary resources adapted for use in the writing of these guidelines include:

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2. WHO. **WHO consolidated guidelines on tuberculosis: Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update.** 2022. <https://www.who.int/publications/i/item/9789240063129>
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7. National strategic plan for Tuberculosis and Leprosy control 2020/2021-2024-2025
<https://www.health.go.ug/cause/national-strategic-plan-for-tuberculosis-and-leprosy-control-2020-21-2024-25/>
8. Uganda National Guidelines for the programmatic Management of Drug-Resistant Tuberculosis, Second edition, 2016
9. Addendum to the National Guidelines for the Programmatic Management of Drug -Resistant Tuberculosis, 2019

Abbreviations

AFB	Acid fast bacilli
AIDS	Acquired immunodeficiency syndrome.
ART	Antiretroviral therapy
ARV	Antiretroviral
BCG	Bacillus Calmette-Guérin
CBO	Community-based organization
CI	Confidence interval
CNS	Central nervous system
CPT	Co-trimoxazole preventive therapy
CXR	Chest x-ray
DHIS2	District health information system II
DHO	District health officer
DNA	Deoxyribonucleic acid
DOT	Directly observed therapy
DR-TB	Drug-resistant tuberculosis
DST	Drug sensitivity testing
DTLS	District tuberculosis and leprosy supervisor
ECG	Electrocardiogram
FBO	Faith-based organization
FDC	Fixed-dose combination
FQ	Fluoroquinolone
GDF	Global Drug Facility
HC	Health centre
HIV	Human immunodeficiency virus
HMIS	Health management information system
HRD	Human resource development
IC	Infection control
IDP	Internally displaced person
IRIS	Immune reconstitution inflammatory syndrome
LJ	Lowenstein-Jensen
LMIS	Logistics Management Information System
LPA	Line probe assay
MDR-TB	Multidrug-resistant tuberculosis
M&E	Monitoring and evaluation
MGIT	Mycobacteria Growth Indicator Tube
MOH	Ministry of Health
MOTT	Mycobacteria other than tuberculosis
MTB	Mycobacterium tuberculosis
MUAC	Mid-upper arm circumference
NGO	Non-governmental organization
NMS	National Medical Stores
NTLP	National Tuberculosis and Leprosy Program
NTM	Non-Tuberculous mycobacteria

NTRL	National Tuberculosis Reference Laboratory
PAS	Para-amino salicylic acid
PLHIV	People living with human immunodeficiency virus
PMDT	Programmatic management of drug-resistant TB
QA	Quality assurance
QPPU	National Quantification, Planning, and Procurement Unit
RR-TB	Rifampicin-resistant tuberculosis
R&R	Recording and reporting
RTLFP	Regional tuberculosis and leprosy focal person
SOP	Standard operating procedure
SRL	Supranational reference laboratory
TSH	Thyroid stimulating hormone
TSRS	TB specimen referral system
UMTAC	Uganda Medicines and Therapeutic Advisory Committee
WHO	World Health Organization
XDR-TB	Extensively drug-resistant tuberculosis

[Anti-TB drug abbreviations can be found in Chapter 6, Table 6.1]

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Chapter 1:

Introduction to DR-TB epidemiology and causal factors

This chapter reviews the global and Uganda-specific epidemiology of DR-TB and describes causal factors that contribute to its development.

Global epidemiology of DR-TB

MDR/RR-TB poses a significant global health challenge because of the complex treatment regimens, longer treatment duration, and higher treatment costs in comparison to drug-susceptible TB. Globally, 3.6% of the new TB cases and 18% of previously treated TB cases have MDR/RR-TB, resulting in an estimated 465,000 MDR/RR-TB cases each year worldwide. The proportion of MDR/RR-TB varies significantly across WHO regions, ranging from 2.8% in the WHO African Region to 26% in the WHO European Region among new cases. Among previously treated cases, the proportion ranges from 7.9% in the Eastern Mediterranean Region to 57% in the European Region. However, two-thirds of the global MDR/RR-TB burden is concentrated in seven countries: India, the Russian Federation, Pakistan, South Africa, China, Indonesia, and the Philippines. Globally, the burden of drug-resistant TB (DR-TB) is also estimated to have increased between 2020 and 2021, with 450 000 (95%CI: 399 000–501 000) new cases of Rifampicin-resistant TB (RR-TB) in 2021. The number of people provided with treatment for RR-TB and multidrug-resistant TB (MDR-TB) declined between 2019 and 2020. The reported number of people started on treatment for RR-TB and MDR-TB in 2021 was 161 746, covering only about one in three of those in need. The treatment success rate for drug-resistant TB, at 60% globally, remains low. In the WHO Afro region, some areas with higher burdens of TB, tend to have higher rates of MDR-TB, the proportion of MDR/RR-TB among new TB patients remained at about 3–4% and 18–21% among those previously treated for TB. [WHO Global Tuberculosis Report, 2022].

Epidemiology of DR-TB in Uganda

DR-TB is an emerging problem in Uganda. Results of a national DR-TB survey carried out in 2010 (limited to smear-positive samples) indicate an MDR-TB prevalence of 1.4% and 12.1% among new and retreatment cases, respectively [Lukoye et al., PLoS ONE, 2013], yet more are still missed from the surveillance systems. Sub-national surveys indicate an MDR-TB prevalence ranging from 0–4.5% among new cases and 4.4–24% among retreatment cases (see table 1.1 below). Since the inception of the PMDT in Uganda, the program has registered a growing trend in MDR TB notifications; cumulatively the program has enrolled 3,554 patients on MDR/RR-TB treatment from 2012 till December 2021(Figure 1). However, there was a dip in notification in 2020 following the outbreak of Covid-19 pandemic. Since then, the country has experienced a sharp increase in notified cases beyond 2021. From the 2020 MDR/RR-TB Cohort(n=445), males still suffer proportionately at 72.8% of the patients in this cohort and those aged 25–44 years at 52%. In addition, children between 0–14 years accounted for 7.7% and the MDR/RR/HIV coinfection rates were 37.3%, the country has and has also seen TSR improve from 47% in 2012 to 88% in 2020 this is higher when compared to 71% in WHO Afro region and 60% at the global level, the highest ever since implementation, though falls short 2 percentage points of the global target of 90%. Mortality in the 2020 cohort stands at 8%. Uganda is yet to implement molecular epidemiological investigation

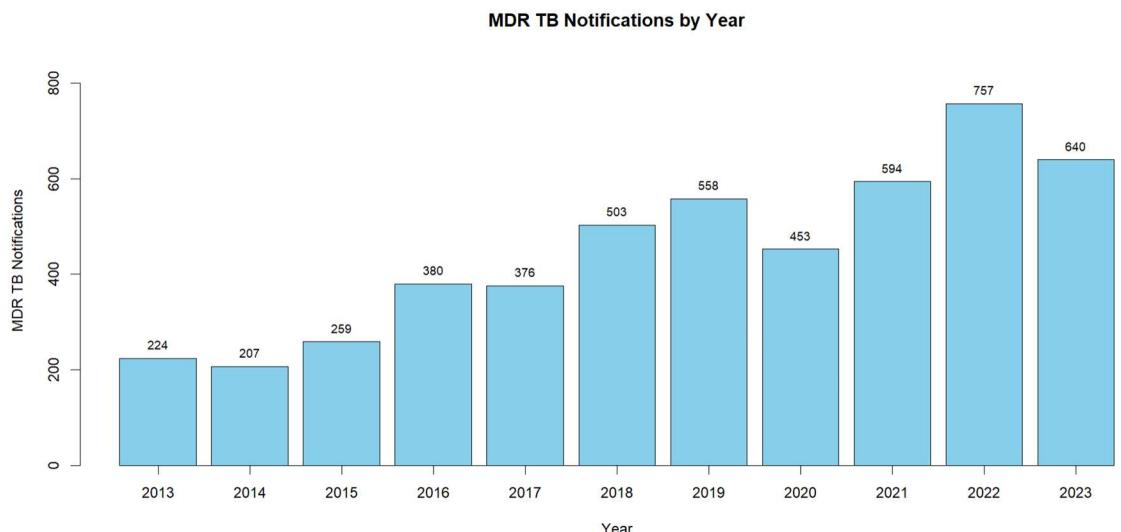


Figure 1: MDR TB Notifications from 2013 – 2023

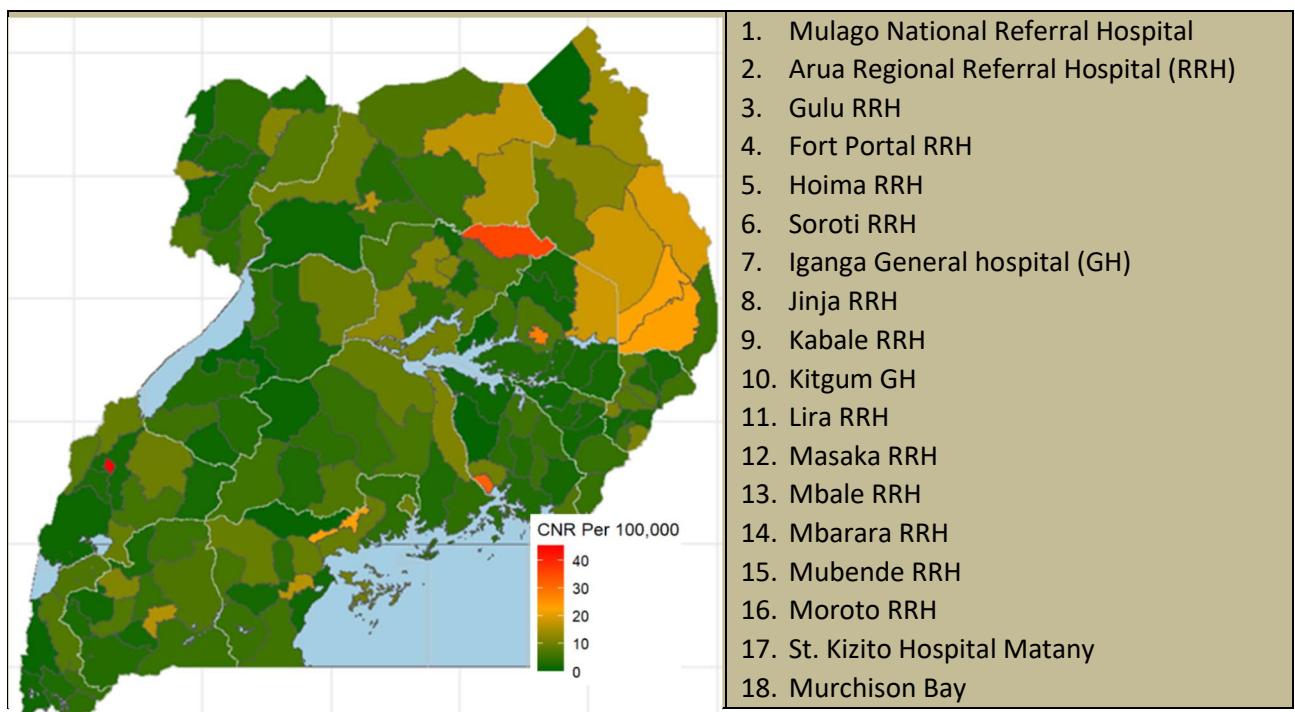
Table 1.1: Summary of TB drug resistance surveys in Uganda

Adapted from the Uganda Expansion Plan 2012-2016, and operational guidance on PMDT; updated with national data from Lukoye et al., PLoS ONE, 2013

Institution	Year of study	Survey location	% MDR per patient category		Survey coverage
			New No. (%)	Previous Rx No. (%)	
GLRA	1996-97	Rural	374 (0.5)	45 (4.4)	Sub-national
UMDNJ Welcome Trust	2001	Urban	0 (0)	75 (24)	Sub-national
UMDNJ Welcome Trust	2006	Urban	107 (4.5)	287 (11.5)	Sub-national
MSF	2007-08	Rural	123 (0)	22 (13.6)	Sub-national
Kampala-EU	2009	Urban	472 (1.1)	61 (11.5)	Sub-national
NTLP/GoU	2010	Rural/Urban	1,397 (1.4)	140 (12.1)	National
GF USAID	2022	Rural/Urban	Ongoing	Ongoing	Sub-national

An Increase in MDR TB notification rate is linked to epidemic clusters of TB identified with in the country, though not evenly spread out across the regions. The geographic distribution shows the highest burden of MDR-TB per 100,000 to be Fort-portal City, Jinja City, Otuoke, Butambala, Soroti, Kalangala, Nakapiripiti, Nabilatuk, Katakwi, Masaka City (Figure 2). The same districts bear a high burden for DS-TB above the national 199 per 100,000. [12.1%] to date, 18 DR-TB treatment initiation facilities have been started in the highest-burden districts with regional distribution as outlined in figure 1.1.

Figure 1.1 Map of burden for MDR-TB cases in the country and treatment initiation facilities



DR-TB causal factors

Although its causes are microbial, DR-TB is essentially a man-made problem. From a microbiological perspective, resistance is caused by a genetic mutation that makes a drug ineffective against the bacilli. From a clinical and programmatic perspective, it is an inadequate or poorly administered treatment regimen that allows a drug-resistant strain to become dominant in a patient infected with TB. Ongoing transmission of established drug-resistant strains within a population is also a significant source of new drug-resistant cases. The following table lists some of the factors that contribute to the risk for developing DR-TB.

Table 1.2 Factors contributing to poor outcomes and risk for development of DR-TB

Adapted from Lambregts-van Weezenbeck et al., *Tubercle and Lung Disease*, 1995

Health care providers: Inappropriate treatment	Drugs: Inadequate supply/quality	Patients: Inadequate drug intake or treatment response
<ul style="list-style-type: none"> • Inadequate treatment regimens: wrong dose or combination of drugs by prescribers • Poor DOT or lack of proper treatment monitoring • Inadequately organized or underfunded TB control programs • Non-compliance with guidelines • Poor management of adverse drug reactions 	<ul style="list-style-type: none"> • Stock-outs (at all levels) or interrupted supply of drugs • Poor storage conditions at peripheral facilities • Poor quality of drugs • Poor regulation of medications 	<ul style="list-style-type: none"> • Lack of patient health education on TB • Poor adherence • Lack of transport/long distances to facilities • Side effects • Malabsorption • Social barriers, denial, cultural issues, substance dependence/abuse • Comorbidities (HIV, diabetes, malnutrition, psychiatric condition)

Any identified sources of DR-TB should be addressed urgently. The framework approach described in these guidelines helps to identify and curtail possible sources of DR-TB. It is important to prevent the development of resistance since mortality for patients infected with resistant strains is high. It is also important not to lose sight of the role of high-quality DOT and appropriate care for drug-susceptible TB as the primary means to prevent development of drug resistance.

Key messages for DR-TB prevention:

- Well-administered first-line treatment using the most effective regimen and high-quality DOT for drug susceptible cases is the best way to prevent further resistance.
- Timely identification of DR-TB and adequate DR-TB treatment regimens administered early in the course of the disease are essential to stop primary transmission.

Chapter 2

Definitions for DR-TB classification, registration groups, and treatment outcomes

This chapter will explain the different definitions and classification groupings for DR-TB based on type of drug resistance, registration groups, bacteriology, and outcomes for reporting purposes. The updates of the chapter are based on the 2022 WHO update on treatment of drug-resistant TB.

Note: The registration and outcome definitions here are consistent with newer WHO recommendations adapted from the operational handbook on tuberculosis, 2022 update

Chapter 2:

Definitions for DR-TB classification, registration groups and treatment outcomes

Drug-resistant TB (DR-TB) refers to TB disease caused by a strain of *Mycobacterium Tuberculosis* that is resistant to any TB medicines. This is confirmed using conventional laboratory methods based on growth in culture media (phenotypic testing) or using molecular methods that identify mutations associated with resistance to specific drugs (genotypic testing). Patterns of DR-TB are classified into the following groups:

- **Mono-resistant TB:** TB disease caused by a strain of *M. tuberculosis* complex that is resistant to one first-line anti-TB drug only.
- **Poly-resistant TB:** TB disease caused by a strain of *M. tuberculosis* complex that is resistant to more than one first-line anti-TB drug, other than both Isoniazid and Rifampicin.
- **Multidrug-resistant TB (MDR-TB):** TB disease caused by a strain of *M. tuberculosis* complex that is resistant to Rifampicin and Isoniazid.
- **Bacteriologically confirmed:** when a biological specimen is positive by smear microscopy, culture or a rapid diagnostic test for TB recommended by WHO.
- **Drug susceptibility testing (DST):** in vitro testing using either molecular or genotypic techniques to detect resistance-conferring mutations, or phenotypic methods to determine susceptibility to a medicine.
- **Extensively drug-resistant (XDR-TB):** TB disease caused by a strain of *M. tuberculosis* complex that is resistant to Rifampicin (and may also be resistant to Isoniazid), and that is also resistant to at least one fluoroquinolone (Levofloxacin or Moxifloxacin) and to at least one other “Group A” drug (Bedaquiline or Linezolid).
- **Rifampicin resistance (RR-TB):** resistance to Rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs; includes any resistance to Rifampicin in the form of mono-resistance, poly-resistance, MDR, or XDR
- **RR diagnosed by the Xpert MTB/RIF test or other WHO-recommended rapid molecular test** means that, thus far, only resistance to Rifampicin has been tested for and established. Additional drug susceptibility testing (DST) should be conducted to identify if additional resistance to other anti-TB drugs is present.

DR-TB is further diagnostically classified as:

- **Confirmed MDR-TB or RR-TB:** These are patients in whom MDR-TB or RR-TB is confirmed by a laboratory DST.
- **Presumptive MDR-TB or RR-TB:** Patients may be registered and started on a second-line anti-TB regimen based on significant risk for drug resistance and before laboratory confirmation of resistance, or on the basis of a rapid molecular test results. This would include cases without laboratory confirmation, deemed to be clinically diagnosed MDR-TB or RR-TB based on recommendations of the DR-TB Expert Panel and approved to begin treatment with an MDR-TB regimen.

Further classification of cases is done to document the site of TB involvement:

- **Pulmonary:** TB involving the lung parenchyma or tracheobronchial tree, including miliary disease. A patient with both pulmonary and extrapulmonary TB disease should be classified as a pulmonary case. If the TB is confined to intrathoracic adenopathy (hilar and/or mediastinal) or TB-related pleural effusion alone without radiographic involvement of the lung parenchyma, classification would be considered extrapulmonary.
- **Extrapulmonary:** TB of organs other than the lungs (e.g., pleura, lymph nodes, abdomen, genitourinary tract, skin, meninges, joints, and bones). The definition of an extrapulmonary case with several sites affected should be based on the site representing the most severe form of disease.

MDR-TB patient registration groups

Patients are assigned to a registration group based on the most recent treatment history at the time of collecting the biological specimen that was used to confirm MDR-TB or RR-TB.

- **New:** A person with TB disease who has never been treated for TB or has only previously ever taken TB drugs for less than 1 month.
- **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 a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection).
- **Treatment after loss to follow-up:** A patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.
- **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.
- **Other:** A previously treated TB patient whose outcome after the most recent course of treatment is unknown or undocumented, or who has an unknown previous TB treatment history.

For the purposes of registration on second-line treatment for MDR-TB, patients are considered New if DST was performed within one month of the start of treatment, even if they had received more than one month of first-line drug treatment for TB by the time that the DST results returned (and subsequently registered for second-line TB treatment)

- **Treatment failure of a first-line treatment regimen:** A sputum smear or culture that is positive at five months or later during treatment. The identification of MDR-TB at any point during a first-line treatment is no longer automatically assigned a *Treatment failure* outcome, considering that effective second-line treatment may be immediately available.

For more information on proper reporting and recording information for MDR-TB patient registration and completion of the MDR-TB register, refer to Chapter 19.

MDR-TB treatment outcomes

Treatment monitoring for DR-TB mainly relies on sputum culture with bacteriological conversion or reversion. The WHO 2022 revised definitions for patients with drug resistance are provided in table 2.1 below.

Outcome	Definition
Treatment failed	A patient whose treatment regimen needed to be terminated or permanently changed ^a to a new regimen or treatment strategy
Cured	A patient with pulmonary TB with bacteriologically confirmed TB at the beginning of treatment who completed treatment as recommended by the national policy, with evidence of bacteriological response ^b and no evidence of failure.
Treatment completed	A patient who completed treatment as recommended by the national policy but whose outcome does not meet the definition for cure or treatment failure
Died	A patient who died ^c before starting treatment or during the course of treatment.
Lost to follow-up	A patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.
Not evaluated	A patient for whom no treatment outcome was assigned. ^d
Treatment success	The sum of all patients cured and treatment completed.
<i>An optional definition was also proposed for use in operational research only</i>	
Sustained treatment success	An individual assessed at 6 months (for DS-TB and DR-TB) and at 12 months (for DR-TB only) after successful TB treatment, who is alive and free of TB-

^a Reasons for the change include:

- no clinical response or no bacteriological response, or both (see note ^b);
- adverse drug reaction; or
- evidence of additional drug-resistance to medicines in the regimen.

^b "Bacteriological response" refers to bacteriological conversion with no reversion:

- "bacteriological conversion" describes a situation in a patient with bacteriologically confirmed TB where at least two consecutive cultures (for DR-TB and DS-TB) or smears (for DS-TB only) taken on different occasions at least 7 days apart are negative; and

• "bacteriological reversion" describes a situation where at least two consecutive cultures (for DR-TB and DS-TB) or smears (for DS-TB only) taken on different occasions at least 7 days apart are positive either after the bacteriological conversion or in patients without bacteriological confirmation of TB.

^c Patient died for any reason.

^d This includes cases "transferred out" to another treatment unit and whose treatment outcome is unknown; however, it excludes those lost to follow-up.

- **Extensive (or advanced) pulmonary TB disease:** the presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography. In children aged below 15 years, advanced disease is usually defined by the presence of cavities or bilateral disease on chest radiography.

Additional clarification for Treatment failure:

- If the clinician changes two or more anti-TB drugs during the intensive phase because of lack of response or adverse drug reactions, then the case is not considered a Treatment failure and the same treatment episode needs to be monitored for outcomes.
- However, if such a change or termination of regimen occurs during the continuation phase for the reasons presented in table 2.1, then the Treatment failure outcome is fulfilled.

Bacteriology and sputum conversion

Bacteriological examinations used in patients with DR-TB include sputum smear microscopy, culture, and DST, as well as molecular techniques such as Xpert MTB/RIF and line-probe assay (LPA).

The mainstays for testing patient response to treatment (monitoring specimens) are sputum smear microscopy and culture.

- Xpert MTB/RIF and LPA are recommended for diagnostic testing for the presence of *Mycobacterium tuberculosis* (MTB) and detection of mutations associated with rifampicin resistance; molecular tests are not recommended for treatment monitoring.
- DST may be used during treatment to assess for any acquisition of additional resistance or reinfection (also see Chapter 9 for more information on monitoring response to treatment and recommended frequency of DST during treatment).

Given that decisions on the treatment of patients depend to an important degree on the bacteriological findings, it is crucial that the tests are performed in conformity to international standards.

DR-TB confirmation at baseline: In order for a patient to be considered bacteriologically positive at the start of second-line treatment, the following criteria must be met:

- At least one pre-treatment specimen was positive for sputum smear microscopy, Xpert MTB/RIF, or culture.
- The collection date of the sample on which the laboratory examination was performed was less than 30 days before, or 7 days after, initiation of second-line treatment. A sample obtained within this time frame should be considered the **baseline specimen**.

Examinations are required at the start of treatment to confirm the diagnosis of TB, and to determine the infectiousness of the patient. Patients with positive sputum smear are the most infectious. Both smear and culture should be used to monitor patients throughout therapy.

- At least one sputum sample should always be cultured at the start of second-line TB treatment.
- The monitoring of sputum culture is important for decisions on changes in treatment.

Key point: Obtaining baseline and monthly monitoring specimens for documenting smear and culture status is used to track response to treatment and is needed for timely documentation of month of conversion.

Month of culture conversion determines:

- Duration of intensive phase s [at least 6 months and 4 months post-culture conversion]
- Total duration of treatment (at least 20 months total treatment and 18 months post culture conversion, choosing whichever duration is longer)

The terms conversion and reversion of culture results are defined as follows:

- **Conversion (to negative):** The culture is considered to have converted to negative when two consecutive cultures taken at least 30 days apart are found to be negative. In such case, the date of the first negative culture is used as the date of conversion.
- **Reversion (to positive):** The culture is considered to have reverted to positive when, after an initial conversion, two consecutive cultures taken at least 30 days apart are found to be positive. For the purpose of defining *Treatment failed*, reversion is only considered when it occurs in the continuation phase (or after eight months if no continuation phase is used).

Chapter 3

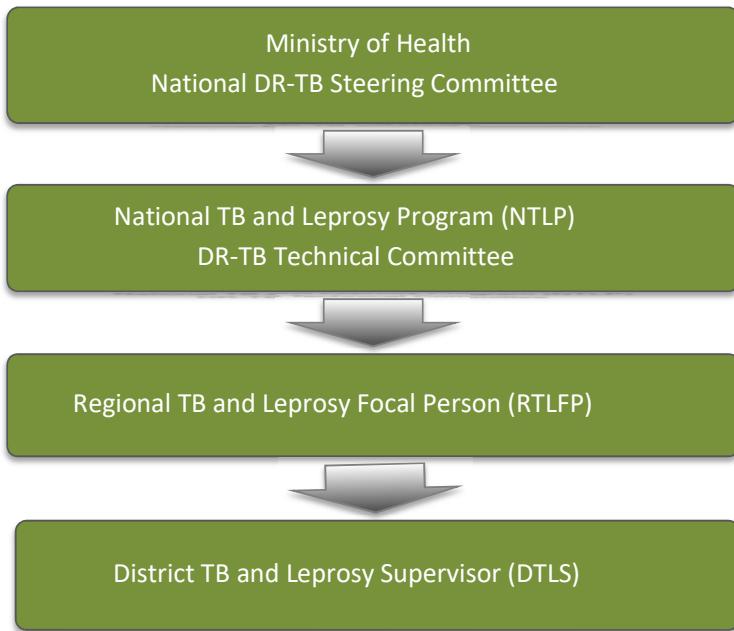
Structure of PMDT, oversight, and delivery of care

This chapter reviews the PMDT regulatory framework, structure of oversight and service delivery (including DR-TB Expert Panels), and PMDT coordination with other specialized health care systems (prisons and immigrant/refugee services).

PMDT regulatory framework and coordination

The relational structure for oversight of the PMDT program is presented below in figure 3.1.

Figure 3.1 Regulatory framework of the PMDT program



National DR-TB Steering Committee: The National DR-TB Steering Committee will be the overall policy formulating body. The Director General of Health Services chairs the committee. It comprises members of the National Disease Control Department, NTLP, development partners, civil society organizations, non-governmental organizations (NGOs), implementing partners, and AIDS Control Program. The Steering Committee is responsible for reviewing and updating policy guidelines, resource mobilization, advocacy communication and social mobilization, coordination, governance, planning, and monitoring and evaluation (M&E) of DR-TB activities.

Core functions of the Steering Committee include the following:

- Provide strategic and technical support to program planning, implementation, M&E, and capacity development.
- Provide guidance for mainstreaming of PMDT issues within overall TB control policies and programming instruments.
- Prepare joint, interagency annual work plans and national action plans for PMDT
- Oversee and support revision of PMDT guidelines regarding case finding, treatment, and overall case management.
- Promote mobilization of human and financial resources for PMDT operations and implementation of national expansion plans
- Promote documentation of evidence-based best practices

Steering Committee meetings: The Steering Committee will meet once every quarter to review progress with implementation of the joint work plan, and to receive and review reports on activities, address constraints, and provide guidance as required.

National TB and Leprosy Program (NTLP): NTLP is the central coordinating body for the activities described in the program strategic framework, including PMDT. Commitment of the necessary resources, particularly for a strong central management team, ensures that all elements are in place, from the procurement of second-line drugs to the appropriate implementation and monitoring of the DR-TB control program. As needed, the NTLP will build partnerships with all relevant health care providers. DR-TB care and prevention activities will be implemented as an integral part of NTLP. M&E and reporting of programmatic outcomes and indicators are coordinated by the NTLP. Training and capacity building initiatives, programmatic and implementation research, and the prioritization and development of such activities are also coordinated and directed through oversight by the NTLP.

DR-TB Technical Committee: One function of the NTLP is to have a DR-TB Technical Committee. The Technical Committee is an advisory group comprised of technical leadership with expertise in DR-TB clinical care and control and program planning, as well as linkages to essential services (laboratory, drug procurement, M&E). The Technical Committee is the central technical body tasked with advising on and leading guideline and policy development for approval by the NTLP and National DR-TB Steering Committee. The NTLP DR-TB Coordinator reports directly to the NTLP Program Manager and provides primary leadership for the Technical Committee.

Core functions of the DR-TB Technical Committee include the following:

- Lead development, review, and dissemination of DR-TB, guidelines, standard operating procedures (SOPs), and protocols
- Organize and participate in quarterly DR-TB cohort reviews.
- Promote best practices and procedures for routine DR-TB surveillance, diagnosis, and treatment, including appropriate follow-up testing for patients on treatment and proper documentation and communication of results to treatment sites.
- Develop appropriate strategies for DR-TB case finding, care, and treatment.
- Strengthen recording and reporting for PMDT and support full integration into the NTLP M&E system.
- Participate in resource mobilization activities for DR-TB
- Ensure DR-TB diagnostic and treatment supplies and medicines are prioritized for procurement.
- Organize and participate in capacity building and mentorship activities in DR-TB care and prevention.
- Promote documentation of evidence-based best practices, including the writing of scientific papers for publication
- Support development and implementation of relevant research protocols

Meetings of the DR-TB Technical Committee: The Committee will meet monthly to plan and review program activity implementation, DR-TB case finding, patient enrolment and monitoring, status of second-line medicine stock, and other key issues as identified by the program.

Regional TB and Leprosy Focal Person (RTLFP): Previously, an NTLP zonal level existed under the TB program structure. The zonal level has now been modified and restructured to align with the MOH regional performance monitoring chain structure. The regional level of the NTLP system will assist in implementation of policies and M&E activities of the DR-TB services under their care. Integration of the DR-TB services and oversight of the existing regional and district framework remain areas of development. RTLFP activities include the following:

- Receives and reviews DR-TB data reports from treatment initiation sites and DTLS.
• (see Chapter 19 for more details on PMDT data flow)
- Ensures proper tracking and transfer of patients between regions and districts.
- Analyses district-level DR-TB data for quality assurance and conducts data audits.
- Presents DR-TB quarterly report and analysis to the central level and shares results with district DHO and DTLS teams (process to be integrated into district health information system II [DHIS2])
- Incorporates DR-TB data and issues into regional performance review meetings with each DTLS and supports DTLS efforts to implement PMDT activities.
- Works with treatment initiation sites and DTLS/DHO for technical support for facilities implementing DR-TB activities.
- Assists in coordination and facilitation of quarterly DR-TB Cohort Reviews
- Participates in treatment initiation site Expert Panel Review meetings.
- Participates in training, supervisory, and mentorship activities with central PMDT/NTLP staff.
- Collaborates with central PMDT/NTLP staff and DR-TB Technical Committee to develop action plans for DR-TB and assists in regional implementation.

District TB and Leprosy Supervisor (DTLS): The DTLS, under the supervision of the DHO, organizes implementation of DR-TB activities at the district level.

- The **District Health Officer (DHO)**, who leads the district TB surveillance activities, will support the integration of these activities into the district surveillance system.

The DTLS, with the support of the DHO, will be responsible for:

- Ensuring intensified case finding for DR-TB with rapid DST performed for all patients considered high risk for DR-TB, including all retreatment cases and other priority groups (see Chapter 4)
- Reporting newly diagnosed RR-TB patients in the weekly, monthly, and quarterly health management information system (HMIS) reports
- Maintaining a list and informing the DHO of all patients diagnosed with DR-TB in the district
- Ensuring referral of DR-TB patients to the nearest DR-TB treatment initiation facility
- Ensuring coordination of care and tracking of transfers between facilities, particularly DR-TB treatment initiation facilities and community-based follow-up sites
- Supporting follow-up facilities to ensure DR-TB patients are on DOT, have access to proper monitoring tests, and that care remains coordinated with supervising DR-TB treatment initiation sites.
- Participating in training and supervision of healthcare staff at follow-up facilities on PMDT diagnosis, treatment, and care
- Ensuring appropriate home assessment, screening of DR-TB contacts, and proper investigations of symptomatic contacts are completed, and records of contacts screened are kept
- Actively following up with and supporting patients not adhering to treatment
- Supporting implementation of recommended infection control practices within all health care facilities in the district
- Organizing resources for TB and DR-TB control within the district
- Promoting social mobilization and PMDT information dissemination within the district and between stakeholders
- Ensuring patients at high risk for DR-TB are being screened (see Chapter 4, table 4.1)

The DTLS will provide an update to the DHO at least monthly and/or as needed on all the above activities.

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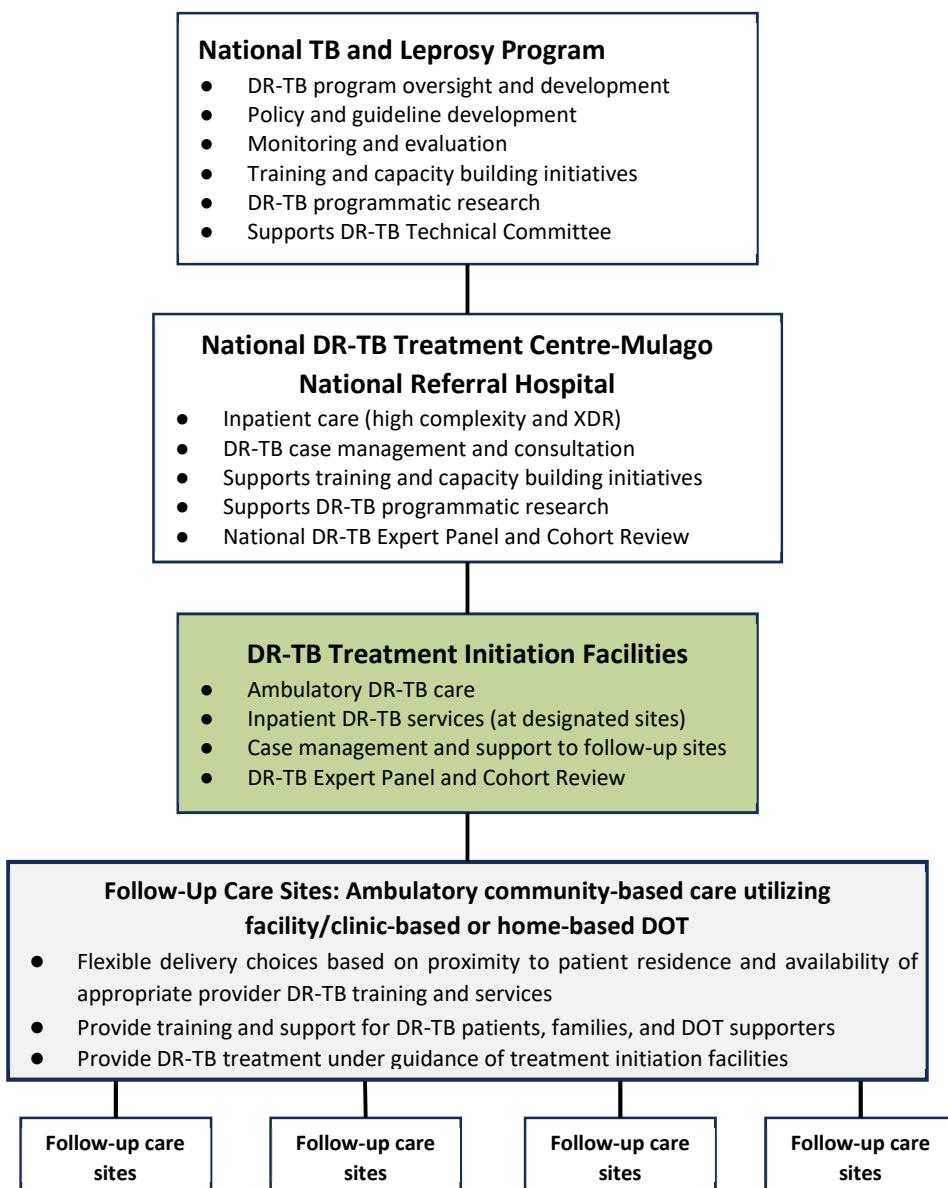
Structure of PMDT oversight and delivery of care

DR-TB care in Uganda is primarily ambulatory and community-based provided through local facility/clinic-based DOT or home-based DOT delivery systems. Treatment initiation and case management oversight is provided by regional or district treatment initiation facilities under ambulatory conditions unless medical instability or extensive resistance requires hospitalization. DR-TB cases that require hospitalization will be cared for at regional DR-TB treatment sites, with higher complexity cases or cases with extensive resistance referred to the DR-TB Centre of Excellence at Mulago Hospital.

For more information and **details regarding flow of patient care and referral systems, refer to Chapter 8.**

The structure, responsibilities, and hierarchy of DR-TB oversight and clinical service delivery is diagrammed in figure 3.2 below.

Figure 3.2 Structure of PMDT oversight and service delivery



The general roles and responsibilities of the NTLP and DR-TB Technical Committee are reviewed in the preceding section 3.1.

Mulago National Referral Hospital: The Mulago Hospital DR-TB unit will serve as the national reference centre for the management of DR-TB. The facility and providers have managed the heaviest burden of identified DR-TB cases in Uganda to date and are equipped to admit complex and/or XDR-TB cases. Mulago Hospital has access to a wide range of specialty consultation services as a national referral hospital and through their affiliation with Makerere University. The site also serves as the central DR-TB treatment initiation facility for the Kampala jurisdiction.

- With the high degree of experience and access to joint NTLP Technical Committee members, the Expert Panel convened at Mulago will serve as the **National Expert Panel** group to assist in reviewing complex cases and issues brought forth from regional centres.
- Mulago National Referral Hospital will also support and participate with the coordination of **National DR-TB Cohort Review** sessions organized through the NTLP or other national DR-TB training initiatives.
- With special isolation capacity, the unit will serve as the national referral centre for complex and/or extensively resistant DR-TB cases.
- The centre will conduct TB/DR-TB clinical and operational research.

Regional DR-TB treatment initiation facilities:

- Designated regional DR-TB treatment initiation facilities have **both inpatient and ambulatory care** capacity for the care and management of DR-TB.
- Providers have had appropriate training to initiate and **offer “start-to-finish” case management oversight** for DR-TB.
- Sites will conduct monitoring tests and monthly clinical reviews for all patients initiated on DR-TB treatment.
- Sites will ensure availability and proper handling of second-line drugs.
- Sites are responsible for timely and accurate completion of DR-TB recording and reporting forms, including entry into the electronic database in coordination with the RTLFP.
- Experienced clinical providers and nurses from these sites serve as **peer-to-peer mentors** for capacity building and supportive supervision of other treatment initiation sites through the direction and support of the NTLP.
- Treatment initiation sites will also convene and support **Regional Expert Panels** and participate in **national and/or regional DR-TB Cohort Review** sessions, as organized through the NTLP.

District general hospitals:

- If accredited by NTLP/MOH, designated district DR-TB treatment initiation facilities may initiate second-line treatment on an ambulatory basis for patients who do not require hospitalization.
- Sites will refer critically ill MDR-TB and other complicated patients to a regional (or national if XDR) treatment initiation facility for admission and further management.
- Providers have had appropriate training to initiate and offer “start-to-finish” case management oversight for DR-TB.
- Sites will conduct monitoring tests and monthly clinical reviews for all patients initiated on DR-TB treatment.
- Sites will ensure availability and proper handling of second-line drugs.

- Sites are responsible for timely and accurate completion of DR-TB recording and reporting forms, including entry into the electronic database in coordination with RTLFP.
- District treatment initiation sites will also convene and support District Expert Panels and participate in national and/or regional DR-TB Cohort Review sessions as organized through the NTLP.
- All district hospital and ambulatory care settings will support and participate in intensified DR-TB case finding.

Community-based follow-up care: Facility/clinic or home-based DOT

- Delivery of DR-TB care at the peripheral health system level is tailored to fit the local infrastructure and patient needs.
- Choice of facility or provider for DR-TB services follows a patient-centred approach to optimize access to care and enhance adherence.
- Based on proximity to the patient and availability of DR-TB trained staff, peripheral level follow-up facility care may take place in the nearest local health unit/clinic that has been trained to offer treatment to DR-TB patients.
- Where available, community-based DR-TB teams may be mobilized to deliver homebased care to patients.
- Follow-up care sites provide daily DOT to DR-TB patients.
- All community-based care or peripheral facility sites will have oversight and case management linkages with the referring DR-TB treatment initiation facilities responsible for the DR-TB patient.
- In collaboration with the treatment initiation facility and the DTLS, these sites will ensure home assessment, contact tracing, and investigation for all DR-TB patients under their care.

DR-TB Expert Panels

DR-TB Expert Panels and their role: The DR-TB Expert Panel is a case management and review committee with expertise in DR-TB diagnosis and management, or knowledge regarding essential services critical to DR-TB care. Panels should be organized at each DRTB treatment initiation site. The panel located at the Mulago Hospital DR-TB Centre of Excellence will serve as the National DR-TB Expert Panel. General district hospitals accredited to start patients on second-line treatment will have smaller panels and will be supported by the regional panels monthly.

- The site panels shall include DR-TB trained clinical providers (doctors, clinicians, or medical officers), DR-TB nurses, lab personnel, social workers, and a radiologist, if available (or provider trained on chest x-ray [CXR] reading), as well as and key representatives of associated essential services (e.g., laboratory; social work/services; community linkage; nutrition; ear, nose, throat; and drug procurement) for the DR-TB program, RTLFP, and DTLS.
- The National Expert Panel shall also include members of the PMDT Technical Committee at the NTLP.
- The committee will meet regularly when needed or monthly, at a minimum, to confirm DR-TB diagnoses, approve initiation of treatment and choice of regimen, advise if complications arise, assess response to treatment, advise when issues of nonadherence to treatment or infection precautions arise, advise on ways forward for patients failing second-line treatment, and determine final outcomes through a consensus using standards based on the NTLP Guidelines for PMDT.
- If urgent clinical decisions are required between scheduled meetings, an ad hoc assembly of members may be convened for a timely response.

- The DR-TB Expert Panel will review issues related to individual case complications, and adherence problems, and will address local solutions to programmatic challenges (e.g., case management response to temporary anti-TB drug or supply stock-outs, linkage to service issues, or access to ancillary medications).
- Complex case or programmatic issues at the regional or district level may warrant further review or elevation to the national level for consideration. Issues may be brought to the National Expert Panel as part of the Cohort Review process (see Chapter 19), or on an ad hoc basis if urgent, and should be coordinated through the NTLP PMDT Coordinator.
- Expert Panels will be responsible for reviewing and determining the treatment outcomes of patients started on treatment.

Delivery of DR-TB services for key populations (prisons, military, schools, refugees/IDPs)

Coordination among the different components of public and private health care programs and organizations is essential for successful program implementation.

Coordination with prisons: Transmission in prisons may be an important source of spread of DR-TB and infection control measures can substantially reduce incidence. In many cases, inmates may be released from prison before they finish treatment. Close coordination and communication with the civilian TB control program, advance planning, targeted social support, and specific procedures for transferring care are essential to ensure that patients complete treatment after release from prison.

Initially DR-TB cases diagnosed from prison shall be managed at accredited DR-TB facilities with prisons working as follow-up facilities after discharge of patients from the hospitals. Based on clinical stability and availability of trained DR-TB staff, Uganda prison health services may directly manage cases within the prison health service units.

Coordination with other key population services: Capacity for appropriate DR-TB risk assessment and screening should be coordinated between other agencies that serve the needs of key populations and the NTLP. This includes communication and DR-TB service linkages to facilitate proper evaluation and advice. Collaborative efforts include (but are not limited to) outreach and coordination with:

- **Immigrants and refugees/internally displaced persons (IDPs) services**
- **Military services**
- **Schools**

A memorandum of understanding shall be written delineating responsibilities and funding where different ministries, such as Internal Affairs and Defense, for the prison system, military health service system, or other departments are involved.

Chapter 4:

DR-TB case finding and diagnosis (including use of rapid molecular DST)

This chapter describes strategies for case finding and diagnosis of patients with either suspected or confirmed DR-TB.

Key recommendations of this chapter:

- All patients at high risk for DR-TB should be screened for drug resistance using a rapid molecular DST method (e.g, Xpert MTB/RIF Ultra or Truenat) for early identification.
- If Xpert MTB/RIF Ultra or Truenat results identify resistance to Rifampicin, this client should be immediately referred to the nearest DR TB treatment centre for further evaluation and initiation of DR TB treatment.
- An Xpert MTB/XDR assay for detection of fluoroquinolone resistance should be done at the DR TB treatment centre prior to DR TB treatment initiation.
- At the DR TB treatment centre, an additional sputum specimen must be collected and sent to the NTRL for culture and standard phenotypic DST before initiation of DR TB treatment.
- Full profile phenotypic DST for both first line (Rifampicin and Isoniazid, ethambutol, pyrazinamide) and 2nd line (Moxifloxacin, Levofloxacin, Bedaquiline, Linezolid and Clofazimine, Delamanid, Pretomanid, Amikacin) anti TB drugs will be done for the baseline culture positive samples from all the RR TB cases received at the NTRL.

Background and general considerations

Early identification and prompt initiation of adequate treatment for drug-resistant cases minimizes mortality among these patients, and prevents patients from spreading the disease to others, acquiring further resistance, and progressing to a state of permanent lung damage. Surveillance data for drug resistance among new and re-treatment TB patients (smear positives, treatment failure, relapse or return after lost to follow-up) and other high-risk groups is important for informing NTLP of planning needs, which include:

- Identification of high-risk groups for prioritization and targeted DST testing
- Design of effective case-finding strategies and treatment regimens
- Estimation of the number of patients to be enrolled, medication supply, and other procurement requirements.

INH mono resistance surveillance is currently limited to the DR TB patients diagnosed using a rapid molecular assay prior to initiation of DR TB treatment. This is done using the Xpert MTB/XDR assay available at each of the DR TB treatment centres. However, it is recommended that all clients that remain sputum smear positive at 2,3 or 5 months of treatment of susceptible TB treatment should have their sputum samples collected and referred to the nearest DR TB treatment initiation site for Isoniazid testing or sent to the NTRL for culture and 1st line phenotypic DST.

Risk groups for DR-TB

The NTLP recommends **intensified case finding and targeted use of a rapid molecular DST** for specific groups of patients at increased risk for DR-TB in Uganda. Uganda is currently using the Genexpert TB testing (Xpert MTB/ RIF ultra) and Truenat testing platforms as the rapid molecular diagnostic DST assay for the identification of Rifampicin Resistant TB. Specific elements of the history that suggest an increased risk of drug resistance are reviewed in table 4.1 below, which represents the list of high-risk target groups for DST. Stronger risk factors are placed higher in the table. Risk factors for XDR-TB are discussed in section 4.3.

Table 4.1 NTLP target groups for DST based on risk factors for DR-TB

Target Group for DST	Reason for inclusion as a target group
All bacteriologically confirmed cases	These will include all that have not received a DST at all e.g. use of urine LF-LAM, microscopy/smear, TBLAMP etc.
Failure to convert	Failures of treatment TB regimen are defined as patients who remain sputum smear positive at the end of a supervised treatment regimen. These patients have the highest MDR-TB rates of any group, often approaching 90%.
Exposure to a known DR-TB case	Close contacts of MDR-TB patients have high rates of MDR-TB. Management of DR-TB contacts is described in Chapter 15.
Patients who remain sputum smear positive at month 2/3 & 5 of first-line anti-TB treatment	This group of patients is at risk for DR-TB, rates can vary considerably. There are some DR TB strains that might be missed by the molecular assays and might require a phenotypic DST for identification. Therefore, all patients still smear positive at month 2,3 and 5. send a sample for phenotypic culture and DST at NTRL.
Relapse or return after loss to follow-up, without recent treatment failure	Cases of relapse or return after loss to follow-up with a history of erratic anti-TB drug use may be more strongly associated with risk for DR-TB. Early relapses are also associated with DR-TB.
Exposure in institutions that have DR-TB outbreaks or a high DR-TB prevalence (includes health care workers)	Prisoners and health care workers in health facilities can have high rates of DR-TB.
HIV-positive patient presumed to have TB	It is strongly recommended that all individuals with HIV-associated TB have DST to rule out DR-TB to avoid high rates of mortality due to unrecognized DR-TB.

Strategies for DR-TB case finding and diagnosis.

Algorithm for rapid molecular DST testing

A key component of the NTLP strategy for intensified DR-TB case finding is implementation of rapid molecular DST testing for all high-risk patients (as listed in table 4.1).

- Case-finding strategies can be greatly enhanced with rapid molecular DST, which significantly improves the ability to quickly identify cases of DR-TB that should be isolated and started on treatment.
- Rifampicin is the most potent anti-TB drug of the first-line regimen, and Rifampicin resistance most commonly occurs with concomitant Isoniazid resistance. A positive rapid molecular DST for Rifampicin is a strong indicator that a patient may have MDR-TB, while a negative test makes diagnosis of MDR-TB highly unlikely.
- Figure 4.1 presents the algorithm for the use of rapid molecular DST using Xpert MTB/RIF Ultra and Truenat for identification and initial management of patients suspected of TB who are at increased risk of DR-TB.

Figure 4.1: Algorithm for TB screening, diagnosis and management

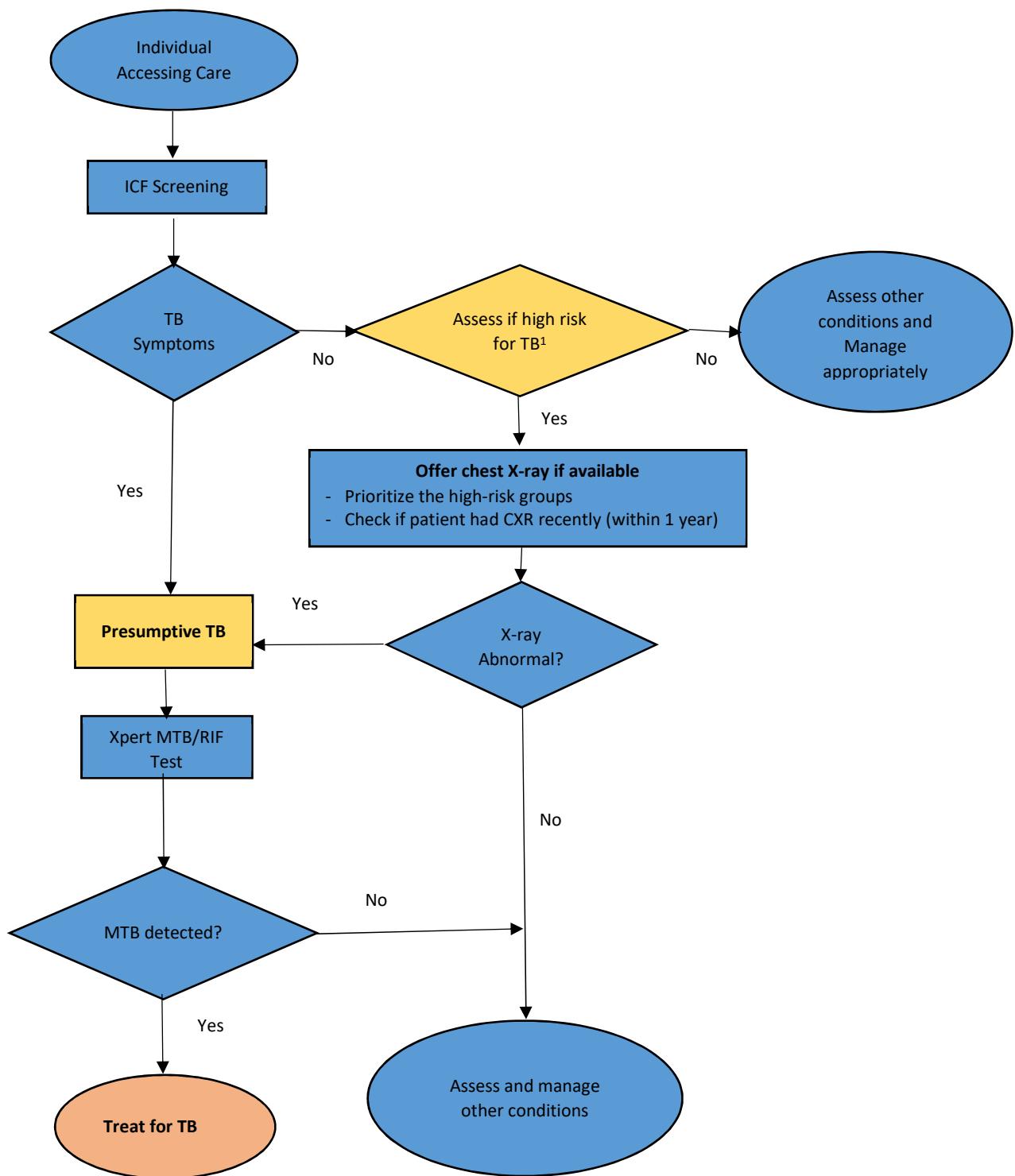
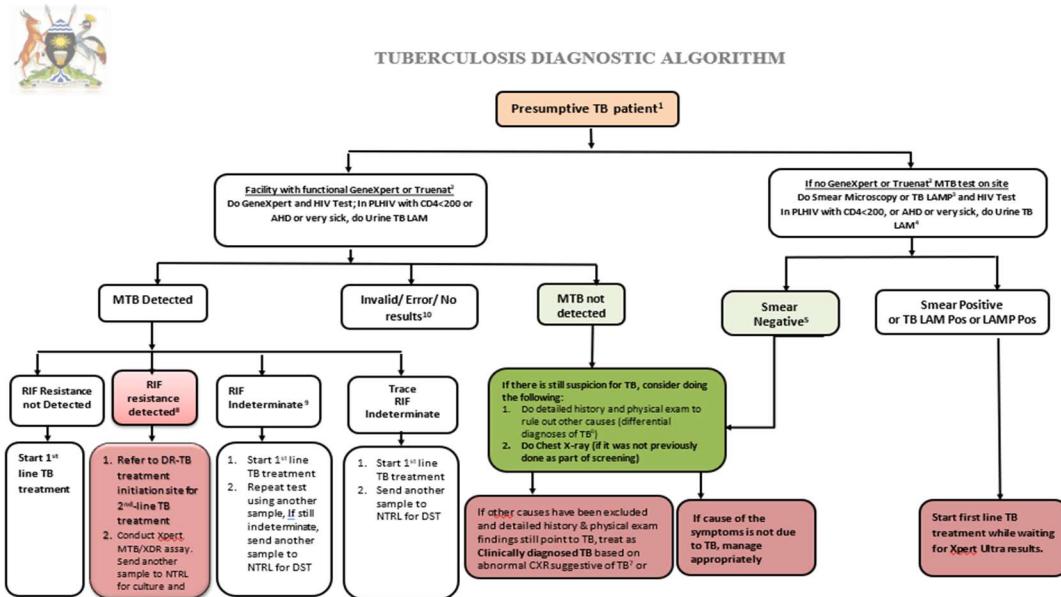


Figure 4.2: Tuberculosis Diagnostic Algorithm

1. **Presumptive TB** is presence of any or a combination of the following symptoms; cough≥2 weeks or current cough with any other TB symptom, fever, night sweats, history of contact with a TB case, weight loss or poor weight gain for children. Also consider abnormal chest x-ray in a high-risk patient as presumptive TB
2. **Truenat** is a molecular test for diagnosis of TB and Rifampicin resistance
3. **TB LAMP Positive**- Only Positive TB-LAMP should be sent for Xpert testing. **Smear positive** (AFB positive): is defined as at least one positive smear
4. **Urine TB LAM** test should be offered to HIV positive individuals with CD4 ≤ 200 (AHD) or very sick (**Temperature >39°C, Respiratory Rate >30 breaths/min, Heart Rate >120 beats/min, New Seizure, Unable to walk without assistance / Bed-ridden**). If Urine TB LAM is positive, the Patient should be started on TB Treatment and a sputum sample should be collected for Genexpert testing to rule out Rifampicin resistance.
5. **Smear negative**: defined as at least one negative smear. Carry out other investigations such as CXR **if available**. Those with **CXR suggestive of TB** should be treated as clinically diagnosed TB. **If not available** or CXR not suggestive, do further history, physical examination and other investigations to exclude **other causes of chronic cough, fever and weight loss**.
6. **Differential Diagnoses of TB**: Chronic Obstructive Pulmonary Disease (COPD), heart disease, asthma, bronchiectasis, emphysema; Histoplasma pneumonia, trypanosomiasis, brucellosis; Fungal infection of the lung; Malignancy (lung cancer, lymphoma etc.)
7. **Features of abnormal X-ray suggestive of TB**: Heterogeneous opacities and cavitation in the upper parts of the lung, mediastinal L/nodes, pleural effusion and mililiary picture
8. **If MTB detected RIF resistance detected**, Refer patient for MDR-TB treatment. Conduct Xpert MTB/XDR assay. Send another sample to NTRL for culture and DST (Sample should be sent by DR-TB treatment initiation site).
9. **If MTB detected Rifampicin Resistance Indeterminate**: Start first line TB treatment, Repeat Test using another sample. If still indeterminate, send another sample to NTRL for DST.
10. If Error/No result on Xpert, repeat the test with a new cartridge. If Invalid on Xpert, repeat the test with a new sample and new cartridge. For Truenat, repeat the test and follow algorithm to interpret. If both Truenat tests give indeterminate, treat with 1st line TB regimen and promptly conduct additional investigations to assess resistance to rifampicin e.g., DST. Review treatment based on DST result.

Interpreting Rifampicin-resistance results from molecular testing

Discussion on different methods of testing for drug resistance (conventional/phenotypic DST versus rapid molecular/genotypic DST) can be found in the laboratory section of these guidelines (Chapter 5). This section will discuss the application and interpretation of rapid molecular DST for case finding and diagnosis.

Rapid DST using molecular testing methods (Xpert MTB/RIF Ultra, Truenat and LPAs) have been found to have a high sensitivity and specificity for detection of Rifampicin resistance. Molecular methods do not have perfect concordance with phenotypic culture-based DST methods and patient details such as treatment history and risk factors for DR-TB should always be considered when interpreting laboratory results.

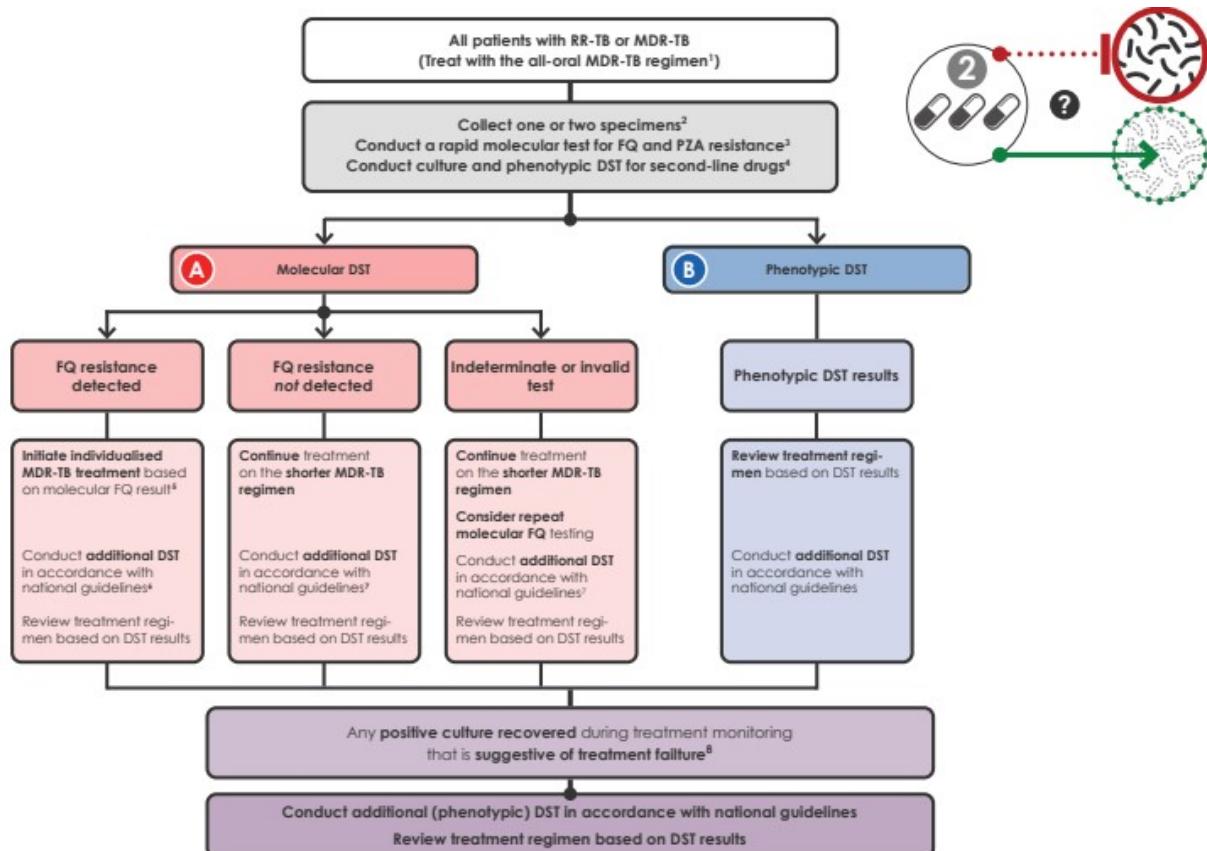
The rapid DST molecular methods detect mutations in the rpoB region of MTB DNA, which are responsible for >95% of Rifampicin-resistant strains. Given the resultant high sensitivity of molecular methods, a negative result generally excludes Rifampicin resistance and no further testing to confirm negative results is required. In rare instances, when a patient is strongly presumed to have RR-TB even after a negative molecular test, follow-up testing using conventional (phenotypic) culture-based DST or sequencing may be used to test for Rifampicin resistance resulting from a small number of mutations occurring outside the rpoB region.

The rapid DST molecular methods also have high specificity for detection of Rifampicin resistance. Nevertheless, any diagnostic test with a specificity of less than 100% when used in a population with a low prevalence of the condition can result in a lower positive predictive value, which means that a number of false-positive results are present among those diagnosed as having the condition. Increasing evidence, however, is showing that the occurrence of apparently false-positive Rifampicin resistance by Xpert MTB/RIF, compared to phenotypic culture-based DST methods, may be linked to detection by molecular methods of strains that are truly resistant to Rifampicin, yet are not detected by culture-based DST. Such strains appear to have clinically relevant mutations in the rpoB region conferring resistance to Rifampicin, causing disease that is likely to fail first-line treatment. A study by Van Deum A, et al, showed that an epidemiologically significant proportion (close to 10-13%) of Rifampicin-resistant strains in first failure and relapsed patients are missed by rapid phenotypic DST.

The interpretation of molecular results and follow-on steps will depend on the result itself, as well as on the patient group from which the patient originated. All patients identified by molecular methods should be initiated on an appropriate recommended treatment regimen as soon as possible. Prompt treatment initiation will have a positive effect on patient outcomes, and the treatment regimen can be refined when additional testing results become available.

Figure 4.2 Algorithm for DST for second line drugs for RR-or MDR TB patients

From WHO Operational handbook on tuberculosis: Module 3-Diagnosis.Rapid diagnostics for tuberculosis detection



Foot notes to figure 4.2

BDQ: Bedaquiline; CFZ: Clofazimine; DLM: Delamanid; DST: drug-susceptibility testing; FQ: fluoroquinolone; INH: Isoniazid; LC-aNAAT: low complexity automated NAAT; LZD: Linezolid; MDR-TB: multidrug-resistant tuberculosis; MDR/RR-TB: multidrug- or Rifampicin-resistant tuberculosis; NAAT: nucleic acid amplification test; PZA: pyrazinamide; RR-TB: Rifampicin-resistant tuberculosis; SL-LPA: line-probe assay for second-line drugs; TB: tuberculosis; WHO: World Health Organization.

1. Patients should be promptly initiated on an MDR-TB regimen in accordance with national guidelines and WHO recommendations. A shorter all-oral BDQ-containing treatment regimen of 9–12 months in duration is the preferred option for eligible MDR/RR-TB patients.
2. If molecular and phenotypic testing are performed in the same laboratory, one specimen may be sufficient. If testing is performed in two laboratories, two specimens should be collected, and the molecular and phenotypic testing conducted in parallel.
3. WHO recommends getting the rapid DST results for FQs before the start of treatment, although this testing should not delay the start of treatment. Currently, LC-aNAAT and SL-LPA are the WHO-approved rapid molecular tests for detecting FQ resistance.
4. Phenotypic DST should be conducted for each of the drugs included in the treatment regimen for which there are accurate and reproducible methods. Reliable phenotypic DST methods when performed in a quality-assured laboratory are available for BDQ, FQ, CFZ, INH, PZA, DLM and LZD. A new molecular class of tests, the reverse hybridization high complexity NAAT, is available for PZA resistance detection on culture isolates. The initiation of treatment should not be delayed while awaiting the results of the phenotypic DST.
5. For more details regarding individualized regimens, see the *WHO consolidated guidelines on drug-resistant tuberculosis treatment* (58).
6. For FQ-resistant MDR/RR-TB, a specimen should be collected and submitted for phenotypic DST to the WHO Group A (BDQ and LZD), B and C drugs, if not already being done as described in note 4.
7. In settings with a high underlying prevalence of resistance to FQs or for patients considered at high risk of FQ resistance, a specimen should be referred for culture and phenotypic DST for FQs.
8. If resistance to an individual drug (e.g. BDQ) is suspected and DST for these drugs is not available in the country, laboratories will need to have mechanisms to store the isolate and ship it to a WHO supranational laboratory for DST.

When a molecular method detects Rifampicin resistance, all RR-TB patients detected by rapid molecular tests (Xpert MTB/RIF Ultra and Truenat) will be referred to DR-TB treatment initiation facilities for further evaluation and treatment.

- The patient should be registered as having bacteriologically confirmed RR-TB, and a sputum sample (taken immediately, prior to treatment onset) for testing with Xpert MTB/XDR at the DR TB treatment site as well as collect another sputum sample to the NTRL for phenotypic culture and DST. Consideration for treatment regimen initiation based on Xpert MTB/XDR or SL LPA results and clinical evaluation should be made (see Annex 9) and appropriate DR-TB regimen started. The DR-TB Expert Panel should be consulted for the appropriate regimen in the event of fluoroquinolone resistance detected by the available diagnostics like Xpert MTB/XDR or SL LPA. When phenotypic (full) DST results are available, the MDR-TB treatment regimen may be reconstructed based on the results and patient registration may be updated accordingly.

In case of discordance in Rifampicin resistance results between a molecular method and phenotypic DST or another molecular method, consider the highest level of resistance to manage the patient.

Molecular methods are not suitable for monitoring of treatment response. Results can stay positive for MTB by detection of DNA in dead organisms after viable bacteria have been eliminated, resulting in false-positive results. Therefore, culture remains the preferred method for monitoring patient response to DR-TB therapy.

Presumptive MDR-TB

The groups eligible for the presumptive diagnosis of MDR-TB and direct enrolment into an MDR-TB regimen include:

- Failures of treatment regimens with first-line drugs:** Patients in whom treatment with first-line drugs (HREZ) fails may have MDR-TB. If the quality of the drugs the patient received is uncertain or if the quality of DOT is poor or unknown (i.e., if regular ingestion of medicines is uncertain), treatment regimens may fail for reasons other than drug resistance.
- Close contacts of DR-TB cases who develop active TB disease:** These patients can be enrolled for treatment with MDR regimens, pending DST results. See Chapter 15 for more details on the management of contacts of DR-TB patients.
- For all patients started on empiric MDR-TB regimens, the standard of care is to receive DST to confirm the diagnosis. However, it should be noted that
- Under circumstances where DST results are not available to guide the management of individual patients, an empirical regimen can be continued throughout the course of treatment under the guidance of the Expert MDR TB Panel. *Remark:* If DST results become available later, regimens should be adjusted appropriately.

Case finding and diagnosis for XDR-TB and other specific populations

Case finding for XDR-TB: Additional risk factors may raise concern for potential expanded resistance. The two strongest risk factors for XDR-TB are:

- Failure of a TB treatment that contained second-line drugs, including a fluoroquinolone and either Bedaquiline or Linezolid (or both).
- 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.
- Full profile DST for all available drugs should be assessed: Bedaquiline, Linezolid, Clofazimine, Moxifloxacin and Levofloxacin. Other specific DST might be requested on special request e.g. Delamanid, Ethionamide, Amikacin etc.
- HIV-infected individuals with risk factors for XDR-TB should have either liquid or other validated rapid techniques for DST of first- and second-line drugs requested due to the high and rapid risk of death with coinfection.

The National TB Reference Laboratory (NTRL) currently has the capacity to perform DST of representative second-line drugs using conventional and rapid molecular techniques as per the table below

Table 5: NTRL DST capacity.

Type of DST	2nd line Drugs tested
LJ DST	Levofloxacin, Moxifloxacin, Amikacin
MGIT DST	Levofloxacin, Moxifloxacin, Amikacin, Bedaquiline Clofazimine, Linezolid, Delamanid, Ethionamide, Pretomanid
MKIT DST	Amikacin, Prothionamide, Cycloserine, Para Amino Salicilic acid (PAS), Moxifloxacin, Levofloxacin and Linezolid
Broth micro dilution	Bedaquiline, Delamanid, Clofazimine
Xpert MTB/XDR	Fluoroquinolones, Ethionamide, Amikacin, Kanamycin, Capreomycin
Sequencing	Levofloxacin, Moxifloxacin, Cycloserine, Bedaquiline, Clofazimine, Linezolid, Delamanid, Ethionamide, Amikacin, Capreomycin, Kanamycin, PAS

Case finding of patients with mono- and poly-drug resistance: Mono- and poly-drug resistant strains are strains that are resistant to anti-TB drugs but not to both Isoniazid and Rifampicin. DST will identify cases of mono- and poly-drug resistance, in addition to MDR-TB cases. These patients may require modifications to their anti-TB regimens or be considered for a DR-TB regimen (see Chapter 7).

Case-finding in pediatric patients: (Also refer to Chapter 11.) The diagnosis of TB is more difficult in children than in adults; similarly, DR-TB case finding in pediatric cases can be difficult. Pediatric cases therefore require adjustments in diagnostic criteria and indications for treatment. Younger children, especially those less than five years old, may not be able to produce sputum specimens on demand but it is possible to test their stool using the Xpert MTB/Rif Ultra assay. Measures such as taking a careful history; enlisting important physical signs; and performing investigations such as CXR, sputum induction or gastric aspiration for sample collection, and a tuberculin skin test may be considered, if available.

- It is highly recommended that any sample, including sputum, stool and/or gastric aspirates, received from children (0–14 years) should be referred for Xpert MTB/RIF Ultra testing as the initial test (see algorithm in figure 4.1 above).
- Children should not be excluded from treatment solely because a sputum specimen is not available. Collection of specimens from extrapulmonary sites should be attempted where appropriate.
- Children with active TB who are close contacts of patients with DR-TB should be presented to the DR-TB Expert Panel to approve initiation of empiric DR-TB treatment.

Case-finding in HIV-infected patients: (Refer also to Chapter 12.) Unrecognized MDR-TB and XDR-TB are associated with high mortality in HIV-infected patients.

- Initial testing with Xpert MTB/RIF Ultra or Truenat should be performed on all people living with HIV (PLHIV) with presumptive TB in Uganda, regardless of sputum smear status, to increase early identification and treatment initiation in those with DR-TB (see figure 4.1).

Case finding for extrapulmonary TB: in cases where the anatomic location of disease includes sites outside the pulmonary parenchyma, fine needle aspiration or biopsy should be considered in settings with appropriate facilities and technical expertise. The WHO operational handbook on tuberculosis: module 3: diagnosis: rapid diagnostics for tuberculosis detection, 2021 update recommends the following for the diagnosis of extrapulmonary TB:

- In adults and children with signs and symptoms of extrapulmonary TB, Xpert MTB/Rif may be used in lymph node aspirate, lymph node biopsy, pleural fluid, cerebrospinal fluid, peritoneal fluid, pericardial fluid, synovial fluid or urine specimens as the initial diagnostic test for the corresponding form of extrapulmonary TB rather than smear microscopy or culture.
- In adults and children with signs and symptoms of extrapulmonary TB, Xpert MTB/RIF Ultra should be used for detection of RIF resistance rather than culture and phenotypic DST.
- In adults and children with signs and symptoms of extrapulmonary TB, Xpert Ultra may be used in lymph node aspirate and lymph node biopsy as the initial diagnostic test for the detection of lymph node TB, rather than smear microscopy or culture. Testing of extrapulmonary specimens with Xpert MTB/RIF Ultra should be discussed and planned with the laboratory.
- Specimens obtained by aspiration or biopsy may also need to be sent to the pathology laboratory for examination, in addition to the microbiological laboratory for testing, to rule out other diseases.

Management of specimens and next steps

Management of specimens, next steps, and other considerations once a diagnosis of DR-TB has been made can be found in the following areas of these guidelines:

- Procedures for collecting and transporting sputum specimens are described in Chapter 5 which also addresses different techniques, limitations, quality assurance requirements, and other issues of culture and DST.
- Infection control measures for sputum collection must be in place so as not to risk infecting others (see Chapters 5 and 16).
- Once the results have been received at the facility or by the health care provider, the patient should have an immediate follow-up medical visit to initiate appropriate treatment. Next steps in the referral process and initiation of care are covered in Chapter 8.

Chapter 5: Laboratory

This chapter describes laboratory services needed to diagnose and treat DR-TB.

Background

Based on current laboratory methods available, a definitive diagnosis of DR-TB requires MTB bacteria to be isolated on culture, identified, and DST completed.

Early detection of drug resistance through rapid molecular testing using Xpert MTB/RIF Ultra or Truenat is available and its use in appropriate cases (see Chapter 4) should be prioritized. Rapid identification allows for the use of appropriate treatment regimens earlier during care, which has an important impact on improved TB control. Conventional culture and DST methods require prolonged lengths of time to confirm mycobacterial growth and detect drug resistance. During this prolonged wait, patients may be inappropriately treated, drug-resistant strains may continue to spread, and amplification of resistance may occur. Therefore, early and rapid diagnosis of TB and drug resistance will have obvious benefits for patients and public health, including better prognosis, increased survival, prevention of acquisition of further drug resistance, and reduced spread of drug-resistant strains to vulnerable populations.

General definitions for the laboratory and DST

The following are definitions of terms used when dealing with DR-TB testing:

- **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 anti-TB drug.
- **Genotypic DST (molecular DST):** Genotypic testing detects mutations in the TB genome associated with specific drug resistance. (Note: genotypic testing is also used to identify MTB by detecting the presence of TB-specific mycobacterial DNA).
- **Direct testing:** Direct testing refers to testing directly from a clinical sample (most commonly a sputum specimen).
- **Indirect testing:** Indirect testing refers to testing performed on cultured isolates of MTB. In indirect DST, processed clinical samples are directly inoculated onto media with and without anti-TB drugs, or processed for molecular testing.
- **Critical concentration** of an anti-tuberculous agent has been adopted and modified from international convention. The critical concentration is defined as the lowest concentration of an anti-TB agent *in vitro* that will inhibit the growth of 99% (90% for pyrazinamide) of phenotypically wild type strains of *M. tuberculosis* complex.
- **Minimum inhibitory concentration (MIC)** – the lowest concentration of an antimicrobial agent that prevents growth of more than 99% a microorganism in a solid medium or broth dilution susceptibility test.
- **Clinical breakpoint** – is the concentration or concentrations of an antimicrobial agent which defines an MIC above the critical concentration that separates strains that will likely respond to treatment from those which will likely not respond to treatment. This concentration is determined by correlation with available clinical outcome data, MIC distributions, genetic markers, and PK/PD data including drug dose. A dose increase can be used to overcome

resistance observed at lower dosing, up until the maximum tolerated dose, and therefore a higher clinical breakpoint above which the particular drug is not recommended for use. The clinical breakpoint is used to guide individual clinical decisions in patient treatment.

- **Reproducibility:** The ability of a test or experiment to be accurately reproduced, or replicated, under independent conditions. Reproducibility relates to the agreement of test results across different laboratories and laboratory technicians.
- **Reliability:** The extent to which a test result remains consistent when repeated under identical conditions. Reliability does not imply validity. A reliable test generates a consistent result, which may not necessarily be accurate (e.g., clinical efficacy may not be accurately predicted even if a test is highly reliable).
- **Validity:** The validity of a test refers to whether a test is measuring what it is supposed to be measuring. Ideally, a DST result should predict clinical efficacy.
- **Cross-resistance** is resistance to multiple anti-tuberculosis agents caused by a single genetic change (or multiple changes, in case the given resistance mechanisms requires several genetic alterations), although in practice, such mutations may not be known. Resistance mutations to one anti-TB drug may confer resistance to some or all of the members of the drug family and, less commonly, to members of different drug families e.g. cross resistance between the fluoroquinolones: Moxifloxacin and Levofloxacin, cross resistance between Bedaquiline and Clofazimine and cross resistance between Delamanid and Pretomanid (References 31 and 32 in the 2022 WHO operational handbook, Module 4-treatment Drug resistant tuberculosis treatment).

Essential laboratory services and infrastructure

Optimal management of DR-TB requires both mycobacterial and clinical laboratory services. At a minimum, the required mycobacteriology laboratory services include rapid molecular DST (Xpert MTB/RIF Ultra and Truenat), culture, identification to confirm MTBC, and DST to Isoniazid and Rifampicin. Clinical laboratory services for adequate evaluation and monitoring of patients should include basic haematology, biochemistry, serology, and urine analysis (see Chapter 9).

In addition to diagnostic services, laboratory services play a critical role in surveillance of drug resistance patterns to provide information on the magnitude and trends in drug resistance, for developing appropriate treatment modalities, and for evaluating the impact of control program interventions.

Adequate resource allocation (human and financial) to laboratory services is essential to ensure availability of sufficient and adequately qualified and trained laboratory staff, as well as a safe and functioning laboratory infrastructure with appropriate levels of biosafety, well-maintained equipment, and sufficient laboratory consumables.

Transmission of TB, including MDR- and XDR-TB, is a well-recognized risk for laboratory workers. Specific precautions, good microbiological practices, engineering controls, proper training, and containment measures are needed to ensure safe handling of MTB at all levels of the laboratory network.

Comprehensive laboratory quality management systems are mandatory, including internal quality control and external quality assurance.

Organization of the laboratory network

The TB laboratory network has a pyramidal structure based on many peripheral (Level I) laboratories accessible to all patients in need of TB evaluation, a moderate number of intermediate (Level II)

laboratories, and a central (Level III) laboratory—the NTRL. Functions and responsibilities at the different laboratory levels are outlined in the following table.

Table 5.1 Functions and responsibilities of TB laboratory service levels I-III

Level I: The peripheral laboratories (HC III, HC IV, district hospitals)
<ul style="list-style-type: none"> ● Receipt of specimens ● Preparation and staining of smears. ● Ziehl-Neelsen and/or fluorescence microscopy and recording of results. ● Dispatch of results ● Maintenance of laboratory register ● Cleaning and maintenance of equipment ● Management of reagents and laboratory supplies ● Internal quality control ● Proper waste management ● Perform as a Hub (if accredited) ● Perform rapid DST (Xpert MTB/RIF Ultra or Truenat) where applicable or refer samples to the hub, nearest GeneXpert or Truenat site, or to the NTRL
Level II: The intermediate laboratory (Regional referral hospital)
<ul style="list-style-type: none"> ● All the functions of a Level I laboratory ● Training of microscopists ● Support to and supervision of peripheral-level staff with respect to microscopy and rapid molecular methods like GeneXpert and Truenat. ● Preparation and distribution of reagents for microscopy at peripheral sites ● Quality improvement and proficiency testing of microscopy at peripheral sites
Level III: The central laboratory (National TB Reference laboratory)
<ul style="list-style-type: none"> ● All the functions of Level I and II laboratories ● DST (first- and second-line anti-TB drugs) for MTB isolates ● Identification of mycobacteria other than MTB ● Technical control of and repair services for laboratory equipment ● Updating and dissemination of laboratory manuals, including guidelines on diagnostic methods, care and maintenance of equipment, and quality assurance ● Close collaboration with the central level of the NTLP ● Supervision of lower-level laboratories regarding bacteriological methods and their support (particularly training and supervision) to the peripheral laboratories ● Quality assurance of microscopy, molecular methods: GeneXpert and Truenat (culture and DST, if applicable in the future) performed at lower- level sites ● Training of lower-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 the NTLP

The NTRL in Uganda is also recognized as a WHO Supranational Reference Laboratory (SRL). As an SRL, the NTRL participates in proficiency testing to maintain external quality assurance and validation of DST results

Mycobacteriology laboratory services for DR-TB programs

The NTLP, through NTRL, provides SOPs and policy guidelines on TB tests important in the diagnosis and monitoring of DR-TB. Some important considerations for providers when using these tests include the following:

- **Microscopy:** Microscopy for acid-fast bacilli (AFB) cannot distinguish viable from non-viable organisms, drug-susceptible versus drug-resistant MTB, or between different species of mycobacteria. Microscopy for DR-TB is therefore limited to assessing initial infectiousness of patients, triaging specimens to different algorithms for culture and DST, and confirming that organisms growing on (or in) culture media are mycobacteria rather than contaminants.
- **Xpert MTB/RIF Ultra (also referred to as GeneXpert):** This assay is a cartridge-based automated test that uses real-time polymerase chain reaction (PCR) on the GeneXpert platform to identify MTBC and mutations associated with RIF resistance directly from sputum and other extra pulmonary specimens in less than 2 hours. This assay uses the same GeneXpert platform as the MTB/RIF and was developed to improve the sensitivity and reliability of detection of MTBC and RIF resistance. To address sensitivity, Xpert Ultra is more sensitive than Xpert MTB/RIF (16 colony forming units [cfu]/mL and 131 cfu/mL, respectively). At very low bacterial loads, Xpert Ultra can give a “trace” result, which is not based on amplification of the rpoB target and therefore does not give results for RIF susceptibility or resistance. Trace results should be handled as guided by the TB diagnostic algorithm. The GeneXpert assay has similar sensitivity, specificity, and accuracy as culture on solid media and has been recommended by WHO as the initial diagnostic test among persons at risk of MDR-TB. Xpert MTB/RIF Ultra should be used rather than conventional microscopy, culture, and DST as the initial diagnostic test for TB.
- **Xpert MTB/XDR:** The Xpert MTB/XDR detects *Mycobacterium tuberculosis* complex (MTBC) DNA and genomic mutations associated with resistance to Isoniazid (INH), fluoroquinolones (FQs), Ethionamide (ETH) and second-line injectable drugs (Amikacin [AMK], kanamycin and capreomycin) in a single cartridge. Xpert MTB/XDR tests are run on Cepheid's GeneXpert instruments, using 10-colour modules that differ from the 6-colour modules traditionally used for Xpert MTB/RIF and Xpert MTB/RIF Ultra (Xpert Ultra) testing. Xpert MTB/XDR is intended for use as a reflex test in tuberculosis (TB) specimens (unprocessed sputum or concentrated sputum sediments) determined to be MTBC-positive. WHO recommends the use of Xpert MTB/XDR assay for people with bacteriologically confirmed pulmonary TB on sputum for initial detection of resistance to INH and FQs, rather than culture based phenotypic drug-susceptibility testing (DST). Xpert MTB/XDR assay performs well as a follow-on test for patients with bacteriologically confirmed TB for the detection of resistance to INH, FQ, ETH and AMK. This assay should be used for all newly diagnosed RR TB or MDR TB for detection of FQ resistance prior to initiation of DR TB treatment.
- **Truenat MTB, MTB Plus and MTB-RIF Dx assays:** The Truenat MTB and MTB Plus assays use chip-based real-time micro PCR for the semiquantitative detection of MTBC directly from sputum specimens and can report results in under an hour. The assays use automated, battery operated devices to extract, amplify and detect specific genomic DNA loci. The assays are designed to be operated in peripheral laboratories with minimal infrastructure and minimally trained technicians, although micro pipetting skills are required. If a positive result is obtained with the MTB or MTB Plus assay, an aliquot of extracted DNA is run on the Truenat MTB-RIF Dx assay to detect mutations associated with RIF resistance.
- **LPAs:** LPAs are a family of DNA strip-based tests that detect mutations associated with drug resistance. They do this either directly, through binding DNA amplification

products (amplicons) to probes targeting the most commonly occurring mutations (MUT probes), or indirectly, inferred by the lack of binding the amplicons to the corresponding wild-type probes.

1. **First-line LPAs (FL-LPAs)** such as GenoType MTBDR plus and NTM+MDRTB Detection Kit allow the detection of resistance to RIF and INH. WHO recommends using FL-LPAs for people with a smear-positive sputum specimen or a cultured isolate of MTBC, commercial LPAs may be used as the initial test instead of phenotypic DST to detect resistance to RIF and INH
2. **Second-line LPAs (SL-LPAs)** such as the GenoType MTBDRsl test allow the detection of resistance to FQs and AMK. WHO recommends using SL-LPAs for patients with confirmed MDR/RR-TB, an SL-LPA may be used as the initial test, instead of phenotypic DST, to detect resistance to FQs and AMK. LPA testing requires appropriate infrastructure (three separate rooms are required) and is currently available through the NTRL
- **Culture:** Culture in liquid media is the current reference method for bacteriological confirmation of TB. Both solid (Lowenstein- Jensen [LJ]) and liquid media (Mycobacteria Growth Indicator Tube [MGIT]) culturing methods are used at the NTRL. Turnaround time for results is faster with liquid culture (four to six weeks), compared to solid media methods (six to eight weeks). In general, the recovery of tubercle bacilli is higher with liquid culture than with solid culture methods. However, liquid culture media, being a more sensitive culture system, has higher contamination rates than solid media. Non-tuberculous mycobacteria are more frequently isolated with liquid media than with solid media. It is therefore essential to differentiate MTB isolates from other mycobacteria.
- Quality of culture results may be compromised by delays in specimen transport, sample quality and volume, and quality of laboratory processing (appropriate digestion and decontamination, as well as good quality culture media and incubation conditions). Laboratory errors, such as mislabelling or cross-contamination between specimens during aerosol-producing procedures, may lead to false-negative or false-positive results. In this context, laboratory findings should always be correlated with the patient's clinical condition and any diagnostic test should be repeated if necessary.
- Identification of MTB: Since Uganda is a high TB burden country, most mycobacterial isolates will be MTB. However, the prevalence of non-tuberculous mycobacteria (NTM, also referred to as MOTT for mycobacteria other than TB) can be more common in patients infected with HIV. Unless the species is confirmed as MTB, mycobacterial isolates appearing phenotypically resistant to first-line anti-TB may represent infection with NTM and not DR-TB.
- Treatment of NTM is different from treatment of DR-TB. In Uganda, NTM is detected using a TB antigen test (SD MPt64) applied to culture growth. NTM is reported as MOTT on solid media (Lowenstein- Jensen [LJ]) results and as NTM on reports from liquid media (Mycobacteria Growth Indicator Tube [MGIT]). The NTRL will identify the specific NTM when: they are isolated in multiple specimens collected at different times or when isolated from a sterile source e.g. cerebrospinal fluid. The specific identification of the NTMs is by use of LPAs like HAIN CM/AS at the NTRL.
- **DST:** Identification of DR-TB is based on DST on targeted risk groups and treatment of the identified DR-TB patients based on recommended strategies. These guidelines recommend that any patient in whom resistance is considered likely should have a DST done. There are a number of DST methods used that include: solid (LJ), liquid (Bactec-MGIT), and molecular tests (LPA, Xpert MTB/RIF Ultra, Xpert MTB/XDR)
- DST for XDR-TB: Rapid molecular testing for detection of Pre-XDR-TB (SL LPA or Xpert MTB/XDR) is available in Uganda. Conventional and newer liquid DST techniques that test for

fluoroquinolone, repurposed drugs (Bedaquiline, Linezolid, Clofazimine) and aminoglycoside resistance are considered the most reliable methods for determining XDR-TB and are available through the NTRL.

Limitations of DST

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

- DST for first-line anti-TB drugs is most accurate for Rifampicin and Isoniazid and less reliable and reproducible for Ethambutol and Pyrazinamide.
- DST results for some second-line anti-TB drugs (aminoglycosides, polypeptides, Bedaquiline, repurposed drugs-Linezolid/ Clofazimine and fluoroquinolones: Moxifloxacin and Levofloxacin) have been shown to be relatively reliable and reproducible. (in 2023, WHO released critical concentrations for testing Pretomanid and Cycloserine). Various phenotypic DST assays are available at the disposal of the NTRL, these include LJ DST, MGIT DST, MKIT DST and micro broth dilution test.

For Rifampicin resistance, there is not complete concordance between phenotypic and genotypic detection methods. Emerging evidence suggests that DNA sequencing of the *rpoB* gene (the gold standard method for genotypic DST) may be a better, although not perfect, reference method than phenotypic DST.

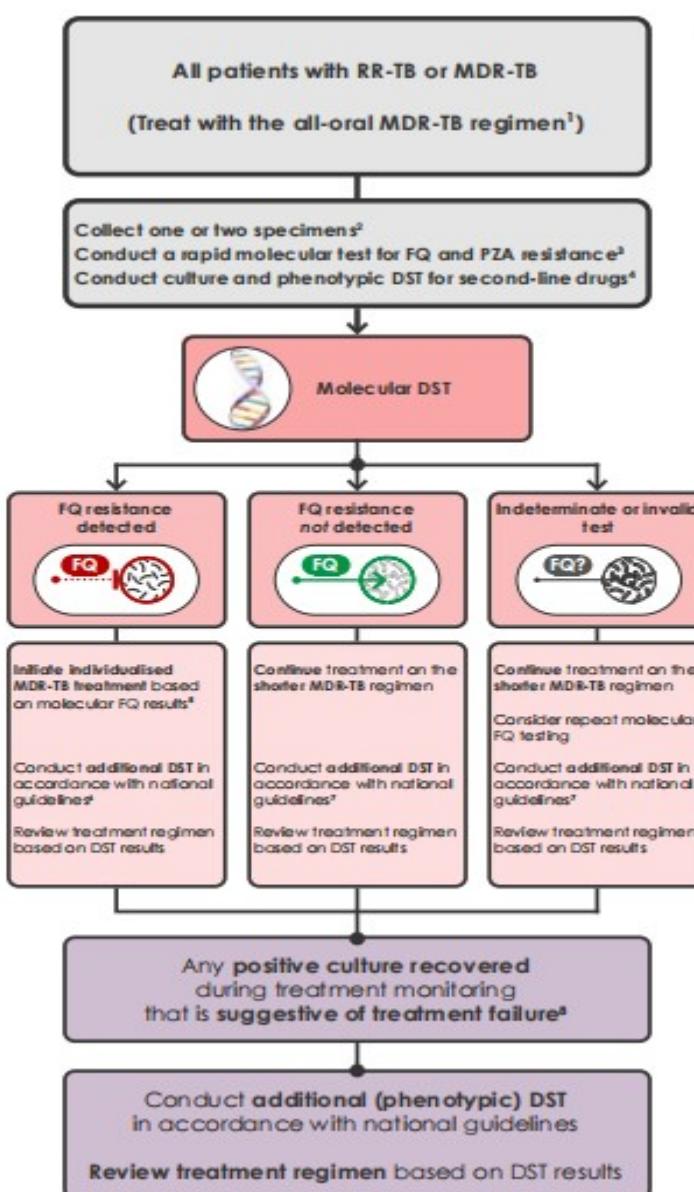
Cross-resistance

Cross-resistance and lack of understanding of the molecular mechanisms underlying TB drug resistance further confound the interpretation of DST results. Emerging evidence shows a clear association between phenotypic drug resistance and specific molecular mutations for most anti-TB drugs; however, not all mutations conferring resistance to second-line anti-TB drugs have been described, and neither have the underlying molecular mechanisms for the detected mutations been elucidated. Consideration for potential cross-resistance can influence the choice of anti-TB drug regimens and a summary of known cross-resistance between anti-TB drugs can be found in Chapter 6, table 6.2.

Sequencing: Next-generation sequencing (NGS) is a powerful tool with the capacity to improve tuberculosis (TB) management and control through the rapid and accurate detection of all clinically relevant mutations, and thereby the rapid diagnosis of drug-resistant TB (DR-TB) in clinical specimens. This information is crucial for clinicians to make prompt decisions regarding the best therapy to adopt for treatment of multi- and extensively resistant tuberculosis.

Figure 5.1 DST for second line drugs for RR-TB or MDR-TB patients)

From WHO operational handbook on tuberculosis. Module 3-Diagnosis: Rapid diagnostics for tuberculosis detection

**Foot notes to figure 5.1**

BDQ: Bedaquiline; CFZ: Clofazimine; DLM: Delamanid; DST: drug-susceptibility testing; FQ: fluoroquinolone; INH: Isoniazid; LC-aNAAT: low complexity automated NAAT; LZD: Linezolid; MDR-TB: multidrug-resistant tuberculosis; MDR/RR-TB: multidrug- or Rifampicin-resistant tuberculosis; NAAT: nucleic acid amplification test; PZA: pyrazinamide; RR-TB: Rifampicin-resistant tuberculosis; SL-LPA: line-probe assay for second-line drugs; TB: tuberculosis; WHO: World Health Organization.

1 Patients should be promptly initiated on an MDR-TB regimen in accordance with national guidelines and WHO recommendations. A shorter all-oral BDQ-containing treatment regimen of 9–12 months in duration is the preferred option for eligible MDR/RR-TB patients.

2 If molecular and phenotypic testing are performed in the same laboratory, one specimen may be sufficient. If testing is performed in two laboratories, two specimens should be collected, and the molecular and phenotypic testing conducted in parallel.

3 WHO recommends getting the rapid DST results for FQs before the start of treatment, although this testing should not delay the start of treatment. Currently, LC-aNAAT and SL-LPA are the WHO- approved rapid molecular tests for detecting FQ resistance.

4 Phenotypic DST should be conducted for each of the drugs included in the treatment regimen for which there are accurate and reproducible methods. Reliable phenotypic DST methods when performed in a quality-assured laboratory are available for BDQ, FQ, CFZ, INH, PZA, DLM and LZD. A new molecular class of tests, the reverse hybridization high complexity NAAT, is available for PZA resistance detection on culture isolates. The initiation of treatment should not be delayed while awaiting the results of the phenotypic DST.

5 For more details regarding individualized regimens, see the WHO consolidated guidelines on drug-resistant tuberculosis treatment (58).

6 For FQ-resistant MDR/RR-TB, a specimen should be collected and submitted for phenotypic DST to the WHO Group A (BDQ and LZD), B and C drugs, if not already being done as described in note 4.

7 In settings with a high underlying prevalence of resistance to FQs or for patients considered at high risk of FQ resistance, a specimen should be referred for culture and phenotypic DST for FQs.

8 If resistance to an individual drug (e.g. BDQ) is suspected and DST for these drugs is not available in the country, laboratories will need to have mechanisms to store the isolate and ship it to a WHO supranational laboratory for DST.

Table 5.1 Utilization of the various laboratory tests for DR TB diagnosis and management.

Diagnostic test	Role in DR TB diagnosis and management
Sputum smear microscopy (bullet removed)	<ul style="list-style-type: none"> • Zeihl-Nielsen/ bright field microscopy • Auramine-O/ Fluorescent microscopy <ul style="list-style-type: none"> • For diagnosis of TB in the absence of a rapid molecular DST assay but a follow up sputum sample has to be referred to the nearest molecular DST site (XprtMTB/RIFUltra or Truenat). • For treatment monitoring prior to receipt of culture results from the NTRL
Rapid molecular DST assays	<ul style="list-style-type: none"> • GeneXpert <ul style="list-style-type: none"> 1. Xpert MTB/ RIF Ultra 2. Xpert MTB/ XDR • Truenat MTB, MTB Plus and MTB-RIF Dx (Truenat) assays <ul style="list-style-type: none"> • Xpert MTB/ RIF Ultra or Truenat assays for the rapid detection of Rifampicin resistant TB • Xpert MTB/ XDR assay for the detection of fluoroquinolone, Ethionamide, Isoniazid, Amikacin, kanamycin & capreomycin resistance prior to initiation of the DR TB treatment
Culture	<ul style="list-style-type: none"> • Solid: Lowenstein-Jensen-LJ • Liquid: Mycobacteria Growth Indicator Tube-MGIT <ul style="list-style-type: none"> • Both solid and liquid culture are used for the isolation and identification of Mycobacterium tuberculosis complex. • Used for the routine monthly treatment monitoring of the sputum to assess treatment effectiveness: <ol style="list-style-type: none"> 1. Negative or No growth of cultures imply that the drugs are effective in killing the TB germs. 2. Positive or Growth of the cultures for Mycobacterium tuberculosis complex implies that the TB germs are still viable and such a client is still infectious requiring adequate infection control measures. 3. Positive or Growth for Non-Tuberculosis Mycobacteria/ NTM or Mycobacterium Other Than Tuberculosis/ MOTT: These clients should be managed after isolation and identification of the NTM/ MOTT and choice of treatment should be guided by the DST outcome from the laboratory 4. Contaminated culture results indicate that other flora other than TB have been recovered or isolated. Contaminations are caused by multiple factors that could be attributed to the testing laboratory or to the sputum sample factors like sample transit time from collection to receipt at the laboratory. • For post DR TB treatment follow up to verify no re-occurrence or relapse of DR TB.
Phenotypic DST	<ul style="list-style-type: none"> • LJ DST • MGIT DST • MKIT DST • Micro broth dilutions <ul style="list-style-type: none"> • Confirmation of RR TB and MDR TB: Rifampicin and Isoniazid DST results for all newly diagnosed RR TB cases by the rapid molecular assays. • Extended second line DST for all baseline or newly diagnosed RR TB cases or treatment failures (culture conversion from negative to positive cultures during the course of treatment): Levofloxacin, Moxifloxacin, Bedaquiline, Linezolid and Clofazimine, Delamind, pretomanid • Extended DST for any pre-XDR TB, XDR TB or Fluoroquinolone resistance identified by the rapid molecular assays e.g. Xpert MTB/ XDR. Extended DST can include DST for the following drugs: Delamanid, Amikacin, Ethionamide, high dose Isoniazid and Moxifloxacin (clinical breakpoint)
Sequencing	<ul style="list-style-type: none"> • For the detection of mutations to predict TB drug-resistance phenotypes and guide clinical decisions regarding treatment. • For the identification of strain lineage and resistance mechanisms for TB surveillance. • For the recognition of genetically related strains for the resolution of transmission chains to direct TB control efforts.

	<ul style="list-style-type: none"> For trouble shooting discordant results between the rapid molecular tests and phenotypic DST.
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Repeat 2nd line DST

The NTRL will be mandated to repeat 2nd line DST under these conditions:

- Treatment failure at 4 months of DR TB treatment i.e. when all the follow up samples from baseline to month of treatment are still culture positive.
- In the event of culture conversion (negative to positive) during the course of DR TB treatment especially after month 4 of treatment.
- In the event of return after loss to follow up of a known DR TB patient.

Interpretation of discordant results (order of statements below changed)

Each discordant result will need to be investigated on a case-by-case basis. General considerations are outlined below.

(excerpt from the 2021 WHO Operational handbook on tuberculosis. Module 3: Diagnosis, Rapid diagnosis for tuberculosis detection)

	Discordant results	Implications
1	Molecular WHO rapid diagnostic (mWRD e.g. geneXpert and Truenat) result "MTBC detected other than trace", culture negative (see Point 5 for trace)	<ul style="list-style-type: none"> i. The mWRD result and clinical judgement should be used to guide the treatment decision, pending additional testing. ii. The mWRD result should be considered as bacteriological confirmation of TB, if the sample was collected from a person who was not recently receiving treatment with anti-TB drugs. Cultures from individuals with pulmonary TB may be negative for several reasons, including that the patient is being treated for TB (effective treatment rapidly renders MTBC non-viable), transport or processing problems have inactivated the tubercle bacilli, cultures have been lost to contamination, the testing volume was inadequate, or a laboratory or clerical error occurred. iii. Follow-up actions may include re-evaluating the patient for TB, reassessing the possibility of prior or current treatment with anti-TB drugs (including FQ use), evaluating response to therapy, and evaluating the possibility of laboratory or clerical error.
2	mWRD result "MTB not detected", culture positive	<ul style="list-style-type: none"> i. Treatment decision should be based on the culture result. If the patient started treatment based on clinical judgement, continue treatment. Record the patient as having bacteriologically confirmed TB. ii. The culture-positive result should be considered as bacteriological confirmation of TB because culture is the current gold standard for the laboratory confirmation of TB. Using a sputum specimen, WRDs have a pooled sensitivity of 83–90% for detecting pulmonary TB compared with culture. Their sensitivity is lower in PLHIV, children and other specimen types such as CSF. iii. False positive cultures can result from a variety of causes, such as cross-contamination in the laboratory (e.g. from inappropriate specimen processing) or sample labelling problems. In well-functioning laboratories, such errors are rare. iv. Follow-up actions may include re-evaluating the patient for TB, conducting additional testing using mWRDs, culturing additional samples, and evaluating the possibility of laboratory or clerical error. If the patient was initiated on anti-TB therapy based on clinical judgement, evaluate the response to therapy.

3	mWRD result “MTBC detected, RIF resistance detected”; RIF-susceptible by phenotypic DST	<ul style="list-style-type: none"> i. Use the mWRD result to guide treatment decisions pending additional testing. ii. Borderline resistant mutations are known to generate this discordant result, particularly in the BACTEC Mycobacterial Growth Indicator Tube (MGIT) system (i.e. a false-susceptible phenotypic result). Patients infected with strains carrying these mutations often fail treatment with RIF-based first-line regimens. iii. In some settings with a low prevalence of MDR-TB, silent mutations have been observed that generate a false-resistant mWRD result, but these are rare. iv. A review of the probe melting temperatures when available or banding pattern on the FL-LPA can aid in determining of inferring the specific mutation (e.g. borderline resistant or silent). v. False RIF-resistant results have been observed with the Xpert MTB/RIF G4-Ultra cartridge when the MTBC detected result was “very low” and associated with probe binding delay. Follow-up action may include mWRD testing of the culture. vi. Follow-up actions may include DNA sequencing, confirmatory testing on other mWRD testing platform, phenotypic DST using solid media and evaluation of the possibility of laboratory or clerical error.
4	mWRD result “MTBC detected, RIF resistance not detected”; RIF resistant by phenotypic DST	<ul style="list-style-type: none"> i. The treatment regimen should be modified based on the results of the phenotypic DST. ii. False RIF-susceptible mWRD results are rare but have been observed in 1–5% of RIF resistant TB cases tested with the Xpert MTB/RIF test in various epidemiologic settings. Mutations in the region of the <i>rpoB</i> gene sampled by the Xpert MTB tests have been shown to account for 95–99% of RIF resistance. The remainder of RIF resistance arises from mutations outside the sampled region, which produce an Xpert MTB result of “RIF resistance not detected”. In settings with a prevalent clone that harbours a mutation outside the RRDR, for example Eswatini, this may be more common; however, this has not been identified as a major concern in other settings. Surveillance to monitor emergence of such clones over time should be considered. iii. Follow-up actions may include DNA sequencing, repeating the phenotypic DST and evaluating the possibility of laboratory or clerical error.
5	Xpert Ultra “MTBC detected trace”, culture negative	<p>The interpretation of this result must consider patient characteristics, specimen type and whether the person had been previously treated for TB:</p> <ul style="list-style-type: none"> i. Cultures may be negative for several reasons, including the patient being treated for TB or treated with Fluoroquinolones, transport or processing problems that inactivated the tubercle bacilli, culture contamination or inadequate testing volume, or laboratory or clerical error. ii. The small numbers of bacilli in a sample that generates an “MTBC detected trace” result may be due to active TB disease, laboratory cross-contamination, recent exposure to (or infection with) tubercle bacilli (incipient TB), and current or past treatment for TB. iii. The FIND multicentre study revealed that many of the samples that generated results of “MTBC detected trace” and culture negative were from individuals who had completed therapy within the past 4–5 years, presumably because of the presence of small numbers of non-viable or non-replicating bacilli. Thus, “MTBC detected trace” results must be interpreted within the context of prior treatment. a. For PLHIV and children who are being evaluated for pulmonary TB, or when extrapulmonary specimens (CSF, lymph nodes and tissue specimens) are tested, the benefits of the increased sensitivity for the detection of MTBC (i.e. true positives) outweighs the potential harm of decreased specificity (i.e.

	<p>false positives).</p> <p>i. The “MTBC detected trace” result is considered as bacteriological confirmation of TB (i.e. true positive results) and such patients should have been initiated on therapy based on the Xpert Ultra result. Consider the possibility that the culture result was a false negative result.</p> <p>ii. Follow-up actions may include assessing the response to therapy (culture results are often not available for weeks after specimen collection), reassessing the possibility of prior or current treatment with anti-TB drugs (including Fluoroquinolones use), and evaluating the possibility of laboratory or clerical error.</p> <p>b. For adults being evaluated for pulmonary TB who are not at risk of HIV, the balance of benefit and potential harm varies, based on whether the person had been treated previously for TB because of decreased specificity (i.e. false positives).</p> <p>i. For individuals in whom a history of current or prior TB treatment can be reliably excluded:</p> <ol style="list-style-type: none"> 1. Although the “MTBC detected trace” results should be considered as bacteriological confirmation of TB (i.e. true positive results), any clinical decision (e.g. to treat for TB) should be made based on all available laboratory, clinical and radiological information, and clinical judgement. 2. Consider the possibility that the culture result was a false negative result, if the samples were collected from a person who was not receiving treatment with anti-TB drugs, because of the paucibacillary nature of the sample. Follow-up actions for patients placed on anti-TB therapy may include re-evaluating the patient for TB, assessing the response to therapy, reassessing the possibility of prior or current treatment with anti-TB drugs (including Fluoroquinolone use), repeating Xpert Ultra testing, evaluating the possibility of laboratory or clerical error, and repeating culture (preferably using liquid culture). <p>ii. For adults with a history of recent TB treatment:</p> <ol style="list-style-type: none"> 1. Consider the possibility that the Xpert Ultra “MTBC detected trace” result was a false positive result because of the presence of non-viable bacilli. A culture-negative result is consistent with this possibility. 2. If these patients had been initiated on anti-TB therapy based on clinical judgement, follow-up actions may include assessing the response to therapy, conducting additional testing in accordance with national guidelines, repeating culture (preferably using liquid culture), and evaluating the possibility of laboratory or clerical error.
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Collection and transport of infectious substances

Collection of sputum: For any person presumed to have pulmonary TB disease, sputum should be obtained using the following instructions:

- An adequate amount of sputum not less than 5 ml should be collected.
 - The patient must be educated on the need to prevent spread of TB infection and the importance of providing an adequate amount of sputum using the provided standard sterile, plastic, wide-mouthed, screw-capped container.
 - One sample should be produced on day one when the patient is seen (spot sample) and the second sample on the early morning of day two (early morning sample) when a patient wakes up and after rinsing the mouth with water (before brushing).
 - The patient should be instructed to produce the sample in a well-ventilated open space away from others using the following technique:
1. Inhale deeply two to three times

2. Cough out deep from the chest (should avoid producing only saliva)
3. Open the container and spit sputum into it, close the container, then immediately deliver the sample to the lab for processing.
- In the laboratory, the sample container must be labelled appropriately.

Note: Specimens other than sputum used in the diagnosis of TB may be collected and sent for diagnostic testing according to national guidelines. Refer to discussion of diagnosis of extrapulmonary TB in Chapter 4 for more information.

Packaging and transport of specimens: Given the risks associated with transport of specimens and/or cultures from patients suspected of having DR-TB, NTLP recommends the following for safe packaging and transportation of infectious materials.

- Triple packaging system is recommended: In this system, the sample is physically contained in three receptacles: primary receptacle (sputum in falcon tube wrapped in absorbent material [e.g., cotton, wool]), secondary receptacle (a resealable plastic bag), and a tertiary receptacle (safety box). For details, see the TB specimen referral system (TSRS) training manual and NTRL clinician handbook.
- Warnings on the safety box: Sputum and other specimens suspected to contain infectious mycobacteria or other infectious agents are classified as “Infectious substance, Category B.” Infectious substances in Category B are assigned a specific UN number: UN 3373. From January 1, 2007, the shipping name labelled on containers with such specimens is “BIOLOGICAL SUBSTANCE CATEGORY B.” This name is already labelled on all the safety boxes, as shown to the right.
- **Transportation:** Transport instructions may differ based on local logistics but currently Uganda is utilising an integrated sample specimen referral system using the hub system. This system involves the collection of samples from the specific peripheral health facilities using either moto bike riders or vehicles and transported to the nearest testing point (hub) or the NTRL in Kampala.



Triple-packaged safety box for transporting specimens

What to do in case of damaged/leaking packages in transit: If leakage is noted at any point during transit, seal the package in two polythene bags (PIL® is adequate) and take it to the nearest health centre IV or hospital for destruction, according to the hospital’s routine method of handling biological wastes. Inform the sending health facility and NTRL for action.

Note: Leaking specimens will not be processed at the NTRL or Xpert MTB/RIF Ultra site.

Causes of rejection of samples at NTRL/Xpert MTB/RIF lab include:

- Leakage
- Wrong containers
- No labels on the sputum container
- Wrong sample for the test requested.
- Request form with no sample.

Time for testing (turnaround time) and reporting of results.

Anticipated turnaround time for reporting of results on solid methods is the longest (8–10 weeks), with shorter turnaround times for liquid (6 weeks) and molecular tests (2 days).

Reports are provided to the requesting facility, through a soft copy PDF result by email from the NTRL.

- Timeliness of actions based on results has a significant impact on the quality of care for DR-TB patients.

- The laboratory is responsible for ensuring that reports are sent to both providers and the appropriate NTLP personnel.
- Providers are responsible for tracking results, and should make inquiries to find results if unexpected delays occur.

Infection control and biosafety in the laboratory

WHO classifies the relative hazards of infective microorganisms handled in the laboratory according to their risk of causing human disease, the potential for laboratory spread, and whether effective treatment and prevention measures are available. Related biosafety levels for laboratories have been defined, considering the pathogenic agent; the facilities available; and the equipment, practices, and procedures required to ensure a safe laboratory working environment.

MTB is classified by WHO as a Risk Group 3 laboratory pathogen. Mycobacteriology culture and DST generate high-concentration aerosols requiring biosafety level 3 containment precautions. Laboratory standards require the following essential measures to be in place and enforced:

- Appropriate and specific administrative controls (including good laboratory practice, SOPs, 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 and expert engineering consultation sought when establishing laboratory infrastructure for DST.

The laboratory managers shall ensure that health and medical surveillance of laboratory personnel involved in mycobacteriology culture and DST is done. Surveillance shall 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.

Laboratory workers who disclose to their supervisors a status as HIV-infected should be offered safer work responsibilities and should be discouraged from working with DR-TB specimens.

The use of infection control measures is discussed in more detail in Chapter 16.

Quality control and 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 program must be in place to ensure the accuracy, reliability, and reproducibility of DST results. As a minimum performance indicator, proficiency testing should correctly identify resistance to Isoniazid and Rifampicin in more than 95% of two out of three recent rounds of panels.

As an SRL, the NTRL participates in external quality assurance and proficiency testing to maintain the quality of laboratory services and the validation of DST results.

Chapter 6:

Treatment strategies for MDR/RR-TB

This chapter describes DR-TB regimen options, medications, principles, and general treatment strategies for constructing regimens for the treatment of MDR/RR-TB, and XDR-TB. It also outlines the treatment regimens recommended in Uganda and the basic steps for treatment initiation. For more information on management and monitoring for treatment initiation, see Chapters 8 and 9.

- Note:** The guidance and recommendations contained in this chapter were adapted from
- WHO operational handbook on tuberculosis, Module 4: Treatment Drug-resistant tuberculosis treatment 2022 update. Can be accessed at <https://iris.who.int/bitstream/handle/10665/36533/9789240065116-eng.pdf?sequence=1>
 - WHO. Key updates to the treatment of drug-resistant tuberculosis: rapid communication. June 2024. <https://www.who.int/publications/i/item/B09123>

Definition of terms for DR-TB treatment strategies

DR-TB treatment strategies may be described using the following terms:

- **Standardised treatment:** DR-TB regimen is designed based on drug resistance surveillance data from representative patient populations and all patients in a defined group or category receive the same regimen. This is usually done in the absence of Individualised DST and may be changed once individual results are received.
- **Individualised treatment:** DR-TB regimen is designed based on the patient's past history of TB treatment and individual DST results.
- **Empiric treatment:** This refers to the initiation of treatment prior to a laboratory confirmation of drug resistance based on risk assessment, clinical presentation, and DR-TB Expert Panel recommendations. In most cases, a Standardised MDR-TB regimen will be the starting choice for empiric treatment. Contacts of confirmed MDR-TB patients should be empirically treated with the same regimen as the confirmed index case until the contact's DST result is finalized.

DR-TB treatment regimen options in Uganda

In patients with MDR/RR-TB, there are several regimens that can be used in Uganda. The key factors that define treatment regimen choice include drug-resistance profile, prior exposure to TB medicines, patient history, drug-resistance profile of the index DR TB patient, the patient's age, extent of pulmonary TB disease and localization of extra pulmonary TB lesions. Below we describe the regimen options:

All patients with MDR/RR-TB, including those with additional resistance to fluoroquinolones, need to benefit from effective all-oral treatment regimens, either shorter or longer, implemented under programmatic conditions.

The 2022 update of the DR-TB treatment guidelines added and prioritized a new 6-month regimen – **BPaLM** as a treatment of choice for eligible patients. The **new BDLLfxC** regimen can expand the use of the 6-month regimens to additional patient groups, like children, adolescents, and pregnant

women, who could not benefit from the currently recommended BPaLM regimen (due to the absence of safety and dosing data for pretomanid).

Drug susceptibility testing (DST) to fluoroquinolones is strongly encouraged, but DST should not delay treatment initiation with regimens that are also effective in patients with pre-XDR-TB.

Tabel 6.1: Nationally Recommended DR-TB treatment regimens in Uganda

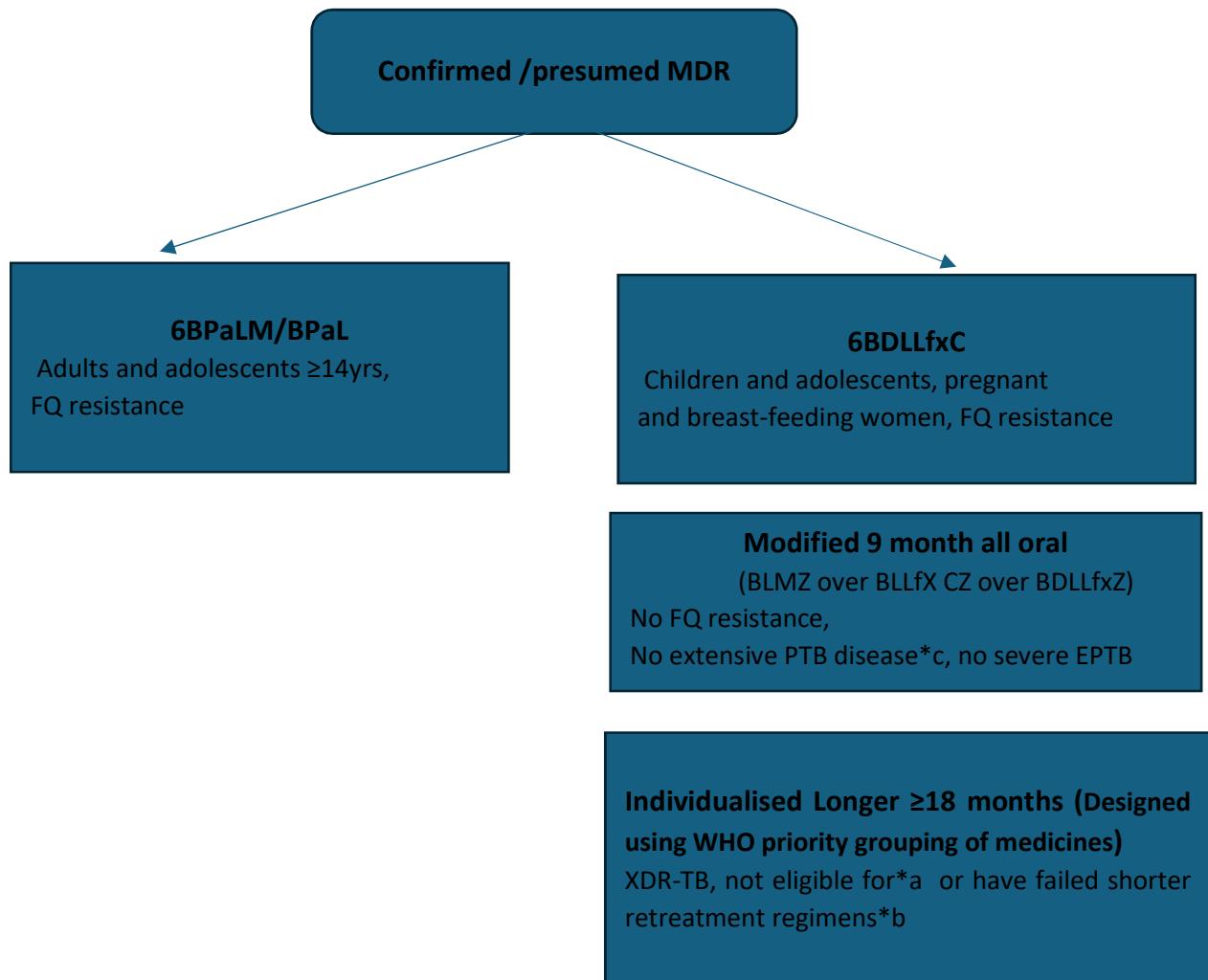
Regimen Type	Regimen composition	Eligibility criteria
The 6-month BPaLM / BPaL	6 Bedaquiline-Pretomanid-Linezolid-Moxifloxacin (BPaLM) or BPaL (without Moxifloxacin)	Can be used in FQ resistance Preferred regimen for most patients >14 years except pregnant and breast-feeding mothers
The 6-month BDLLfxC regimen	6BDLLfxC (Bedaquiline-Delamanid-Linezolid-Levofloxacin-Clofazimine) or BDLC (without Levofloxacin) or BDLLfx (without Clofazimine)	Can be used in FQ resistance Preferred for children, adolescents, pregnant and breastfeeding women
The modified 9-month, all-oral regimens	BLMZ , BLLfxCZ , BDLLfxZ and Bdq-Lzd-LfxCfz-Cs BLMZ is preferred over BLLfxCZ, and BLLfxCZ is preferred over BDLLfxZ and BDLLfxZ is preferred over BLLfxCCs.	Cannot be used in FQ resistance For patients not eligible for 6 months regimens
Longer regimens (>18 months)	designed using atleast 4-5 effective drugs from the priority grouping of medicines recommended in current WHO guidelines	for patients not eligible for or have failed the shorter regimens
Rifampicin-susceptible Isoniazid resistant TB (Hr-TB).	6 (RHZE-Lfx)	Recommended irrespective of previous use of RHZE

- **The 6-month BPaLM regimen**, comprising bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin, may be used programmatically in place of 9-month or longer (>18 months) regimens, in patients (aged ≥14 years) with MDR/RR-TB who have not had previous exposure to bedaquiline, pretomanid and linezolid (defined as >1-month exposure). This regimen may be used without

moxifloxacin (BPaL) in the case of documented resistance to fluoroquinolones (in patients with pre-XDR-TB).

- **The 6-month BDLLfxC regimen**, composed of bedaquiline, delamanid, linezolid (600 mg), levofloxacin, and clofazimine, may be used programmatically in place of 9-month or longer (>18 months) regimens, in all patients with MDR/RR-TB who have not had previous exposure to bedaquiline, delamanid and linezolid (defined as >1-month exposure). The regimen may be used without either levofloxacin or clofazimine depending on fluoroquinolone DST results - BDLLfxC can be initiated without delay in case of unknown FQ-resistance at time of diagnosis of RR-TB (and may be continued with both levofloxacin and clofazimine if FQ-DST results cannot be obtained); BDLLfx is continued for FQ-sensitive TB; BDLC for FQ-resistant TB. The available evidence included children, adolescents, pregnant and breastfeeding women, flagging the possible use of the regimen in these population groups.
- **The use of the modified 9-month, all-oral regimens (BLMZ, BLLfxCZ and BDLLfxZ)** is preferred over currently recommended longer (18-month) regimens in patients with MDR/RR-TB who have not had previous exposure to bedaquiline, delamanid and linezolid (defined as >1-month exposure) and in whom resistance to fluoroquinolones has been excluded. Amongst these regimens, using BLMZ is suggested over BLLfxCZ, and BLLfxCZ is suggested over BDLLfxZ. Access to rapid DST for ruling out fluoroquinolone resistance is required before starting a patient on one of these regimens.
- **The 9-month, all-oral, bedaquiline-containing regimens** are preferred over the longer (>18 months) regimens in adults and children with MDR/RR-TB, without previous exposure to second-line treatment (including bedaquiline), without fluoroquinolone resistance and with no extensive pulmonary TB disease or severe forms of extrapulmonary TB. In these regimens, 2 months of linezolid (600 mg) can be used as an alternative to 4 months of ethionamide. Access to rapid DST for ruling out fluoroquinolone resistance is required before starting a patient on one of these regimens.
- Patients with extensive forms of DR-TB (e.g., XDR-TB4) or those who are not eligible for or have failed shorter treatment regimens will benefit from **individualized longer (≥ 18 months) regimens** designed using the priority grouping of medicines recommended in current WHO guidelines.
- Decisions on appropriate regimens should be made according to clinical judgement and patient preference, considering DST results, treatment history, risk of adverse events, and severity and site of the disease.
- All treatment should be delivered under WHO-recommended standards, including patient-centered care and support, informed consent where necessary, principles of good clinical practice, active drug safety monitoring and management, and regular monitoring of patients and drug resistance to assess regimen effectiveness.

Figure 6.1: Approach to treatment initiation of MDR/RR TB among children, Adolescents and Adults in Uganda



Foot notes

*a Not eligible for includes; previous exposure to BPaL(defined as >1 month) XDR- TB, CNS, Miliary, osteoarticular TB)

*b Have failed shorter retreatment regimens includes treatment regimen needed to be terminated or permanently changed to a new regimen or treatment strategy.

*c Extensive PTB disease is the presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography.

BPaLM is the regimen of choice for patients with MDR/RR TB with absent or unknown fluoroquinolone resistance

In cases where resistance to fluoroquinolones is identified before or after treatment initiation, moxifloxacin can be omitted and the BPaL regimen without moxifloxacin should be initiated or continued, because there is probably no added benefit of using a drug with demonstrated resistance that may have toxicities. If resistance to Bedaquiline, linezolid or Pretomanid is confirmed or suspected, the BPaLM/BPaL regimen should be stopped, and patients should be referred for a longer individualized regimen.

The duration of BPALM regimen is largely standardized for 6 months (26 weeks), whereas BPAL can be extended to a total of 9 months (39 weeks).

Table 6.1: Regimen options and factors to be considered for selection of treatment regimen for patients with RR/MDR-TB

Regimen	MDR/RR-TB fluoroquinolone susceptible	Pre-XDR- TB	XDR- TB	Extensive pulmonary TB	Extrapulmonary TB	Age <14 years
6-month BPALM/BPAL	Yes (BPALM)	Yes (BPAL)	No	No	Yes – except TB involving CNS, miliary TB and osteoarticular TB	No
6 months 6BDLLfxC	Yes	Yes BDLC	No	No	Yes -except TB involving CNS, miliary TB and osteoarticular TB	Yes
9-month all-oral	Yes	No	No	No	Yes – except TB meningitis, miliary TB, osteoarticular TB and pericardial TB	Yes
Longer individualized 18-month	Yes ^a /No	Yes ^a /No	Yes	Yes	Yes	Yes
Additional factors to be considered if several regimens are possible	Drug intolerance or adverse events					
	Treatment history, previous exposure to regimen component drugs or likelihood of drug effectiveness					
	Patient or family preference					
	Access to and cost of regimen component drugs					

BPAL: Bedaquiline, Pretomanid and Linezolid; BPALM: Bedaquiline, Pretomanid, Linezolid and Moxifloxacin; CNS: central nervous system; MDR/RR-TB: multidrug- or Rifampicin-resistant TB; TB: tuberculosis.

XDR-TB: extensively drug-resistant TB.

^a When 6-month BPALM/BPAL and 9-month regimens could not be used.

Drug regimens

The 6-month Bedaquiline, Pretomanid, Linezolid and Moxifloxacin (BPALM) regimen

BPALM refers to the new short, 6-month (or 26-week) treatment regimen for MDR/RR-TB: the Bedaquiline, Pretomanid, Linezolid and Moxifloxacin (BPALM) regimen. This is the regimen of choice for patients diagnosed with MDR/RR-TB with absent or unknown fluoroquinolone resistance.

BPALM regimen includes four components – Bedaquiline, Pretomanid, Linezolid and Moxifloxacin. All these possess some bactericidal activity, making them effective anti-mycobacterial drugs when used in combination.

DST for fluoroquinolones is strongly encouraged in people with MDR/RR-TB, and although it should not delay initiation of the BPALM, results of the test should guide the decision on whether Moxifloxacin can be retained or should be dropped from the regimen – in cases of documented resistance to

fluoroquinolones, BPaL without Moxifloxacin would be initiated or continued. The BPaLM/BPaL regimen may be offered to patients with MDR/RR-TB in the following situations:

Eligibility for BPaLM/BPaL regimen.

- Pulmonary TB or all forms of extrapulmonary TB, except TB involving the CNS, osteoarticular TB and disseminated (miliary) TB.
- Patient is aged 14 years or older.
- No known allergy to any of the BPaLM component drugs.
- No evidence of resistance to Bedaquiline, Linezolid, Delamanid or Pretomanid,
- Patient has not been previously exposed to any of the component drugs for 4 weeks or longer; when exposure to the component drugs is greater than 4 weeks in duration, the patient may receive the BPaLM regimens if resistance to the specific medicines with such exposure has definitively been ruled out.
- All people regardless of HIV status; Care should be taken when CD4 counts are below 100 cells/mm³.
- No XDR-TB according to the 2021 WHO definitions; and
- Patient is not pregnant or breastfeeding or, if the patient is a premenopausal woman, is willing to use effective contraception.

In cases of possible fluoroquinolone resistance (e.g. a history of >4 weeks of fluoroquinolone use or close contact with a person infected with a fluoroquinolone-resistant strain), it is best to initiate a BPaLM regimen until DST for fluoroquinolones is available, to decide whether Moxifloxacin should be continued. If the result of fluoroquinolone DST is never determined or not done, the BPaLM regimen should be used throughout. This is often done even if fluoroquinolone resistance is suspected, because the toxicity of adding Moxifloxacin is low and some patients with past use of a fluoroquinolone or contact cases may still be infected with susceptible strains. If resistance is highly likely (i.e. a treatment with a fluoroquinolone failed or the patient is a close contact of a fluoroquinolone-resistant case and was unlikely to get TB from another source, or in a setting with a high prevalence of fluoroquinolone resistance and in the absence of DST) it is reasonable to omit the Moxifloxacin and use the BPaL regimen for treatment.

Reasons for exclusion from the BPaLM regimen.

- The BPaLM/BPaL regimen may be excluded to patients with MDR/RR-TB in the following situations:
- Patients with a known history of cardiac disease; Caution should be taken seriously while administering BPaLM/BPaL regimen because Bedaquiline and Moxifloxacin can prolong QTc.
- Patient with a known allergy or hypersensitivity to any of the BPaLM component drugs.
- Patient aged below 14years.
- Pregnant and breast-feeding women.
- Pulmonary TB patients with radiological evidence of bilateral disease or radiological evidence of cavitation.
- Patient with Extrapulmonary TB involving the CNS, Osteomyelitis and arthritis.
- XDR-TB according to the 2021 WHO definitions.

Considerations when initiating the BPaLM/BPaL regimen

- Linezolid is associated with anaemia and thrombocytopenia, and care should be taken in patients with anaemia. Care should also be taken for patients who have a haemoglobin level of less than 8 g/dL or a platelet count less than 75,000 platelets/mm³. Consideration of a Linezolid-sparing option or longer regimen may be a safe option.

- Patients with a very low body mass index (BMI) (<17 kg/m²) should be monitored. Low BMI should not be an absolute contraindication in commencing the BPaLM/BPaL regimen, but patients should be monitored closely.
- Patients with liver enzymes at levels three times greater than the upper limit of normal. This is because Bedaquiline and Pretomanid are both associated with increases in liver enzymes.
- Linezolid is associated with peripheral neuropathy; therefore, those with pre-existing peripheral neuropathy of Grade 3–4 should be treated with caution when commencing the BPaLM/BPaL regimen. Alternatively, to decrease the risk of peripheral neuropathy exacerbation, the Linezolid -free regimen could be used.
- Patients who are moribund or with advanced disease should have considerations made for symptoms control and palliative care over initiation of treatment. Decisions should be guided by clinical judgement and the patient’s preferences.

Reasons for drug substitution.

Drug substitution should be considered when certain medications are prescribed concurrently with the BPaLM/BPaL regimen for example:

- Efavirenz may induce the metabolism of Bedaquiline; Substitution should be considered for patients who are on Efavirenz.
- Efavirenz also reduces Pretomanid exposures significantly; therefore, Substitution with an alternative antiretroviral agent (potentially dolutegravir,) should be used if Pretomanid or the BPaLM/BPaL regimen is considered.
- Individuals who are prescribed both Bedaquiline and ritonavir should be monitored closely for adverse events, including QTc prolongation.
- Linezolid is known to be associated with serotonin syndrome; therefore, caution should be taken with other serotonergic drugs (e.g. sertraline and fluoxetine).
- Regimens including zidovudine should be avoided, if possible, because both zidovudine and Linezolid may cause peripheral nerve toxicity and are known to have myelosuppression cross-toxicity.
- Concomitant drugs that prolong QTc should be avoided if possible – such drugs require extra vigilance and monitoring with electrocardiography (ECG) if prescribed with Bedaquiline and Moxifloxacin; for example, Ondansetron, Methadone, Amitriptyline and Clarithromycin, Neuroleptics-Phenothiazines (E.G. Thioridazine, Haloperidol, Chlorpromazine, Trifluoperazine, Pericycline, Prochlorperazine, Fluphenazine, Sertindole and Pimozide), Quinoline Antimalarials (E.G. Halofantrine, Chloroquine, Hydroxychloroquine and Quinacrine) and Anti-Arrhythmic Drugs (E.G. Quinidine, Procainamide, Encainide, Disopyramide, Amiodarone, Flecainide And Sotalol).
- **CYP3A4 inhibitors and CYP3A4 inducers can interact with Bedaquiline:**
 1. CYP3A4 inhibitors include the azole antifungals (Ketoconazole, Voriconazole and Itraconazole), ketolides such as Telithromycin and macrolide antibiotics other than Azithromycin; the azole antifungals in general can safely be used for less than 2 weeks whereas fluconazole could potentially be used for more than 2 weeks.
 2. CYP3A4 inducers include Phenytoin, Carbamazepine, Phenobarbital, St. John’s wort (*Hypericum perforatum*), rifamycins and glucocorticoids.
- Drugs inducing myelosuppression should also be used with caution (e.g. Azathioprine and cytotoxic agents).

BPaLM drug composition

BPALM regimen includes four components – Bedaquiline, Pretomanid, Linezolid and Moxifloxacin. All these possess some bactericidal activity, making them effective anti-mycobacterial drugs when used in combination.

In the BPALM regimen, Pretomanid is administered at 200 mg once daily. Bedaquiline is dosed at 400 mg once daily for 2 weeks, then 200 mg three times per week afterwards, according to the product label. Linezolid dosing is 600 mg once daily and Moxifloxacin 400 mg once daily.

Table 6.2. Dosing of component drugs for adults and adolescents (aged ≥14 years) for BPALM

Drug	Dose
Bedaquiline (100mg tablet)	400mg once daily for 2 weeks, then 200mg 3 times per week afterwards OR 200 mg daily for 8 weeks then 100 mg daily
Pretomanid (200 mg tablet)	200 mg once daily
Linezolid (600 mg tablet)	600 mg once daily
Moxifloxacin (400 mg tablet)	400 mg once daily
BPALM: Bedaquiline, Pretomanid, Linezolid and Moxifloxacin	

BPAL regimen

The BPAL regimen includes three components-Pretomanid, Bedaquiline and Linezolid. The regimen can be prescribed for those who have proven fluoroquinolone resistance.

If fluoroquinolone resistance is acquired while an individual is on the BPALM regimen, in the absence of evidence of acquired resistance to other drugs, Moxifloxacin can be omitted and BPAL should be continued, because there is no added benefit to continuing a noneffective drug that may have toxicities. If resistance to Bedaquiline, Linezolid or Pretomanid is confirmed or suspected, the treatment is considered to have failed, and individuals should be referred to the longer Individualised regimen.

Treatment duration of BPALM and BPAL regimen

All medicines in the regimen are to be used throughout treatment duration, Ideally, missing doses of all three or four drugs in the regimen should be avoided. When the regimen is BPAL from the start or is changed to BPAL, BPAL can be extended to a total of 9 months (39 weeks) continuing from the start of the therapy with BPALM/BPAL.

Below are situations when to consider extension of treatment.

- Extension of the BPAL regimen to a total of 9 months can occur in cases where there is a delayed culture conversion between months 4 and 6,
- There is a proven fluoroquinolone resistance while an individual is on the BPALM regimen.
- There are persons with extensive disease (i.e. bilateral, cavitary disease with significant fibrosis, or scarring/cavities in 3 or more lung zones).
- Any interruption with BPALM/BPAL of longer than 7 days should be made up for by extending the treatment duration (for the number of missed doses).
- Any treatment interruption with BPALM/BPAL up to 1 month nonconsecutively can be added to the overall treatment duration if there is a need to make up the missed doses.
- Reintroduction of the full regimen could be considered after a cessation of not more than 14 days of consecutive treatment interruption or up to a cumulative 4 weeks of non-consecutive treatment interruption.

Key note-

- Extension of BPAL to 9 months should be done with caution in patients with missed Linezolid dosages for two weeks – switching to an Individualised longer regimen may be considered instead of a BPAL extension.
- 26 weeks of BPALM or 39 weeks of BPAL of prescribed doses should be completed within an overall period of 7 or 10 months, respectively.
- 9months BPAL regimen and long Individualised regimen are recommended for management of Pre-XDR TB, however the National Panel will decide basing on a case scenario.

Linezolid dosing in the BPALM/BPAL regimen

Linezolid is by far the most toxic drug in the BPALM and BPAL regimens; it requires significant monitoring and at times a mitigation strategy to reduce adverse effects. It is preferred to continue Linezolid at the full dose for the entire duration; however, the dose of Linezolid can be reduced to 300 mg or can be discontinued (and restarted when possible) if there is significant toxicity (depending on the severity of specific adverse events or serious adverse events) associated with Linezolid, including optic neuritis, peripheral neuropathy or myelosuppression.

Action should be taken in the following manner for the common toxicities associated with Linezolid:

- For optic neuritis diagnosed at any grade, permanent discontinuation of Linezolid is indicated.
- peripheral neuropathy Grade 2, reduce the dose of Linezolid to 300 mg per day with a possible drug holiday for 1–2 weeks before dose reduction. For peripheral neuropathy Grade 3 or 4, in most cases permanent suspension of Linezolid will be needed; in some cases, after a 1–2-week drug holiday and reversion to Grade 2, the Linezolid can be restarted and tolerated, provided it does not revert back to a Grade 3 or 4 (caution is warranted with this approach because patients can be left with a severe painful and disabling permanent peripheral neuropathy).
- Myelosuppression (even of Grade 3 or 4) is often reversible with a short 1-to-2-week drug holiday followed by reducing the dose of Linezolid to 300 mg per day; severe anaemia may need to be treated with transfusions or erythropoietin. Dose modification of Linezolid should be avoided, if possible, in the first 9 weeks of therapy.
- If Linezolid (or any of the drugs) is being intermittently stopped and started on the BPALM/BPAL regimen, there may be concern for development of resistance to the other component medicines in the regimen. This may be more of a concern for patients receiving BPAL because during single drug disruption the regimen will consist of only two effective drugs. Acquired resistance to the two remaining agents in pre-XDR-TB cases can be catastrophic to both the patient and the society.

Modification of treatment

Dose modifications for Bedaquiline, Moxifloxacin and Pretomanid are not allowed, and neither the substitution of Moxifloxacin with Levofloxacin.

Modification of the regimen through early discontinuation or replacement of any of the component drugs may result in poor treatment outcomes. Dose modification of Bedaquiline, Moxifloxacin and Pretomanid is not recommended.

Although the only drug that can be dose modified in BPALM/BPAL is Linezolid, dose modification of Linezolid is acceptable after the first 9 weeks of treatment in cases of adverse events. Although dose modification of Linezolid should be avoided in the first 9 weeks of therapy, this principle should not override the need to avoid permanent disabilities. In some circumstances, the Linezolid may need to be permanently stopped and a decision made on whether to continue the other drugs to complete treatment or start a new treatment. After 9 weeks of consecutive administration of Linezolid, the dose of Linezolid can be reduced to 300 mg if necessary (see examples in Box 6.1).

Box 6.1. Some examples of changes in Linezolid dosing within the BPALM/BPAL regimen

- A patient diagnosed with MDR/RR-TB (based on GeneXpert results) completes 4 weeks of treatment with BPALM, with 600 mg of Linezolid, when they experience symptoms of severe paresthesia in the feet, preventing them from completing their daily life activities. This adverse event necessitates the cessation of Linezolid within the first 9 weeks of therapy. Because permanent discontinuation of Linezolid was needed, the entire regimen has to be discontinued and a new regimen started.
- A patient completing treatment with BPAL, with 600 mg of Linezolid, for MDR/RR-TB with fluoroquinolone resistance, experiences Grade 3 optic neuritis in week 20 of therapy. Linezolid must be ceased permanently, however, because there is less than 8 weeks of treatment remaining, the patient completes a further 6 weeks of therapy with Bedaquiline and Pretomanid and has a negative sputum culture at the end of 26 weeks, achieving a successful treatment outcome on BPAL therapy. The optic neuritis improves slowly after cessation of Linezolid.

Termination of treatment.

Regarding the cessation of any component drug of the BPALM/BPAL regimen because of severe toxicity, the following factors should be considered:

- If either Bedaquiline or Pretomanid needs to be permanently discontinued, the entire BPALM/BPAL regimen should also be discontinued.
- If Linezolid is permanently discontinued during the initial 9 consecutive weeks of treatment, the entire regimen should be discontinued.
- If Linezolid is withheld in the later weeks of the regimen, with the total remaining duration of the regimen not exceeding 8 weeks, the regimen can be considered to be completed with the remaining component drugs; and
- If Moxifloxacin alone is discontinued, the regimen can be continued as the BPAL regimen.

Criteria for discharging patients from treatment.

- Identify and replace missed doses before discharging a patient.
- Must have a month 4 culture results for decision making.
- Patients must have a chest x-ray at month six (6).

Individualised regimen

Table 6.3 Groupings of medicines recommended for use in longer MDR-TB regimens

Groups and steps	Medicine and abbreviation	
Group A: Include all three medicines	Levofloxacin or Moxifloxacin	Lfx Mfx
	Bedaquiline ^{b,c}	Bdq
	Linezolid ^d	Lzd
Group B: Add one or both medicines	Clofazimine	Cfz
	Cycloserine or Terizidone	Cs Trd
Group C: Add to complete the regimen, and when medicines from Groups A and B cannot be used	Ethambutol	E
	Delamanid ^{c,e}	Dlm
	Pyrazinamide ^f	Z
	Imipenem–Cilastatin or Meropenem ^g	Ipm–Cln Mpm
	Amikacin or Streptomycin ^h	Am S
	Ethionamide or Prothionamide ⁱ	Eto Pto
	P-aminosalicylic acid ^j	PAS

^aDST: drug susceptibility testing; ECG: electrocardiography; GDG: Guideline Development Group; IPD: individual patient data; LPA: line probe assay; MDR-TB: multidrug-resistant TB; TB: tuberculosis.

This table is intended to guide the design of individualized, longer MDR-TB regimens. Medicines in Group C are ranked by decreasing order of usual preference for use, subject to other considerations. The 2018 IPD meta-analysis for longer regimens included no patients on thioacetazone and high-dose isoniazid, for a meaningful analysis. No recommendation on perchlozone, interferon gamma or sutezolid was possible owing to the absence of final patient treatment outcome data from appropriate studies (1).

^b Bedaquiline is usually administered 400 mg orally once daily for the first 2 weeks, followed by 200 mg orally thrice weekly for 22 weeks (total duration of 24 weeks). As a result of multiple reviews following new data gradually becoming available, the use of bedaquiline is not restricted by age of the patient. Evidence on the safety and effectiveness of bedaquiline use beyond 6 months was insufficient for review in 2018. Therefore, the use of bedaquiline beyond 6 months was implemented following best practices in “off-label” use (66). New evidence on the safety profile of bedaquiline use beyond 6 months was available to the GDG in 2019, but the GDG was not able to assess the impact of prolonged bedaquiline use on efficacy, owing to the limited evidence and potential residual confounding in the data. However, the evidence supports the safe use of bedaquiline beyond 6 months in patients who receive appropriate schedules of baseline and follow-up monitoring. The use of bedaquiline beyond 6 months still remains as off-label use and, in this regard, best practices in off-label use still apply.

^c Evidence on the concurrent use of bedaquiline and delamanid was insufficient for review in 2018. In 2019, new evidence on both the safety and effectiveness of concurrent use of bedaquiline and delamanid was made available to the GDG. In relation to safety, the GDG concluded that the data suggested no additional safety concerns regarding concurrent use of bedaquiline and delamanid. More evidence was added to that regard between 2020 and 2022 (67). Both medicines may be used concurrently in patients who have limited other treatment options available to them, and if sufficient monitoring (including baseline and follow-up ECG and electrolyte monitoring) is in place. The data on the effectiveness of concurrent use of bedaquiline and delamanid were reviewed by the GDG in 2019, but owing to the limited evidence and potential residual confounding in the data, the GDG could not proceed with a recommendation on effectiveness (1).

^d Use of linezolid for at least 6 months was shown to increase effectiveness, although toxicity may limit its use. The analysis suggested that using linezolid for the whole duration of treatment would optimize its effect (about 70% of patients on

linezolid with data received it for more than 6 months, and 30% for 18 months or the whole duration). No patient predictors for early cessation of linezolid could be inferred from the IPD subanalysis.

e Evidence on the safety and effectiveness of delamanid beyond 6 months was insufficient for review. The use of delamanid beyond these limits should follow best practices in “off-label” use (66). As a result of multiple reviews following new data gradually becoming available throughout the years the use of delamanid is not restricted by age of the patient.

f Pyrazinamide is only counted as an effective agent when DST results confirm susceptibility.

g Every dose of imipenem–cilastatin or meropenem should be preceded by the oral administration of oral clavulanic acid 30–60 minutes beforehand; oral clavulanic acid is only available in formulations combined with amoxicillin. Amoxicillin–clavulanic acid is not counted as an additional effective TB agent and should not be used without imipenem–cilastatin or meropenem.

h Amikacin and streptomycin are only to be considered if DST results confirm susceptibility and high-quality audiology monitoring for hearing loss can be ensured. Streptomycin is to be considered only if amikacin cannot be used (unavailable or documented resistance) and if DST results confirm susceptibility (streptomycin resistance is not detectable with second-line molecular LPAs and phenotypic DST is required). Kanamycin and capreomycin are no longer recommended for use in MDR-TB regimens.

i These agents only showed effectiveness in regimens without bedaquiline, linezolid, clofazimine or delamanid and are thus only proposed when other options to compose a regimen are not possible.”

6-month treatment regimens

Final results from the BEAT-Tuberculosis clinical trial on the use of a new 6-month regimen composed of bedaquiline, delamanid, linezolid (600 mg), levofloxacin, and clofazimine (BDLLfxC) were available to assess whether this new regimen can be used for patients with MDR/RR-TB or pre-XDR-TB when compared with the currently WHO-recommended regimens. The trial used an approach in which either levofloxacin or clofazimine was dropped from the regimen depending on fluoroquinolone drug susceptibility testing (DST) results - BDLLfxC initiated without delay in case of unknown FQ-resistance at the time of RR-TB diagnosis (and continued with both levofloxacin and clofazimine if FQ-DST results could not be obtained); BDLLfx continued for FQ-sensitive TB; BDLC for FQ-resistant TB. Within the trial, all of these regimens were compared with the recommended all-oral, bedaquiline-containing regimens (most of the control group received a 9-month linezolid-containing regimen). The dataset included patients with severe TB disease, people living with HIV, children, adolescents, and a small group of pregnant women.

The Guideline Development group concluded that the 6-month regimen may be used programmatically in MDR/RR-TB patients without prior exposure to these medicines (defined as > 1-month exposure)⁶ in place of the previously recommended 9-month or longer (≥ 18 months) regimens. The BDLLfxC regimen showed favorable efficacy and safety when compared with the regimens given in the control arm of the BEAT-Tuberculosis trial.

When exposure is greater than one month, these patients may still receive this regimen if resistance to the specific medicines with such exposure has been ruled out

The following recommendation was agreed upon:

WHO suggests the use of a 6-month treatment regimen composed of bedaquiline, delamanid, linezolid (600 mg), levofloxacin, and clofazimine (BDLLfxC) in MDR/RR-TB patients with or without fluoroquinolone resistance (conditional recommendation, very low certainty of evidence)

The 6-month BDLLfxC regimen showed high treatment success and is composed of medicines that have been recommended and used widely in all patient groups. The trial's evidence suggests that this regimen may be effectively and safely used in eligible patients with MDR/RR-TB and pre-XDR-TB regardless of their HIV status. The available evidence included children, adolescents, pregnant

and breastfeeding women, flagging the possible use of the regimen in these population groups. Thus, the evidence provided by the study will support new recommendations for the programmatic use of the regimen in many population groups.

9-month treatment regimens

Final results from the endTB clinical trial on the use of five different 9-month regimens were available to assess whether these all-oral regimens comprising different combinations of bedaquiline, levofloxacin or moxifloxacin (M), linezolid, clofazimine, delamanid, and pyrazinamide (BLMZ, BLLfxCZ, BDLLfxZ, DCLLfxZ, and DCMZ) may be used in MDR/RR-TB patients without resistance to fluoroquinolones and no previous exposure to second-line drugs (defined as > 1-month exposure)⁶ when compared with the WHO-recommended longer (≥ 18 months) regimens. Within the trial, each of these regimens was compared with the currently recommended longer (≥ 18 months), all-oral, bedaquiline-containing regimens. The dataset included patients with severe TB disease, people living with HIV, adolescents, and a small group of pregnant women. The evidence provided by the study will support new recommendations for the programmatic use of the regimens in many population groups, including children, adolescents, pregnant and breastfeeding women.

The Guideline Development group concluded that in eligible MDR/RR-TB patients with confirmed drug susceptibility to fluoroquinolones, three (BLMZ, BLLfxCZ, and BDLLfxZ) of the five 9-month all-oral regimens studied may be effectively and safely used instead of the longer (≥ 18 months) regimens. The review suggested against using DCLLfxZ and DCMZ regimens that were associated with high rates of treatment failure/relapse and acquired drug resistance.

The following recommendation was agreed upon:

WHO suggests using the 9-month all-oral regimens (BLMZ, BLLfxCZ and BDLLfxZ) over currently recommended longer (>18 months) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded. Amongst these regimens, using BLMZ is suggested overusing BLLfxCZ, and BLLfxCZ is suggested over BDLLfxZ (conditional recommendation, very low certainty of evidence)

Longer individualised regimen

The construction of longer Individualised regimens (18–20 months) is founded on grouping of medicines recommended for use in longer regimens based on the drug-resistance profile (Table 6.2). In ideal conditions, only a small proportion of MDR/RR-TB patients should opt for longer regimens, because this indication is mainly for those who cannot benefit from either BPaLM/BpaL or the 9-month all-oral (STR) regimen.

Reasons for not using the shorter regimens may be related to the age of the patients, additional resistance (including fluoroquinolone resistance and other Group A medicines, i.e. XDR-TB), intolerance to key medicines used in shorter regimens, severity of disease, pregnancy, certain types of extrapulmonary TB or other complications needing an Individualised approach.

Under many of these circumstances, only less potent and more toxic drugs are left to be used for treatment and lengthy regimens are therefore needed to cure without relapse. Longer regimens, especially if clinical conditions are complex (e.g. advanced disease with higher burden of bacilli and severe disease affecting critical organs) are usually associated with higher likelihood of toxicity, owing to factors such as longer drug exposure, higher intolerance, adverse effects and greater potential for drug–drug interactions in critically ill patients.

All DR-TB patients need a patient-centred approach with treatment adherence support and aDSM, but in longer regimens these activities become more crucial. Patients will need support to overcome the hardships associated with TB and its treatment, including daily adherence challenges, adverse drug reactions, indirect costs and stigma.

Note:

In multidrug- or Rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of treatment if Bedaquiline or Linezolid is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it.

Figure 6.X Stepwise approach to building the 18-20 months all-oral regimen.

STEP 1	Choose all drugs in Group A unless there is intolerance or resistance
STEP 2	Choose all drugs in Group B unless there is intolerance or resistance
STEP 3	Choose drugs in Group C if unable to compose a regimen using Group A and B drugs

Eligibility

A longer treatment regimen should be proposed mainly when the 6 months or 9-month all-oral short regimens cannot be used.

A longer regimen is expected to be used in the following situations:

- Severe extrapulmonary TB(CNS TB, osteo-articular and miliary TB);
- Additional resistance to key medicines of the BPaLM/BPaL regimen (except Moxifloxacin) or the 9-month all-oral regimen;
- Lack of response to shorter treatment regimens (e.g. treatment failure due to no bacteriological conversion, no clinical response, emerging resistance or loss to follow-up);
- Drug intolerance to the component medicines of the BPaLM/BPaL regimen (except Moxifloxacin) or 9 months shorter all-oral treatment regimen; and
- Pregnant and lactating women who could not benefit from the 9-month shorter all-oral regimen owing to certain clinical conditions or children aged below 14 years who could not be treated with BpaLM/BpaL or who, for any reason, cannot opt for a 9-month regimen.

Any patient eligible for a longer regimen should undergo a pre-treatment assessment to optimize the drug selection, reduce the chances of adverse events and thus increase the probability of the favourable treatment outcomes. The pre-treatment assessment includes:

- A detailed clinical history (including all comorbidities, medications and known intolerances), a physical examination, a blood test, chest X-ray or other imaging and bacteriological tests; and
- A list of current effective TB medicines available based on a clinical history of drugs taken before this treatment episode and guided by the DST results or sequencing of the most recent sample from the patient (or the index case). In addition to the eligibility criteria and preclinical assessment, a clinician should also consider:
- Development of a personalized treatment approach (patient-centred approach) and close follow-up, including food support if needed, to increase bioavailability of drugs, improve nutritional status and facilitate adherence;
- Provision of advice on contraception for women of childbearing age;
- Availability of ancillary medications (e.g. corticosteroids in the case of disseminated TB or TB meningitis or pericarditis, pre-treatment blood transfusion in the case of severe anaemia and nutritional support) and other interventions (e.g. intravenous [IV] medication in the case of severe malnutrition and malabsorption, insertion of peripherally inserted central catheter, or surgery in the case of restricted options and meeting criteria for intervention).
- Provision of counselling, depending on the patient's comorbidities (e.g. HIV or diabetes) or pre-existing conditions needing to be treated to optimize TB treatment outcomes.

Composition and duration of the regimens

When constructing longer regimens, several basic principles need to be respected, in line with the best available evidence on composition of the regimens, as per the recommendations listed below.

No.	Recommendation
3.2	Kanamycin and capreomycin are not to be included in the treatment of MDR/RR-TB patients on longer regimens. (Conditional recommendation, very low certainty of evidence)

3.3	Levofloxacin or Moxifloxacin should be included in the treatment of MDR/RR-TB patients on longer regimens. (Strong recommendation, moderate certainty of evidence)
3.4	Bedaquiline should be included in longer multidrug-resistant TB (MDR-TB) regimens for patients aged 18 years or more. (Strong recommendation, moderate certainty of evidence) Bedaquiline may also be included in longer MDR-TB regimens for patients aged 6–17 years. (Conditional recommendation, very low certainty of evidence) In children with MDR/RR-TB aged below 6 years, an all-oral treatment regimen containing Bedaquiline may be used. (Conditional recommendation, very low certainty of evidence)
3.5	Linezolid should be included in the treatment of MDR/RR-TB patients on longer regimens. (Strong recommendation, moderate certainty of evidence)
3.6	Clofazimine and Cycloserine or Terizidone may be included in the treatment of MDR/ RR-TB patients on longer regimens. (Conditional recommendation, very low certainty of evidence)
3.7	Ethambutol may be included in the treatment of MDR/RR-TB patients on longer regimens. (Conditional recommendation, very low certainty of evidence)
3.8	Delamanid may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens. (Conditional recommendation, moderate certainty of evidence) In children with MDR/RR-TB aged below 3 years Delamanid may be used as part of longer regimens. (Conditional recommendation, very low certainty of evidence)
3.9	Pyrazinamide may be included in the treatment of MDR/RR-TB patients on longer regimens. (Conditional recommendation, very low certainty of evidence)
3.10	Imipenem–cilastatin or meropenem may be included in the treatment of MDR/RR-TB patients on longer regimens. (Conditional recommendation, very low certainty of evidence)
3.11	Amikacin may be included in the treatment of MDR/RR-TB patients aged 18 years or more on longer regimens when susceptibility has been demonstrated and adequate measures to monitor for adverse reactions can be ensured. If Amikacin is not available, streptomycin may replace Amikacin under the same conditions. (Conditional recommendation, very low certainty of evidence)
3.12	Ethionamide or prothionamide may be included in the treatment of MDR/RR-TB patients on longer regimens only if Bedaquiline, Linezolid, Clofazimine or Delamanid are not used, or if better options to compose a regimen are not possible. (Conditional recommendation against use, very low certainty of evidence)
3.13	P-aminosalicylic acid may be included in the treatment of MDR/RR-TB patients on longer regimens only if Bedaquiline, Linezolid, Clofazimine or Delamanid are not used, or if better options to compose a regimen are not possible. (Conditional recommendation against use, very low certainty of evidence)
3.14	Clavulanic acid should not be included in the treatment of MDR/RR-TB patients on longer regimens. ¹⁰ (Strong recommendation against use, low certainty of evidence)

¹⁰ Imipenem–cilastatin and meropenem are administered with clavulanic acid, which is available only in formulations combined with amoxicillin. Amoxicillin–clavulanic acid is not counted as an additional effective TB agent, and should not be used without imipenem– cilastatin or meropenem.

Choice of components for the longer Individualised MDR-TB regimens

A stepwise approach guides the design of longer MDR-TB regimens (Table XX).

- The selection of medicines follows a priority order based on the revised classification of regimen components, and a fully oral regimen is preferred.
- At least four drugs must be selected, starting from Group A and then from Group B. Group C drugs are usually included in a longer regimen if it cannot be composed with Group A and B agents alone.
- The choice of drugs from Group C is usually determined by the order in which the medicines are ranked, and by the individual circumstances of the patient and the setting.

A recent review of the observational data found no additional safety concerns when Bedaquiline was used for longer than 6 months; however, no clear evidence was available to indicate whether longer use added efficacy. The clinicians may therefore consider continuing Bedaquiline for longer than 6 months and adding some flexibility for regimen design and the number of effective drugs.

In the case of longer treatment regimens, an individual approach is needed. Therefore, apart from the drug classification, it is crucial to optimize drug selection according to the patient's clinical condition and the drug-resistance pattern.

Considerations include:

- The clinical history of drugs taken in the past by the patient or the index case, or according to local resistance epidemiology in the country or region;
- The DST results – where available, is it of utmost importance to guide the drug selection using phenotypic or genotypic DST; in patients with extensive patterns of resistance, whenever possible, it is advised to perform whole genome sequencing; and
- Selecting drugs according to their special features – in addition to susceptibility, key drug features and clinical particularities of the patient that may boost survival must be considered (e.g. likelihood of effectiveness, CNS penetration, drug–drug interaction profile, tolerance and patient preference, oral absorption and bioavailability).

Most anti-TB drugs are used once daily to achieve a high peak serum concentration that increases the bactericidal and sterilizing effect and to support adherence (to avoid missed or partial doses).

The doses of anti-TB drugs by weight bands are outlined in the Annex.

Table 6.2. Summary algorithm for longer MDR-TB regimen composition in commonplace situations of resistance pattern or contraindication^a

Medicines to which there is resistance or contraindication of use	Consider adding medicines likely or confirmed to be effective			Examples of regimens or contraindication
	Group A	Group B	Group C ^b	
1 Two Group A medicines	Remaining medicine	Both medicines	At least 1 medicine	17 Bdq _(6 m or longer) -Cfz-Cs- Dlm _(6 m or longer) -(Z or E) 18 Lzd-Cfz-Cs-Dlm _(6 m or longer) - (Z or E) 18 Lfx-Cfz-Cs-Dlm _(6 m or longer) - (Z or E) If there is a suspected resistance to E or Z, replace with Group C drugs
2 One Group B medicine	Remaining medicine All 3 medicines	Remaining medicine	May not be needed	18 Bdq _(6 m or longer) -(Lfx or Mfx)-Lzd-(Cfz or Cs)
3 Both Group B medicines	All 3 medicines	None	1 or 2 medicines	17 Bdq _(6 m or longer) -(Lfx or Mfx)- Lzd – Dlm _(6 m or longer) -(Z or E) If there is a suspected resistance to E or Z, replace with Group C drugs
4 One Group A and both Group B medicines	Remaining 2 medicines	None	At least 3 medicines	18 Bdq _(6 m or longer) -(Lfx or Mfx)- Dlm _(6 m or longer) -Z-E 18 (Lfx or Mfx)-Lzd- Dlm _(6 m or longer) -Z-E 18 Bdq _(6 m or longer) -Lzd- Dlm _(6 m or longer) -Z-E If there is a suspected resistance to E or Z, replace with Group C drugs
5 All Group A medicines	None ^c	Both	3 or more medicines	18–20 Cfz-Cs-Dlm-Z-E or other combinations of Group C drugs, depending on known or suspected resistance

Bdq: Bedaquiline; CB: clinical breakpoint; Cfz: Clofazimine; Cs: Cycloserine; Dlm: Delamanid; E: Ethambutol; Lfx: Levofloxacin; Lzd: Linezolid;

m:months; MDR-TB: multidrug-resistant TB; MDR/RR-TB: multidrug- or Rifampicin-resistant TB; Mfx: Moxifloxacin; MIC: minimum inhibitory concentration; TB: tuberculosis; WHO: World Health Organization; Z: pyrazinamide.

a The situations shown are not exhaustive. Other factors may influence choice, such as patient risk for poor outcome or drug-drug interactions, clinician and patient preference and availability of a medicine. More medicines may be added than the recommended minimum if there is limited confidence in the effectiveness of regimen components, or if the patient was exposed in a setting where second-line TB drug resistance is frequent and longer MDR-TB regimens perform poorly despite good programmatic management of MDR/RR-TB. For MDR-TB with confirmed fluoroquinolone resistance, no fluoroquinolone is used and, if Group C agents are needed, the recommended WHO grouping will be followed based on benefit versus risk and individual circumstances.

b The choice and number of Group C medicines to include depends on the confidence in the effectiveness of medicines in this group and the other components of the regimen, thus:

- if 4 Group A and B agents are included and there is confidence in all of them, then Group C agents are not needed;

- if 3 Group A and B agents are included and there is confidence in all of them, then at least one Group C agent is added; and
 - if 2 Group A and B agents are included and there is confidence in all of them, then at least three Group C agents are added.
- c Moxifloxacin, a later-generation fluoroquinolone, may still be effective at a high dose when the fluoroquinolone MIC is below the CB. If the MIC is elevated, then fluoroquinolones are not used, and additional Group C agents will be needed.

Anti-TB drugs: Groups A–C

The classification of medicines used in MDR/RR-TB treatment regimens was revised following the evidence-informed update of the WHO guidelines on DR-TB treatment in 2018. TB medicines to be used for treatment of MDR/RR-TB are categorized into Groups A, B and C (Table #). This classification is based on drug class and level of certainty in the evidence on effectiveness and safety (i.e. balance between benefits and risk of harm). Groups A–C feature the medicines to be used to compose longer MDR-TB regimens. WHO considers that, under programmatic conditions, only these medicines (Groups A–C) have a role in longer MDR-TB treatment regimens.

The most notable differences between the classification of longer regimen components used before 2018 and the current guidelines are an upgrade in the priority of Bedaquiline, Linezolid, Clofazimine and Cycloserine/Terizidone; placement of Delamanid in Group C; and lowering of priority for Pyrazinamide, Amikacin, streptomycin, Ethionamide/Potionamide and p-amino salicylic acid, relative to other treatment options. Several agents that were featured previously in these groups are no longer included because they are:

- No longer recommended (e.g. Ofloxacin, capreomycin and kanamycin);
- Rarely used in longer regimens (e.g. High-dose Isoniazid); or
- An adjunct agent that is not intended to be used alone (e.g. Clavulanic acid is used only in combination with the carbapenems).

The classification facilitates design of the treatment regimen for patients with DR-TB who are not eligible for the BPALM/BPAl or 9-month treatment regimens.

Group A

Group A includes fluoroquinolones (Levofloxacin and Moxifloxacin), Bedaquiline and Linezolid. These medicines were found to be highly effective in improving treatment outcomes and reducing deaths in the evidence reviewed in 2018 for the WHO guidelines (1), and it is strongly recommended that they be included in all longer MDR-TB regimens and used for all MDR/RR-TB patients eligible for longer regimens unless there is a toxicity issue or drug resistance.

Levofloxacin and Moxifloxacin

Levofloxacin and Moxifloxacin are later-generation fluoroquinolones, and their use in the meta-analysis that informed the WHO guidelines (2018 update) resulted in a significantly lower risk of treatment failure or relapse and death (1, 11, 68, 69). Levofloxacin and Moxifloxacin appear to be equally effective in fluoroquinolone-sensitive patients receiving longer regimens, and either of these drugs can be considered for MDR/RR-TB treatment using these regimens. Ciprofloxacin and ofloxacin are less effective in MDR-TB treatment and are no longer recommended.

Reliable rapid molecular DST is available for Levofloxacin and Moxifloxacin (including Xpert MTB/XDR and second-line LPA). Not all point mutations present the same resistance profile. Despite some mutations having consistently high minimum inhibitory concentrations (MICs) (i.e. gyrA D94N or

D94Y), most mutations present a range of phenotypic resistance that may cross critical concentration (CC) and clinical breakpoint (CB) levels. Therefore, once fluoroquinolone resistance has been detected by molecular methods and treatment has started, a phenotypic method may be used as a reference test for distinguishing between high-level (>CB) and low-level (>CC and <CB) resistance mutations, possibly allowing for the use of a high-level fluoroquinolone dose. Where these mutations are detected, the composition of the longer regimen should be re-evaluated based on phenotypic DST results at the CB (70).

If DST for Moxifloxacin confirms high-level resistance, or if the patient's history suggests that Moxifloxacin has not been effective (e.g. if used in a failing regimen for more than 15–30 days), Moxifloxacin should not be used.

Bedaquiline

There is growing experience of its use in children, adolescents and older people, patients with extrapulmonary TB disease and PLHIV.

Currently, there is no age restriction for the use of Bedaquiline, including in longer regimens. The recent data review for the WHO consolidated guidelines suggests no additional safety concerns for the use of Bedaquiline beyond 6 months, used concurrently with Delamanid or in pregnancy. The available data suggests that the concurrent use of Bedaquiline and Delamanid does not increase the risk of clinically meaningful QT prolongation.

Fluoroquinolone resistance testing should be performed to prevent Bedaquiline resistance acquisition, and the levels of resistance should be monitored when possible. Bedaquiline presents cross-resistance with Clofazimine in cases of Rv0678 gene mutation (which lead to upregulation of efflux pumps) and pepQ mutations.

Resistance may occur spontaneously, even without prior exposure to Bedaquiline or Clofazimine (4.1% in some studies). Mutations at the *atp-E* gene may confer high-level resistance to Bedaquiline.

Linezolid

Linezolid has shown anti-TB activity in vitro and in animal studies, and its effectiveness in humans was demonstrated in the meta-analysis conducted for the WHO guidelines, as well as in recent trials involving XDR-TB patients (1, 84–88).

Linezolid is associated with considerable toxicity, which necessitates close monitoring for signs of bone marrow suppression and neuropathies.

The evidence from the WHO consolidated guidelines (1) suggests that Linezolid should be used for as long as it is tolerated. There may be improved outcomes if Linezolid is used for the full duration of treatment. However, it probably has its greatest added effect (including protection of other second line drugs against acquired drug resistance) during the first months of treatment when the bacillary load is highest (90). If toxicity develops, dosing of Linezolid should be reduced or replaced by another bactericidal drug (17).

Linezolid is not affected or metabolized by the cytochrome p450; however, it is an inhibitor of monoamine oxidase (MAO), leading to an increase in serotonin and tyramine levels. Serotonergic syndrome, which can be serious and life threatening, can result when Linezolid is given concomitantly with other MAO drugs that are often used in clinical practice in TB patients (e.g. antidepressants, opioid pain killers such as tramadol, common cold medications or antitussives such as dextromethorphan) (91).

Group B

Group B medicines include Clofazimine and Cycloserine or Terizidone, which were found to be effective in improving treatment outcomes but limited in reducing deaths in the evidence reviewed in

2018 for the WHO guidelines (1). One or both drugs can be added to ensure that a longer regimen starts with at least four effective medicines.

Clofazimine

Clofazimine is an antileprosy medicine that has shown in vitro activity against *M. tuberculosis* and has been used as a second-line TB medicine for several years. The meta-analysis conducted for the WHO guidelines reinforced the evidence for the effectiveness and safety profile of Clofazimine. When used with drugs that prolong the QT interval (e.g. Bedaquiline, fluoroquinolones and Delamanid), Clofazimine may cause additive QT prolongation. ECG monitoring should be implemented when Bedaquiline is used or when several QT-prolonging drugs are also part of the regimen. Non-TB drugs that cause QT prolongation should be avoided if possible.

Cycloserine

Cycloserine is a bacteriostatic drug that inhibits cell wall synthesis, and it has no known cross-resistance to other TB medicines. Terizidone (composed of two molecules of Cycloserine) may be used instead of Cycloserine, and Cycloserine and Terizidone are considered interchangeable. Because of difficulties in interpreting DST (there is no reliable genotypic or phenotypic DST for Cycloserine or Terizidone), Cycloserine or Terizidone should only be considered when other criteria of likelihood of effectiveness are met; for example, any reliable evidence on population levels of drug resistance, and prior use of Cycloserine or Terizidone based on a reliable clinical history.

Group C

Group C comprises both TB and repurposed medicines that are positioned at a lower priority than the Group A and B agents, either because they are less effective (Ethambutol, Delamanid, Pyrazinamide, Ethionamide/Prothionamide and p-aminosalicylic acid) or because they are more toxic and cumbersome to administer parenterally (imipenem–cilastatin, meropenem, Amikacin and streptomycin). These drugs are usually included in a longer regimen if it cannot be composed with Group A and B agents alone.

Ethambutol

Ethambutol is a TB medicine that is used in the treatment of DS-TB and may be added to longer MDR-TB regimens. At recommended dosages, the safety profile of Ethambutol is good. Owing to difficulties in interpreting its DST, Ethambutol should only be considered when other criteria of likelihood of effectiveness are met (e.g. evidence on a population level of low prevalence of drug resistance in circulating MDR/RR-TB strains and no prior use of Ethambutol based on a reliable clinical history).

Delamanid

Based on current evidence on its effectiveness and safety, Delamanid is recommended for use as a Group C agent (1). Delamanid has a potent in vitro bactericidal activity and potential sterilizing activity; it is thought that nitroimidazooxazole derivatives generate reactive nitrogen species, including nitrogen oxide, which are responsible for cell poisoning in low metabolic states. There is no age restriction for use of Delamanid and there are currently dispersible formulations that are preferred over crushing and dispersing adult tablets (47, 92). Delamanid is strongly bound to plasma proteins, resulting in low CNS penetration; however, studies in humans and animals with CNS TB suggest that Delamanid could potentially play a beneficial role when other options are not available (93). The recent data review for the WHO guidelines (1) suggested that there are no additional safety concerns for concurrent use of Delamanid with Bedaquiline.

Pyrazinamide

Pyrazinamide has been routinely added to MDR-TB regimens except where there is a reasonable clinical contraindication for its use (e.g. hepatotoxicity), or other serious adverse event or drug resistance. However, reliable DST for Pyrazinamide is not widely accessible; hence, this drug has often been used without DST or regardless of documented resistance. In the longer regimens, Pyrazinamide is recommended for inclusion only when DST results confirm susceptibility (in such cases it is counted as one of the effective agents); in any other cases, if Pyrazinamide is included in the regimen, it is not counted as one of the four effective drugs (94, 95). There are synergies between Pyrazinamide and other medicines such as Bedaquiline, through complex mechanisms of action targeting dormant bacteria.

Imipenem–cilastatin and Meropenem

Imipenem–cilastatin (not used in patients aged <15 years) and meropenem are the only carbapenems that have an established role in MDR-TB regimens. They are administered intravenously – a major drawback that limits their more widespread use outside hospitals, especially in resource-constrained settings (96–100). Daily IV injections are not usually feasible unless there is a surgically fitted port (a port-a-cath) or a peripherally inserted central catheter connected to a major vein. Meropenem with clavulanate as part of regimens (usually also containing Linezolid) for patients with MDR-TB and XDR-TB has been shown to improve culture conversion and survival (101–103). Clavulanic acid (as Co-Amoxyclav) is not a TB medicine but is an adjunct agent that is given orally each time a carbapenem dose is administered, about 30 minutes before the IV infusion. When included in a regimen, clavulanic acid is not counted as one of the TB agents, and it should not be used without the carbapenem.

Amikacin and streptomycin

Amikacin and streptomycin are the only two aminoglycoside antibiotics that can be used when options for composition of the treatment regimen are limited. Based on the evidence reviewed in 2018, Amikacin and streptomycin were associated with lower rates of treatment failure or relapse and death when used in people with *M. tuberculosis* strains susceptible to Amikacin or streptomycin. However, these drugs share the disadvantages and serious toxicities (i.e. ototoxicity and nephrotoxicity) of other injectable agents that are no longer recommended (i.e. Kanamycin and Capreomycin). Given the high frequency of streptomycin resistance in patients with MDR/RR-TB in many settings, and its extensive historical use as part of older first-line TB regimens in many countries, streptomycin is unlikely to have much use in MDR-TB regimens.

Ethionamide and Prothionamide

In WHO guidance, Ethionamide and prothionamide are considered interchangeable. The WHO consolidated guidelines make a conditional recommendation against their use in longer MDR-TB regimens, reserving them for situations where multiple, more effective agents (e.g. Bedaquiline, Linezolid and Clofazimine) cannot be used. Apart from the low bactericidal profile, use of Ethionamide and Prothionamide is limited because of poor gastrointestinal tolerance, which could be potentially linked to bad adherence. In pregnant women, these drugs are usually not recommended owing to poor tolerance, decrease in thyroid stimulating hormone (TSH) levels (which are fundamental for the development of the fetus) and concerns raised by effects in animal reproductive studies.

P-aminosalicylic acid

P-aminosalicylic acid (PAS) can be considered as the last resource for treatment of MDR/RR-TB. It is often poorly tolerated and has a modest bacteriostatic activity. The drug is recommended in the WHO consolidated guidelines only for use in the treatment of MDR/RR-TB patients on longer regimens if Bedaquiline, Linezolid, Clofazimine or Delamanid are not used, or if better options to compose a

regimen are not possible. There is no indication of cross-resistance of p-aminosalicylic acid to other anti-TB drugs (1). Use of p-aminosalicylic acid is limited owing to poor gastrointestinal tolerance.

Other medicines

Some medicines previously recommended as potential components of MDR-TB longer treatment regimens do not feature in Groups A–C.

High-dose Isoniazid

High-dose Isoniazid is not included in Groups A–C given the rarity of its use in longer regimens for adults. It is considered a relatively safe medicine, as shown recently in experience with its use at the 10 mg/kg dose. Other evidence suggests that high-dose Isoniazid may also be useful in the longer MDR-TB regimens. A more recent early bactericidal activity study among patients with MDR-TB – in which the Isoniazid resistance was mediated by isolated inhA mutations – demonstrated that doses of 10–15 mg/kg of Isoniazid daily exhibited bactericidal activity similar to standard-dose Isoniazid (5 mg/kg) given to patients with DS-TB.

Strains with isolated katG or both katG and inhA mutations are unlikely to respond even to high-dose Isoniazid, given the typically high Isoniazid MICs in those strains. In the absence of information on Isoniazid mutation patterns for an individual patient, knowledge of the prevalence of both mutations among locally circulating RR-TB strains (e.g. from DRS in the relevant epidemiological setting) may also inform decisions as to which treatment regimens would be most appropriate.

Duration of the regimen

The total length of a long treatment regimen is 18 to 20 months.

Note: all-oral longer MDR-TB regimens have no intensive phase. The duration of use of different medicines will depend on their clinical indication, patient tolerability (e.g. Linezolid used for as long as no serious adverse event emerges) and individual treatment response (e.g. culture negativity), until completion of the expected total duration of treatment or time after culture conversion.

Although the total length of treatment is expected to be about 18–20 months in most patients, it may be modified based on the patient’s clinical situation and response to treatment.

NTLP may choose a fixed duration (e.g. 18 months) for implementation purposes.

Principles of MDR-TB treatment

Early MDR-TB detection and the prompt initiation of effective treatment are important factors in obtaining successful outcomes.

The intensive phase of MDR-TB treatment should consist of at least four second-line anti-TB drugs likely to be effective (including an injectable anti-TB drug), with the addition of Pyrazinamide. If there is unclear evidence about the effectiveness of a certain medication, the medication can still be part of the regimen, however, it should not be counted as one of the four core medications. See below for advice on predicting medication effectiveness.

MDR regimens should include at least Pyrazinamide, a fluoroquinolone (later-generation), an injectable anti-TB drug, Ethionamide (or Prothionamide) and Cycloserine. This is the basis of the preferred standard regimen implemented in Uganda.

Avoid medications with a strong contraindication for the patient due to drug-drug interactions, overlying toxicities, co-morbidities, history of severe allergy or other adverse reactions, and/or pregnancy.

In some circumstances, laboratory confirmation of drug-susceptibility will not be available and a determination of likelihood of effectiveness based on available information is required.

Adjuncts to MDR-TB treatment

Surgery in the treatment of MDR/XDR-TB

Surgery has been employed in the treatment of TB since before the advent of chemotherapy. With the challenging prospect that more cases of MDR/XDR-TB are virtually untreatable with all available drugs or risk having serious sequelae, there has been re-evaluation of the role of pulmonary surgery as a way to reduce the amount of lung tissue with intractable pathology and to reduce the bacterial load. Large case series have reported that resection surgery may be safe and an effective adjunct when skilled thoracic surgeons and excellent postoperative care are available.

The updated WHO consolidated guidelines include a conditional recommendation for elective partial lung resection (lobectomy or wedge resection) as an adjunct to the chemotherapy of MDR/RR-TB patients with resistance to additional medicines. The recommendation does not apply to radical pneumonectomy, which had no statistically significant effect. The recommendation was based on evidence from an IPD meta-analysis to evaluate the effectiveness of different forms of elective surgery as an adjunct to combination medical therapy for MDR-TB, and a systematic review and study-level meta-analysis.

The relative benefits of surgery are expected to depend substantially on the population subgroups that are targeted. The reviews for the guideline update in 2016 could not provide a refined differentiation of the type of patient who would be best suited to an intervention, or the type of intervention that would carry the most benefit. The effect is expected to be moderate in the average patient considered appropriate for surgery. The odds of success for patients with MDR/RR-TB and resistance to fluoroquinolones and injectable agents were significantly lower when they underwent surgery compared with other patients ($aOR: 0.4$, 95% CI: 0.2–0.9). This finding is likely to be biased, given that patients who underwent surgery would have had other factors predisposing them to poor outcomes – factors that could not be adjusted for. Programmes with limited access to surgery may target patients who remain sputum smear positive, who have resistance to many drugs and who have localized pulmonary disease. Computerized tomography, pulmonary function testing and quantitative lung perfusion or ventilation may have a role in the preoperative work-up.

Resection surgery should be timed to give the patient the best possible chance of cure with the least risk of harm. Thus, the timing of surgery may be earlier in the course of the disease when the patient's risk of morbidity and mortality are lower (e.g. when the disease is still localized to one lung or one lung lobe). Generally, at least 2 months of therapy should be given before resection surgery, to decrease the bacterial infection in the surrounding lung tissue. Prognosis appears to be better when partial lung resection is performed after culture conversion. Even with successful resection, the total duration of treatment and the duration of treatment after culture conversion should be guided by the recommendations in Section 5, Section 6 and Section 7.

Partial lung resection for patients with MDR/RR-TB is only to be considered when good surgical facilities, staffed by trained and experienced surgeons, are available. Many programmes will have limited access to surgical interventions. In programmes with suboptimal surgical facilities and with no trained thoracic surgeons, resection surgery may increase morbidity or mortality. Specialized surgical facilities should include stringent infection control measures (given that infectious material and aerosols are generated in large quantities during surgery), mechanical ventilation and postoperative pulmonary hygiene manoeuvres. After resection, direct laboratory testing of the resection material (lung lesion) will be useful. If the results of laboratory testing differ between the resected material and other clinical specimens, the treating clinician may need to adjust treatment based on the results obtained from the resected material or other clinical specimens.

There are still many uncertainties about the role of surgery in MDR-TB treatment. All data available for the 2016 recommendations were from observational data from case series, which may be biased. For instance, it is likely that in choosing patients to be operated on there would have been systematic exclusion of patients deemed unfit for surgery and anaesthesia, such as older patients and those who were very sick with comorbidities (e.g. no patient with HIV in the dataset had undergone surgery) or extensive disease. There were not enough data on adverse events, surgical complications or long-term sequelae – some of which may be fatal – to allow for a meaningful analysis. Conversely, the effectiveness of surgery may have been underplayed in the analysis because of the lack of a suitable control group.

Use of corticosteroids

Corticosteroids have been used to support the treatment of serious and severe consequences of TB, such as miliary TB, respiratory insufficiency, CNS involvement and pericarditis. The WHO Guidelines for treatment of drug-susceptible TB and patient care, 2017 update made the following recommendations:

- In patients with tuberculous meningitis, an initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks should be used. (Strong recommendation, moderate certainty in the evidence).
- In patients with tuberculous pericarditis, an initial adjuvant corticosteroid therapy may be used. (Conditional recommendation, very low certainty in the evidence)

The recommendations are limited to these two forms of extrapulmonary TB. In patients with TB meningitis, evidence from RCTs showed lower rates of death, severe disability and relapse when patients received steroids with TB treatment. The mortality benefit increased with increasing severity of TB meningitis. Adverse events and severe adverse events, including severe hepatitis, were lower in patients receiving steroids. In patients with TB pericarditis, studies showed a benefit to steroid treatment in relation to death, constrictive pericarditis and treatment adherence.

Although the evidence and the recommendations primarily relate to non-MDR-TB, these recommendations could also apply to patients with MDR/RR-TB, on the condition that the patient is still receiving the TB treatment regimen. Corticosteroids are immunosuppressive and therefore can weaken the body's response to fight TB; hence, they should only be used if clearly indicated and if the patient is on an adequate effective regimen. If corticosteroids are used in an inadequate regimen, this could accelerate the patient's deterioration. Oral treatment can be given, but when a more immediate response is needed, injectable corticosteroids are often used initially.

Treatment of MDR/RR-TB patients with HIV

With regard to HIV infection, a specific recommendation was made in 2011 on the use of ART in all patients with HIV and DR-TB:

ART is recommended for all patients with HIV and drug-resistant TB requiring second-line anti-tuberculosis drugs irrespective of CD4 cell count, as early as possible (within the first 8 weeks) following initiation of anti-tuberculosis treatment (Strong recommendation, very low quality of evidence)

Delaying ART increases the risk of dying among TB patients living with HIV; therefore, ART should be started in all TB patients living with HIV, regardless of their CD4 cell count. The therapy should be initiated as soon as possible within the first 8 weeks of TB treatment, or within the first 2 weeks in patients with profound immunosuppression (e.g. CD4 counts <50 cells/mm³). In children with HIV and active TB, ART should be initiated as soon as possible and within 8 weeks following the initiation of anti-TB treatment, regardless of the CD4 cell count and clinical stage.

There may be a potential for overlapping, additive toxicities or drug–drug interactions between some antiretroviral medicines and the injectable agents, Moxifloxacin and Clofazimine; however, there are usually no grounds to warrant modifications of the MDR-TB or the ART regimens. It is not recommended to use Bedaquiline and Efavirenz in combination. Antiretroviral treatment regimens need to be optimized, and should be initiated early, in accordance with WHO recommendations. Close monitoring for response and toxicity is advised for patients on both TB and HIV treatment. Other comorbidities (e.g. diabetes and mental health disorders) should be managed accordingly.

Chapter 7:

Regimen for Rifampicin susceptible and Isoniazid resistant TB

This section refers to an Hr-TB treatment regimen that has a duration of 6 months and uses oral agents. WHO recommends Rifampicin, Ethambutol, pyrazinamide and Levofloxacin for 6 months in patients with confirmed Rifampicin-susceptible, Isoniazid resistant tuberculosis.

The basic regimen can be summarized as:

Hr-TB regimen: 6(H)RZE-Lfx

All medicines in this regimen are to be used daily for 6 months. When fixed-dose combination (FDC) formulations are used, Isoniazid is included but it is not obligatory for the regimen

If levofloxacin cannot be used because there is fluoroquinolone resistance or intolerance or other contraindications to the use of fluoroquinolone, then 6(H)RZE may be prescribed daily for 6 months.

Eligibility:

The Hr-TB regimen is recommended once Isoniazid resistance has been confirmed and Rifampicin resistance excluded. Rifampicin resistance needs to be excluded using rapid molecular tests (e.g. Xpert MTB/RIF) before Levofloxacin is used, to avoid the inadvertent treatment of MDR/RR-TB with an inadequate regimen. Ideally, rapid DST for fluoroquinolones and pyrazinamide is also performed.

It is not advisable to give a regimen for Hr-TB unless Isoniazid resistance is confirmed or highly suspected (e.g. confirmed TB patient who is the close contact of a documented Hr-TB case). This will avert the unnecessary use of Levofloxacin and prolonged pyrazinamide exposure in TB patients who may be cured with 2HRZE/4HR. Once the Hr-TB regimen has been started, if the results of initial DST reveal Isoniazid susceptibility, the regimen may be modified so that the patient effectively completes a course of first-line TB treatment.

The recommendations apply to both adults and children, including PLHIV. Thus, HIV testing and treatment of PLHIV with ART is important, and the aim is to start ART within 8 weeks of TB treatment initiation (regardless of CD4 count), or within the first 2 weeks in patients with profound immunosuppression (e.g. CD4 counts<50 cells/mm³). The regimen is also likely to be effective in patients with extrapulmonary Hr-TB; however, consultation with appropriate specialists is advised.

Hr-TB treatment is expected to be started if either of the following circumstances apply:

- Hr-TB is confirmed and Rifampicin resistance is ruled out before TB treatment is started – in such cases, the 6(H)RZE-Lfx regimen is started immediately. If the diagnosis is strongly presumed (e.g. close contact of a confirmed Hr-TB source case) but results of DST are still pending, the regimen may be introduced. Should DST results taken at the start eventually show susceptibility to Isoniazid, then Levofloxacin is stopped and the patient continues treatment to complete a 2HRZE/4HR regimen.

- Hr-TB is discovered after the start of treatment with the 2HRZE/4HR regimen (this includes patients who had undiagnosed Isoniazid resistance at the start or who developed Isoniazid resistance while on first-line treatment) – in such cases, rapid molecular testing for Rifampicin resistance must be undertaken (or repeated). Once Rifampicin resistance has been excluded, a full 6-month course of (H)RZE-Lfx is given. The duration is driven by the need to give Levofloxacin for 6 months, which usually implies that the companion first-line medicines are taken for longer than 6 months. The unexpected discovery of resistance to one agent should prompt the clinician to repeat DST for other agents in the regimen. The example in Box 7.1 illustrates a typical situation that could arise.

Box 7.1. Evaluation of a typical scenario – a delayed DST result in a patient on a first-line regimen

Before starting the 2HRZE/4HR regimen, a patient with rifampicin-susceptible TB confirmed by Xpert MTB/RIF has a sputum sample sent to a regional laboratory for phenotypic DST. The results are returned to the treating physician 3 months later; they show resistance to isoniazid. The patient has meanwhile adhered to their treatment regimen, gained weight and been symptom free for 2 months.

What does the clinician need to think about and do?

- Given that the DST results are 3 months old, the initial resistance pattern may no longer be indicative of the current situation, because the bacteria may have acquired additional resistance.
- Since the beginning of the third month, the patient should have been in the continuation phase with isoniazid and rifampicin (usually in FDC); however, the patient is effectively on rifampicin monotherapy. Resistance to rifampicin may have developed and needs to be checked, even if the clinical progress suggests that the regimen is working. Xpert MTB/RIF needs to be repeated.
- If rifampicin resistance is detected, the patient should be started on MDR-TB treatment (as detailed in Chapter 5, Chapter 6 and Chapter 7).
- If rifampicin resistance is not detected, the patient should be switched to the (H)RZE-Lfx regimen for 6 months. Ideally, DST for fluoroquinolones should be performed.

Composition and duration of the regimen

The duration of Hr-TB treatment is driven by the need to complete 6 months of a fluoroquinolone containing regimen. This implies that, when Hr-TB is diagnosed after the start of the regimen for treatment of DS-TB, the companion medicines (HRZE) would end up being given for more than 6 months.

In patients with cavitary disease and with persistent positivity on sputum smear and culture, prolongation of (H)RZE-Lfx beyond 6 months could be considered on a case-by-case basis. Prolongation of treatment increases the risk of toxicity, particularly from pyrazinamide and Ethambutol, which are usually only given for 2 months in the first-line TB regimen.

Levofloxacin is the preferred fluoroquinolone for Hr-TB regimens. The exposure to Moxifloxacin decreases markedly when it is combined with Rifampicin. This effect has not been reported in the case of Levofloxacin; also, Levofloxacin appears to cause less QT interval prolongation than Moxifloxacin.

Levofloxacin is included in Hr-TB regimens except in the following instances: when Rifampicin resistance cannot be tested for, when there is documented resistance or known intolerance to fluoroquinolones, and when there is pre-existing prolongation of the QT interval and pregnancy. If a fluoroquinolone cannot be used, a patient with Hr-TB can still be treated with 6(H)RZE; streptomycin is not required in such cases.

For patient convenience and ease of administration, the HRZE FDC may be used to treat Hr-TB (given that no RZE FDC is currently available). The dosage of other TB medicines in the Hr-TB regimen is the same as in the standardized DS-TB 2HRZE/4HR regimen. The inclusion of Isoniazid in the regimen has not been shown to lead to substantial benefit or harm to patients; however, Isoniazid may increase the hepatotoxicity of pyrazinamide. High-dose Isoniazid (10–15 mg/kg per day) may still be effective when used in combination

regimens in the presence of isolated inhA mutations linked to low MIC, even in “fast acetylators” (i.e. individuals who metabolize Isoniazid rapidly). In the presence of both inhA and katG mutations, addition of Isoniazid (even at a high dose) is unlikely to add value to the regimen.

Patients with Hr-TB may have a higher risk of acquiring additional resistance and MDR-TB, which may manifest during the same treatment episode or in a subsequent relapse. The effect of additional resistance to Ethambutol and pyrazinamide on the treatment of Hr-TB is unclear.

Considerations for implementation

The regimens recommended for treatment of Hr-TB is not divided into an intensive and a continuation phase – this simplifies the delivery and monitoring of treatment. Treatment is given daily, and intermittent treatment should be avoided. Relevant measures to support adherence, social support and the use of digital technologies should be considered to ensure favourable treatment outcomes.

The cost of medicines to compose a full 6(H)RZE regimen with Levofloxacin is slightly higher than the cost of a 2HRZE/4HR regimen used for DS-TB. Nonetheless, the 6(H)RZE regimen is an affordable and feasible intervention, even in low-income settings. Use of FDCs simplifies treatment and lowers costs, and the use of dispersible formulations of HRZ, Ethambutol and Levofloxacin is preferred in children. As with the treatment of other forms of TB, the expenses associated with the proper delivery of care (e.g. DST, adherence support and clinical monitoring) far exceed the cost of medicines.

A new diagnostic platform has been approved for the detection of Hr-TB – the new Xpert MTB/ XDR cartridge, which can detect Isoniazid resistance in less than 90 minutes, matching the rapidity and convenience of Xpert MTB/RIF for Rifampicin resistance. First-line LPA can also detect Isoniazid resistance, Typical processing time for an LPA specimen is about 2–3 days, owing to batching. DST based on liquid culture (or MGIT) could also detect Hr-TB at the level of a reference laboratory, but this means a processing delay of at least 10 days. Testing on solid media is also an option, but it takes several months to obtain results; hence, this approach is of limited use for baseline testing and monitoring of treatment response.

Current epidemiological data indicate that more than three quarters of the global burden of Hr-TB occurs among previously untreated (“new”) TB cases. Previous TB treatment is thus not a strong indicator of risk of Hr-TB – the correlation with previous TB treatment is weaker than it is with MDR-TB. Reserving Isoniazid DST to such patients is therefore unlikely to yield many Hr-TB cases. There are various concerns about empirical Hr-TB treatment of previously treated TB cases, without prior DST.

- First, such treatment will lead to unnecessary overtreatment with fluoroquinolones and prolongation of pyrazinamide use in many patients. Most recurrent cases will not have Hr-TB and can be cured with a 2HRZE/4HR regimen.
- Second, unless Rifampicin resistance is excluded at the baseline, patients with MDR/RR-TB would be exposed to an inadequate regimen, with the risk of acquiring additional resistance, including fluoroquinolones.
- Third, this policy would deflect the focus of the programme from testing new TB patients, who usually harbour the main burden of Hr-TB.
- Finally, this approach would risk creating once again a “re-treatment regimen”, similar to the situation that prevailed in many settings until recently with the indiscriminate use of the streptomycin-containing 8-month “Category 2” regimen in all previously treated TB patients.

In a situation where access to DST is good, a logical diagnostic algorithm would start with Xpert MTB/ RIF as the initial test for all patients evaluated for TB. Cases in whom TB is confirmed and Rifampicin resistance is not detected would be further tested with Xpert MTB/XDR or LPA. Liquid culture may replace LPA, but the additional delay in obtaining results is a disadvantage.

Treatment monitoring

The clinical monitoring of patients on Hr-TB treatment follows similar principles to those that apply to other first-line TB regimens. Bacteriological monitoring of sputum generally follows the same schedule as DS-TB,

with direct microscopy at months 2, 5 and 6. It is desirable, however, to perform a culture together with smear microscopy (or at least in the last month of treatment) to check for any emergent resistance, especially to Rifampicin. Non-response to treatment should be investigated with DST.

Liver and kidney function and other blood tests may be necessary, based on clinical manifestations and medications in use. ECG for patients on 6(H)RZE-Lfx is not usually required unless there are other risks for QT interval prolongation. The first-line TB agents may cause adverse drug reactions, which are mostly mild, not serious and self-limiting or manageable with basic measures. Dosage adjustment, in consultation with a specialist, is recommended if creatinine clearance is below 30 mL/min (17). Adverse drug reactions should be reported to the spontaneous pharmacovigilance systems required by national regulations, as for other drug-related harms. In patients on regimens for Hr-TB, aDSM is not mandatory.

As with all other notifiable TB cases, patients with Hr-TB should be registered in the TB register, regardless of whether treatment has started, or whether a regimen containing second-line TB medicines is being given. The case may be retained in the TB register for the purposes of monitoring the treatment response and the interim or final outcomes. Cases without Hr-TB may be enumerated with the main DS-TB cases for the purposes of treatment outcome reporting. Hr-TB cases given fluoroquinolones or other second-line agents in addition to 6(H)RZE may also be registered in the second-line TB register if the programme wishes to monitor how many patients are being given regimens containing second-line medicines. If this is done, it is important that cases without RR-TB are not enumerated with the MDR/RR-TB cohort for treatment outcome monitoring purposes.

It will be helpful to monitor efforts to improve testing coverage, detection, enrolment and outcomes for Hr-TB separately from other TB or MDR/RR-TB cases. The indicators for MDR/RR-TB may be adapted for this purpose; outcome definitions are the same as for non-MDR/RR-TB. Reporting is at the same frequency as that recommended for standard monitoring of other TB cohorts.

However, treatment of TB patients who do not have Rifampicin resistance with regimens discussed in this section should lead to a successful outcome in most patients, and maximizing the likelihood of success should be the end objective of TB programmes. The use of electronic case-based databases facilitates the grouping of patients by comparable resistance patterns or treatment episodes to undertake more advanced analyses, allowing adjustment for at least some covariates.

Chapter 8:

Flow of care: referrals, initiation of care, transfers, supervision, and adherence

This chapter describes the flow of DR-TB care as patients are identified and referred for treatment initiation. It outlines the structure and approaches for DR-TB treatment delivery from the facility of diagnosis to the treatment initiation sites and down to community-based care, oversight and supervision of clinical care, management of interruptions when second-line anti-TB treatment regimens are required, and considerations to enhance treatment adherence.

Referral for second-line TB treatment

In Uganda, patients with RR-TB who require second-line treatment regimens must be referred to one of the designated DR-TB treatment initiation facilities for treatment start.

Referral from peripheral health facility

When someone is diagnosed with RR-TB by Xpert MTB/RIF, or is presumed or found to have confirmed MDR-TB, the peripheral health facility staff should immediately trace the patient and refer him/her to the nearest DR-TB treatment initiation facility using the NTLP DR-TB Referral/Transfer Form (form 10).

Send one copy of the NTLP TB Patient Referral and Transfer Form (form 10) with the patient to be presented to the clinician at the DR-TB treatment initiation facility

Send one copy of the NTLP TB Patient Referral and Transfer Form to the DTLS to enable the DTLS to follow up with the DR-TB treatment initiation facility where the patient has arrived

File the remaining copy at the referring facility site

Enrolment and treatment initiation

Enrolment

Once a referral is received, the clinician at the treatment initiation facility will complete an initial evaluation, education and counseling of the patient, and then present the patient during the regional **DR-TB Expert Panel meeting** to decide whether the patient meets the criteria for initiating second-line anti-TB treatment. If so:

- Determine appropriate DR-TB regimen
- Discuss the patient information on the DR-TB Treatment Patient Consent Form (form 11) and obtain patient consent for second-line anti-TB treatment
- Complete the NTLP DR-TB Treatment Approval Form (form 9) and register patient in the Second-line TB Treatment Register
- Determine whether the patient should be admitted to hospital for treatment initiation OR
- Determine whether the patient can safely initiate treatment as an outpatient

Treatment initiation

Hospitalization – For patients who are severely sick, have access challenges, or are otherwise determined to need closer monitoring (including access to ECG during first 2 weeks on new drugs or STR), admission to a hospital for treatment initiation will be arranged. During hospitalization:

- Patients should be oriented to the hospital environment and provided with acceptable living conditions including adequate food, fans or cooling systems during hot climates, bed nets, and sufficient activities like TV screens, to avoid boredom.
- Health education on importance of adherence and other key aspects of DR-TB treatment and monitoring should begin (see box 8.1 and Chapter 19 for information that should be covered with the patient and patient's family).
- Proper infection control measures, described in Chapter 16, must be observed.

- Inmates with DR-TB referred from the prison will require special security arrangements from the referring prison or, if available, are admitted at a prison DR-TB treatment facility.
- Planning for transfer to ambulatory or community care will begin and will involve the DTLS, patient, follow-up facility, and, potentially, other family members.

Box 8.1 Checklist to review with the patient before DR-TB treatment starts

Discuss where treatment will start. If at a hospital, estimate the approximate length of stay. If at home, ask about the home living situation and whether or not the patient feels home treatment will be possible.

Inform the patient about the length of treatment—that it will be for at least 20 months but may be longer.

Teach the patient about the drugs: there are at least five anti-TB drugs, of which one is an injectable agent.

Teach the patient about monitoring requirements for smear, culture, and laboratory tests for side effects.

Make a follow-up plan for seeing the doctor and inform the patients that if they have problems, they should be seen sooner. Make sure they know how to make an appointment if they need to be seen before the next routine visit.

Instruct patients on what to do in case of an emergency (like severe shortness of breath).

Teach patients about possible side effects.

Inform patients that they must report any side effects to the medications; remind them to notify you right away if there is any hearing loss or ringing in the ears.

Teach patients how DR-TB can be transmitted and some basics about household infection control. The patient is most infectious during the first few days or weeks of treatment when he/she is still smear positive.

Windows and doors should be left open in the home to increase ventilation.

A smear positive patient should wear a surgical or cloth mask at all possible times.

It is safer to visit with family and friends if the patient is outdoors in the open air.

If started on new drugs (BDQ) or STR, adjust counseling details, Annexes 8 & 9.

Ambulatory/clinic-based – For patients in which outpatient care can be safely administered, treatment can start once baseline examinations have been conducted (see section 8.3) and staff at the treating clinic/facility have been trained on:

- Second-line anti-TB treatment delivery by DOT (six days/week for the injectable)
- Essential monitoring and management involved
- Recording and reporting requirements (see Chapter 19)
- Infection control considerations (see Chapter 16)
- Indications for referral or consultation should problems arise
- Patient-centred care approaches (see Chapter 10) and treatment care plan
- Home assessment and contact investigation (see Chapter 15)

Staff from the regional DR-TB treatment initiation facility should provide close support and oversight during the initial weeks and months (weekly for the first month) of treatment to ensure treatment is well established and tolerated by the patient.

Special attention must be taken to ensure that HIV-infected patients are not exposed to smear-positive DR-TB patients. Discuss with the patient how he/she will get to and from the clinic, as well as any special processing for DR-TB patients (fast-tracking or designated waiting area) available at the clinic to prevent transmission of DR-TB to others while the patient is still potentially infectious early in the treatment course.

Infectious DR-TB patients will require isolation during the early weeks of treatment to prevent ongoing transmission in the community. Patients who are employed or are attending school may need notice from health care authorities that time off of work or school is required for a period of time.

Pre-treatment screening and evaluation

The required initial pre-treatment clinical investigation includes a thorough medical history and physical examination. The purpose of the baseline evaluation is to document the following:

Presence and severity of signs and symptoms of TB, including a detailed description of the CXR, for determining clinical responses to treatment

Co-existing conditions of importance, such as HIV, diabetes or cardiac risks

Baseline laboratory values as reference for monitoring during treatment

Initial evaluation of the patient includes the following investigations (all results charted in the Second-line TB

Treatment Card, except where noted below):

Complete history and physical: document in the MDR-TB Screening Form 8

Check HIV status:

- If found to be HIV positive, prepare patient to start ART as per the TB/HIV guidelines; send sample for CD4 (CD4% in children) and/or viral load.
- If found to be HIV negative, repeat periodically during treatment as indicated.
- If known to have HIV, obtain **current CD4 count** and/or viral load and confirm HIV treatment regimen, assess adherence, and obtain HIV provider contact information.

Acid-fast smear and mycobacterial cultures: Record results by date of specimen collection (not result report date). Send two sputum specimens for smear and culture before starting treatment to ensure the NTRL can provide adequate baseline culture and DST results in addition to Xpert MTB/RIF findings.

DST results: Include rapid DST and full DST results. NOTE: The collection date of the sample sent for full DST should be less than 30 days before, or a maximum 7 days after, the initiation of second-line anti-TB treatment (specimen collected before treatment start is preferred).

Baseline laboratory investigations including liver function tests (total serum bilirubin, SGPT & SGOT, total serum albumin), creatinine, potassium, uric acid, blood glucose and full blood count, and thyroid stimulating hormone (TSH)

Baseline weight, height, and mid-upper arm circumference (MUAC)

Baseline CXR: include brief graphic **description**.

Baseline audiology or hearing evaluation

Social evaluation: Conducted using the Household Assessment Form (form 13a) to ascertain whether the patient has all the necessary social supports to foster treatment adherence. This will include an assessment of income, food security, and providing for the family in terms of clothing, education, shelter, medical care, etc. Social habits (e.g., alcohol consumption, smoking, and other substance abuse) which can affect adherence and treatment outcome should also be assessed and appropriate plans for addressing any potential barriers should be developed with the patient and documented in the Treatment Care Plan (annex 2).

Psychiatric evaluation: Patients with pre-existing mental illness should be assessed by a psychiatric specialist prior to commencing the standard MDR-TB regimen and should be closely monitored during treatment.

Pregnancy test for women of childbearing age: Methods of avoiding pregnancy during treatment should be discussed and agreed upon during the initial assessment. Repeat pregnancy test periodically during treatment as indicated.

If symptoms of hypothyroidism or goitre are present or the patient is of advanced age, test baseline free thyroxine and TSH levels.

If Bedaquiline or STR to be used, or the patient has a history of cardiac disease, obtain baseline electrocardiogram. Also, obtain baseline lipase.

The baseline assessment should document any specific recommendations for medication dose adjustment, plans for management of adverse effects, and frequency of monitoring in patients with pre-existing conditions (e.g., diabetes mellitus, renal insufficiency, acute or chronic liver disease, thyroid disease, and mental illness, drug or alcohol dependence, HIV infection, pregnancy, lactation). The management of DR-TB when these conditions exist is described in Chapters 12 and 13. See box 8.2 for the minimum criteria that must be addressed to assess for suitability to initiate the standard MDR-TB regimen. See box 8.1 for information to cover with the patient who will start second-line anti-TB treatment and Chapter 10 for other important patient-centred support measures.

Transfer, oversight and clinical supportive supervision

Once the patient is well established on treatment and arrangements made for continuation of treatment in or near the patient's home community, day-to-day treatment and follow-up will be transferred from the initiation facility to community-based care and support.

DR-TB treatment initiating facility: Transfer responsibilities

The DR-TB treatment initiation facility team will undertake the following before transferring a DR-TB patient for follow-up treatment and care in the patient's home district:

- Re-emphasize with the patient the importance of adherence to treatment under DOT.
- Establish with the patient how he/she will receive daily treatment and follow-up once transferred (i.e., getting to and from the follow-up facility or provision of home-based treatment).
- Identify responsible staff in a follow-up facility or designated community health care worker closest to the patient or his/her community willing to work under the supportive supervision of the DR-TB treatment initiation facility staff to provide and/or oversee DR-TB treatment.

Train, plan for, and discuss with the follow-up facility staff:

- Support measures needed to ensure patient's adherence to treatment (see section 8.6 and Chapter 10)
 - Potential side effects and how to promptly recognize and manage them (see Chapter 9) as well as when and what to report to the DR-TB treatment initiation facility staff when adverse effects are experienced
 - Essential sputum and laboratory monitoring of the patient during treatment (see Chapter 9)
 - Essential recording in patient's Second-line TB Treatment Card (see Chapter 19)
 - Frequency for DR-TB patient follow-up appointments at the DR-TB treatment initiation facility
 - How to properly and safely store second-line TB drugs, as well as the frequency and method for ordering future supply
 - Identification and required evaluation of household and other close contacts of DR-TB patients with pulmonary disease (see Chapter 15)
 - Frequency of supportive supervision and follow-up that will be provided to the follow-up facility through the DR-TB treatment initiation facility team
1. Assist in identifying and training a DR-TB treatment supporter (staff in follow-up facility or community member) before patient discharge or transfer to community- based care
 2. Deliver the patient's drugs and a copy of the Second-line TB Treatment Card (form 01); transfer process should involve the DTLS

DR-TB treatment initiating facility and DTLS: Oversight and clinical supportive supervision

If a patient has been transferred to a follow-up facility or other community-based care mechanism, the overall management and oversight of the patient's progress on DR-TB treatment "from start to finish" remains the responsibility of the treatment initiation facility DR- TB team and the DTLS. Steps to ensure this oversight and clinical supportive supervision include:

- Ensuring patients return for monthly evaluations and monitoring tests (if not available at the local facilities) to the treatment initiation facility
- Tracking patient data and progress by the DR-TB staff at the treatment initiation facility, and reporting this information at the quarterly DR-TB Cohort Reviews
- Holding supportive supervision and mentorship visits bimonthly, at a minimum, following the initial training and transfer of the patient
- Ensuring the follow-up facility has adequate stock supply of second-line anti-TB medicines and sputum containers
- Ensuring contacts are being evaluated
- Ensuring completion of post-treatment monitoring occurs as per the guidelines

Models of community-based care for treatment of DR-TB

Community management of DR-TB patients aims to bring treatment capacity closer to the patient's home, delivered through an ambulatory/clinic-based or a home-based care model.

Ambulatory/clinic-based care

This involves the patient travelling to a clinic to receive DOT (six days per week for the injection). This works well if the patient lives near a facility that offers DOT for DR-TB, so there is no travel barrier and waiting time is minimized.

- The patient should be given an enabler (transport) for travel in situations where travel to and from the clinic will create a difficulty for the patient and/or patient's family.
- To enhance adherence, the facility should offer patient-centred, patient-friendly services (see Chapter 10). For example, arrange for an early morning or late afternoon appointment for a patient who is working.
- Patient should be smear negative before allowing travel on public transportation or waiting in common waiting rooms.

Home-based care

Home-based care implies that the health system is visiting the patient in his/her home to provide daily injection and oral medications, monitor side effects, and provide health education and psychosocial support alongside infection control and contact tracing. Home-based care has shown the best treatment outcomes in settings where it has been implemented due to the strong psychosocial support component regularly offered to both patient and family. Treatment and care in this model is provided by a team of trained community treatment supporters that includes clinicians (physicians, medical officers, and clinical officers), nurses, social workers, and lay persons. With this model, patients are less likely to get lost to follow-up DR-TB treatment supporters

Function of a community treatment supporter:

- Supervise oral doses and escort the patient(s) for injections at the health centre
- Provide injections (in some authorized cases only)
- Accompany the patient to all medical consultations
- Remind and provide sputum bottles to the patient on monthly basis for sputum collection
- Record daily doses in the Second-line TB Treatment Card
- Collect drugs and supplies in a drug box from the follow-up treatment facility every two weeks or monthly, then return the drug box to the follow-up treatment facility at end of two weeks or month
- Educate the patient's family on the importance of screening for HIV and TB
- Conduct contact tracing, infection control, recording and reporting, training, advocacy, and social support
-

The treatment supporter/DOT provider should be someone who:

- Is chosen by or is acceptable to the patient
- Is committed to support the patient for a long time
- Has received MDR-TB-specific training
- Is available to observe doses twice a day
- Is available to accompany patients to clinic and lab appointments
- Can read and write
- Is not immune suppressed (HIV or diabetes)
- Is over 14 years of age
- Ideally, is not an immediate family member (NOTE: Family relationships are often complicated for the DR-TB patient. A family treatment supporter could be subject to subtle manipulation by the patient, relatives, employers, etc.)

Political will from the health and local community authorities is vital to the success of community-based treatment for DR-TB. Organizations that have expertise in social and community mobilization can be helpful in establishing community support systems.

Ensuring adherence to therapy

Patients with DR-TB who have been treated for TB in the past are more likely to have previously had problems with non-adherence. Even in the best circumstances, adherence to second-line therapy is difficult because of the prolonged treatment duration and large number of drugs that have more serious adverse effects. Thus, DR-TB patients are at increased risk of non-adherence to treatment. Adherence is an essential element in curing DR-TB and preventing the generation of XDR strains capable of spreading within the community and leaving virtually no possibility of cure for the patient. Therefore, adequate support measures must be in place from the start of therapy to give each DR-TB patient the best chance for cure. Essential support measures include patient education, DOT, patient- centred care, prompt management of adverse effects, and close monitoring.

Patient education and treatment care plan

Patient education, being one of the essential interventions, starts with checking what the patient knows or understands about their diagnosis, their past experience with TB treatment, and expectations that they may have. During the initial interviews with the patient, assess for potential barriers to adherence and discuss strategies that the patient would find supportive.

- Obtain informed consent and commitment prior to treatment start (form 11)
- Address patient questions and concerns
- Discuss the phases of treatment (intensive phase and continuation phase)
- Discuss infection control and protecting others (see Chapter 16)
- Discuss anticipated challenges for remaining adherent to treatment
- See box 8.1 and Chapter 10 for important patient information to cover

Once potential barriers to adherence have been identified, a plan of care to address the barriers should be documented using a Treatment Care Plan (see annex 2). A strong treatment care plan will include the following elements:

- Lists the identified barriers to adherence
- Identifies patient-centred approaches to address barriers to adherence
- Documents interventions used
- Is periodically reviewed to evaluate the effectiveness of interventions

Directly observed therapy

As second-line treatment for DR-TB may be the patient's last chance for cure, and because there is a serious public health consequence if treatment fails, it is mandatory that all patients on second-line anti-TB treatment be on DOT. DOT can be provided in the community/home, a health centre/clinic, or a hospital.

DOT for DR-TB

All efforts should be made to ensure DOT arrangements are as convenient for the patient as possible, avoiding long transportation and waiting times.

Who can deliver DOT? The use of injections during the intensive phase generally requires that a health care worker is involved as the DOT provider to DR-TB patients during the initial period of treatment. A health care worker staying near the patient's home should be identified and the location where DOT will take place determined (e.g., either at home or at a nearby health facility). Once the intensive phase is completed, a lay treatment supporter can continue DOT for the remainder of treatment.

Maintaining confidentiality. The DOT treatment supporter should maintain strict confidentiality regarding the patient's disease.

Early and effective management of anti-TB drug side effects

Although rarely life threatening, the adverse effects of second-line drugs can be debilitating. Patients who experience high rates of adverse effects may be at an increased risk of interrupting treatment. Therefore, early and effective management of adverse effects is one of the critical strategies for promoting adherence to DR-TB treatment. Refer to Chapter 9 for details on management of adverse effects.

Monitoring and follow-up of the non-adherent patient

A strong system of monitoring that allows the patient to be followed throughout treatment must be in place. The forms in Chapter 19 are designed to assist the care provider in follow-up. Immediate steps should be

When a patient fails to attend a DOT or monthly clinic appointment:

- Prompt patient follow-up by a DOT worker visiting the patient's home should be done the same day to find out why the patient has missed an appointment.
- Every effort should be made to listen to reasons for the patient missing a dose(s) in a sympathetic, friendly, and non-judgmental manner, and to work with the patient and family to ensure continuation of treatment.
- Ensure that treatment is resumed promptly and effectively.
- Do not double up doses missed. Rather, missed doses should be added to the end of treatment (end of intensive phase or continuation phase depending on when the missed doses occurred).
- Transportation problems, if any, should be promptly addressed.

taken if a patient fails to keep a DOT appointment.

Failure to remain fully adherent to treatment can occur for many reasons. Table 8.1 covers some of the common reasons patients with DR-TB report as reasons for non-adherence, and proposes some possible solutions to these problems, which can be adapted and incorporated into the patient's Treatment Care Plan.

Table 8.1 Common adherence problems and their solutions

Adapted from the PIH Guide to the Medical Management of Multidrug-Resistant Tuberculosis, 2nd ed.

Problem	Possible Solutions
The patient does not want to take treatment because of adverse effects.	This is the most common reason for default. Treat the adverse effects immediately.
The patient does not want to take treatment because he/she is feeling better (e.g., fever and cough resolved) but the medicine makes him/her feel bad (e.g., nausea, dizziness, fatigue for hours after taking medication).	Explain: "Even though you feel better, you are not cured. There is still MDR-TB in your lungs that will start growing again if you stop treatment." Encourage the patient that the side effects from the medication will diminish over time. Consider pre-medication with anti-emetic if indicated (see Chapter 9 for approaches to managing side effects).
The patient has economic problems that affect ability to be adherent.	Assess basic housing, food, and clothing needs and explore ways to address these needs. Explore what services are available through NGOs, faith-based organizations (FBOs), community-based organizations (CBOs), and other partner organizations to support patient needs.

The patient is suffering from alcohol or drug abuse.	Discuss possible alcohol or drug abuse with the family and the patient. Refer patient to drug treatment programs and/or support groups.
The patient has a bad relationship with the health worker supervising treatment.	Discuss these issues with the community team and the health worker supervising treatment. Change the health worker if these problems cannot be resolved.
The patient is experiencing isolation, stigma, or discrimination.	Educate the family and community. Consider involving community leaders if the patient agrees.

Table 8.2: Approach to re-initiation of treatment after lost to follow-up (default)

Adapted from the PIH Guide to the Medical Management of Multidrug-Resistant Tuberculosis, 2nd ed.

Amount of treatment received prior to lost to follow-up	Action
Treatment less than 3 months	<p>Send sputum for culture and DST.</p> <p>Close prior DR-TB treatment episode in the Second-line TB Treatment Register with final outcome as “lost to follow-up.”</p> <p>Counsel patient and family; obtain commitment to complete full course of treatment.</p> <p>Re-register the patient and restart original regimen from the beginning; patient will need a new, full course of treatment.</p> <p>Can adjust regimen once DST results are available</p>
Treatment more than 3 months	<p>Close prior DR-TB treatment episode in the Second-line TB Treatment Register with final outcome as “lost to follow-up” or “treatment failure,” whichever outcome best applies.</p> <p>Counsel patient and family; obtain commitment to complete full course of treatment.</p> <p>Recollect and send sputum for culture and DST prior to restart of treatment.</p> <p>Re-register the patient and restart original regimen from the beginning; patient will need a new, full course of treatment. Adjust regimen if needed once repeat DST results are available.</p> <p>NOTE: If treatment failure was suspected before interruption, consider designing a new regimen instead of restarting original regimen.</p>

Treatment more than 3 months	<p>Restart the regimen the patient was taking before the interruption. If patient was in the continuation phase and there has been no evidence of clinical deterioration during the interruption, the continuation phase can be restarted.</p> <p>NOTE: If the patient has any subsequent positive smears or cultures in the next few months, consider the patient as bacteriologically positive, re-register and restart a full course of MDR-TB treatment (from the injectable phase).</p> <p>Send sputum for culture and DST; total length of treatment will depend on whether the sputum culture is positive. All patients in this category should get a minimum of 24 months of therapy total.</p>
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NOTE: If the interruption is six months or more and the patient is clinically stable and bacteriologically negative, it may be advisable to first determine if the patient has active TB before deciding to restart treatment. See Annex 9 for additional considerations on STR.

If interruption is less than two months (not classified as lost to follow-up), there would be no change in registration, but, similar clinical reasoning regarding repeat testing and considerations for regimen restart or changes may apply as above.

Reinitiating treatment after interruption or lost to follow-up (default)

No matter what the reason for treatment interruption, a careful, systematic approach to re-initiation of DR-TB treatment must be undertaken.

When a patient returns after an interruption in treatment:

- Perform a review of the clinical record and situation leading up to the interruption.
- Examine how much treatment the patient received prior to the interruption.
- Explore what sort of adverse effects the patient may have been experiencing the last time he/she was taking treatment.
- Was the patient smear- or culture-positive at the time he or she stopped treatment?
- What factors led to the interruption and reason(s) why patient stopped therapy?

Perform a careful clinical evaluation looking for evidence of disease progression.

Evaluate symptom status and perform a clinical exam.

Obtain monitoring specimens (and CXR where indicated) based on findings, duration of interruption, and duration of treatment prior to interruption.

Table 8.2 provides a suggested approach to re-initiation of treatment after interruption in treatment of greater than or equal to 2 months (meeting criteria for classification as lost to follow-up), factoring in when the interruption occurred and result of sputum smear and culture upon return to treatment.

Conduct a full clinical evaluation prior to restart of treatment

Assess symptoms and clinical status (including weight): Is the patient asymptomatic, or are symptoms and clinical status similar or worse than prior to break in treatment? If there are signs of worsening status, consider a repeat chest radiograph.

Collect and send sputum for smear, culture, and, if culture-positive, repeat DST.

Meet with the patient and the community team to discuss ways to improve adherence before restarting treatment.

Forced isolation and respect for human rights

Management of DR-TB, which can be a threat to public health, must be balanced with consideration for human rights and patient dignity.

When, in rare situations, the extreme measure of involuntary confinement is deemed necessary, it should be approached in a transparent and accountable manner. If it can be proven that forced isolation is temporarily required, patients must be provided with the quality care that includes, among other rights, free

access to second-line drugs, laboratory support including effective DST, social support, and respect and dignity. Patients should be informed clearly, in their language, of the decision and its details, and of their rights and responsibilities, as outlined in the Patients' Charter for Tuberculosis Care, accompanied by a peer-supporter and/or family member.

The fear of forced isolation without consideration of patients' dignity creates a negative perception of TB Control within the affected community, which discourages people from going for TB testing and raises the stigma attached to the disease. If the conditions of isolation are equated with punishment, the efforts to stop transmission of the disease will be made more difficult.

Certain restrictions on individual rights and liberties may be necessary at times when there is evidence of potential risk to others.

Conclusion

Enduring treatment for DR-TB can be difficult for the patient and patient's family. Treatment delivery is most successful when a strong support network is built around the patient to address all the difficult challenges a patient faces, right from diagnosis. This includes ensuring sufficient support measures are in place to enable uninterrupted treatment, proper monitoring, and management of adverse effects, as well as to address socio-economic problems, stigma, and lack of social support, among others. Whatever treatment delivery model is chosen, a multidisciplinary team of providers must be assembled throughout the patient's care, with adequate oversight and supportive supervision in order for optimal outcomes to be achieved.

Digital Adherence Technologies (DATs) for patient treatment monitoring

In the fight against TB, healthcare providers can enhance patient support using Digital Adherence Technologies (DATs), like Video Observed Treatment and Smart Pill Boxes. These tools empower individuals with MDR TB, allowing them to manage their treatment conveniently. DATs promote a patient-centered care model by overcoming obstacles like limited clinic visits and travel restrictions, enabling healthcare providers to follow and support the patient journey more effectively through online adherence platforms.

Potential benefits of DATs

1. Patient can choose the most suitable time to take medication within their daily routine.
2. Patient can be prompted by daily medication reminders to take their medication.
3. Patient can receive individualized treatment information or support.
4. Healthcare providers can access their patient's real-time medication adherence information through the DAT platform.
5. The adherence platform can send healthcare providers automated alerts and reports about patients prompting the necessary action.
6. Helps healthcare providers identify patients who need more support and shape the most suitable treatment response.

The DATs technologies to support MDR TB treatment

Video supported treatment (VST)

Allows patients video record their medication intake using a secured app on their mobile phone which the healthcare provider can watch to confirm medication intake. After completion the video is sent to the health care provider. Patients are guided through a secured mobile application to record videos of themselves ingesting their daily medication. This is then uploaded to a secure remote server that is accessed by the health care provider to review the doses taken. If a video is not sent when expected or if the medication intake is unclear in the video, the healthcare provider is prompted to contact the patient to determine the problem and provide timely support.

Smart Pill Box

With the use of a low-cost medication container, a battery powered sensor and a mobile data connection, a LED and speaker to enable visual/audible dose reminders, the smart pill box automatically logs patient medication intake each time the patient opens the box to take medication by sending a signal. A smart pill box consists of a battery that lasts up to 6 months before it requires a recharge with a global mobile data subscription for 36 months meaning one container can be used by various patients.

Medication sleeve/label (99 DOTS)

The medication sleeve/label also called 99 DOTS, use customised packaging such as printed sleeves or labels that fit Fixed Dose Combination (FDC) medication. The patient reports medication intake daily by calling a toll-free phone number or sending free SMS messages using a code found on the customized packaging.

Cost considerations

The cost estimates of the DAT interventions are dependent on the type of DAT used, the number of people enrolled on the treatment, the enrolment duration, supportive infrastructure costs, monitoring devices, data, and airtime provided to the healthcare facilities.

DAT Data flow

Dosage/Adherence information from patients enrolled is automatically linked to the DAT platform in real-time for health workers to review and offer the necessary support. The DAT system is in position to send the adherence information to the national data capture systems (DHIS2 and eCBSS) to make use of the adherence information beyond patient monitoring.

Chapter 9:

Monitoring treatment response and management of adverse effects

This chapter provides information on the essential monitoring for patients who have started second-line anti-TB treatment and the management of the associated adverse effects of treatment. It addresses the following:

- Monitoring requirements for determining response to treatment and DR-TB treatment outcomes
- Monitoring actions for early detection of adverse effects and strategies for management

Key recommendations of this chapter:

- Standard monitoring should be implemented for all patients on treatment for DR-TB, as per table 9.1 below.
- To evaluate treatment response, both smear and culture should be monitored monthly until culture conversion is documented. Once culture conversion is achieved, monitor smears monthly and cultures bimonthly.
- Increased monitoring is required in patients with HIV, diabetes, renal impairment, and hepatic disorders, and who are receiving ART.
- Active drug safety monitoring and management (aDSM) should be implemented by Health care workers of DR-TB control programme.
- Ancillary drugs for the management of adverse effects should be available to the patient.

Monitoring treatment response

Patients should be monitored closely for signs of treatment failure. Patients will require evaluation by a treatment initiation facility clinician at least monthly for clinical evaluation and monitoring. The DOT provider should be trained to offer daily patient monitoring and to report and refer the patient to the clinician at the treatment initiation facility if signs or symptoms of TB worsen or if adverse side effects persist.

- Monitoring response to treatment is accomplished through regular history-taking, physical examination, bacteriological examination, and thorough review of chest radiography (see table 9.1 for the recommended frequency of activities to monitor DR-TB treatment response).
- The classic symptoms of TB—cough, sputum production, fever, and weight loss— generally improve within the first few weeks to months of treatment.
- For children, height and weight should be measured regularly to ensure that they are growing normally (see also Chapter 11). A normal growth rate should resume after a few months of successful treatment.
- Cough and sputum production can persist after sputum conversion in patients with extensive lung damage; however, such patients usually show signs of improvement within a month or two of effective treatment.
- Persistent fever, weight loss, or recurrence of any of the classic TB symptoms should prompt investigation of treatment failure or untreated comorbidities. The recurrence of TB symptoms after sputum conversion may be the first sign of treatment failure.

Sputum smears and cultures must be monitored regularly throughout treatment to document treatment outcomes. The most important objective evidence of improvement is conversion of the 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 to detect ongoing active disease and/or treatment failure. Therefore, culture is necessary to monitor the progress of treatment and to determine treatment outcome. Sputum smear and culture examinations are also dependent on the quality of the sputum produced, so care should be taken to obtain adequate specimens and to promptly transport them to the lab for testing according to standard procedures.

Persistently positive sputum cultures for AFB should be assessed for NTM, as colonization or infection with NTM in damaged lung secondary to TB is not uncommon. Usually these NTMs do not need to be treated. However, if DR-TB is adequately treated (cultures remain negative for MTB), and there continues to be clinical evidence of disease (e.g., fevers, cough, and progressive radiographic deterioration) and NTMs are repeatedly isolated, treatment, if available, may need to be directed towards the NTM and referral to a specialist considered.

Culture conversion should not be considered equivalent to cure. A certain proportion of patients may initially convert and later revert to positive sputum culture. These patients have a reversion and eventually will be declared treatment failures.

Table 9.1 Activities for monitoring DR-TB treatment response

Monitoring evaluation	Recommended frequency
Evaluation by the DR-TB treatment initiation facility clinician	At initiation: Every day during the first weeks, if hospitalized, and at least every week, if treated as outpatient, (Ambulatory care), until patient is well established and tolerating treatment. Once stable, patient should be seen at least once a month. Follow-up Assessments: Monthly assessment by the DR-TB treatment initiation facility clinician unless there is a medical necessity to see the patient more often. The DOT provider at the follow-up facility/Community, reviews the patient daily and signals any concerns to the clinical team at the DR-TB treatment initiation facility between monthly reviews.
Treatment adherence and tolerance	At every DOT encounter
Sputum smears and cultures	At baseline, then monthly until end of treatment and at 6- and 12-months post treatment.
Weight	Monthly. For children and others with substantial weight loss prior to diagnosis, check every 2 weeks for the first 3 months.
Height	Monthly for children, along with weight, in order to assess growth (see also Chapter 11)
MUAC	Monthly for all patients
DST	At baseline, but also consider repeating when DR-TB patients remain culture-positive despite treatment, or revert after month 4. It is not necessary to repeat DST within less than 2–3 months of the previous DST.
Chest radiograph	At baseline, and every 6 months. Summarize key findings in the Second-line TB Treatment Card.

These guidelines recommend that the tests be performed at baseline and then monthly as it is in table 9.1 For patients who remain smear- and culture-positive during treatment, or who show other indications of treatment failure, DST can be repeated. Objective bacteriological evidence of improvement often lags behind clinical improvement.

The chest radiograph may be unchanged or show only slight improvement in the first few months of treatment, especially in re-treatment patients with chronic pulmonary lesions. Chest radiographs should be taken at least every six months to document progress, when a surgical intervention is being considered, for MDR/RR patients with resistance to additional medicines, should be done after at least 2 months therapy has been given and after culture conversion or whenever there is clinical deterioration. A chest radiograph at the end of treatment is useful to later manage TB pulmonary sequela post- treatment. See also Figure 9.1 for a summary of the routine monitoring patients on second- line anti-TB treatment should undergo.

Monitoring for adverse effects during treatment

Close monitoring of patients is necessary to ensure that health care personnel recognize the adverse effects of second-line anti-TB medications quickly.

Treatment sites should conduct Active Drug Safety Monitoring and Management (aDSM). aDSM is the active and systematic clinical and laboratory assessment of patients on treatment to detect, manage and report suspected or confirmed drug toxicities.

NDA recommends reporting even for known mild and common reactions. The Serious Adverse Events (SAEs) and Adverse Events (AEs) of special interest (AESI) (Annexure 6). should be reported within 24 hours.

Serious adverse event (SAE): Refers to an 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.

Annexure 6: Adverse events of special interest.

Adverse events of special interest	
Depression	Seizures
Arthralgia	Hypothyroidism
Dizziness/vertigo	Psychosis
Hearing disturbances	Suicidal ideation
Sleep disturbances	Hepatitis (hepatotoxicity)
Electrolyte disturbances	Renal failure (nephrotoxicity)
Peripheral neuropathy	QTc prolongation
Gastritis	Rash
Myelosuppression	Lactic acidosis
Visual disturbance	Allergic reaction
Sexual Dysfunction	Dry Skin

The ability to monitor patients for adverse effects daily is one of the major advantages of DOT over self-administration of DR- TB treatment. The majority of adverse effects are easy to recognize, and patients will often volunteer this information and should be probed during the clinic visit to share any event that happened. (e.g., complain of nausea and vomiting, tingling or numbness in hands or feet, Visual changes). However, it is important to have a systematic method for patient interviewing and documentation of the absence or presence of adverse effects, with comments about severity since some patients may be reticent about reporting even severe adverse effects. The PV Screening tool should be filled for every patient on every clinic visit. This allows them to discover other adverse events that patients may not have reported if they were distracted by one adverse effect and forget to tell the health care provider about others. DOT providers should be trained to

document the regular screening of patients for symptoms of common adverse effects: rashes, gastrointestinal symptoms (nausea, vomiting, and diarrhea), psychiatric symptoms (psychosis, depression, anxiety, and suicidal ideation), jaundice, ototoxicity, peripheral neuropathy, and symptoms of electrolyte wasting (muscle cramping, palpitations). DOT providers should also be trained in simple adverse effect management and when to refer patients to a nurse or physician.

Laboratory screening is invaluable for detecting certain adverse effects that are more hidden (i.e., not obviously noted by taking the history of the patient or by physical examination). DR-TB treatment initiation facilities should have the capacity to provide the recommended laboratory investigations to patients under their care. See table 9.2 and figure 9.1 for recommended minimal frequency of essential laboratory screening. Since this regular screening will generate a large number of laboratory results, it is important to transcribe these results into the laboratory flow chart in the Second-line TB Treatment Card (Form 01) in order to efficiently and safely document the frequency of testing and track the results.

Note: All adverse events should be reported to the National Drug Authority using the Active Drug Safety Monitoring and Management (aDSM) form and entered into PVIMSt. Using Bedaquiline and Delamanid for the Treatment of Drug-Resistant Tuberculosis in Uganda: Guidelines for clinicians; 2016.

1 Culture conversion is defined as two consecutive negative smears and cultures taken 30 days apart

Table 9.2 Routine toxicity monitoring during second-line TB treatment

Monitoring evaluation	Recommended frequency
Serum creatinine	Monthly while receiving injectable drugs. For high-risk patients (patients with HIV, diabetes, renal insufficiency, or who are over 50 years of age), check every 1–2 weeks during first month, then every 1–3 weeks.
Serum potassium	Monthly while receiving an injectable agent. Every 1–3 weeks in patients with HIV, diabetes, other high risk, or when indicated.
Serum magnesium and calcium	If hypokalemia is diagnosed, check serum Mg and Ca. If on Bedaquiline, check monthly and repeat if any ECG abnormalities develop (prolonged QT interval).
TSH	Every 6 months if receiving Ethionamide and/or PAS. Monitor monthly for signs/symptoms of hypothyroidism. It is not necessary to measure T3 and T4 levels.
Liver serum enzymes (SGOT, SGPT, bilirubin)	Periodic monitoring (every 1–3 months) in patients receiving Pyrazinamide for extended periods, or for patients at risk for or with symptoms of hepatitis. For HIV-infected patients, do monthly monitoring.
Mental health/depression screen	Screen monthly for changes in mood or other psychiatric disturbances for patients on Cycloserine. A Standardised depression screening questionnaire may be useful for this purpose. Refer to a psychiatrist when indicated.
Audiometry (hearing test)	Audiogram monthly while receiving an injectable agent. Ask patients about changes in hearing at every clinic visit and evaluate their ability to participate in normal conversation.
Serum glucose	If a patient has diabetes and is taking fluoroquinolone, monitor glucose frequently (weekly) and educate patients on signs and symptoms of hypoglycemia and hyperglycemia. If on Gatifloxacin, monitor glucose closely.
Hemoglobin and white blood count	For patients with baseline anemia, monitor full blood count regularly, as indicated. If on Linezolid, monitor weekly at first, then monthly or as needed based on symptoms; there is little clinical experience with prolonged use of Linezolid.
Vision tests (acuity and color)	For HIV-infected patients on AZT, monitor monthly initially and then as needed based on symptoms.
Lactate	If on Linezolid or ART, lactate should be checked for work up of lactic acidosis.
Lipase	If on Linezolid, Bedaquiline, D4T, ddi, or ddc, check lipase for work-up of abdominal pain to rule out pancreatitis.

Electrocardiogram (ECG)	If on Bedaquiline, obtain ECG at weeks 0, 2, 4, and then monthly after starting treatment and more frequently if heart conditions, hypothyroidism, or electrolyte disturbances are present. If on STR: check at weeks 0, 2, 4, 8 and at change to continuation phase.
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NOTE: Results of sputum smear and culture, DST, Xpert MTB/RIF, SL LPA, laboratory monitoring, audiogram results, and chest radiograph summary need to be charted in the Second-line TB Treatment Card (Form 01) to provide an ongoing summary of initial tests and the patient's response to treatment and adverse effect monitoring.

Monitoring	Recommended Frequency																				
	Month of treatment																				
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Clinical Evaluation	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Weight/ Height/ BMI/ MUAC (and nutritional support)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
TB Symptoms, Treatment Education, DOT, Adherence counselling	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Adverse drug reactions	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Substance use and mental health screen	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Family planning and pregnancy testing	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
GeneXpert/ Xpert XDR assay	x																				
Sputum smear, culture	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
DST	x	If indicated																			
Chest X-ray	x					x															
LFTs (at least ALT, AST and bilirubin)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
RFTs (Creatinine)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Serum electrolytes	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
CBC	Weeks 0, 2	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
TSH (If on Eto)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
HIV/ CD4/ Viral load*	x	Every 3 months																			
Blood glucose	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
ECG (QTcF)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Peripheral neuropathy and visual acuity screen (If on Lzd)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	

Table XX: Clinical, bacteriological and laboratory monitoring schedule for BPALM/BPAL and Individualised regimens

There are a number of relatively common toxicities that are complicated to monitor but can be life threatening; they necessitate extra attention in monitoring and include the following:

Nephrotoxicity. This is a known complication of injectable drugs, both aminoglycosides and capreomycin. The adverse effect is occult in onset and can be fatal. The optimal timing for checking serum creatinine is unknown, but most experts recommend checking at least monthly while the patient is on injectable. In addition, patients with a history of renal disease (including comorbidities such as HIV and diabetes), advanced age, or any renal symptoms should be monitored more closely, particularly at the start of treatment. An estimate of the creatinine clearance (or glomerular filtration rate) may help to further stratify the risk of nephrotoxicity in these patients (see Chapter 13 for information on calculating creatinine clearance). Patients with a low baseline glomerular filtration rate should be monitored closely for nephrotoxicity.

Electrolyte wasting. Electrolyte loss through the kidneys is a known complication of anti-TB injectable drugs, most frequently with capreomycin. It is generally a late effect occurring after months of treatment, and is reversible once the injectable drug is suspended. Since electrolyte wasting is often occult in the early stages and can be easily managed with electrolyte replacement, serum potassium should be checked at least monthly in all patients while they receive an injectable agent. Low serum magnesium can result in an increase in renal potassium loss, therefore, it is recommended that serum magnesium and calcium also be checked if hypokalemia is diagnosed.

Hypothyroidism. Hypothyroidism is an effect provoked by PAS and/or Ethionamide. It is suspected by clinical assessment and confirmed by testing serum TSH. These agents produced hypothyroidism in 3.5% of patients in one study,² while in a different study the rate was greater than 50%.³ The higher rate in the second cohort may be a result of high rates of advanced disease, HIV, and/or malnutrition. Since symptoms can be subtle, it is recommended that patients be screened for hypothyroidism with a serum TSH at baseline, then every six months. Screening with TSH should occur sooner if symptoms of hypothyroidism arise. The dosing of thyroid replacement therapy should be guided using serum TSH levels every month until a stable dose in thyroid replacement hormone is reached. Goitres can develop due to the toxic effects of PAS and/or Ethionamide. In areas where iodine deficiency goitres are endemic, treatment with iodine is indicated, in addition to assessment and treatment for hypothyroidism.

Liver toxicity. Chemical hepatitis can result from Pyrazinamide, PAS, and, less commonly, with other second-line drugs. Liver enzymes should be checked for all patients who exhibit signs of hepatotoxicity. It is recommended to check serum liver enzymes monthly for HIV-positive patients on Pyrazinamide.

Ototoxicity. Ototoxicity refers to damage to the auditory cranial nerve (VIII), usually manifested by hearing loss, tinnitus (ringing in the ear), and/or other vestibular symptoms, such as nystagmus and ataxia; disequilibrium can also occur. Presentation is most commonly observed in patients receiving large cumulative doses of aminoglycosides and/or capreomycin. Concomitant use of furosemide, particularly in the setting of renal insufficiency, may exacerbate ototoxic effects of these medications. Patients starting therapy with hearing loss at baseline from prior aminoglycoside use are at the highest risk. Hearing loss is generally not reversible

² Shin S, Furin J, Alcantara F, Hyson A, Joseph K, Sanchez E, et al. Hypokalemia among patients receiving treatment for multi-drug-resistant tuberculosis. Chest 2004; 125:974–980.

³ Satti H, Mafukidze A, Jooste PL, McLaughlin MM, Farmer PE, Seung KJ. High rate of hypothyroidism among patients treated for multidrug-resistant tuberculosis in Lesotho. IJTLD 2012;16(4):468–472.

upon discontinuation of therapy. Hearing loss begins at higher frequencies and progresses to low frequencies. This often manifests as tinnitus in early stages. Audiological surveillance reveals that even patients without any audiological complaints (tinnitus or hearing loss) may show audiological characteristics of ototoxic hearing loss at higher frequencies. As speech frequencies are affected late in the disease, complaints of difficulty in hearing often indicate a later stage in the progression of ototoxic hearing loss. Thus, audiometry for baseline and/or follow-up testing is required to pick up early hearing loss. Audiometry is recommended every month while on the injectable agent.

Psychiatric disturbances. Psychosis and depression can result in thoughts of suicide and even suicide attempts. Assessment of the patient's psychosocial condition, including the specific question, "Are you having thoughts of suicide or depression?" should be done routinely at the monthly visit. Similarly, signs of psychosis, anxiety, agitation, and depression should be looked for monthly.

QTc prolongation. The QTc interval is a measure of the time between the start of the Q wave and the end of the T wave on an ECG and represents the electrical depolarization and repolarization of the left and right ventricles. A lengthened QTc interval is a biomarker for ventricular tachyarrhythmias, like torsades de pointes, and a risk factor for sudden death. Concomitant use with drugs that prolong the QTc interval may cause additive QTc prolongation, and should be avoided in patients at high risk for cardiac complications (patients with a QTc interval greater than 450 ms, history of torsades de pointes or cardiac ventricular arrhythmias, or history of severe coronary artery disease). Some of the second-line anti-TB drugs are known to prolong the QTc interval (e.g., Bedaquiline, M, Cfz); therefore, an ECG must be obtained at baseline and regularly to monitor the QTc interval when such medicines will be used. See Annexes 8 and 9 for more details.

Management of adverse effects

Second-line anti-TB medications have many more side effects than the first-line drugs. Proper management of adverse effects begins with education of all stakeholders involved in treatment and care. Before starting treatment, the patient, DOT providers, and health care workers should be instructed in detail about the potential adverse effects that could be produced by the prescribed drug regimen.

Remember to always have a discussion with the patient about any event that occurred since they started taking the drug. Document in the screening tool DOT providers should immediately alert the initiating site and ensure that it is reported to NDA.

General principles for management of adverse effects

All anti-TB drugs are associated with adverse effects.

Adverse effects are not a contraindication to appropriate treatment.

Poorly managed adverse effects may lead to non-adherence or inappropriate therapy.

Minor adverse effects are common during initial months of treatment.

Serious reactions are rare but require immediate attention and proper reporting.

Timely diagnosis and early management are crucial.

Community health workers and DOT can help with close surveillance for adverse effects during ambulatory treatment by having close communication with patient and family members.

Exploration of alternative etiologies and contributing factors, as well as correction of underlying abnormalities, is important.

Changes to the MDR-TB regimen as a result of adverse effects are rarely indicated.

Ambulatory management is usually adequate.

A recent systematic review and meta-analysis that examined the frequency and type of adverse effects due to MDR-TB treatment⁴ found that 57.3% of patients developed at least one type of adverse effect during treatment for MDR-TB. The most common adverse effects were gastrointestinal disorders, which were observed in 1,620 of 3,991 patients with a pooled rate of 32.1% (95% confidence interval [CI] 23.5–42.1). Gastrointestinal disorders included the presence of nausea, vomiting, abdominal pain, diarrhoea, epigastric discomfort, hematemesis, melena, and positive endoscopic findings. The next two most common types of adverse effects were ototoxicity (included tinnitus, hearing loss confirmed by physical examination or audiometry, or presence of disequilibrium) with a pooled estimation was 14.6% (95% CI 10.9–19.4), and psychiatric disorders (included presence of depression, anxiety, psychosis, suicide, nightmares, and convulsion) with an overall incidence of 13.2% (95% CI 9.9–17.3).

Table 9.3 summarizes the reported adverse effects, the likely responsible anti-TB agents, and the suggested management strategies. Overlapping toxicities for HIV-infected patients on ART and DR-TB treatment are addressed in Chapter 12.

General Guidance on when to continue with or replace a regimen:

If the adverse effect is mild and not dangerous, continue the treatment regimen with the help of ancillary drugs if needed (see table 9.4 for commonly used ancillary medication). In patients with advanced resistant TB patterns, a satisfactory replacement drug may not be available; therefore, suspending a drug would make the treatment regimen less potent. Some adverse effects may disappear or diminish with time, and patients may be able to continue receiving the drug if sufficiently encouraged and motivated.

The adverse effects of a number of second-line drugs are highly dose dependent. Reducing the dosage of the offending drug is another method of managing adverse effects, but only in cases where the reduced dose is still expected to produce adequate serum levels and not compromise the regimen.

Modification of the regimen by discontinuation or replacement of the offending drug is necessary to avoid permanent disabilities. This applies to serious Adverse events or for grade 3 and 4.

To note in the BPALM regimen, dose modification of Bedaquiline and Pretomanid is not recommended, and dose modification of Linezolid should be avoided in the first 9 weeks of therapy, this principle should not override the need to avoid permanent disabilities.

In some circumstances, the offending drug may be permanently stopped, and a decision made either to continue the other drugs to complete treatment or start a new regimen. For example, Visual changes of any severity, when a patient experiences symptom of severe paresthesia in the feet, preventing them from completing their daily life activities.

Reporting adverse events (AEs): When an adverse effect is suspected to be associated to a second-line anti-TB drug, Active Drug Safety Monitoring and Management (aDSM) Form should be completed. (see Annex Form 19; Once the data on adverse events is captured in the AE form, A copy of this DPS form should be sent to NDA using WhatsApp: +256740002070, Email: druginfo@nda.or.ug, Telephone: 0800101999/ 0417788100/1. The other copy filed in the patient record; AE data should be entered in the DR- TB MIS and PVIMS.

Health care workers can also submit suspected adverse event information online at <https://primaryreporting.who-umc.org/Reporting/Reporter?OrganizationID=UG>.

Please note that any derangement in laboratory findings (see Table 11) should be considered an adverse event and should be reported.

Psychosocial support is an important component of the management of adverse effects. This is one of the most important roles played by DOT providers, who educate patients about adverse effects and encourage them to continue treatment. Patient support groups are another means of providing psychosocial support to patients (see also Chapter 10).

To continuously assess the safety of the regimens prescribed for patients, the NDA and MOH/NTLP will be tracking AE prevalence, aDSM coverage and facility reporting through the indicators in Table 12 below.

Table 12: Indicators for reporting Active Drug Safety Monitoring and Management (aDSM)

	Indicator	Definition
1	Proportion of patients in each RR- TB regimen type reporting an AE during period of assessment	Numerator: Number of RR/MDR-TB, pre-XDR-TB and XDR-TB cases for each treatment regimen type who report an AE during period of assessment Denominator: Number of RR/MDR-TB, pre-XDR-TB and XDR-TB cases for each second line treatment regimen type during period of assessment
2	Proportion of ADEs reported to NDA during period of assessment	Numerator: Number of ADEs identified and reported to NDA during period of assessment Denominator: Number of ADEs identified ADEs during period of assessment
3	Proportion of initiating facilities that have submitted SAE reports during period of assessment	Numerator: Number of initiating facilities that submitted SAE reports during period of assessment Denominator: Number of initiating facilities included in aDSM during period of assessment (once active surveillance commences)

Table 11. Identification and management of adverse events.

Type of adverse event	Likely culprit drugs	Identification	Management
Anemia	LZD	Monthly monitoring of FBC and neutrophils is essential for persons on LZD	If moderate to severe (haemoglobin <8g/dL), initiate medical work up, treat underlying conditions, hold LZD until anemia resolves. A shorter course of LZD could be considered in less extensive disease. If on short regimen and FLQ susceptibility has been confirmed, can discontinue LZD.
Arthritis/ arthralgia	PZA, FLQ	Clinically defined	NSAIDS, physical therapy, massage, topical therapy, consider substitution for or stopping PZA if no improvement.
Depression or anxiety	Life circumstances, CS, high-dose INH	Clinically defined	Counselling, antidepressants, referral to psychiatric support, assess for suicidal/homicidal ideation, consideration of substitution for CS or High- dose INH AVOID USE OF TRICYCLIC ANTIDEPRESSANTS as these can prolong the QTc interval
Diarrhea	Other causes, PAS	Stools> 3 times per day, primarily liquid.	Assess for other causes, rehydration, assess electrolytes, consider drug substitution for PAS..
Electrolyte disturbances (Hypokalemia)	Amikacin, streptomycin, kanamycin, capreomycin	Regular blood testing (potassium)	If potassium is low (<3.5 mEq/L), replace with oral potassium and consider replacing magnesium as well if levels are low. If potassium < 2.5 m eq hospitalise and replace IV.
Hearing problems	Amikacin, streptomycin, kanamycin, capreomycin	Identified through audiology or problems in communication	Stop s the injectable drug if any hearing symptoms or if hearing loss > 26 dB (Grade 1), substituting with an alternative drug such as DLM. Injectable agents should not be used if hearing loss cannot be formally monitored by audiology.
Hepatotoxicity	PZA, ETO, BDQ, PAS, CFZ, DLM, Rifabutin, FLQ, Pa	Tender liver, visible jaundice	Stop all drugs if ALT/AST> 5 times the upper limit of normal or if> 3 X the ULN and patient has symptoms of drug-induced liver injury; Wait for liver function to return to normal < 3X ULN; Re-introduction of RR-TB drugs should be sequentially, every 5-7 days with monitoring of liver function before introducing the next drug. The least hepatotoxic drugs should be added first: CFZ-LZD-LFX/MFX- DLM and

			<p>can be given altogether to provide a backbone regimen. Then introduce the more hepatotoxic one by one every 5-7 days: BDQ, ETO, INH</p> <p>while monitoring liver function tests after each one to identify the responsible drug. PZA should not be re-started.</p>
Ichthyosis/ dry skin	CFZ	Clinical findings	Give emollient creams Monitor for skin and soft tissue infection
Leukopenia/ neutropenia	LZD	Monthly monitoring of FBC and neutrophils is essential for persons on LZD	If moderate to severe (< 1,000 cells/L), initiate medical work up, treat underlying conditions, hold LZD until leukopenia resolves. A shorter course of LZD could be considered in persons with non-severe disease
Nausea and vomiting	ETO, PAS	Clinically	<p>Common adverse event and may lead to non-adherence so intense management is necessary..</p> <p>Consider anti-emetic therapy.</p> <p>Consider separating the dosing of ETO and also of PAS from the other drugs by giving it in the evening; Consider reducing the dose of ETO and building the dose up to full dose over 2 weeks.</p> <p>With new onset nausea and vomiting, should also consider hepatotoxicity, hepatitis, pancreatitis, or increased intracranial pressure.</p>
Peripheral neuropathy	Isoniazid, LZD, Pa	Clinically	<p>Prevent by giving pyridoxine 50mg per day (0.5-1.0mg/ kg/day in children) with INH but dose should not exceed 100mg/day.</p> <p>If clinically evident neuropathy that interferes with patient's daily activities, stop LZD or Isoniazid and substitute with another effective agent (i.e. DLM).</p> <p>Consider the use of pre- gabalin or gabapentin to treat pain. AVOID USE OF TRICYCLIC</p> <p>ANTIDEPRESSANTS as these can prolong the QTc interval Can be challenging to monitor in young children, thus a shorter course of LZD could be considered in young children.</p>
Psychosis	CS, high-dose INH, FLQ	Clinically defined.	<p>Referral to psychiatric support, assess for suicidal/ homicidal ideation, consideration of substitution for CS or High-dose INH. AVOID THE USE OF HALOPERIDOL as this medication can prolong the QTc interval.</p>

QTc prolongation	BDQ, CFZ, DLM, MFX, LFX, Pa	Routine ECG monitoring at week 2 , week 4 then monthly for the first 6 months of treatment, with calculation of the QTc interval	Assess for symptoms Assess if taking other QTc prolonging drugs If symptomatic, consider admission for evaluation. If asymptomatic, and QTc>470msec but <500msec repeat ECG in 1 week., If> 500msec repeat ECG, check and correct electrolytes, check TSH, assess for other causes, consider holding RR-TB medications as detailed below.
Rash (severe), Steven-Johnson Syndrome (SJS)	Any drug, although some drugs are more likely to cause rash, such as PZA	Severe rash, peeling mucus membranes, patient unwell	Stop all drugs; Wait until clinical condition has improved; Re-introduce drugs after consultation with the National DR-TB Panel.
Renal impairment	Amikacin, streptomycin, capreomycin, kanamycin	Regular blood testing, symptoms of high potassium	If creatinine rises (> 1.3 times the upper limit of normal) or potassium is elevated, stop injectable, substitute with alternative drug.
Seizures	CS, high-dose INH, FLO, other causes	Clinically defined	Head CT, rule out other causes, anti-seizure medications, consideration of substitution for CS or High- dose INH
Skin hyperpigmentation	CFZ	Clinically	Counselling and support; plans for managing inadvertent disclosure
Dry Skin	CFZ	Clinically	Use Emollients like Vaseline. Avoid the sun
Dry Eyes	CFZ	Clinically	Lubricate the eyes using artificial tear drops. Steroids/ Antibiotics if inflamed or infected. If moderate to severe (<50,000 cells/L), initiate medical work up, treat underlying conditions, hold LZD until thrombocytopenia resolves. A shorter course of LZD could be considered in persons with non-severe disease
Thrombocytopenia	LZD	Monthly monitoring of FBC is essential for persons on LZD	Consider thyroxine supplementation if a. clinical hypothyroidism, or (b) raised TSH and decreased T4; b. Exclude other causes (e.g. Lithium, amiodarone, previous radioiodine therapy, pregnancy- associated thyroid dysfunction, and Hashimoto's disease) Initiate thyroxine if TSH > 10 IU/mL. Start with 50mcg daily and repeat TSH in one month. Monitor TSH every month and increase the dose by 25 mcg until TSH normalises (TSH < 5 miU/L).
Thyroid dysfunction	ETO, PAS	Regular blood testing (TSH) , clinical hypothyroidism or goitre	

			If raised TSH and normal T4 repeat test in 1 month. Thyroid dysfunction resolves upon discontinuation of the cause agent. Hormone replacement must continue at least 2 to 3 months after completed DR-TB treatment.
Visual problems	EMB, LZD	Regular (i.e. baseline and monthly) testing of visual acuity (with Snellen chart or age appropriate measure including papillary responses and “fixate and follow” response in children < 2 years of age and symbol charts in children ages 3-5 years).	Stop EMB and/or LZD (and do not re-introduce), refer the patient to ophthalmologist for further evaluation and management.

Often, alterations in dosing schedule or order can help mitigate some adverse effects such as gastrointestinal intolerance or fatigue/trouble concentrating. However, management often requires the use of ancillary medications to eliminate or lessen the adverse effects, and therefore, a stock of ancillary medications should be available for health care providers to prescribe to patients. Table 9.4 provides a list of indications and commonly used medications for the management of common adverse reactions.

Table 9.4 Commonly used ancillary medications

Adapted from the WHO Companion Handbook to the WHO Guidelines for the Programmatic Management of DR-TB, 2014

Indication	Medication
Nausea, vomiting, upset stomach	Metoclopramide, dimenhydrinate, prochlorperazine, promethazine, bismuth subsalicylate
Heartburn, acid indigestion, sour stomach, ulcer	H2-blockers (ranitidine, cimetidine, famotidine, etc.), proton pump inhibitors (omeprazole, lansoprazole, etc.) NOTE: Avoid antacids as they can decrease absorption of fluoroquinolone
Oral candidiasis	Fluconazole, clotrimazole lozenges, nystatin suspension
Diarrhea	Loperamide
Depression	Selective serotonin reuptake inhibitors (fluoxetine, sertraline), tricyclic antidepressants (amitriptyline)
Severe anxiety	Lorazepam, diazepam
Insomnia	Dimenhydrinate
Psychosis	Haloperidol, thorazine, risperidone (also include stocks of benzotropine or biperiden to prevent extrapyramidal effects)
Seizures	Phenytoin, carbamazepine, valproic acid, phenobarbital
Prophylaxis of neurological	Pyridoxine (vitamin B6) The recommended dose is 50 mg for every 250 mg of Cycloserine prescribed, not to exceed 150–200 mg daily (dosing is less well defined for other drugs, but generally 100 mg)

complications of Cycloserine, Linezolid, Ethionamide, high-dose Isoniazid.	
Peripheral neuropathy	Amitriptyline, gabapentin
Vestibular symptoms	Meclizine, dimenhydrinate, prochlorperazine, promethazine
Musculoskeletal pain, arthralgia, headaches	Ibuprofen, paracetamol, codeine
Cutaneous reactions, itching	Hydrocortisone cream, calamine, Caladryl lotions
Systemic hypersensitivity reactions	Antihistamines (diphenhydramine, chlorpheniramine, dimenhydrinate), corticosteroids (prednisone, dexamethasone)
Bronchospasm	Inhaled beta-agonists (salbutamol, albuterol, etc.), inhaled corticosteroids (beclomethasone, etc.), oral steroids (prednisolone, prednisone), injectable steroids (dexamethasone, methylprednisolone)
Hypothyroidism	Levothyroxine
Electrolyte wasting	Potassium, magnesium, and calcium replacement therapy (oral and intravenous formulations)

Summary

The timely and intensive monitoring for and management of adverse effects caused by second-line anti-TB drugs is an essential DR-TB program activity. Poor management of adverse effects increases the risk of default or irregular adherence to treatment and may result in death or permanent morbidity. Patients experiencing adverse effects should be referred to health care providers who have experience in treating them.

Chapter 10: Managing DR-TB through patient-centred care

Any patient with presumptive or diagnosed DR-TB should be provided with high-quality, patient-centred care, as outlined in both the International Standards for Tuberculosis Care and the Patients' Charter for Tuberculosis Care. A patient-centred care approach identifies certain rights and responsibilities of the provider, patient, family, and community. It facilitates mutual collaboration to achieve TB cure with dignity.

General considerations

The programmatic management of DR-TB is extremely challenging even in the best of circumstances. Achieving a successful outcome requires:

Coordination and collaboration from a multi-disciplinary team of health professionals

Commitment from the patient to complete a long course of treatment, often involving difficult adverse effects

A supportive environment of mutual respect and consideration drawing upon the strengths of family and community

Certain basic steps should be taken to ensure joint commitment by both the patient and health provider. Some steps involve changing attitudes, perceptions, and behaviours, while others may require refining existing management practices and service delivery systems.

Understanding patient-centred care

Patient-centred care provides the basis for building better patient-provider relations, and can contribute to improved adherence, reduced stigmatization, and better treatment outcomes. It also sends a message to the wider affected community that DR-TB can be successfully treated within a dignified framework of mutual respect, thus facilitating early patient finding and community participation.

Patient Education – During all phases of care, patients should be provided with appropriate and understandable information about the disease and its treatment. An informed patient can better assist health workers in their work of caring for patients.

Peer Support Groups – Information sharing sessions involving expert patients and trained health workers can benefit patients by providing important information about the disease, its treatment, and tips about managing common side effects. These sessions can also inform providers about risk factors for default and other warning signs that can affect treatment outcome. These discussion sessions should be facilitated through two-way communications, mutually deciding on interventions for problem solving.

Dignity from day one

Individuals with presumptive DR-TB should begin what may be a long march towards a cure in a manner to encourage their willing participation. From the first consultation or examination, the patient should be accorded the understanding of innocence, that it is not the fault of the person that bacteria are resistant to certain drugs. Offering solidarity and compassion initially, instead of reproach,

will begin the process in a healthy way, which the patient will remember during the many months of treatment that follow.

Social support

The socioeconomic impact of DR-TB on patients and their families can be devastating. Delays in diagnosis can lead to physical debilitation and inability to work. Extended isolation during the patient's infectious period and long treatment duration (minimum 20 months or more) restrict work options for patients as well.

As part of the patient's baseline evaluations before commencing treatment, an assessment of the means, needs, and financial resources of the patient should be conducted. Areas of need identified during this assessment should be addressed to ensure sufficient social support to enable completion of DR-TB treatment. The social support assessment for patients with DR-TB should examine four specific areas: informational, emotional, community, and material support needs.

Informational support

Patients should be counselled and educated in their local language as soon as they are diagnosed with DR-TB, and this counselling and education should continue throughout treatment. The patient's knowledge and beliefs about DR-TB should be assessed.

Information to cover with patients and family members:

- TB and DR-TB disease and how it is transmitted.
- Household infection control measures early during treatment
- Treatment duration, potential side effects, and management
- DOT as the standard of care for medication administration
- Essential monitoring for adverse effects and for assessing response to treatment.
- Rights and responsibilities as a DR-TB patient
- Rights and responsibilities of the patient's health care team
- Potential role and support that may be available from family and community.
- Who to contact in case of an emergency (e.g., severe reaction or worsening symptoms)

Providing adequate information to patients about the disease and treatment is a basis for reaching good treatment outcomes and is a key element of the Stop TB Strategy under component 5, "Empowering People with TB and Communities". See also Chapter 8, box 8.1, for more detailed information to cover with the patient prior to initiating second-line anti-TB treatment.

Emotional support

Patients on second-line treatment for DR-TB will need encouragement from start to finish to successfully completing the long course of treatment. Considerable stigma is attached to the disease and this may interfere with adherence to therapy. In addition, the long nature of DR-TB treatment combined with the side effects of the drugs may contribute to depression, anxiety, and further difficulty with treatment adherence. Providing emotional support to patients may increase the likelihood of adherence to therapy.

Hospitals managing DR-TB patients should identify a staff member who will serve as the focal person for developing patient-centred care approaches. This individual could help to identify expert patients (peer supporters) who may be willing to encourage and support other DR-TB patients. In this way, a social support network can develop within the clinical facility; such a network can play an essential role in galvanizing adherence, preventing default, and reducing stigma.

In the same way, peer counselling at the community level has been shown to be highly effective in TB in several communities, and it is a key element in scaling-up the response to HIV. MDR-TB cured patients (“Community Champions :) can be identified and trained to function as peer supporters. These “champion-counsellors” can be assigned to a patient from diagnosis through to cure, and can serve as both friend and peer-educator. From the patient’s perspective, having this companion available greatly reduces the psychological burden of the long treatment.

A patient support group facilitated by a trained counsellor, social worker, or facilitator can create an opportunity for DR-TB patients to share problems they are struggling with during different stages of their treatment. Through sharing common challenges and ways of coping, patients can draw encouragement and support from each other.

Community support

Community health care workers play an important role in fostering patient-centred care approaches within communities. Their attitudes and interpersonal skills can support achievement of positive treatment outcomes. Patients are less likely to default on treatment if satisfied with the way they are treated as human beings, and this echoes throughout the wider affected community. Furthermore, it is commonly understood among patients that stigma, like water, flows downward, not upward from the bottom. Thus, health care workers can play a leading role in diminishing stigma by viewing the patient-provider relationship with an appreciation of the challenges each other faces, and viewing the process to cure DR-TB as a joint endeavour.

Information to cover with patients and family members:

Community health workers should be trained appropriately in communicating and interacting positively with both patients and families.

1. Early involvement of the DTLS and sub-county health workers in patient care is necessary, especially for patients transferred to follow-up health centres

Material support

Socioeconomic problems (e.g., hunger, homelessness, unemployment, family responsibilities) must be addressed to enable patients to adhere to DR-TB treatment and to reduce the impact that the disease and treatment have on the patient's family and quality of life. These challenges can be successfully mitigated through socioeconomic interventions. Professional social workers should be used to assess the need for such socioeconomic interventions and monitor their delivery.

Communicating care

Information to cover with patients and family members:

- Tailor material support to the individual needs of the patient and family dependents (e.g., cover school fees for DR-TB patient's dependent children while patient is unable to work)
- Although food packages and transport support may be useful to alleviate some of the difficulties, providing a minimum support package (e.g., rent, business grants for vulnerable patients) may be a worthy investment to ensure adherence and willing participation
- Priority should be given to provide enablers that address barriers that would otherwise be insurmountable for patients (e.g., communicate with employers to ensure DR-TB patients retain their jobs while hospitalized for treatment initiation)
- Involve organizations (NGOs, CBOs, FBOs) that may be able to assist in providing socioeconomic support (e.g., skills training to equip DR-TB patients with skills that can support their reintegration into the community during treatment and following completion)

Although implementing patient-centred quality care will often require resources to scale up programmatic infrastructure and services, part of the process requires simple adjustments in the attitudes and language of the health providers.

Health staffs who seek to manage DR-TB should appreciate the fundamental human resistance to being "controlled." When talking to patients, family, and community members, health workers should avoid the term "TB control" and use "TB care" instead. This seemingly small change in language speaks volumes to the people who must struggle to "win" the challenge of a long and difficult treatment. The word "prevention" is also seen to be more user-friendly to patients, their families, and communities. Prevention language can help engage family and community participation in supporting patients through DR-TB treatment.

Health workers should adopt methods of communicating "with" patients. This means having dialogue with patients and their families, in a manner that builds a positive partnership towards successful treatment completion, hence cure (communicating care).

For patients with literacy limitations, efforts should be undertaken to provide audio or visual supports, such as information by recorded cassette or graphic illustrations. Staff acting as the focal person for patient-centred care and peer supporters can also play an important role as communicators.

Civil society

The involvement of civil society (e.g., patient support groups, NGOs, CBOs, FBOs) in various aspects of the programmatic management of DR-TB is strongly recommended. These organizations can assist through diverse, and important, actions, including:

- Providing social support services
- Referring individuals with signs and symptoms of TB (case finding)
- Prevention campaigns and community sensitization
- Advocating for greater resources for local services

DR-TB is a problem for the affected community, and welcoming the participation of and building working relations with civil society organizations not only brings new resources to confront the problem, but can also serve as a dynamic link between patient and care provider (see also Chapter 8).

Conclusion

Successful management of DR-TB requires putting the patient at the centre of a comprehensive program of care, which includes allowing them to exercise their rights. This, in turn, enables patients to fulfil their responsibilities and assist in the treatment success. The process of adopting the patient-centred care approach is essential for both good program management practices and for scaling up the response to the growing threat of DR-TB

Chapter 11:

Management of DR-TB in children and Adolescents

Unlike adults who acquire DR-TB from prior exposure to TB treatment, DR-TB in children mainly results from transmission of resistant TB strains from adults with whom they are in close contact (primary resistance). The clinical presentation of DR-TB in children is similar to that of drug-susceptible TB. Bacteriological confirmation of MDR/RR-TB disease in younger children is relatively uncommon, and the decision to treat for MDR/RR-TB may rely on clinical signs and symptoms, radiological findings and significant exposure to someone with microbiologically confirmed MDR/RR-TB. In children without microbiological confirmation of TB disease or Rifampicin resistance, the choice of regimen relies partly on the drug-resistance pattern of the isolate obtained from the most likely index case. (primary resistance). The clinical presentation of DR-TB in children is similar to that of drug-susceptible TB.

When to suspect MDR-TB in children

Children with the following situations are at risk of DR-TB and should be evaluated as such:

- A child who is a close contact of a known MDR-TB patient
- A child who is a close contact of a suspected MDR-TB patient, such as a case of treatment failure, retreatment (relapse, loss to follow up), or recent death from TB
- A child with confirmed TB who is still bacteriologically positive after five months of appropriate treatment with first line anti-TB medications (Treatment failure)
- A child who is not responding to first-line anti-TB drugs at two months despite adherence (e.g., failure to gain weight, persistent fevers, failure to regain activity, CXR with radiological worsening)
- A child previously treated for TB presents with recurrence of TB disease

Diagnosis

Just as in drug-susceptible TB, a diagnosis of DR-TB should follow a careful clinical evaluation including detailed history taking (assess for risks mentioned above), clinical examination, and laboratory confirmation.

History and clinical exam

Transmission of DR-TB to a child commonly results from exposure to an infectious adult or adolescent in his/her close environment, often within the immediate household. TB infection can progress rapidly to active TB disease, particularly in young children (less than five years of age) and those with weakened immune systems. For infants, the time between infection and disease can be as short as a few weeks; therefore, the initiation of contact tracing for newly diagnosed pulmonary DR-TB patients should be prioritized when it is known that young children live in the household (see Chapter 15 for further information on contact investigation). In the absence of known contact, the following findings should alert the clinician to consider TB in the differential diagnosis:

Symptom evaluation

For children with symptomatic disease, the most frequent symptoms are chronic and unremitting cough, fever, and weight loss. Ask about and assess for the following in all children being evaluated for DR-TB:

- **Persistent cough:** Ask how long the cough has been present. A cough that is not improving and has been present for two to three weeks or more is suggestive of TB.
- **Persistent fever:** Persistent fever for two weeks after common causes such as malaria or pneumonia, have been excluded.
- **Weight loss or failure to thrive:** Commonly, children with active TB will have poor weight gain, may lose weight, or become malnourished. Always ask about weight loss and measure the child's height and weight and plot it on a growth chart. MUAC should also be checked and referral provided for nutritional support when baseline malnutrition is present.
- **Fatigue, reduced playfulness, less active:** Ask if these have been present since the onset of above symptoms.

Chest x-ray

Chest radiography remains an important tool for diagnosing pulmonary TB in children who are sputum smear-negative, Xpert MTB/RIF negative, TB culture-negative, or who cannot produce sputum. The following abnormalities on CXR are suggestive of active TB in a child:

- Enlarged hilar or mediastinal lymph nodes and opacification in the lung tissue
- Miliary pattern
- Cavitation (tends to occur in older children)
- Pleural or pericardial effusion (though seen on CXR, are forms of extrapulmonary TB that tend to occur in older children)
- Finding of marked abnormality on CXR in a child with no signs of respiratory distress (no fast breathing or chest in-drawing)

Laboratory confirmation

Microbiological confirmation should always be attempted; at least two good quality specimens should be collected and sent separately for Xpert MTB/RIF ultra and mycobacterial culture and DST. Many children will not have microbiological confirmation due to paucibacillary disease or some forms of extra-pulmonary disease

- Most children over six years of age can be coached into producing a sputum sample, or may successfully produce a sample after sputum induction.
- For younger children and infants, a gastric aspirate or induced sputum or stool sample can be obtained (see annex 6 for guidance on obtaining gastric aspirate or induced sputum for TB) and/or nasopharyngeal aspirate or stool for TB, which may yield sufficient organisms to enable culture and DST.

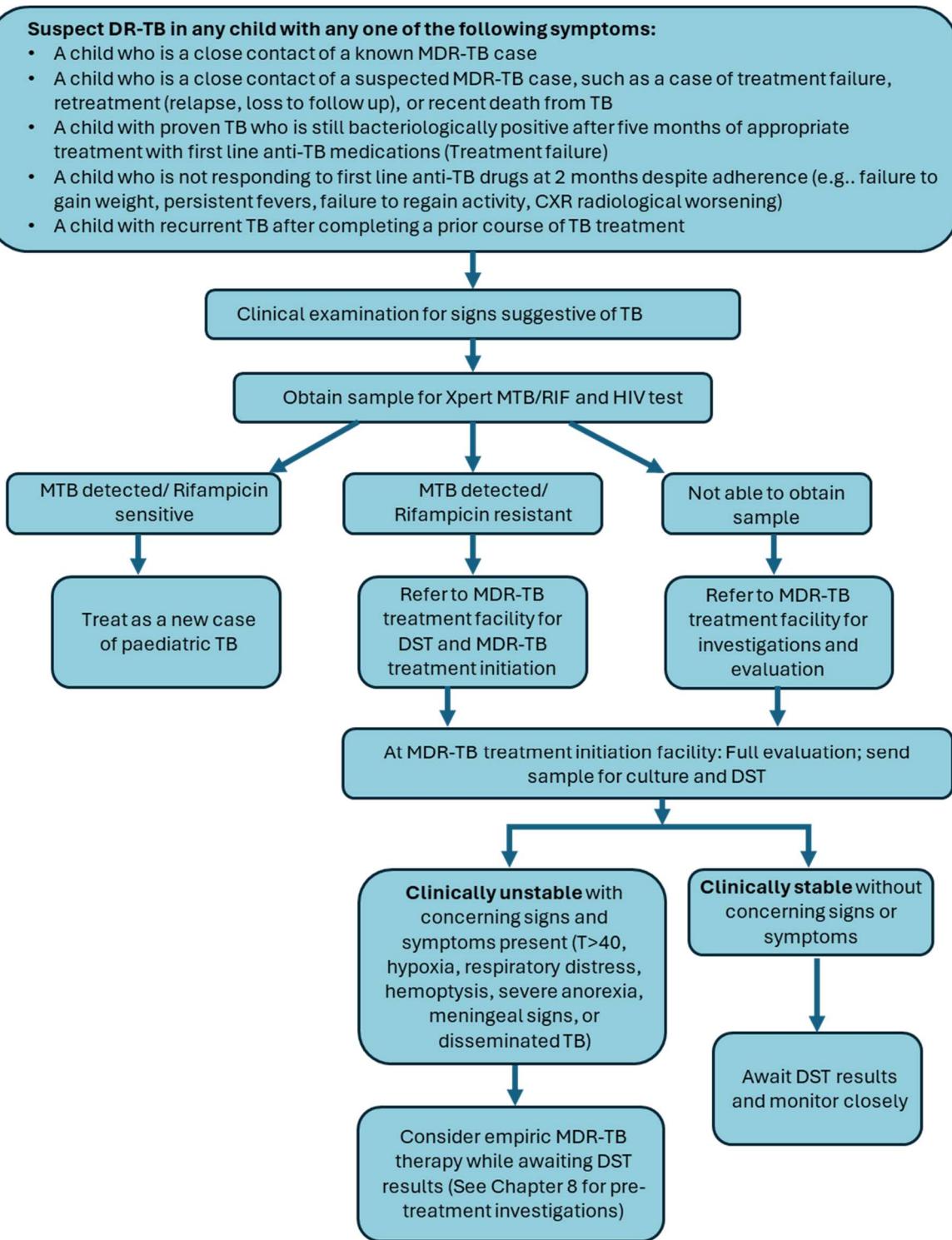
Whenever possible, a sputum specimen should be collected and sent for Xpert MTB/RIF as the initial diagnostic test. The algorithm shown in figure 11.1 below provides guidance to health workers on how to handle children who are at risk of MDR-TB.

The majority of children with MDR-TB will be diagnosed clinically. In addition to the challenge of obtaining a specimen for testing, children are more likely to have extrapulmonary disease or pulmonary TB with low bacillary loads. In children with suspected extrapulmonary disease, collection of a specimen from the affected site may enable confirmation of TB diagnosis and drug susceptibility testing. Examples might include:

- Fine needle aspiration or biopsy from peripheral lymphadenitis
- Pus from draining sinus
- Cerebral spinal fluid in cases of TB meningitis
- Pleural or pericardial fluid if effusions are present
- Stool for TB

Figure 11.1 Algorithm for diagnosis of MDR-TB in children

Adapted from the DR-TB Sentinel Project Field Guide, 2012



Treating MDR-TB in children under 15 years of age

The treatment of MDR-TB in children is guided by the same principles used for adults.

In March 2022, the World Health Organization (WHO) issued updated guidelines for management of tuberculosis in children and young adolescents, which recommend that Delamanid and Bedaquiline can be used in all age groups, along with updated dosing guidance for all TB drugs [13]. Therefore, previous age restrictions on use of these medications in children are no longer relevant.

The WHO-recommended 6-month regimens, BPAL and BPALM, only apply to non-pregnant persons aged 15 years and older, as Pretomanid safety has not been established during pregnancy or in children. However, most children with RR-TB do not require a long 18-month treatment regimen to achieve cure of the disease. Based on the results of the SHINE trial, which focused on treatment shortening for drug susceptible (DS)-TB in children with non-severe disease [14], the WHO now recommends a total duration of only 4 months of treatment in children with smear negative, non-severe DS-TB. A similar approach to shorter treatment has been adopted by clinicians experienced in the management of paediatric RR-TB, and children with non-severe RR-TB disease can be successfully treated with a shorter duration of treatment than is usually recommended for adults. However, close monitoring for recurrent disease, for at least 12 months following completion of treatment, is considered essential for these children.

Local availability of paediatric formulations of TB drugs also determine which regimens are feasible in Uganda, particularly among young children for whom the adult drug formulations are typically poorly tolerated and difficult to administer. Wherever possible, paediatric formulations should be considered for young children and infants or for those who struggle to swallow adult formulation tablets. Paediatric formulations including Delamanid 25 mg dispersible tablet, Levofloxacin 100 mg dispersible tablet, Bedaquiline 20 mg dispersible tablet, Clofazimine 50 mg dispersible tablet are available in Uganda through a donation programme

Therefore, it is important to emphasize the general principles of RR-TB treatment and regimen design in this age group, as there is no standardized treatment regimen for all children under 15 years of age. Composition and duration of treatment regimens may vary between individual children and is based on resistance profile of the organism as well as site and severity of the RR-TB disease. The following recommendations for treatment of RR-TB in children under 15 years of age follows the approach outlined in the Sentinel Guide for Management of MDR-TB in Children [15], considering available programmatic paediatric data, extrapolated efficacy data from adult clinical trials, expert paediatric opinion and the latest WHO recommendations.

Principles of RR-TB treatment in children under 15 years of age

The general approach to paediatric RR-TB regimen design is the same for children of all ages (0- 14 years).

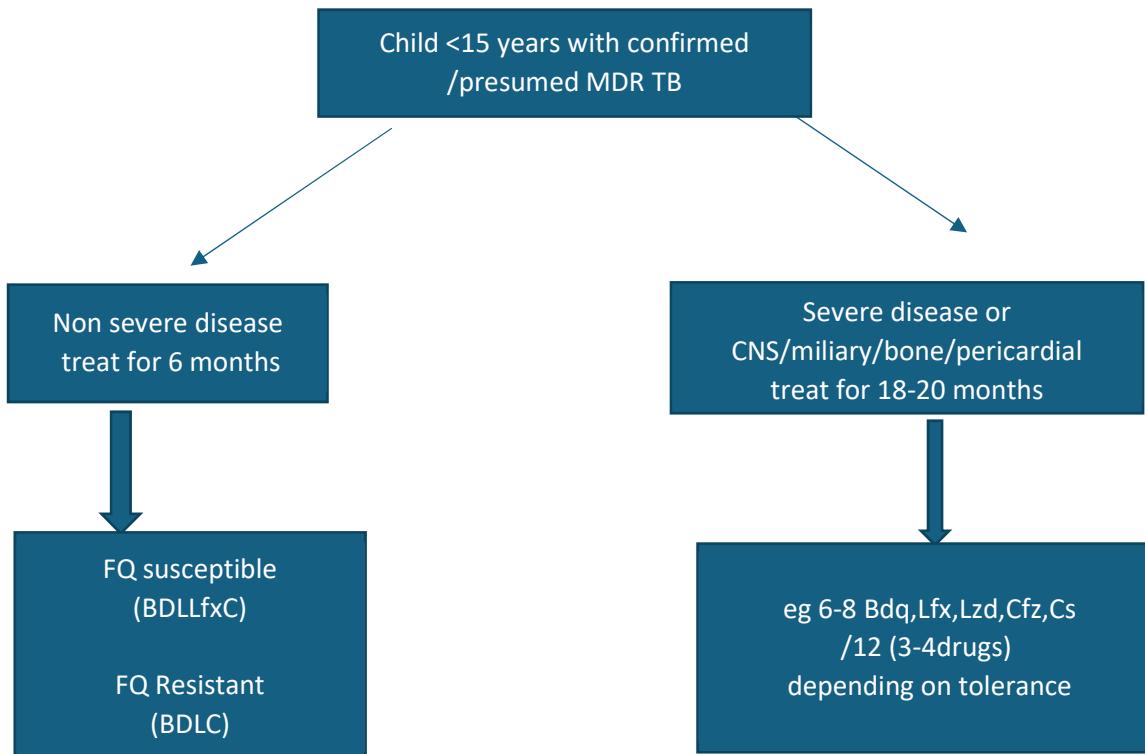
The following principles of treatment are recommended:

In designing treatment regimens for children, the following factors must be considered:

- RR-TB regimen composition is based on the current WHO drug grouping (see Section 2.7). The regimen should include at least 4 drugs considered to be effective, with possible addition of a 5th drug if needed (severe disease, site of infection, or only ≤ 1 group A drug in regimen). Priority must be given to WHO Group A & B drugs and Delamanid; using more than five of these drugs in cases of MDR/pre-XDR-TB may add to the toxicity profile of the regimen without necessarily improving treatment efficacy.
- All-oral regimens must be prioritised (except for rescue regimens where options are limited, and injectable agents are available and likely to be effective).
- Disease severity, i.e., severe versus non-severe disease (based on definitions from the SHINE trial and the WHO 2022 definition for children < 15 years, see Table 3.21 below) – children with severe disease may require five drugs in their regimen initially.
- Site of disease – children with more extensive disease (particularly CNS, miliary, bone or pericardial disease) are likely to require five drugs in their regimen. Treatment of RR-TB meningitis should be guided by the medicines' ability to cross the blood-brain barrier.

- Drug resistance profile – treatment should be based on the DST pattern of the M. tuberculosis strain from the most likely source case if the child does not have an M. tuberculosis isolate of his/her own with DST results. Following up on all DST results for samples from the child and the source patient is therefore essential (with special consideration for checking resistance to the fluoroquinolones, BDQ, CFZ, and LZD)
- Toxicity and tolerability of drugs, and feasibility of adverse effect monitoring – specific medicines, e.g. LZD, may not be a feasible option for some children in view of the considerable risk of toxicity and stringent monitoring requirements (e.g., frequent blood draws to check full blood count (FBC) and differential white cell count) which may be challenging for some children and their families.
- Availability of paediatric formulations – some medicines (e.g., 100 mg CFZ capsules) cannot be easily administered to young children and may have to be substituted with other effective medicines.
 - Drug dosing is based on the child's weight (and age in infants), in accordance with the 2022 WHO RR-TB treatment guidelines [13] – see Annexure 1 for drug dosing in children weighing under 30 kg and for those weighing over 30 kg. Doses of drugs must be modified as children gain or lose weight over the weight band thresholds.
 - Child-friendly formulations of TB medications should be used whenever possible, if acceptable to the child and caregiver. If paediatric formulations are not available, then extemporaneous preparations may be required. These can be prepared daily by cutting or crushing the tablets, and mixing with water, pap, yoghurt or milk. This should be done in consultation with a pharmacist or a pharmacist's assistant.
 - Persons at primary healthcare facilities dispensing the TB medicines to the child/caregiver for administration at home should carefully check the doses of each medicine and that the correct formulation is used, especially if there is more than formulation for a specific medicine (e.g., a 100mg dispersible Levofloxacin tablet is different in mg strength from
 - the 250 mg adult Levofloxacin formulation). Adherence support for the child and the caregivers is essential to ensure optimal outcomes in children. Because preparation and administration of the medications used to treat RR-TB can be complicated, intensive support should be provided to the family throughout treatment.
 - Very young children (under the age of 5 years) with any form of RR-TB disease should be treated under the guidance of a clinician with experience in the management of paediatric RR-TB. This also applies for children with XDR-TB (i.e., MDR plus resistance to fluoroquinolone and resistance to Bedaquiline and/or Linezolid), as individualized longer regimens and in-patient management may be necessary.
 - Treatment duration in children is usually based on site and severity of disease (see Table 3.21 below), as well as extent of drug resistance. Good outcomes have been reported among adults following treatment with 3 or 4 drugs for 6 months (BPaL and BPaLM). Results from the SHINE trial [14] indicate that children with non-severe DS-TB disease can be successfully treated with a shorter (4-month) duration with effective drugs. Therefore, children with non-severe RR-TB disease are also likely to be successfully treated with shorter (6-month) regimens containing at least 4 effective drugs; those with more severe disease are likely to require longer treatment for 9 or 12 months (see Figure 3.1). Clinicians may also extend treatment for individuals in cases of slow or inadequate clinical, radiological and/or microbiological treatment response. There is no specified intensive or continuation phase for paediatric RR-TB regimens and most drugs should be continued throughout treatment, if possible, unless limited by toxicity or intolerance. Bedaquiline and Delamanid are mostly used for 6 months only but can be extended to 9 months in consultation with an expert/specialist. Linezolid is often only tolerated for up to 2 months; however, some children may benefit from Linezolid for the full duration of treatment if tolerated.

Approach to treatment of MDR TB among children <15 years:



Note:

- a. Additional resistance to Bdq, Lzd, Cfz or intolerance to above regimens: use salvage regimen individually designed based on hierarchical grouping of SLDs.
- b. Consider Lzd for only 2 months. Monitor FBC 2 weekly in the first month, then monthly for Myelosuppression, peripheral neuropathy and optic neuritis.

Table : Severe versus non severe disease in children <15 years

Severe versus non-severe of TB disease classification in children <15 years	
Non -Severe TB disease in children <15 Years	severe TB disease in children <15 Years
1 Peripheral lymphadenopathy	CXR: bilateral disease (consolidation, infiltrates, or cavities)
2 CXR-unilateral disease (consolidations, infiltrates in <1 lobe, without cavities)	Mediastinal lymph nodes causing airways compression
3 Small simple pleural effusions	Extrapulmonary forms of disease other than peripheral LNs or simple pleural effusions
4 Mediastinal lymph nodes without airways compression	

Regimen:**Individualised regimens for children under the age of 15 years**

The below provides individualized regimens and duration of treatment that would be appropriate in various situations based on drug susceptibility test pattern and site / severity of disease

Table of individualised regimens for children<15 yrs

DRUG SUSCEPTIBILITY PATTERN	SEVERITY OF DISEASE	REGIMENT AND DURATION	COMMENTS
RR TB that is not FQ resistant and not CNS, osteoarticular or spinal TB	Non-severe	6 BDLLFx C preferred over 9 months regimens and ≥18-month regimen	LZD for first 2 months only. If LZD withdrawn in first 2 months consult Expert panel to replace LZD with a group C drug
	Severe	Individualised ≥18 months regimen	Use Linezolid as long as tolerated and feasible
RR that is resistant to FQ	Non-severe	6 BDLC	
	Severe	Individualised ≥18 months regimen	
RR CNS disease or spinal TB	severe	Individualised ≥18-month regimen eg 6-8 Bdq, Lfx, Lzd, Cfz, Cs/12 Bdq, Lfx, CfZ/ cS	Use Linezolid as long as tolerated and feasible Continuation phase with 3 or 4 drugs depending on tolerance
RR with confirmed or probable resistance to Bdq, Cfz, Lzd	Severe	Individualised salvage regimen	Expert panel guidance

- Monitor for Lzd toxicity particularly bone marrow suppression Hb <8g/dl, Neutrophils <0.75 particularly bone marrow suppression (Hb < 8 g/dL neutrophils < 0.75 x 10⁹ /L and/or platelets <50 x 10⁹ /L) which may require frequent blood draws, and the ability to monitor for peripheral neuropathy/optic neuritis.
- Pyridoxine needs to be prescribed in patients receiving Cycloserine and High dose Isoniazid

Alternative Regimen

The WHO suggests that the 9-month all-oral regimen (4–6 Bdq(6 m)-Lfx/Mfx-Cfz-Z-E-Hh-Eto or Lzd(2 m)/5 Lfx/MfxCfz-Z-E) may be offered to children and adults without bacteriological confirmation of TB or resistance patterns but who require MDR/RR TB treatment based on clinical signs and symptoms (including radiological findings) and history of contact with someone with confirmed MDR/RR TB. However, the benefits of this regimen for a child with MDR/RR-TB should be weighed. Bedaquiline is relatively well tolerated and easy to administer to children; adult formulation Bedaquiline tablets suspended in water have been shown to have the same bioavailability as tablets swallowed whole. This regimen, however, was not adopted by Uganda because of the high pill burden and the difficulties of administering each of the seven drugs in this regimen, particularly if child-friendly formulations of the drugs are not available

Annex 1: Weight Based dosing of Medicines used in MDR TB regimens, adults and children (page 93 of (World Health Organisation 2022 operational handbook)

11.5. Management of RR-TB in children above 15 years of age and non-pregnant adults**11.5.1 Key points regarding the (BPALM/BPAL) regimen**

- Most People with a diagnosis of RR-TB will be eligible to receive the 6BPALM
- The short regimen contains the following medication Bedaquiline, Pretomanid and Linezolid with or without additional Moxifloxacin for 6 months. This can be extended to 9 months at the clinician's discretion.
- If fluoroquinolone resistance is detected, BPAL can be used without Moxifloxacin for 9 months.

- Prior use of Bedaquiline, Delamanid or Pretomanid and Linezolid (>1 month) is not a contraindication for BPaLM. However, resistance to these agents must be excluded. If found to be resistant to Bedaquiline, Linezolid, Delamanid or Pretomanid the client is no longer eligible for BPaL-L regimen.
- Severe extra-pulmonary RR-TB meningitis, pericarditis, osteoarticular, abdominal or disseminated/miliary disease may not be treated with BPaL-L.
- Linezolid dose is 600 mg/daily. This should be given for at least 8 weeks. In the case of toxicity or intolerance the dose can be interrupted (while other medicines in the regimen are continued) for a total of a maximum of 8 weeks throughout the treatment course.
- There is no specified intensive or continuation phase for these regimens and all drugs should be continued throughout treatment, if possible, unless limited by toxicity or intolerance
- HIV-positive patients with any CD4 count, regardless of ART status, qualify to receive the short RR-TB regimen if they meet the inclusion criteria listed above.
- Pyridoxine does not need to be prescribed in patients receiving BPaLM/BPaL

Other considerations:

- When a liquid formulation is available, it should be used for patients weighing less than 15 kg.
- Most second-line TB drugs do not have pediatric liquid or tablet formulations, so it may be necessary to split the pills to approximate the correct dose. To split tablets into 3/4 tab, it is suggested to split the tablet in half and then split a half tablet in half. Discard the smaller quarter tablet and give the child a half tablet plus the remaining quarter tablet.
- For Cycloserine, the capsule can be opened and dissolved in 10 ml of water. When using this method, ensure the contents of the capsule are fully dissolved in the water before drawing up the desired amount in a syringe for administration.
- Doses of most anti-TB drugs have not been established for children below 5 kg, but often the potential benefit outweighs the risks. In such cases, the child should be dosed as close to the middle of the mg/kg range as possible.

Tips for administering medication to small children and infants:

- Mix crushed or cut tablets into a small amount of soft food.
 - Give a small amount of soft food (without medicine) before the medication dose, between spoonfuls, and after the dose.
 - Some powder will suspend into liquid well and can pass through a syringe. A dispenser with a bigger opening, such as a medicine dropper, is better than a syringe and will deliver a greater proportion of the drug without sticking in the syringe.
 - If mixing the medicine in soft food before delivery, use only a small amount. The child will not want to take many spoonfuls of the drug. Many children will prefer the crushed pills or granules delivered with soft food (e.g., banana).
 - Alternatively, a thin layer of soft vehicle can be placed on the spoon, the powder or pill fragment layered on top, followed by another layer of soft vehicle (making a medication “sandwich” and preventing drug taste in the vehicle itself).
- Immediately after the medication is given, offer some food the child likes or a drink to clear away any taste of the medication. Breastfeed infants after administering medication dose to help clear away any taste of the medication.
- Give lots of praise and encouragement to the child.

Monitoring the child and Adolescent DR-TB patient

The main objective of monitoring is to:

- Ascertain response to medicines
- Ensure timely adjustment of doses
- Have early detection and limitation of adverse events

In children, microbiological monitoring of the response to treatment is often difficult (for the same reasons it is difficult to obtain a microbiological diagnosis). This makes it particularly challenging to diagnose treatment failure in children. Persistent abnormalities on chest radiographs do not necessarily signify a lack of improvement. In children, weight loss or, more commonly, failure to gain weight adequately in the presence of proper nutritional intake is of particular concern and often one of the first (or only) signs of treatment failure.

Clinical monitoring

- **Weight and height:** Weight and height should be taken at each visit and used to track gains in nutritional status. Medicine doses should be adjusted for any change in weight bands. Evaluate for treatment failure in a child with failure to gain weight or weight loss while on treatment and with adequate nutritional intake.
- **MUAC:** Measure MUAC at each visit to track gains in nutritional status.
- **Symptoms:** Resolution of symptoms including cough, fevers, and change in weight should be evaluated and documented at each visit in the Second-line TB Treatment Card.
- **Adherence:** Adherence is often a challenge, particularly in adolescents and especially during the continuation phase. Counselling of the child and family about the importance of completing the full course of anti-TB treatment is important and should be reinforced regularly. See Chapter 8 for more information on strategies for ensuring adherence to treatment, and Chapter 10 for information on patient-centred care and support.
- **Adverse effects:** Adverse effects are common in patients taking second-line anti-TB regimens. For information on monitoring and managing adverse effects, see Chapter 9.
- Record adverse effects in the Second-line TB Treatment Card. Additionally, the Suspected Adverse Drug Reaction Reporting Form (Form 17) should be completed.
- **Laboratory monitoring:** See monitoring schedule in table 11.2. Arrange for sputum induction or gastric aspirate (see annex 6) for children, especially in younger children who are unable to produce sputum on their own.
- **Radiologic monitoring:** See monitoring schedule in table 11.2.

Adjvant therapy

Corticosteroids: As in drug-susceptible TB, corticosteroids are indicated in MDR-TB meningitis, MDR-TB pericarditis, and patients with severe respiratory distress.

Pyridoxine (Vitamin B6): Pyridoxine should be given to all patients on Cycloserine (as well as Linezolid, high-dose Isoniazid, Ethionamide/prothionamide, and Terizidone) to prevent neurological side effects. The optimal prophylactic dose of pyridoxine for children has not been established. However, 1–2 mg/kg/day has been recommended in some references, with a usual range of 10–50 mg/day for paediatric patients at risk for neurological sequelae.

Supportive management

Nutrition: A child with MDR-TB requires more calories than a healthy child of the same age given the wasting that occurs with TB and extra energy expended fighting the infection. The primary caregivers should be educated on the need to provide a balanced diet using affordable, locally available foods. Failure to improve nutritional status in a child with MDR-TB is an early indicator that the MDR-TB may not be under control.

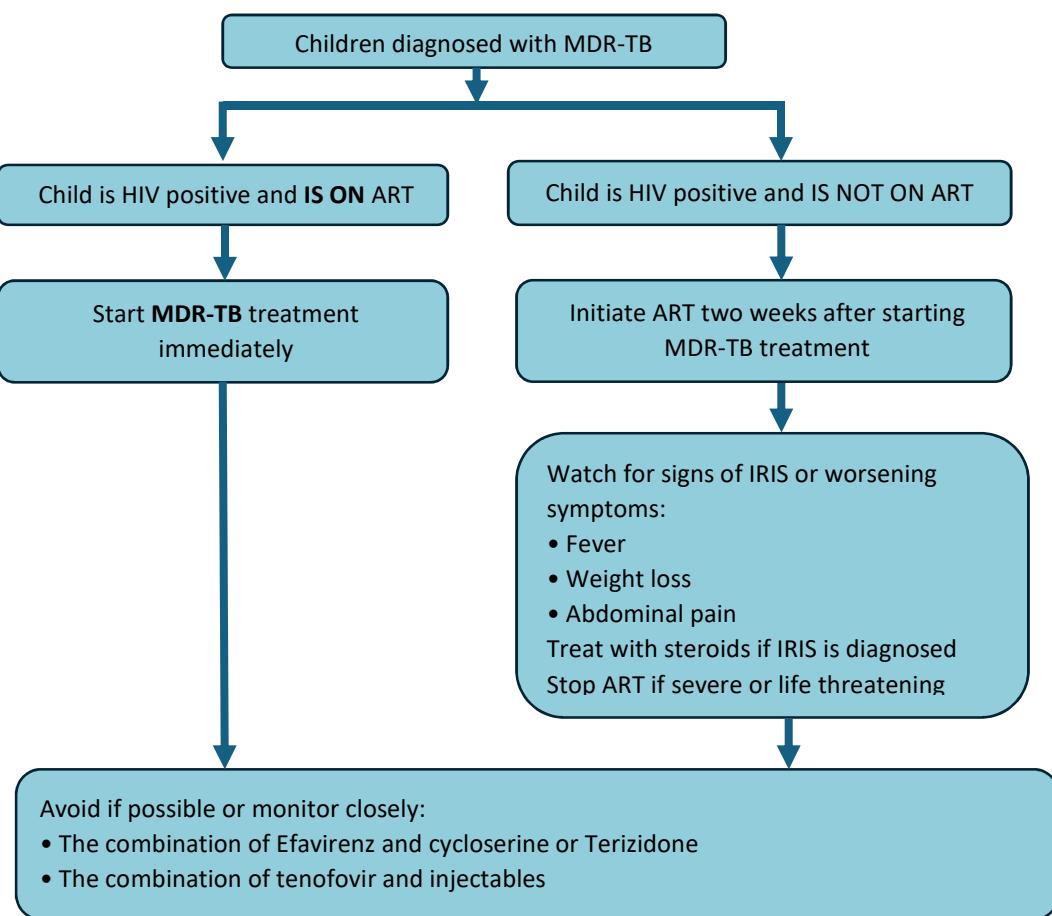
Family support: The family members need to be counselled and supported psychologically given the long duration of treatment and unfavourable treatment outcomes associated with non-adherence to treatment.

Management of MDR-TB/HIV coinfection in children

All children with presumed or confirmed DR-TB should be screened for HIV infection as part of their initial pre-treatment investigations. All patients diagnosed with TB and HIV should be initiated on ART irrespective of WHO stage and CD4 counts. ART should be started within two to eight weeks of anti-TB treatment initiation in HIV-infected children with presumed or confirmed MDR-TB. Children who are on MDR-TB treatment and ART should be monitored for drug-drug interactions and signs of IRIS. In addition to early ART initiation, all co-infected child TB cases should receive cotrimoxazole prophylaxis and pyridoxine supplementation.

Figure 11.2 Algorithm for management of children on treatment for MDR-TB and HIV

Adapted from the DR-TB Sentinel Project; Field Guide, 2012



11.4 Management of child contacts of MDR-TB diagnosed cases

The MOH in Uganda does not recommend any preventive therapy for contacts of patients diagnosed with MDR-TB. Therefore, Isoniazid should not be used as preventive therapy for MDR-TB.

- All contacts of patients with diagnosed MDR-TB should be screened for symptoms and signs of TB (see also Chapter 15).
- All symptomatic children should be referred to a health facility for further evaluation including history taking, clinical examination, and investigations (see section 11.2).
- Asymptomatic children should be evaluated for signs and symptoms of TB at 3 months following the index patient's diagnosis of DR-TB, then at 6, 12, 18, and 24 months. If a child develops signs and symptoms of TB during the follow-up period, he/she should be referred to a health facility for further evaluation.

Summary

Early diagnosis coupled with strong social support, parental and family counselling, and a close relationship with the health care providers may help improve outcomes in children. Weight is an important clinical marker to monitor regularly in a child, both for determining proper medication dosage as the child gains weight and for assessing response to treatment. Weight loss and/or failure to gain weight may be early indicators of treatment failure in a child who is receiving proper nutrition.

Chapter 12:

DR-TB in patients with HIV

This chapter illustrates where the management of DR-TB differs in the presence of known or suspected HIV infection and provides guidance on the management of HIV-related DR-TB.

Key recommendations of this chapter:

- Use Xpert MTB/RIF for rapid diagnosis of TB and RR-TB
- Provide chronic HIV care (including provision of cotrimoxazole preventive therapy [CPT], nutritional support, viral load monitoring and coordination of care with HIV provider)
- Introduce ART promptly in DR-TB/HIV patients
- Ensure effective infection control
- Watch for overlapping toxicity with ART and DR-TB therapy

General considerations

Uganda has a high prevalence of HIV (5.5%) (Uganda AIDS Indicator Survey Dec 2021) among the general population and approximately 37.3% were HIV infected among the 2020 MDR TB cohort of 445 patients. HIV is a powerful risk factor for all forms of TB and presents a significant challenge for the prevention, diagnosis, and treatment of DR-TB.

There are high mortality rates among HIV-infected patients with DR-TB, and alarming mortality rates in patients co-infected with XDR-TB and HIV compared to non-infected individuals. Early diagnosis of DR-TB and HIV, prompt treatment with adequate regimens, sound patient support, and strong infection control measures are all essential components in the management of DR-TB in PLHIV. Prompt initiation of ART in addition to treatment of DR-TB improves outcomes of DR-TB in individuals infected with HIV.

The principles for treatment of active TB disease in HIV-infected patients remain the same as those for HIV-uninfected patients. In addition, the following also apply:

- All HIV-infected patients with diagnosed active TB should be started on TB treatment immediately.
- All HIV-infected patients with diagnosed active TB should be treated with ART.
- All TB patients co-infected with HIV should be offered ART irrespective of CD4 cell count no later than eight weeks and within two weeks of starting TB treatment.
- In HIV-infected patients with TB meningitis, ART should be deferred until two months after initiation of TB treatment.
- In all HIV-infected pregnant women with active TB, ART should be started as early as feasible, both for maternal health and for prevention of mother-to-child transmission of HIV.

It is important to anticipate and to manage the immune reconstitution inflammatory syndrome that is likely to occur with earlier initiation of ART in patients with TB or other opportunistic infections. Particular attention should be paid to the interaction between antiretroviral (ARV) and anti-TB drugs (see section 12.4.3).

- For newly diagnosed HIV infection at the beginning or during RR-TB treatment, patients should be started on the recommended first line ART regimen in Uganda (TDF/3TC/DTG in fixed dose combination) and have a CD4 count done.
- For patients already on ART and starting RR-TB treatment with BDQ, ART options include dolutegravir, nevirapine, or atazanavir/ritonavir depending on ART history and current viral load results. If there are no CD4 or viral load results within 6 months of RR-TB treatment initiation, persons newly diagnosed with RR-TB who are HIV positive on ART should have a CD4 count and viral load tested at the start of RR-TB treatment. The treatment initiating center should notify the central public health laboratory (CPHL) of the indication of any repeat viral loads to avoid sample rejection.
- If the viral load at start of RR-TB treatment is suppressed ($VL < 1000$ regardless of plasma or dried blood spot sample), continue current regimen
- If the viral load at start of RR-TB treatment is not suppressed ($VL > 1000$ regardless of sample type), the ART regimen will need modification based on current regimen and ART history
- For patients diagnosed with RR-TB who have defaulted ART and are currently not on ART, restart on TDF/3TC/DTG and monitor viral load per national HIV guidelines (viral load at 6 months, 1 year, then yearly)
- AZT also causes toxicity to the bone marrow and substitution should be considered in persons on LZD (Table 10)
- For persons not yet on ART, antiretroviral therapy is recommended for all patients with HIV and DR-TB requiring second-line anti-TB drugs, irrespective of CD4 cell count, as early as possible (within the first 8 weeks, with special attention to initiate ART within 2 weeks when the CD4 count is < 50) following initiation of RR-TB treatment.
- Co-trimoxazole therapy should also be provided regardless of CD4 count, and can be used with LZD and monitoring for anemia
- Identification and management of other co-morbid opportunistic infections is required for persons with RR-TB and HIV
- Additional counselling support will be needed to help people with RR-TB and HIV be successful in their treatment; key points to address in counselling include increase pill burden, and warning signs of opportunistic infections that require presentation to care

Table . Guidance for modification of ART regimens for adults during RR-TB treatment

Current ART regimen	Proposed ART regimen	
TDF or ABC/3TC/EFV	Viral load < 1000 copies/mL (plasma or dried blood spot sample) <ol style="list-style-type: none"> 1. Persons should remain on ABC if they have a contraindication to TDF 2. TDF/3TC/DTG 3. TDF/3TC/LPV/r (or ATZ/r) 4. TDF/3TC/NVP 	Viral load > 1000 copies/mL (plasma or dried blood spot sample) AZT/3TC/DTG*(ensure HBsAg is negative prior to discontinuing TDF)
TDF or ABC/3TC/NVP	Keep on same ART regimen	Review previous VL and history. If history of treatment interruptions, poor adherence, or clinically un- well/CD4 <50 , switch NVP to LPV/r (or ATZ/r)* If no change is made, address adherence and re-check VL in 3 months. If VL > 1000 , switch to AZ-T/3TC/DTG*
TDF or ABC or AZ-T/3TC/LPV/r or DTG	Change AZT to TDF (or ABC if renal impairment, Amikacin use), keep rest of regimen unchanged	Review and address reason for high VL. Refer to HIV guideline guidance on genotyping if VL remains elevated*

*Clinicians should consult the National DR-TB Panel or AIDS Control Program for management of complex RR-TB/HIV co-infected patients.

DR-TB and HIV collaborative activities

The following list is based on the WHO and national policy on TB/HIV collaborative activities and has been adapted to be specifically applicable to DR-TB.

- **Perform provider-initiated HIV testing and counselling in all patients with presumptive and diagnosed DR-TB.** HIV testing for all patients with presumptive TB or diagnosed with TB (both drug-susceptible and drug-resistant) is recommended and can be done at the same time the sputum is sent for Xpert MTB/RIF. This approach is preferred over referring patients elsewhere for HIV testing and counselling, as there is less opportunity for patient drop out. It is important to educate and counsel patients on HIV prevention.
- **Include HIV testing in anti-TB drug resistance surveillance:** Incorporating HIV testing with anti-TB drug resistance surveillance offers an opportunity to expand HIV testing and improve understanding of the relationship between HIV and DR-TB at the population level. It also provides critically important individual benefits to PLHIV, including better access to testing, early case detection, and rapid initiation of treatment for DR-TB. Unlinked anonymous testing for HIV is not recommended in Uganda because the results cannot be traced back to individuals who need HIV care and treatment.
- **Use wMRDTs in PLHIV with presumptive TB (see Chapter 4).** This rapid DST method is more sensitive in detecting TB cases than smear microscopy and it detects mutations associated with Rifampicin resistance, thus shortening the time to diagnosis of MDR-TB. WHO recommends Xpert MTB/RIF as the initial diagnostic test in settings with high prevalence of HIV-associated TB and/or MDR-TB. The national TB diagnostic algorithms were revised so that PLHIV presumed to have TB can access Xpert MTB/RIF as the initial TB diagnostic test.
- **Use mycobacterial cultures in PLHIV with presumptive TB.** TB in HIV-infected patients is more likely to be smear-negative or extrapulmonary. Smear microscopy alone has significant limitations and is insufficient to reliably diagnose a significant proportion of HIV co-infected patients. When Xpert MTB/RIF is negative but TB is still suspected (or if Xpert MTB/RIF is not available), mycobacterial cultures of the sputum or other fluids and tissues are recommended to help in the diagnosis of sputum smear-negative and extrapulmonary TB in PLHIV. Mycobacterial cultures are also important for phenotypic DST and testing for resistance to other first- and second-line drugs.
- **Perform DST and GeneXpert XDR Assay at the start of TB therapy.** Unrecognized DR-TB carries a high risk of mortality in PL HIV. Prompt initiation of appropriate anti-TB treatment can reduce mortality among PLHIV who also have DR-TB. Because unrecognized MDR- and XDR- TB are associated with such high mortality in HIV-infected patients, DST or rapid DST for all TB/HIV co-infected patients is recommended. At present, Xpert MTB/RIF is the initial test of choice and if Rifampicin resistance has been detected, patients should be referred to DR-TB treatment initiation facilities to start second-line TB treatment. A baseline sputum sample should be sent to NTRL for culture plus GeneXpert XDR Assay before the start of treatment to detect fluoroquinolone, Isoniazid, Ethionamide and Aminoglycoside resistance
- **Consider empirical treatment with second-line anti-TB drugs.** Patients at high-risk for MDR-TB should be started on an empiric MDR regimen, even before laboratory confirmation of MDR-TB (see Chapter 6 for standard MDR-TB regimen). This strategy can be applied to all patients regardless of HIV status but is especially important in HIV-positive patients.
- **Initiate ART promptly in DR-TB HIV patients.** ART should be started promptly in all HIV-infected patients with MDR-TB, regardless of CD4 cell count. Second-line anti- TB drugs should be initiated first, followed by ART as soon as second-line anti-TB regimen is tolerated. Generally, this should be within the first two weeks of initiating MDR-TB treatment.
- **Provide CPT for patients with active TB and HIV.** Provide CPT to all patients with HIV according to national guidelines on collaborative TB/HIV activities. CPT is not known to interact significantly with any of the second-line anti-TB medications. There are, however, overlapping toxicities between ART, second-line

anti-TB drugs, and cotrimoxazole (see table 12.2), and co-infected DR-TB patients should be monitored closely.

- **Implement sound patient follow-up and monitoring system.** Care providers should be familiar with the clinical aspects of the treatment of both DR-TB and HIV. There should be close monitoring of potential adverse effects, including psychiatric assessments and nutritional status (see Chapter 9 for monitoring for adverse effects and table 12.2 for overlapping toxicities of ART with second-line anti-TB drugs). There should also be periodic assessments of therapeutic response to both infections (see Chapter 9 for information on monitoring response to second-line anti-TB treatment).
- **Implement additional nutritional and socioeconomic support.** Patients with DR-TB and HIV may suffer from severe wasting, diarrheal diseases, and malabsorption syndromes. The NTLP recommends that a comprehensive package of prevention, diagnosis, treatment, and care interventions (continuum of care) should be provided to all PLHIV. Additionally, treatment with second-line anti-TB medications may result in adverse effects that affect treatment adherence and require more frequent visits to health facilities. Wherever possible, patients with DR-TB living with HIV should be offered socioeconomic and nutritional support.
- **Provide integrated TB and HIV services (one stop shop model).** Co-treatment of DR-TB and HIV is particularly difficult due to the long duration, heavy pill burden, and numerous side effects of these diseases. These patients should receive treatment for TB and HIV—and any other comorbidities—at the same place and time, as possible. Ensure DOT for both ART and DR-TB treatment. This improves adherence and quality of care, as a single care team understands and manages all of the needs of the patient (see below).
- **Ensure effective TB infection control.** Strict application of TB infection control measures is mandatory. Implementation of the Uganda infection control policy recommendations can greatly decrease the risk of DR-TB transmission and protect HIV-infected patients (see also Chapter 16).
- **Involve key stakeholders in DR-TB and HIV activities.** Effective coordinating bodies that operate at all levels, and which include the participation of all stakeholders—from HIV and TB programs, civil society organizations, patients, and communities—are feasible and ensure broad commitment and ownership. These key stakeholders should be involved in the planning and monitoring of DR-TB and HIV activities and programs.

Clinical features and diagnosis of DR-TB in PLHIV

The diagnosis of TB (including MDR-TB and XDR-TB) in PLHIV is more difficult and may be confused with other pulmonary or systemic infections. The presentation is more likely to be extrapulmonary or sputum smear-negative than in HIV-uninfected TB patients, especially as immunosuppression advances. This can result in misdiagnosis or delays in diagnosis, and hence, delays in initiation of treatment. In turn, these delays lead to higher morbidity and mortality.

To make a diagnosis of TB and DR-TB in persons with HIV coinfection, all available clinical investigations should be utilized, including molecular tests (i.e., Xpert MTB/RIF for prompt diagnosis of RR-TB [see Chapter 4, figure 4.1]), culture, and radiography. For patients with advanced HIV disease, molecular tests and/or mycobacterial culture of other fluids (e.g., blood, pleural fluid, ascitic fluid, cerebrospinal fluid, and bone-marrow aspirates) and histopathology (e.g., lymph node biopsies) may be helpful in diagnosis. Remember, a prompt diagnosis and initiation of appropriate treatment can be lifesaving to a patient with HIV, and, for those found to have RR-TB, appropriate treatment will halt the spread of DR-TB in the community.

Concomitant treatment of DR-TB and HIV

The treatment of DR-TB in patients with HIV is very similar to that in patients without HIV and is described in Chapter 6, with the following exceptions:

- ART plays a crucial role, as mortality in MDR-TB/HIV without the use of ART is extremely high. Some observational cohort studies have shown that ART improves survival of HIV-infected MDR-TB patients⁵

- and XDR-TB patients.⁶ However, DR-TB patients often have advanced clinical disease that puts them at increased risk of IRIS, in addition to frequent drug interactions and co-toxicities if ART is started early.
- Drug-drug interactions with second-line anti-TB drugs can occur (see section 12.4.3).
 - 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, result in a high incidence of side effects. Some toxicities are common to both anti-TB treatment and ART, which may result in increased rates of adverse events (see table 12.2).
 - Monitoring needs to be more intense for both response to therapy and adverse effects.
 - IRIS may complicate therapy (see section 12.4.6).

ART in patients with DR-TB

ART in HIV-infected patients with TB improves survival for both drug-resistant and susceptible disease. Cohorts of patients treated for MDR- and XDR-TB without the benefit of ART have experienced mortality rates often greater than 90%. Undue delay in the start of ART could result in significant risk of HIV-related death among patients with advanced disease.

For drug-susceptible TB, it is now well established through randomized clinical trials that earlier initiation of ART is associated with decreased mortality. This decrease in mortality is more pronounced among patients with a CD4 count less than 50 cells/mm³. Similar randomized clinical trials have not been performed with DR-TB patients, but clinical experience supports the strategy of early ART initiation in MDR- and XDR-TB patients. Furthermore, evidence reviewed from 10 studies by WHO to assess patient treatment outcomes when ART and second-line anti-TB drugs were used together resulted in the following recommendation:

ART is recommended for all patients with HIV and DR-TB requiring second-line anti-TB drugs, irrespective of CD4 cell-count, as early as possible (within the first eight weeks) following initiation of anti-TB treatment (strong recommendation/very low-quality evidence**).**

⁵ Palacios E, Franke M, Munoz M, Hurtado R, Dallman R, Chalco K, et al. HIV-positive patients treated for multidrug-resistant tuberculosis: clinical outcomes in the HAART era. *IJSTD* 2012; 16:348–354.

⁶ Dheda K, Shean K, Zumla A, Badri M, Streicher EM, Page-Shipp L, et al. Early treatment outcomes and HIV status of patients with extensively drug-resistant tuberculosis in South Africa: a retrospective cohort study. *Lancet* 2010; 375:1798–1807.

Initiating ART as soon as possible with second-line anti-TB drugs may be challenging because many second-line anti-TB drugs can produce serious side effects, but a well-trained clinical team can usually initiate ART within two to four weeks of starting MDR-TB treatment.

DR-TB in patients already receiving ART

There are two issues to consider in patients who are diagnosed with DR-TB while on ART:

1. Whether modification of ART is needed due to drug-drug interactions or to decrease the potential of overlapping toxicities. These concerns are discussed in section 12.4.3.
2. Whether the presentation of active DR-TB in a patient on ART constitutes ART failure. Refer to the National ART guidelines for guidance on assessment for ART failure. If ART failure has been diagnosed, it is **not** recommended to begin a new second-line ART regimen at the same time as initiation of a DR-TB regimen. Instead, continue the present ART regimen and switch to the second-line ART regimen two to eight weeks after the start of DR-TB treatment.

Important drug-drug interactions in the treatment of HIV and DR-TB

It is important to consider drug–drug interactions when administering TB and HIV medications in combination.

- **The antiretroviral drug Efavirenz** induces metabolism of Bedaquiline, so its co-administration with Bedaquiline may result in reduced Bedaquiline exposure and loss of activity; therefore, co-administration is to be avoided.
- **Efavirenz** also reduces Pretomanid exposures significantly (26); therefore, an alternative antiretroviral agent (potentially dolutegravir, although there is currently insufficient evidence for this) should be used if Pretomanid or the BPaLM/BPaL regimen is considered.
- **Ritonavir** may increase Bedaquiline exposure, which could potentially increase the risk of Bedaquiline-related adverse reactions (27); however, increased risk has not been noted in studies administering both drugs concurrently (27–29), including in the current ZeNix trial.
- Individuals who are prescribed both Bedaquiline and ritonavir should be monitored closely for adverse events, including QTc prolongation.

Finally, regimens including zidovudine should be avoided, if possible, because both zidovudine and Linezolid may cause peripheral nerve toxicity and are known to have myelosuppression cross-toxicity.

Potential drug toxicities and overlapping adverse effects in the treatment of HIV and DR-TB

There is limited evidence on the frequency and severity of toxicities and adverse events from ART and second-line anti-TB drugs. In general, HIV patients have a higher rate of adverse drug reactions to both TB and non-TB medications, and the risk of adverse drug reaction increases with the degree of immunosuppression. Identifying the source of adverse effects in patients receiving concomitant therapy for DR-TB and HIV is difficult. Many of the medications used to treat DR-TB and HIV have overlapping, or in some cases additive, toxicities. Often, it may not be possible to link side effects to a single medication, as the risk of resistance for ART precludes the typical medical challenge of stopping all medications and starting them one by one.

Adverse effects that are common to both ARV and anti-TB drugs are listed in table 12.2. When possible, avoid the use of agents with shared side effect profiles. Often, however, the benefit of using medications that have overlying toxicities outweighs the risk. Therefore, if two medications with overlapping toxicities are determined to be essential in a patient’s regimen, these guidelines recommend increased monitoring of adverse effects rather than disallowing a certain combination. See Chapter 9 and section 12.5.5 for monitoring of adverse effects in HIV-infected patients. Side effects that are common to both ARV and anti-TB drugs are listed in table 12.2. Table 12.2 is meant to alert the clinician to potentially overlapping and additive toxicities.

Table 12.2 Potential overlapping and additive toxicities of ART and anti-TB treatment

Toxicity	ARV agent*	Anti-TB agent	Comments
Skin rash	ABC, NVP, EFV, d4T and others	H, R, Z, PAS, Fluoroquinolones, and others	<p>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.</p> <p>Also consider cotrimoxazole as a cause of skin rash if the patient is receiving this medication.</p>

Peripheral neuropathy	d4T, ddI	Lzd, Cs, H, aminoglycosides Eto/Pto, E	Avoid use of d4T or ddI in combination with Cs or Lzd because of an increased risk of peripheral neuropathy. Generally, d4T and ddI are no longer recommended for use in Uganda due to their associated toxicities. If these agents must be used in combination and peripheral neuropathy does develop, replace ARVs with a less neurotoxic agent. Patients taking H, Cs, or Lzd should receive prophylactic pyridoxine.
CNS toxicity	EFV	Cs, H, Eto/Pto, FQ	EFV has a high rate of CNS side effects (dizziness, impaired concentration, insomnia, depersonalization, abnormal dreams, and confusion) in the first two to three 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 CNS 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, CNS toxoplasmosis, CNS TB, 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, d4T, 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 ARVs have been associated with abd. 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).

Toxicity	ARV agent*	Anti-TB agent	Comments
Pancreatitis	d4T, ddI	Lzd	Avoid use of these agents together. If an agent causes pancreatitis, suspend it permanently and do not use any of the potentially pancreatitis-producing ARVs (d4T or ddI) in the future. Also consider gallstones or excessive alcohol use as potential causes of pancreatitis.
Diarrhea	All protease inhibitors, ddI (buffered formulation)	Eto/Pto, PAS, FQ	Diarrhea is a common adverse effect. Also consider opportunistic infections as a cause of diarrhea, or <i>Clostridium difficile</i> (pseudomembranous colitis).
Hepatotoxicity	NVP, EFV, all protease inhibitors (RTV > others), all NRTIs	H, R, E, Z, Bdq, PAS, Eto/Pto, FQ	Also see Chapter 9 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. Consider cotrimoxazole as a cause of hepatotoxicity if the patient is receiving this medication. Rule out viral etiologies as cause of hepatitis (hepatitis A, B, C, and cytomegalovirus).
Lactic acidosis	d4T, ddI, AZT, 3TC	Lzd	If an agent has caused 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 high lactate 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, hypophosphatemia, hypouricemia, proteinuria, normoglycemic 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 (see Chapter 9 for recommended monitoring frequency). In the presence of renal insufficiency, ARVs and anti-TB medications need to have their doses adjusted (see Chapter 13).
Nephrolithiasis	IDV	None	No overlapping toxicities regarding nephrolithiasis have been documented between ART and anti-TB medications. Adequate hydration prevents nephrolithiasis in patients taking IDV. If nephrolithiasis develops while on IDV, substitute with another protease inhibitor.

Electrolyte disturbances	TDF (rare)	Cm, aminoglycosides	<p>Diarrhea and/or vomiting can contribute to electrolyte disturbances.</p> <p>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 (see Chapter 9).</p>
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Toxicity	ARV agent*	Anti-TB agent	Comments
Bone marrow suppression	AZT	Lzd, R, Rfb, H	<p>Monitor blood counts regularly (see Chapter 9). Replace AZT if bone marrow suppression develops.</p> <p>Consider suspending or decreasing the dose of Lzd.</p> <p>Consider cotrimoxazole as a cause if the patient is receiving this medication.</p> <p>Consider adding folinic acid supplements, especially if the patient is receiving cotrimoxazole.</p>
Optic neuritis	ddl	E, Eto/Pto (rare)	Suspend agent responsible for optic neuritis permanently and replace with an agent that does not cause optic neuritis.
Hyperlipidemia	Protease inhibitors, EFV	None	No overlapping toxicities regarding hyperlipidemia have been documented between ARVs and anti-TB drugs.
Lipodystrophy	NRTIs (d4T and ddl, especially)	None	No overlapping toxicities regarding lipodystrophy have been documented between ARVs and anti-TB drugs. Generally, d4T and ddl are no longer recommended for use in Uganda due to their associated toxicities.
Dysglycemia (disturbed blood sugar regulation)	Protease inhibitors	Gfx, Mxf, Lfx, Eto/Pto	<p>Protease inhibitors tend to cause insulin resistance and hyperglycemia.</p> <p>Eto/Pto tends to make insulin control in diabetics more difficult, and can result in hypoglycemia and poor glucose regulation.</p>
Hypothyroidism	D4T	Eto/Pto, PAS	<p>There is potential for overlying toxicity, but evidence is mixed.</p> <p>Several studies show subclinical hypothyroidism associated with some ARVs, particularly d4T.</p> <p>PAS and Eto/Pto, especially in combination, can commonly cause hypothyroidism (see Chapter 9 for monitoring and management).</p>
Arthralgia	Indinavir, other protease inhibitors	Z, Bdq	<p>Protease inhibitors can cause arthralgia and there have been case reports of more severe rheumatologic pathology.</p> <p>Arthralgia is very common with Z and has been reported as one of the most frequent adverse effects (>10%) in controlled clinical trials with Bdq.</p>

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 are sparse. The additive effects of combining ART and the known second-line anti-TB drugs with respect to QTc prolongation is not known.
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*Medications that are more strongly associated with the adverse effect appear in bold.

Note: ABC=abacavir, NVP=niverapine, EFV=Efavirenz, d4T=Stavudine, ddl=didanosin,

AZT=zidovudine, RTV=ritonavir, 3TC=lamivudine, TDF=tenofovir, IDV=indinavir

Monitoring of DR-TB and HIV therapy in co-infected patients

HIV treatment must be taken daily without exception to prevent the evolution of drug resistance. Since DOT is an important component of DR-TB therapy, HIV treatment should also be taken under DOT to promote adherence (see Chapter 8), which can be compromised due to large pill burden and numerous potential adverse effects that render taking ARVs more difficult.

The complexity of ART in conjunction with second-line anti-TB treatment, each with its own toxicity profiles that may be potentiated with concomitant therapy, demands rigorous clinical monitoring (See details in Chapter 9).

If the patient shows signs of TB treatment failure, the evaluation described in Chapter 14 is warranted. In addition, the ART regimen should be evaluated for possible treatment failure in such situations.

Given that the regimens together are particularly difficult to take, the stigma of both diseases can result in serious discrimination, and the risk of mortality is high, patients with HIV- associated DR-TB may require special socioeconomic, nutritional, and psychosocial support in order to successfully complete treatment.

Immune reconstitution inflammatory syndrome

IRIS has emerged as an important complication of ART. IRIS is relatively common in mild to moderate forms in patients with TB started on ART (seen in up to one third of patients in some studies); however, it is relatively rare in its severe forms. This syndrome can present as a paradoxical worsening of the patient's clinical status, often due to a previously subclinical and unrecognized opportunistic infection. These reactions may present as fever, enlarging lymph nodes, worsening pulmonary infiltrates, respiratory distress, or exacerbation of inflammatory changes at other sites, including the CNS. It generally presents within three months of the initiation of ART and is more common when CD4 cell count is low (less than 50 cells/mm³).

It is important to note that IRIS is a diagnosis of exclusion. Patients with advanced AIDS may show clinical deterioration for a number of other reasons. Consider the full differential diagnosis when evaluating the patient with suspected IRIS, including:

- Treatment failure due to non-adherence, drug resistance, or malabsorption (investigation to rule out this possibility should be done including collecting additional specimen for culture and DST)
- New opportunistic infections or previously subclinical infections that have been unmasked following immune reconstitution causing clinical worsening
- Malignancy
- The management of IRIS is complex and depends on the clinical status of the patient and the site and extent of involvement.
- In most cases, TB treatment and ART can and should be continued.
- Mild symptoms usually resolve over time and can often be managed with the use of non-steroidal inflammatory drugs.
- In situations with moderate to severe symptoms, the use of corticosteroids to suppress the immune response may be necessary (see Chapter 6 for dosing information).

XDR-TB and HIV

XDR-TB has been described in a number of countries, including settings with a high prevalence of HIV. Treatment strategies for XDR-TB are outlined in Chapter 6.

Implications of HIV for MDR-TB infection control

Delay in recognition of DR-TB, prolonged periods of infectiousness, crowded wards, and mixing TB and HIV patients all contribute to nosocomial transmission of DR-TB. These practices have contributed to DR-TB outbreaks that affect both HIV-infected and non-infected patients.

Implementation of adequate infection control precautions at health facilities significantly reduces nosocomial transmission. It is important that DR-TB/HIV patients are managed in the DR-TB unit for both diseases to minimize mixing at crowded HIV clinics. Staff managing DR-TB patients should receive the required training to offer quality HIV/TB services to the patients under their care. The HIV and TB clinics should collaborate to enable all diagnosed HIV/TB patients to have HIV care transferred to the TB clinic for the period the patient will be receiving anti-TB treatment. Patients can return to the HIV clinic after completion of the DR-TB treatment to continue HIV care services. At the community level, home-based measures such as separate living quarters, personal respiratory protection for visitors, and adequate ventilation are recommended. See details on infection control in Chapter 16.

Coordination of HIV and TB care: National level TB/HIV coordination committee

Coordination shall be through having a joint strategic plan to collaborate successfully and systematically in carrying out the recommended joint activities. The joint plan shall seek to diagnose TB in such patients, determine the drug susceptibility of the strain, and provide adequate and appropriate treatment and referral of patients infected with both HIV and DR-TB. Coordinated training activities shall focus on developing a group of providers in a specialized multidisciplinary team with adequate expertise in both areas. Communities and patients should be involved in program design from an early stage.

Facility level TB/HIV: Delivery of services should be integrated at all levels.

- It is recommended that DR-TB/HIV patients receive their care in the DR-TB clinic for both diseases.
- When a DR-TB/HIV co-infected patient is registered at the second-line treatment facility, efforts should be made to establish and link with the HIV treatment provider. The patient will be educated and an explanation of why it is necessary to get care for both diseases at the same time will be provided.
- The DR-TB care team should then access and provide ART and second-line TB treatment and monitor patients for both diseases as recommended.
- Health workers managing TB should be trained in HIV management and ART.
- In DR-TB/HIV, give FDCs for ART whenever possible to reduce pill burden for the DR-TB/HIV co-infected patients.

Conclusion

DR-TB in HIV-infected patients is highly lethal and a growing problem in many parts of the world. Improved case detection, timely and appropriate therapy, close clinical monitoring, management of adverse effects, and appropriate infection control measures are the essential components for successful prevention, control, and management of HIV-related DR-TB.

Chapter 13:

Treatment of DR-TB in special conditions and situations

This chapter describes the management of DR-TB in special conditions and situations, including pregnancy, breastfeeding, contraception, diabetes mellitus, renal insufficiency, liver disorders, seizure disorders, psychiatric disorders, and substance dependence. See Chapter 11 for DR-TB in paediatrics and Chapter 12 for DR-TB in HIV.

Pregnancy and Breastfeeding women

All female patients of childbearing age should be tested for pregnancy during the initial evaluation. Pregnancy is not a contraindication for treatment of active DR-TB, which poses great risks to the lives of both mother and foetus.

The dosing and safety data to support the optimal use of second-line TB medicines are generally sparse because pregnant and breastfeeding women are usually excluded from clinical trials and early access programs.

Pregnant patients should be carefully evaluated, taking into consideration the gestational age and severity of the DR-TB. The risks and benefits of treatment should be carefully considered, with the primary goal of cure; but smear conversion prior to birth is the initial goal of therapy to protect the health of the mother and child, both before and after birth. The following are some general guidelines.

- The benefits (to both parent and child) of providing effective MDR/RR-TB treatment to the parent far outweigh the potential risks posed to the foetus in-utero or the breastfed infant.
- **Start treatment of DR-TB in the second trimester or sooner if the condition of the patient is severe.** Since the majority of teratogenic effects occur in the first trimester, therapy may be delayed until the second trimester in stable, HIV-negative patients. The decision to postpone the start of treatment should be agreed upon by both patient and doctor after analysis of the risks and benefits and after discussion with the National DR-TB Expert Panel. The decision is based primarily on clinical judgment of signs/symptoms and severity/aggressiveness of the disease (usually reflected in extent of weight loss and lung affection during the previous weeks).
- **Treat with the individualised short treatment regime.** Treat with three or four oral second-line anti-TB drugs that are highly likely to be effective (see Chapter 6, box 6.1) against the infecting strain.
- **Linezolid:** Due to the physiological effects of pregnancy which lead to low haemoglobin (dilutional effect of increased blood volume), and higher risk of peripheral neuropathies, these might be exacerbated by Linezolid. Despite that, Linezolid should be considered in pregnant and breastfeeding patients who meet the eligibility criteria with closer monitoring.
- **Avoid injectable agents.** Aminoglycosides can be particularly toxic to the developing foetal ear. Because there is little experience or evidence for the use of capreomycin in pregnancy, the risks/benefits of its use should be discussed with the mother. Capreomycin may also carry a risk of ototoxicity, but it is the injectable drug of choice if an injectable agent cannot be avoided due to an immediate life-threatening situation due to MDR-TB. The option of using capreomycin thrice weekly from the start can be considered to decrease the drug exposure to the foetus.
- **Avoid Ethionamide.** Ethionamide can increase the risk of nausea and vomiting associated with pregnancy, and teratogenic effects have been observed in animal studies.
- Avoid Pretomanid; at this point in time, there is currently not safety data for Pretomanid in pregnancy therefore this drug should be avoided.

- Total treatment duration is the same as MDR-TB treatment (see Chapter 6).
- The child should receive a bacillus Calmette-Guérin (BCG) vaccine BCG at birth, as per national policy.

There is limited data on the safety and long-term use of fluoroquinolones, Cycloserine, PAS, and amoxicillin/clavulanate in pregnancy, but these are considered the drugs of choice for MDR-TB treatment in pregnancy.

If the injectable agent, Ethionamide/prothionamide or other drugs, were withheld because of pregnancy, they can be added back post-partum if needed to make a more complete regimen. There may not be a clear transition from the intensive phase or continuation phase, and it may be decided to use the injectable agent for three to six months post-partum, even when that occurs in the middle of treatment. Alternatively, if the patient is doing well and past the normal six-month period for the injectable agent, one may consider not using the injectable agent. Any addition of drugs should consider the principle of never adding a single drug to a failing regimen.

Care providers must also pay particular attention to seamless continuity of care between antenatal and TB services.

A breastfeeding mother with active DR-TB should receive a full course of anti-TB treatment. Timely and properly applied chemotherapy is the best way to prevent transmission of tubercle bacilli to her baby.

- In lactating mothers on treatment, most anti-TB drugs will be found in the breast milk in concentrations that would equal only a small fraction of the therapeutic dose used in an infant. Any effects of such exposure on infants during the full course of DR-TB treatment have not been established. Consider formula feeding only if affordable, feasible, accessible, safe, and sustainable. HIV-positive mothers should be encouraged to exclusively breastfeed for six months, and up to one year with complimentary feeds. For more details on infant feeding options for HIV-positive mothers, refer to Uganda ART guidelines.
- The mother and her baby should not be completely separated. However, if the mother is sputum smear-positive, the care of the infant should be left to family members until she becomes sputum smear-negative, if this is feasible. When the mother and infant are together, this common time should be spent in well-ventilated areas or outdoors. The mother should use a surgical mask until she becomes sputum smear-negative.

Contraception

Birth control is strongly recommended for all non-pregnant, sexually active women receiving therapy for DR-TB because of the potential consequences for both mother and foetus resulting from DR-TB treatment during pregnancy.

There is no contraindication for the use of oral contraceptives with non-rifamycin-containing regimens. Patients who vomit directly after taking an oral contraceptive can be at risk of decreased absorption of the drug, and therefore of decreased efficacy. These patients should be advised to take their contraceptives separate from times when they may experience vomiting caused by the anti-TB treatment. Patients who vomit at any time directly after, or within the first two hours after, taking a contraceptive tablet should use a barrier method of contraception until a full month of the contraceptive tablets can be tolerated.

For patients with mono- and poly-resistant TB that is susceptible to Rifampicin, the use of Rifampicin interacts with contraceptive drugs, resulting in decreased efficacy of protection against pregnancy. A woman on oral contraception who is receiving Rifampicin treatment may choose between two

options: use of an oral contraceptive pill containing higher estrogen (50 µg), following consultation with a physician; or use of another form of contraception.

Condoms are a reasonable solution for patients who do not want to take additional pills and/or when protection against sexually transmitted diseases is also needed. Patients should be aware that condom use is not as effective as contraceptive pills, especially when not used correctly. Medroxyprogesterone intramuscular injections, and other methods of contraception, can also be considered.

Patients with anaemia

Patients with TB commonly have anaemia of chronic disease, and treatment with an effective drug regimen (even one that includes Linezolid) may lead to improvement or resolution of the anaemia once the disease is properly treated. Many patients with TB also suffer with nutritional deficiencies, and low haemoglobin may also be a result of iron deficiency and low iron stores. This deficiency may resolve naturally once effective TB treatment (even including Linezolid) leads to resolution of TB symptoms and improvement in the patient's diet and appetite. Extended use (≥ 2 weeks) of Linezolid has been associated with reversible myelosuppression. Therefore, the Linezolid-containing 9-month regimen must not be offered to patients with a pretreatment serum haemoglobin below 8 g/dL that cannot be rapidly corrected (i.e. with blood transfusions) before starting MDR/RR-TB treatment. Similarly, owing to the morbidity associated with severe neutropenia and thrombocytopenia, the Linezolid-containing 9-month regimen is not suitable in patients with neutrophils below $0.75 \times 10^9/L$ (or 750/mm³) or platelets below $150 \times 10^9/L$ (or 50 000/mm³) before starting treatment. Some patients respond well to an initial blood transfusion that raises their haemoglobin above 8 g/ dL and allows them to at least start a Linezolid-containing regimen – Linezolid will not necessarily cause myelosuppression in patients with baseline anaemia, although a baseline haemoglobin below 10.5 g/dL has been reported as a risk factor for Linezolid-induced anaemia (54). It is not uncommon for haemoglobin to drop again shortly after blood transfusion in a person with untreated chronic TB disease, but the temporary increase in haemoglobin may allow enough time for a Linezolid-containing regimen to be effective in treating the TB disease, and the patient's haemoglobin is likely to improve as the disease is brought under control.

Blood transfusions may not be a lasting solution in situations where haemoglobin drops significantly from baseline because of Linezolid toxicity when Linezolid is continued. Although blood transfusions may help to reverse anaemia following withdrawal of Linezolid, they may not resolve Linezolid-induced myelosuppression with ongoing exposure to the drug. Therefore, if Linezolid toxicity leads to a drop in haemoglobin below 8 g/dL during the first 2 months of treatment, Linezolid should be withdrawn and the regimen switched appropriately. More research is needed on the role of iron supplementation to treat anaemia during MDR/RR-TB treatment; however, oral supplementation of iron is often not well tolerated and is not immediately effective at the start of treatment, at a time when the pill burden can be overwhelming and the risk of multiple drug side-effects is high.

Diabetes mellitus

Patients with both diabetes and MDR-TB are at risk of poor outcomes and diabetic care must be managed closely throughout the treatment of DR-TB. The presence of diabetes mellitus may potentiate the adverse effects of anti-TB drugs, especially renal dysfunction, gastrointestinal upset, and peripheral neuropathy. Precautions must be taken; however, none of the anti-TB drugs are contraindicated.

- Management considerations for DR-TB patients with diabetes include:
- All patients with DR-TB should be screened for diabetes as part of the initial evaluation.

- The 9-month all-oral regimen may be used to treat MDR/RR TB in patients with DM.
- Type 2 diabetes is associated with several liver disorders therefore it is prudent to monitor closely for hepatotoxicity among these patients.
- The provider responsible for DR-TB should be in close communication with the provider team managing the patient's diabetes. The responsibility for the management of diabetes, however, often falls to those treating the patient for DR-TB.
- Providers and patients should adhere closely to the foundations of diabetes management, including the adoption of a diabetic diet, monitoring of symptoms of hypo and hyperglycemia, and practicing good foot care.
- Health workers should provide disease-specific counseling and support regarding diabetes and DR-TB.
- The concomitant use of metformin at high doses and Linezolid may increase the risk of lactic acidosis. Also, the long-term use of Linezolid, high doses of Isoniazid, and Cycloserine in patients with diabetes can lead to an increased risk of peripheral neuritis. Baseline optic nerve or retinopathy or maculopathy may worsen after Linezolid use; hence, eye evaluation is recommended before and during treatment.
- Patients with diabetes usually have some underlying chronic diabetic nephropathy. This increases the risk of injectable nephrotoxicity.
 - Creatinine and potassium levels should be monitored frequently—weekly for the first month and then at least monthly thereafter—while receiving the injectable.
 - An angiotensin-converting-enzyme (ACE) inhibitor should be considered in all patients with diabetes to prevent progression of diabetic nephropathy.
 - Patients should have regular monitoring of blood glucose levels and other important markers of diabetes management.
 - Goal blood glucose levels are 80–120 mg/dL before meals and 100–140 mg/dL before bedtime. Higher levels are appropriate if a patient has a history of hypoglycemia. Patients may need intensive glucose monitoring until these goals are met.
 - Goal hemoglobin A1c is less than 7%. Levels should be checked every three months (as available) if treatment changes, or patient is not meeting goals. Checks can be extended to every six months in stable clinical situations.
 - Patients with diabetes should undergo a yearly retinal exam.
 - Blood pressure should be checked monthly.
- Tight control of blood glucose can be achieved through pharmacologic therapy.
 - Oral hypoglycemic drugs can be used during the treatment of DR-TB but may require dosage adjustment due to drug-drug interactions.
 - Some experts recommend the use of insulin for tight blood glucose control in all patients with diabetes and TB.
 - Use of Ethionamide or prothionamide may be associated with hypoglycemia and difficulties in glucose control.

Table 13.1 Adjustment of anti-TB drugs in renal insufficiency^a

Drug	Recommended dose and frequency for patients with creatinine clearance <30 ml/min or for patients receiving hemodialysis (unless otherwise indicated dose after dialysis)
Isoniazid	No adjustment necessary
Rifampicin	No adjustment necessary
Pyrazinamide	25–35 mg/kg per dose, three times per week (not daily)
Ethambutol	15–25 mg/kg per dose three, times per week (not daily)
Rifabutin	Normal dose can be used, if possible monitor drug concentrations
Rifapentine	No adjustment necessary
Streptomycin	12–15 mg/kg per dose, two or three times per week (not daily) ^b
Capreomycin	12–15 mg/kg per dose, two or three times per week (not daily) ^b
Kanamycin	12–15 mg/kg per dose, two or three times per week (not daily) ^b
Amikacin	12–15 mg/kg per dose, two or three times per week (not daily) ^b
Ofloxacin	600–800 mg per dose, three times per week (not daily)
Levofloxacin	750–1,000 mg per dose, three times per week (not daily)
Moxifloxacin	No adjustment necessary
Gatifloxacin	400 mg three times a week
Cycloserine	250 mg once daily, or 500 mg/dose three times per week ^c
Terizidone	Recommendations not available
Prothionamide	No adjustment necessary
Ethionamide	No adjustment necessary
P-aminosalicylic acid ^a	4g/dose, twice daily maximum dosed
Bedaquiline	No dosage adjustment is required in mild to moderate renal impairment (dosing not established in severe renal impairment, use with caution)
Linezolid	No adjustment necessary
Clofazimine	No adjustment necessary
Amoxicillin/clavulanate	For creatinine clearance 10–30 ml/min, dose 1,000 mg as amoxicillin component twice daily; for creatinine clearance <10 ml/min, dose 1,000 mg as amoxicillin component once daily
Imipenem/cilastatin	For creatinine clearance 20–40 ml/min, dose 500 mg every 8 hours; for creatinine clearance <20 ml/min dose 500 mg every 12 hours
Meropenem	For creatinine clearance 20–40 ml/min, dose 750 mg every 12 hours; for creatinine clearance <20 ml/min dose 500 mg every 12 hours
High-dose Isoniazid	Recommendations not available
Clarithromycin	500 mg daily

^aAdapted from the Tuberculosis Drug Information Guide, 2nd Edition, 2012, published by the Curry International Tuberculosis Center and California, Department of Public Health

^bCaution should be used with the injectable agents in patients with renal function impairment because of the increased risk of both ototoxicity and nephrotoxicity. If on dialysis, dose after dialysis.

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

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

Renal insufficiency

Renal insufficiency caused by longstanding TB infection itself, or previous use of aminoglycosides, is not uncommon. Great care should be taken in the administration of second-line drugs in patients with renal insufficiency, and the dose and/or interval between dosing should be adjusted according to table 13.1. Patients with renal failure may present a baseline anemia (possibly a clinical complication) that may be made worse by the use of Linezolid or another myelotoxic drug. The dosing is based on the patient's **creatinine clearance**, which is an estimate of the glomerular filtration rate or renal function. The 9 month all oral regimen may be used to treat MDR/RR-TB in patients with renal failure provided the dose or dosing interval of renally excreted drugs is adjusted for the patient's creatinine clearance. Levofloxacin (but not Moxifloxacin), Ethambutol and pyrazinamide require dose or frequency adjustment for adults with creatinine clearance of less than 30 mL/min. Treatment does not have to be extended unless indicated by lack of smear conversion at month 4 of treatment, as for patients with normal renal function.

An example of **how to estimate a patient's creatinine clearance** is provided in box 13.1.

Box 13.1 An example of calculating the creatinine clearance

$$\text{Estimated GFR} = \frac{\text{Weight (kg)} \times (140 - \text{age}) \times (\text{constant})}{\text{Serum creatinine } (\mu\text{mol/L})}$$

- The creatinine is measured in the serum of the blood.
- The **constant in the formula = 1.23 for men and 1.04 for women.**
- If creatinine is reported in conventional units (mg/dl) from the laboratory, one can convert it to an SI Unit ($\mu\text{mol/L}$) by multiplying by 88.4. For example, creatinine = 1.2 mg/dl is equivalent to $(88.4 \times 1.2) = 106.1 \mu\text{mol/L}$.
- Normal values for the creatinine clearance are:

Men: 97 to 137 ml/min

Women: 88 to 128 ml/min

Example: A female patient has a serum creatinine = 212 $\mu\text{mol/L}$ (age = 46, weight = 50 kg). What is the creatinine clearance?

Calculate the creatinine clearance:

$$\text{Weight (kg)} \times (140 - \text{age}) \times (\text{constant}) / \text{serum creatinine} = 50 \times (140 - 46) \times (1.04 \text{ for women}) / 212 = \mathbf{23.0 \text{ ml/min}}$$

The creatinine clearance is below 30. Refer to table 9.1. Every drug in the regimen should be examined and adjusted if necessary, according to the table.

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

Online calculator sites may also be helpful, such as <http://www.mdcalc.com/creatinineclearance-cockcroft-gault-equation>.

Liver disorders

The first-line drugs Isoniazid, Rifampicin, and pyrazinamide are all associated with hepatotoxicity. Of the three, Rifampicin is least likely to cause hepatocellular damage, although it is associated with cholestatic jaundice. Pyrazinamide is the most hepatotoxic of the three first-line drugs. Among the second-line drugs, Ethionamide, prothionamide, and PAS can also be hepatotoxic, although less so than any of the first-line drugs. Hepatitis occurs rarely with the fluoroquinolones.

Patients with a history of liver disease can receive the usual DR-TB regimens provided there is no clinical evidence of severe chronic liver disease, hepatitis virus carrier, recent history of acute hepatitis, or excessive alcohol consumption. However, hepatotoxic reactions to anti-TB drugs may be more common in these patients and should be anticipated.

In general, patients with chronic liver disease should not receive pyrazinamide. All other drugs can be used, but close monitoring of liver enzymes is advised. If significant aggravation of liver inflammation occurs, the drugs responsible may have to be stopped.

Uncommonly, a patient with TB may have concurrent acute hepatitis that is unrelated to TB or anti-TB treatment and 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. Viral hepatitis should be treated if medically indicated and treatment, if available, can occur during DR-TB treatment. The 9-month all-oral regimen may not be the most appropriate option for people with chronic liver disease because this regimen contains several potentially hepatotoxic drugs (e.g. pyrazinamide, Isoniazid and Ethionamide). Although this regimen may still be offered with close monitoring of liver enzymes in people with chronic stable liver dysfunction, a longer regimen with fewer hepatotoxic drugs may be preferable in some settings where closer monitoring is not feasible.

Seizure disorders

Some patients requiring treatment for DR-TB will have a previous or current medical history of a seizure disorder. The first step in evaluating such patients is to determine whether the seizure disorder is under control and whether the patient is taking anti-seizure medication. If the seizures are not under control, initiation or adjustment of anti-seizure medication will be needed before the start of DR-TB therapy. In addition, any other underlying conditions or causes of seizures should be evaluated and corrected.

Cycloserine (and Terizidone, which is a dimer of Cycloserine) should be avoided in patients with active seizure disorders that are not well controlled with medication. However, in cases where Cycloserine is a crucial component of the treatment regimen, it can be given and the anti-seizure medication adjusted as needed to control the seizure disorder. If Cycloserine is used, appropriate adjuvant use of pyridoxine (vitamin B6) should be added. The risks and benefits of using Cycloserine should be discussed with the patient and the decision of whether to use Cycloserine made together with the patient.

High-dose Isoniazid also carries a higher risk of seizure and should be avoided in patients with active seizure disorders.

In mono- and poly-resistant cases, the use of Isoniazid and Rifampicin may interfere with many of the anti-seizure medications. Potential drug interactions should be checked before use.

Seizures that present for the first time during anti-TB therapy are likely to be the result of an adverse effect of one of the anti-TB drugs. However, other causes could include TB-related IRIS in HIV-positive patients. More information on the specific strategies and protocols to address adverse effects is provided in Chapter 9.

Psychiatric disorders

It is advisable for psychiatric patients to be evaluated by a health care worker with psychiatric training before the start of treatment for DR-TB. The initial evaluation documents any existing psychiatric condition and establishes a baseline for comparison if new psychiatric symptoms develop while the patient is on treatment. Any psychiatric illness identified at the start of or during treatment should be

fully addressed. There is a high baseline incidence of depression and anxiety in patients with MDR-TB, often connected with the chronicity and socioeconomic stress factors related to the disease.

Treatment with psychiatric medication, individual counseling, and/or group therapy may be necessary to manage the patient suffering from a psychiatric condition or an adverse psychiatric effect caused by medication. Group therapy has been very successful in providing a supportive environment for MDR-TB patients and may be helpful for patients with or without psychiatric conditions. (Adequate measures to prevent infection risk should be in place for the group therapy.)

The use of Cycloserine is not absolutely contraindicated for the psychiatric patient. Adverse effects from Cycloserine may be more prevalent in the psychiatric patient, but 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. Other second-line anti-TB drugs associated with potential psychiatric adverse effects are listed in Chapter 9.

All health care workers treating DR-TB should work closely with a mental health specialist and have an organized system for psychiatric emergencies. Psychiatric emergencies include psychosis, suicidal tendencies, and any situation involving the patient being a danger to oneself or others.

Substance dependence

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

Cycloserine will have a higher incidence of adverse effects (as in the psychiatric patient) in patients dependent on alcohol or other substances, including a higher incidence of seizures. However, if Cycloserine is considered important to the regimen, it should be used and the patient closely observed for adverse effects, which are then adequately treated.

Older patients

TB-related morbidity and mortality tends to be higher among older people than in the younger population. Patients aged 65 years and older with MDR/RR-TB are more vulnerable to the adverse effects of TB medications owing to physiological changes of ageing (e.g. increase in QT interval and decrease in estimated glomerular filtration rate [eGFR]), other comorbidities and overlapping, additive drug toxicities (owing to a higher likelihood of polypharmacy in older people). Advanced age has also been reported as a risk factor for Linezolid-induced anaemia (54). Whereas the 9-month all-oral regimen may be offered to eligible patients of any age, older people may require closer monitoring for drug-related adverse events as well as closer adherence support and assistance to administer treatment daily or as prescribed.

Chapter 14:

Management of DR-TB patients after treatment failed

This chapter describes the essential investigations and management of DR-TB patients on second-line anti-TB regimens that are suspected of and/or confirmed to be failing treatment. As defined in Chapter 2, a DR-TB patient is considered to have failed a second-line treatment regimen when:

A patient whose treatment regimen needed to be terminated or permanently changed (see note ‘a’) to a new regimen or treatment strategy.

‘a’

Reasons for the change include:

- No clinical response or no bacteriological response, or both (see note ‘b’);
- Adverse drug reaction; or
- Evidence of additional drug-resistance to medicines in the regimen.

‘b’

“Bacteriological response” refers to bacteriological conversion with no reversion:

- “Bacteriological conversion” describes a situation in a patient with bacteriologically confirmed TB where at least two consecutive cultures (for DR-TB and DS-TB) or smears (for DS-TB only) taken on different occasions at least 7 days apart are negative; and
- “Bacteriological reversion” describes a situation where at least two consecutive cultures (for DR-TB and DS-TB) or smears (for DS-TB only) taken on different occasions at least 7 days apart are positive either after the bacteriological conversion or in patients without bacteriological confirmation of TB.

Signs of treatment failed

Treatment failed should be suspected if there is:

1. Lack of signs of improvement, particularly after completing at least four months of full adherence to what is deemed to be an effective second-line treatment regimen
2. Clinical, radiographic, or bacteriological evidence of progressive active disease
3. Reappearance of disease (clinical, bacteriological, or radiographic worsening after an initial response to treatment)

Investigating and addressing potential treatment failed

The following steps are recommended when treatment failure is suspected:

1. **Use a drug-o-gram** to assess breaks or changes in treatment, as well as serial changes in bacteriology, DST results, weight, symptoms, and radiographic exams (see annex 3).
 - a) **Assess treatment regimen:** Examine whether the anti-TB drugs, doses, and frequency of dosing have been consistently appropriate for the patient’s weight, drug resistance pattern, and medical history.
 - i. All DST results should indicate the date on which the specimen was collected. When examining the adequacy of the treatment regimen in relation to the DST result, keep in mind that the DST result reflects only the pattern of resistance that existed at the point the specimen was first collected from the patient.
 - ii. When signs of treatment failed are present and the regimen is determined to have been suboptimal, expert consultation should be sought and prompt action taken

- to determine treatment and management options. Repeat culture and second-line DST should be expedited.
- b) Assess bacteriology: Positive smears and cultures are the strongest evidence that a patient is not responding to treatment. However, single laboratory results must be viewed in the context of the full clinical picture.
- i. A single positive culture in the presence of an otherwise good clinical response can be caused by a laboratory contaminant or error. In this situation, treatment should continue uninterrupted and repeat smear and culture should be expedited. Negative cultures following a single positive culture can be viewed as evidence that the patient is not failing treatment.
 - ii. Positive smears with negative cultures may be caused by dead bacilli, particularly in patients with extensive pulmonary disease. When such a patient is otherwise showing clinical improvement, treatment failed can be ruled out and treatment should continue uninterrupted.
- c) Radiographic changes: Negative smear and culture results in a patient with clinical and radiographic deterioration suggest the possibility of a disease other than MDR-TB treatment failed (e.g., other infectious pneumonias or malignancy). In a patient with confirmed MDR-TB, second-line treatment should continue while other causes for the radiographic changes are explored. Patients should be discharged from care with evidence of radiological improvement
- d) DST result changes: DST results showing evidence of acquired resistance to any of the second-line drugs depending on the patient's current treatment regimen (particularly Group A drugs i.e Floroquinolones, Bedaquiline or Linezolid) could suggests treatment failed. In such a case, expert consultation should be sought and prompt action taken to determine treatment and management options.
- e) Weight loss: Trending weight loss should prompt investigation into:
- i. Patient's nutritional intake, as loss of weight may indicate food insecurity
 - ii. Gastrointestinal problems (e.g., nausea, vomiting, diarrhea) as loss of weight may be caused by medication side effects or other gastrointestinal infections or conditions
 - iii. Disease progression and potential treatment failed

2. Evaluate the patient clinically

- Look for undetected, uncontrolled comorbidities.
- Consider illnesses that decrease absorption of medicines (e.g., chronic diarrhea) or may result in immune suppression (e.g., HIV/AIDS).
- Consider illnesses that mimic failure (chronic infection with non-tuberculous mycobacteria).

3. Assess adherence carefully

- Review the patient's DR-TB Treatment Card for doses signed off as DOT and compare with the medication count remaining at the site where DOT is being supervised.
- Interview the patient in a non-confrontational manner (with and without the DOT provider/supporter present). Questions should assess:
 - i. Adherence problems and potential solutions
 - ii. Possible manipulation of the DOT provider/supporter by the patient
 - iii. Whether DOT provider/supporter is fulfilling their duties
- If manipulation by the patient is suspected:
 - i. – Counsel the patient, examining the patient's understanding of and beliefs about DR-TB, how it is transmitted to others, and benefits of treatment

- ii. – Consider relieving the DOT provider/supporter of DOT responsibilities with the patient; provide additional training and closer supervision whenever assigned another DOT provider/supporter role
- iii. –Consider changing the way the patient receives DOT (e.g., switch clinics, switch DOT provider/supporter, etc.)
- 3. If the DOT provider/supporter is not fulfilling his/her duties for any reason, consider switching the DOT provider/supporter.
- 4. See Chapter 8 and 10 for other strategies to address adherence.

What to do when treatment failed is confirmed

Change treatment regimen

When a patient fails to respond to MDR-TB treatment, it is necessary to reassess the regimen and treatment plan. Changes in treatment may be made as early as four to six months if conversion is not seen and if there is clinical deterioration. (Additional considerations apply with using the standardized treatment regimens, see Annex 9 for details).

- Whenever a regimen change is indicated because of treatment failed, a final outcome should be recorded in the Second-line TB Treatment Register and a new DR-TB Registration number given.
- The new treatment regimen should include **at least four likely effective anti-TB drugs**; it may be necessary to request for compassionate use of new anti-TB drugs. Never add just one drug to a failing regimen.
- If surgical resection is feasible, it should be considered.

Permanent Suspension of therapy

If the patient continues to deteriorate despite the measures described in the previous section, permanent suspension of therapy may be considered when the medical personnel are confident that all the medications have been ingested and there is no possibility of adding other medications or carrying out surgery.

There are at least three important considerations to bear in mind when deciding whether to continue or permanently suspend treatment and move to a supportive, palliative care approach.

1. **Patient's quality of life:** The medications used in MDR-TB treatment have significant adverse effects, and continuing them while treatment is failing may cause additional suffering.
2. **Public health concern:** Continuing a treatment that is failing can amplify resistance in the patient's strain, and will result in a waste of resources. These highly resistant strains may subsequently infect others and be extremely difficult to treat.
3. **Model of care available:** Examine the capacity to provide end-of-life care *and* proper TB infection control to patients who have no effective treatment alternatives, while remaining a source of TB infection.

Indications for permanent suspending of treatment

There is no single set of parameters to indicate that cure is possible (or impossible), nor an absolute timeframe to determine whether a treatment regimen is failing. While there is no simple definition to determine failure, sometimes it just becomes clear that the patient is not going to improve despite the treatment delivered. Signs indicating treatment failed with no further options to achieve cure include the concurrence of several of the following:

- Persistent positive smears or cultures in the past 8–10 months of treatment
- Progressive extensive and bilateral lung disease on chest radiograph with no option for surgery
- High-grade resistance (often XDR-TB + additional resistance) with no option to add at least two additional effective agents (all possible second-line regimen choices have been used)
- Overall deteriorating clinical condition that usually includes weight loss and respiratory insufficiency

Approach to permanent suspending of therapy

The approach to suspending therapy includes:

- Discussions should be held among the clinical team involved in the patient's care, followed by discussion and decision to be made by the National DR-TB Panel.
- Once the decision is made that treatment should be permanently suspended, a clear plan should be prepared for approaching the patient and the family.
- The transition from treatment to supportive care may be best accomplished in the patient's home environment through discussion with the patient and family over the course of several weeks. It is not recommended to suspend therapy before the patient understands and accepts the reasons for doing so and agrees with the supportive care offered (see box 14.1 for palliative care measures that should be included in the patient's supportive care plan).

Provide palliative care

Palliative care may be considered for patients in whom all the possibilities of MDR-TB treatment have failed. It is important that medical visits continue and that the patient is not abandoned. The types of supportive measures that may be offered are summarized in box 14.1.

Conclusion

Signs of treatment failed should prompt immediate investigation and action. Tools such as a **drugogram** should be used to help assess the full clinical picture, potential cause(s) of treatment failed, and to guide decisions on regimen changes.

Suspension of therapy (confirmed by the National DR-TB Panel) may be considered only after all other options for treatment have been explored. Suspending therapy in a patient who has failed MDR-TB treatment is a delicate situation and difficult for family members and caregivers; but, it is especially difficult for the patient as treatment is often viewed as his or her only hope. Strong support, care, and sympathy must be given to the patient and family.

Box 14.1 End-of-life supportive measures

- | |
|--|
| <ul style="list-style-type: none">• Hospitalization, hospice care, or nursing home care. Having a patient die at home can be difficult for the family. Hospice-like care should be offered to families who want to keep the patient at home. Inpatient end-of-life care should be available to those for whom home care is not available. Ability to provide respiratory isolation is an essential consideration when inpatient end-of-life care will be required for an infectious DR-TB patient.• Preventive measures. Oral care, prevention of bedsores, bathing, and prevention of muscle contractures are indicated in all patients. Encourage patients to move their bodies in bed if able and assist in repositioning the bedridden patient who may need assistance. Keeping beds dry and clean is also important. |
|--|

- **Infection control measures.** The patient who is taken off anti-TB treatment because of failure often remains infectious for a long period of time. Infection control measures should be continued (see Chapter 16) with reinforcement of environmental and personal measures, including N-95 mask use for caregivers.
- **Pain control and symptom relief.** Paracetamol, or codeine with paracetamol, offers relief from moderate pain. Codeine also helps control cough. Other cough suppressants can be added. If possible, stronger analgesics, including morphine, should be used when appropriate to keep the patient adequately comfortable. See the WHO analgesic guides, pain scales, and three-step “ladder” for pain relief (<http://www.who.int/cancer/palliative/painladder/en/>).
- **Relief from respiratory insufficiency.** Oxygen can be used to alleviate shortness of breath.
- **Corticosteroids** (prednisolone) may be beneficial in severe respiratory insufficiency. Morphine also provides significant relief from respiratory insufficiency and should be offered according to established clinical protocols whenever necessary.
- **Nutritional support.** Small and frequent meals are often best for a person at the end of life. It should be accepted that the intake will reduce as the patient’s condition deteriorates and during end-of-life care. Nausea and vomiting or any other conditions that interfere with nutritional support should be treated.
- **Regular medical visits.** When therapy stops, regular visits by the treating physician and support team should be continued in order to address medical needs and to ensure that infection control practices are being followed.
- **Continuation of ancillary medicines.** All necessary ancillary medications should be continued as needed. Depression and anxiety, if present, should be addressed. Antiemetics may still be needed and fever treated if the patient is uncomfortable.
- **Psychosocial support.** Psychological counselling to the patient and family caregivers is critical at this stage, especially to assist patients in the planning of decisions related with the end of life, and to provide emotional support, especially in settings in which strong stigma is attached to the disease.
- **Respect for patient’s beliefs and values at the end of life.** It is common for the patient and family caregivers to develop or increase their interest in spiritual and religious matters once they perceive that the end of life is approaching. Health care providers should respect those beliefs and should not impose personal values and practices that prevent the patient from seeking and finding comfort in the services delivered by faith-based organizations.

Chapter 15:

Management of contacts of DR-TB patients

Contact tracing is critical to identify further cases of MDR/RR-TB, prevent ongoing transmission and ultimately work towards the global EndTB strategy. Assessment should be offered for household contacts where feasible, especially for children aged below 5 years. Measures available for screening should include symptom assessment, chest X-ray and sputum testing (preferably using WHO recommended molecular tests) (33).

This chapter describes the management of adult and child contacts of a DR-TB patient.

Key recommendations of this chapter:

- Investigate contacts of DR-TB as a matter of high priority, and of XDR-TB as an emergency.
- Household and close contacts of DR-TB patients should receive an initial detailed clinical evaluation and follow-up evaluation at 6, 12, 18 and 24 months after the index case's diagnosis and initiation of second-line treatment.
- Children under age five and all contacts with HIV, and other immunocompromised contacts regardless of age, should receive an additional evaluation three months after the index case's diagnosis and treatment start.
- Routine treatment of latent MDR-TB with second-line anti-TB drugs or Isoniazid preventive therapy is not recommended currently.

General considerations

Opportunities to halt the transmission of DR-TB in communities and to treat DR-TB in a timely fashion are often missed due to:

- Delay in diagnosis of drug resistance.
- Lack/Inadequate of investigation of contacts of DR-TB patients.
- Failure to ask patients presenting with active TB disease about any history of exposure to DR-TB
- Poor access to second-line drugs and/or DST

TB contact investigation is a high-yield case finding strategy.

Contact investigation is a systematic process to identify previously undiagnosed cases of TB among the contacts of an index case. Studies have shown that TB contact investigation is a high-yield case finding strategy.

- The frequency of detecting TB among contacts of MDR-TB has varied from zero to as high as 8% in various studies.
- The risk for new incidence cases is highest in the first 12 months after the index patient's diagnosis of TB, with half or more of the cases found among contacts during the time of the initial contact evaluation.
- Secondary TB cases found among contacts are not uniformly distributed across households (e.g., no secondary cases will be found for most TB cases, but multiple secondary cases will be detected among the contacts of others). This variation likely results from differences in the infectivity among TB cases and variation in the susceptibility of the contacts (e.g., young children and HIV-infected contacts are more likely to progress to active TB).

In general, contact investigation activities are most efficient when integrated into routine programmatic management of TB and DR-TB. There are multiple opportunities during routine TB program work to investigate contacts of DR-TB patients. While all contacts of TB require investigation,

DR-TB requires the most vigilance. Because of the severe risk of morbidity and mortality of XDR-TB, investigation of contacts to an XDR-TB patient should be done as **an emergency**.

A contact is any person who has been exposed to someone with new or recurrent TB. In the case of DR-TB, contacts are those persons exposed to someone with confirmed pulmonary DR-TB. Household and other close contacts i.e. neighbours, workplace and social contacts of DR-TB patients who develop active TB could have drug-resistant disease.

Household contacts are those who shared the same enclosed living space with the index case for one or more nights or for frequent or extended periods during the day within **three months** prior to the index case's diagnosis and DR-TB treatment start.

- NOTE: The definition of "household" needs to consider the housing arrangement in some communities in which a cluster of multiple households of an extended family may include multiple nearby structures for sleeping, yet the entire family share meals and living space throughout the day. In these settings a "household" may be defined as all the individuals who regularly share meals together.

Close contacts of DR-TB patients are defined as those not living in the same household but who spent many hours a day with the index case in the same indoor living, working, or social space within three months prior to the index case's diagnosis and DR-TB treatment start.

Evaluating contacts of DR-TB patients for active TB disease

In Uganda, health care staff at multiple levels should screen family members and other close contacts of patients with DR-TB for signs and symptoms of active TB.

Prompt notification of DR-TB patients is crucial, allowing for the early initiation of contact tracing. Rapid evaluation of close contacts allows timely identification of those who have active disease and, if active disease has been excluded, allows initiation of treatment of LTBI for newly infected contacts before disease occurs.

Investigating household and other close contacts

According to WHO guidelines, contacts of patients diagnosed with MDR-TB should be closely evaluated and followed. WHO further advises that children under five and people of all ages living with HIV should receive a clinical evaluation every six months for two years after their last MDR-TB exposure, whether they are symptomatic. Given that separating out just children under age five and those with HIV coinfection to follow every six months for two years creates logistical challenges, Uganda will focus contact tracing efforts on all household and close contacts for the two years following the index case's diagnosis. Additional attention will be given to those contacts at highest risk for rapid progression to TB disease in the first three months following index case diagnosis (e.g., children under five years, symptomatic patients, HIV-positive individuals). Contact tracing should be done even when the index patient has died.

Once the health facility receives DR-TB results, a home assessment should be conducted within the first week of index case diagnosis (see Form 13a for Household Assessment for DR-TB) and screening of all household contacts initiated. The index patient should be interviewed to identify where the patient spent time during the period preceding his/her diagnosis of DR-TB. This will provide information about the locations in which contacts may have had indoor exposure and will need to be identified for follow-up. The most common important location is the home, but other locations may need to be considered (e.g., a classroom for an elementary school teacher). All this information is collected using Household Assessment and Contact Screening form and is collected in collaboration with the health worker from the treatment initiation facility.

Household surveillance of contacts will be conducted every six months for the period the index patient is on treatment. Generally, four visits will be conducted during the two years following the index case's diagnosis to assess contacts and conduct investigations on symptomatic contacts (see figure 15.1).

- Household and close contacts deemed high risk (those under five years of age and those with HIV) should have an additional evaluation three months after index case diagnosis, as TB infection can progress to active disease quickly in young children and those who are immunocompromised. Parents of child contacts should be counselled to seek immediate medical attention should their child begin to show signs of failing to thrive.
- For deceased DR-TB patients (upon receipt of the results or after initiating treatment), contact tracing will be done immediately and six months later because there is still risk of disease from exposure prior to the patient's death. The last visit should be six months after the death of the index patient.

Prioritisation of Contacts

As the circumstances in each contact investigation are unique, and risk of infection and disease to individual contacts cannot be determined precisely, the classification of contacts into 'close' and 'casual' is recommended to guide the decision-making process. Contacts with a cumulative total exposure to an infectious TB patient exceeding eight hours within a restricted area should be regarded as close contacts i.e. equivalent to household contacts. A reduced cumulative total exposure time of ≥ 4 hours should be considered for vulnerable contacts such as young children aged less than 5 years and immunocompromised contacts.

Classification of contacts for prioritising contact tracing

Contact classification	Description
Close contacts	<ul style="list-style-type: none"> • All household contacts (an individual sharing a bedroom, kitchen, bathroom, or sitting room) • All other immunocompetent adult contacts with a cumulative total exposure ≥ 8 hours in a restricted area equivalent to a domestic room (may include girlfriend, boyfriend, close friends, sexual partners, frequent visitors to the home, etc.) • A reduced cumulative total exposure time of ≥ 4 hours may need to be considered for vulnerable contacts exposed in a restricted area such as children aged < 5 years and immunocompromised individuals, immunocompromised either due to disease e.g. HIV or therapies, individuals receiving $>15\text{mg}$ prednisone or equivalent for more than four weeks, or other immunosuppressive agents for cancer, chemotherapeutic agents, anti-rejection drugs for organ transplantation and TNF-α antagonists or as defined by the attending consultant. • Individuals exposed during medical procedures (e.g. bronchoscopy, sputum induction or autopsy) where no infection control practices were in place
Casual contacts	<ul style="list-style-type: none"> • Generally all other contacts such as work colleagues, team/ club members, etc. (some such contacts may be assessed as being close contacts following risk assessment)

Expanding a contact investigation

Consideration should be given to extending screening if there is evidence of transmission based on any of the following:

- There is an unexpectedly high rate of infection or TB disease in close contacts (e.g. if $\geq 10\%$ of close contacts have TB infection or active disease)
- TB disease is identified in a casual contact or a contact with low screening priority
- Infection is identified in any contact (close/casual) under five years of age.

The Contact Tracing Interview

A newly diagnosed MDR/RR patient should be interviewed by a trained member of staff in the hospital, TB clinic, in the patient's home or anywhere that will ensure the patient's privacy. Interviews should be completed as soon as possible. The interview provides an opportunity to exchange information, for the patient to acquire information about TB and its control, and for the health professional to learn to adapt treatment and education strategies to the patient's specific requirements. The Centers for Disease Control and Prevention (CDC) developed standard procedures for interviewing TB patients in 1999.²⁹²

The following principles as proposed by CDC are recommended for use:

1. **Building rapport with a patient** is an important part of contact tracing. This can be achieved by assuring patient privacy, helping the patient decide how to share information about their diagnosis to contacts, and allowing approximately one hour for exchange of information (depending on the patient's health and endurance).
2. **Exchanging information** should allow the interviewer to obtain missing information e.g. date of symptom onset, and the patient to improve their understanding of disease causation/transmission and clarify their treatment plan requirements.

3. **Transmission settings** i.e. places the patient attended while infectious should be identified so contacts attending those venues can be identified and prioritised for screening based on time spent by the index case in those settings. Topics for discussion could include where the patients worked, spent their leisure/recreational time, where they visited, ate, spent nights, etc. The interviewer should ask specifically about time spent in congregate settings (e.g. schools, prisons, hospitals/healthcare settings, etc.)
4. **Lists of contacts** should be made for those attending each potential site of transmission, including name of contact, approximate types, frequency and duration of exposure. Recent illness among contacts should be discussed.
5. **Closure:** The interviewer should express appreciation for the patient's contribution, and indicate how screening will proceed, that site visits will be conducted and confidentiality respected.
6. **Follow-up interviews** should be scheduled if further information is required.

Site investigation

Site visits may need to be undertaken to complement interviews. It is important that consideration is given to the index patient's lifestyle so that places of intense contact other than the household may be determined (e.g. work or leisure sites). Site visits may add contacts to the list and are the most reliable source of information regarding transmission settings. Physical conditions at each setting can contribute to transmission. At congregate settings, the size of the room(s), ventilation system and airflow patterns should be considered along with information about how long and how often the patient was in that setting. Failure to visit all potential sites of transmission has contributed to TB outbreaks. Visiting the index patient's residence is especially helpful for finding children who are contacts. Certain sites (e.g. congregate settings) require special arrangements to visit. Communication and liaison with management in congregate settings is an essential component of site investigation. Maintaining confidentiality for an index patient can be difficult. The index case should be informed that information needs to be shared with management. Every effort should be taken to maintain patient confidentiality.

Contact investigation for patients whose culture converts back to positive.

In some instances, a DR-TB patient's culture may convert to negative and then become positive again. This may happen if a patient is lost to follow-up and discontinues medications before completing treatment or if treatment was not adequate because of multidrug resistance. If the patient is located after a treatment lapse of three months or longer and if the patient's cultures have become positive again or if the patient relapses while on treatment after becoming culture negative, a second window period should be defined, and the patient should be re-interviewed. Contacts identified during the initial investigation should be re-evaluated if they were exposed again. If new contacts are identified, they should be tested and evaluated.

Contact investigation among children and adolescents.

Contact investigations for children with suspected TB are generally conducted to identify the adult source patients. Because TB among infants and young children usually occurs within weeks to months of contracting infection with *M. tuberculosis*, having a child with disease is a marker of recent transmission from someone in the child's environment. Children younger than 10 years with pulmonary TB are rarely contagious because their pulmonary lesions are small (paucibacillary disease), cough is not productive, and few or no bacilli are expelled. However, children or adolescents of any age with characteristics of adult-type TB (i.e. productive cough and cavitary or extensive upper lobe lesions on chest X-ray) should be considered potentially infectious at the time of diagnosis.

Management of newborn infant contact of DR-TB

Management of the newborn infant is based on categorisation of the maternal (or household contact) infection. Although protection of the infant from TB disease is of paramount importance, contact between infant and mother should be allowed when possible.

Mother (or household contact) with DR-TB disease

Investigation of all household members should be conducted without delay. If the mother has DR-TB disease, the infant should be evaluated for congenital TB. The mother (or household contact) and the infant should be separated until the mother (or household contact) has been evaluated and the mother (or household contact) and infant are receiving appropriate anti-TB therapy, the mother wears a mask, and the mother understands and is willing to adhere to infection control measures. Once the infant is receiving Isoniazid, (DS-TB) separation is not necessary unless the mother (or household contact) has possible MDR-TB or has poor adherence to treatment and DOT is not possible.

DR-TB Outbreaks. A DR-TB outbreak indicates potential extensive transmission. An outbreak implies that the patient was contagious, that contacts were exposed for a substantial period and that the interval since exposure has been sufficient for infection to progress to disease. An outbreak investigation involves several overlapping contact investigations, with a surge in the need for public health resources.

Congregate Settings

Overall concerns associated with congregate settings include:

- The substantial numbers of contacts
- Incomplete information regarding contact names and locations
- Incomplete data for determining priorities
- Difficulty in maintaining confidentiality
- Collaboration with officials and administrators who are unfamiliar with TB
- Legal implications and
- Media coverage.

Increased resources will be necessary when the scope or duration of an investigation is expected to disrupt other essential TB control functions.

Maintaining confidentiality for an index patient is particularly challenging if the patient was conspicuously ill or was absent from the setting while ill. Collaboration with officials at the setting is essential for obtaining access to employee and occupancy rosters, ascertaining contacts, performing on-site testing and offering education to associates (e.g. classmates, friends or co-workers) of the index patient. For congregate settings, the types of information for designating priorities are site specific, and therefore a customised algorithm is required for each situation. The general concepts of source-case characteristics, duration and proximity of exposure, environmental factors that modify transmission, and susceptibility of contacts to TB should be included in the algorithm. The optimum approach for a setting-based investigation is to interview and test contacts on site. If this is not possible, then the contacts should be invited for evaluation at a designated health facility.

Workplaces

Many people spend the majority of their waking hours in their workplaces. Duration and proximity of exposure can be greater than for other settings. Details regarding employment, hours, working conditions and workplace contacts should be obtained during the initial interview with the index

patient, and the workplace should be visited and examined after accounting for confidentiality and permission from workplace administrators or managers. Employee lists are helpful for selecting contacts, but certain employees might have left the workplace and thus have been omitted from current employee lists. Customers of a business workplace may also need to be considered.

Workplace administrators or managers are likely to express concern regarding liability, lost productivity and media coverage. In addition, they might have limited obligations to protect patient confidentiality. All of these issues can be addressed during the planning phase of the investigation.

Hospitals and other Healthcare Settings

The primary TB risk to other patients and staff in hospitals/healthcare settings is the undiagnosed or unsuspected patient/staff member with infectious TB disease. The issue of potential exposure of patients, some of whom may have reduced immunity, may result in considerable resources being directed at identifying exposed patients, many of whom are likely to be at minimal risk. Unnecessary screening of contacts with minimal risk should be avoided as yields from contact investigation in healthcare settings can be low.

Healthcare-associated transmission of *M. tuberculosis* has been linked to close contact with persons with TB disease during aerosol-generating or aerosol-producing procedures, including bronchoscopy, endotracheal intubation, suctioning, other respiratory procedures, open abscess irrigation, autopsy, sputum induction and aerosol treatments that induce coughing.

Effective contact tracing requires liaison between public health services, hospital infection prevention and control and occupational health services. Coordination of contact tracing is most appropriately led by hospital infection prevention and control (vis. consultant microbiologist) in those healthcare settings where this is in place. This will include the initial alerting of public health and occupational health services. In all other healthcare settings, coordination should be undertaken by the public health service.

Contact tracing should be initiated where:

- A person with DR-TB has been examined at a healthcare setting, and TB disease was not diagnosed and reported quickly, resulting in failure to apply recommended TB infection controls or
- Environmental controls or other infection control measures have malfunctioned while a person with infectious TB was in the setting or
- A HCW DR-TB and exposes other persons in the setting.

Contact tracing should be carried out only for patients for whom the risk is regarded as significant. No two episodes of this kind are likely to be identical in all respects, and narrowly drawn guidelines are thus inappropriate. A repeat risk assessment should also be made if investigation of the household contacts of the index case has an unusually high yield.

Guidance for contact tracing in hospitals and healthcare settings:

DR-TB in a hospital inpatient

- Following diagnosis of DR-TB in a hospital inpatient in an open ward, a risk assessment should be undertaken. This should take into account the degree of infectivity, the length of time before the infectious individual was isolated, the proximity of the contact, and whether other patients were unusually susceptible to infection

In general, patients should be regarded as at risk of infection if they spent more than eight hours in the same section (rather than the whole ward) as an inpatient with infectious/presumed infectious

TB. If patients were exposed to a patient with DR-TB for long enough to be equivalent to household contacts (as determined by the risk assessment), or an exposed patient is known to be particularly susceptible to infection, they should be managed as equivalent to household contacts

Where an inpatient has MDR-TB, or if exposed patients are immunocompromised, specialist expert advice should be sought

Staff in casual contact with a patient of smear positive TB should be reassured and reminded of the possible symptoms of TB to report. Staff who have undertaken mouth-to-mouth resuscitation without appropriate protection, prolonged care of a high dependency patient or repeated chest physiotherapy on a patient with undiagnosed respiratory TB should be managed as close contacts.

DR-TB in a HCW

If the HCW has been at work while infectious, it will be necessary to identify patients, other staff and visitors who may have had significant contact and manage as per contact tracing procedures.

Other healthcare settings

Elderly people residing in nursing homes are almost twice as likely to acquire TB as those living in the community. Certain considerations for control of TB in hospitals apply also to such extended care facilities, including maintaining a high index of suspicion for the disease, promptly detecting cases and diagnosing disease, isolating infectious persons and initiating standard therapy and identifying and evaluating contacts (contact investigation).

Schools

The notification of a patient of DR-TB in a school setting, whether a staff member or pupil, requires particular attention because of the potential for spread of infection and also because of the anxiety that can be generated among pupils, parents, staff and the wider public. The typical features of contact investigations in schools are the potentially substantial numbers of contacts and difficulties in assigning priorities to contacts who have undetermined durations and proximities of exposure.

If the index patient is a staff member, the aim of contact tracing is generally to detect secondary patients in the school. This may also be the aim if the index is an infectious adolescent patient. If the patient is a younger child or a non-infectious adolescent, the main purpose is to detect a source patient in addition to the possibility of detecting other secondary patients from a common source.

Guidance following notification of a patient of DR-TB in a pupil or staff member:

- Case risk assessment

The case risk assessment should include an early visit to the school to check indoor spaces, observe general conditions and enquire about ventilation.

Communication

- Early meeting with school management to explain prevention and control measures
- Early consideration of how to best communicate with the wider school population and how to keep updated
- Early anticipation of, and planning for, media communication aspects. The presence of TB in schools often generates publicity. Ideally, the public health department should communicate with the school and parents (and guardians) before any media report a story.

School pupil with DR-TB

- Screen class (if single class group) or year (who share classes) o Screen relevant staff members (class teachers/games/school bus/other)
- Screen (by symptom enquiry and single chest X-ray) all other members of staff in the school if the index patient of a school pupil's TB infection is not found. This is especially relevant if evidence of recent infection has been found in fellow pupils in order to exclude a potential index patient among staff.

Teacher with DR-TB

- Screen, where in contact during preceding three months, relevant class pupils/games etc.
- Screen staff member contacts.

Screening extension

- Contact tracing may need to be extended to include children and teachers involved in extracurricular activities (e.g. sport, school bus travel, etc.) and non-teaching staff on the basis of degree of infectivity of index patient/length of time the index patient was in contact with others/whether contacts are unusually susceptible to infection/the proximity of contact. Outdoor activities would not normally pose a transmission risk, unless this involved confined spaces for prolonged time periods.

Secondary patient

- Any secondary patients of sputum smear positive TB should be treated as index patients for the purposes of contact tracing.

Further pupil patient within 12 months

- Should further patients of TB occur in a child within a twelve-month period, all adult staff in the school should be screened with a single chest X-ray (in order to exclude a potential index patient among staff).

Pre-schools

Children aged < five years who have been identified as contacts of patients of infectious TB should receive a clinical evaluation, including a TST and chest X-ray, to rule out active TB. TB disease in children aged < five years typically indicates that the infection must be recent. For this reason, it is a sentinel public health event. Young children usually do not transmit TB to others and their contacts are unlikely to be infected because of exposure to them. In a source case investigation of a child aged < five years in a pre-school setting, all adults in the facility should be included if the source case has not been found in the family or household.

Child < five years with DR-TB

- Screen all adults in the pre-school setting by symptom enquiry and single chest X-ray if the source patient has not been found in family/household.

Adult with DR- TB

- Screen all children
- Screen all adults as close contacts

Transportation

Prolonged journeys (i.e. eight hours or longer) in a confined space and recirculation of air on various modes of transport may increase the risk of transmission of M. tuberculosis. Although the risk of exposure relative to the frequency and duration of journeys and modes of transport has not been demonstrated, this risk is likely to be similar to that in other circumstances where people are together in confined spaces.

WHO have published guidelines for preventing and controlling TB transmission on aircraft in 2008, which are available at: www.who.int/TB/features_archive/aviation_guidelines/en/.303 Between 1992 and 1994, CDC conducted seven contact investigations, six of which were undertaken for passengers, and one for an infectious cabin crew member. Evidence of TB transmission (as indicated by the detection of latent infection) was determined in only two investigations: one from a cabin crew member to other crew members with a minimum of 12 hours' exposure, and the other from a passenger to other passengers seated in the same section of the aircraft, on a flight lasting more than eight hours.^{304;305} To date, no patient of clinical or bacteriologically confirmed TB disease has been identified as a result of exposure on a commercial aircraft.

The risk of exposure to a patient of MDR-TB or XDR-TB during a flight causes considerable concern among travellers, health authorities, airline companies and the media. At present, little evidence exists to suggest that drug-resistant strains of TB would be more easily transmitted during air travel. In other settings drug-resistant TB has been found to be more transmissible than drug-sensitive strains. However, the consequences of infection with drug-resistant strains are more complex, the outcomes are not as good as for drug-susceptible TB, and therefore the consequences for exposed contacts are also more important. On these occasions, medical authorities, airline representatives and members of the public are advised to seek guidance from the DoHC and HPSC

To prevent exposure on flights, WHO recommends that infectious TB patient should not travel by public air transportation until at least two weeks of adequate treatment have been completed or until the person is Guidelines on the Prevention and Control of Tuberculosis in Ireland 2010 HSE/HPSC - 110- sputum smear negative. Patients with MDR-TB or XDR-TB should not travel until they have been proved to be non-infectious (i.e. culture-negative). Health authorities and/or physician(s) should conduct a risk assessment of the potential infectivity, potential drug resistance, duration of the

proposed flight, and the possible consequences of transmission to other passengers when a TB case wishes to travel. The public health authority and/or physician must give clear advice or instruction on whether or not to travel. Patients intending to travel against this advice should be reported to the MOH of the relevant HSE area for any necessary action.

Contact tracing of infectious or potentially infectious TB patients on aircraft should be limited to flights which were ≥ 8 hours duration and took place during the previous three months. All patients of respiratory TB who are sputum smear positive and culture positive (if culture available) are deemed infectious. All patients of respiratory TB who are sputum smear negative and culture positive are deemed potentially infectious.

The following criteria should also be used when determining the infectiousness of a patient at the time of travel:

- i presence of cavitations on chest X-ray,
- ii presence of symptoms at the time of the flight and
- iii documented transmission to close contacts.

2. If the index patient is a passenger, obtain contact details of passengers sitting in the same row and the two rows ahead and behind (from one side of the aircraft to the other because of ventilation patterns) the index patient. Inform contacts of possible exposure and advise screening of these flight contacts and cabin crew who served the section in which the TB patient was seated. 3. If the index patient is an aircraft crew member, contact tracing of passengers should not routinely take place. Contact tracing of other members of staff is appropriate, in accordance with the usual principles for screening workplace colleagues.

Clinicians should immediately inform the MOH in the relevant HSE area of any patients with infectious pulmonary or laryngeal TB who have a history of air travel ≥ 8 hours.

The MOH should then inform HPSC of the case. Case and air flight details should also be forwarded to HPSC. HPSC will then verify with the airline(s) that:

- The patient was on the flight
- The flight time (≥ 8 hours) and
- \leq three months have elapsed since the flight.

If the TB patient travelled on more than one airline, HPSC will contact each airline on which the patient travelled on a flight for ≥ 8 hours total flight duration.

Once this is verified, HPSC (as the country where the patient was reported) will then inform the counterpart public health authorities in all countries where the flight(s) departed and landed. HPSC will then request from the airline(s) the list of relevant flight contacts will also inform the public health authorities of the countries of residence of the identified contacts and advise them of the situation. In countries of residence of the contacts, the public health authorities should follow national policy for TB contact investigation. In some circumstances such patients (as outlined in the WHO TB and Air Travel Guidance) may need to be reported to WHO under the International Health Regulations (IHR).

Recommendations on the prevention and control of TB transmission on aircraft is based on best currently available scientific evidence and medical practice. Over time, if new evidence emerges in relation to this, it will be reviewed by the committee and the recommendations revised if deemed appropriate.

Prisons

Prisons are a significant reservoir of infection. Infected inmates can spread TB both within the prison and in the community after release. A 2002 survey of the WHO European region found a mean notification rate of 232 new cases per 100,000 prisoners (range: 0-17,808). Highest rates were observed in countries of the former Soviet Union, and have been attributed to overcrowding, poor hygiene and ventilation.

Outbreaks of TB have been reported in prisons in the US and UK. Although TB in prisons was not thought to be a problem in England and Wales in the 1980s, routine surveillance has recently shown an increase in patients in this setting. Prisons in London have been associated with a large outbreak of Isoniazid resistant TB since 2001.

Maintaining control of TB in prisons is challenging because of difficulties with practicalities such as prompt diagnosis of patients, identification of contacts, screening and compliance with prophylaxis and treatment. Contact tracing is typically complex in prison settings due to short stays and mobility of inmates. A multidisciplinary team, led by the local public health department (who will undertake the contact tracing), should be convened to manage the intervention. In addition to key prison staff and prison medical services, the team may include other staff who have regular contact with prisoners such as social worker/ education worker/probation officer representatives. CDC guidelines highlight the important role of correctional information systems (e.g. an inmate medical record system and inmate tracking system) in efficient contact tracing. Any contacts who are HIV positive or immunosuppressed should be among those receiving the highest priority evaluation for infection.

If a suspect infectious TB patient is encountered on contact tracing there should be prompt transfer out of the facility for diagnostic evaluation if airborne infection-isolation rooms are not available. If the process is delayed, a substantial number of persons might be exposed as a result of the congregate living arrangements that characterize correctional facilities.

Continuity of care following transfer between prisons and release into the community is seen as a major barrier to treatment completion. For this reason, DOT is recommended for all prisoners receiving treatment for LTBI and active disease. Prison medical services in liaison with local public health departments are encouraged to make arrangements to facilitate treatment completion.

Recommendation:

A multidisciplinary team approach to effectively manage TB contact tracing in prisons is required. This team should be led by the local public health department who will undertake contact tracing. DOT is recommended for all prisoners receiving treatment for active disease and should be considered for those receiving treatment for LTBI.

Other High-Risk Settings

Homeless shelters are important sites for transmission of M. tuberculosis and an important cause of the continuing high incidence of TB among the homeless population. Contact investigations may be wide ranging. Genotyping may help with the rapid identification of clustered cases and site

Cross border contact tracing

As an airborne disease, the transmission and spread of TB does not respect international borders, meaning that the movements of people across national borders pose real risks that lead to the increased transmission and spread of the disease.

Cross-border population movement is therefore a major social determinant of health associated with the transmission of TB, including multi-drug resistant TB (MDR-TB) and extensively drug resistant TB (XDR-TB) in the ECSA-HC region.

Serious intervention between bordering countries should be put in place.

- Both countries should come up with a joint TB preventive/contact tracing committee
- All diagnosed DR-TB persons with due-citizenship should be exchanged among countries for effective contact tracing
- All country nationals diagnosed with DR-TB as visitors from another country and initiated on second line treatment should be shared with health professional from their mother country for contact tracing and DOT monitoring
- Data collected should be shared with the country initiated the patient for register completeness and data management

Evaluation of Contact Tracing

The evaluation of outcomes from contact tracing is important for evaluating the TB control programme, determining the appropriateness of decisions made regarding the contact investigation and future planning. The results of the investigation of each circle of contacts should be evaluated to determine the risk of transmission, attack rates, etc. The following information should be collected:

- The number of contacts identified (particularly close contacts)
- The number of contacts who underwent a full evaluation
- The number of contacts diagnosed with active disease
- The number eligible for preventive therapy and
- The number who accepted and completed preventive therapy.

Recommendation:

Evaluation of all contact tracing activities is recommended. The following information should be collected: (a) number of contacts identified, (b) number of patients of active disease and LTBI and (c) the number of persons who accepted and completed preventive therapy.

Symptomatic adult contacts

Close contacts with TB symptoms should receive a more aggressive diagnostic workup. The **initial evaluation should include:**

- History and physical exam by a clinician
- Sputum investigations (ideally a rapid diagnostic method such as Xpert MTB/RIF Ultra, Truenut or, if not available, sputum smear microscopy, culture, and DST)
- Chest radiograph
- HIV test

If the contact appears to have active TB disease:

- Ensure that Xpert MTB/RIF, culture, and DST have been performed and other baseline evaluations obtained according to the treatment guidelines (See Chapter 8 for details on baseline evaluations prior to treatment initiation).
- While awaiting full DST results, **seek the approval of the National DR-TB Expert Panel** to start an empirical regimen based on the resistance pattern of the index patient.

- In contacts suspected of having extrapulmonary TB, bacteriological confirmation may be difficult. One of the more common presentations of extrapulmonary TB among recently infected contacts is pleural TB. Sputum culture should always be done, since patients with extrapulmonary TB often have subtle pulmonary involvement, but sputum cultures will be positive in at least approximately 30% of patients with pleural TB. DST should also be ordered for all MDR contacts with a suspicion of extrapulmonary TB.

If the initial investigation is not suggestive of active TB:

- Household contacts and close contacts, if possible, should have follow-up evaluations at 6, 12, and 18 months after the index case is diagnosed and started on second-line treatment (figure 15.1).
- A chest radiograph should be kept on file by the clinical team because it is often helpful to compare subsequent radiographs for continued symptoms or development of new symptoms in the future.

Figure 15.1 Steps in contact tracing following the diagnosis of an index DR-TB case

DR – TB Patient diagnosed	
1st visit	<p>When: Within the first week</p> <p>Activities:</p> <ol style="list-style-type: none"> 1. Complete the Home Assessment form 2. List all contacts using the DR-TB Contact Tracing form and evaluate each for TB signs or symptoms 3. Collect sputum from all symptomatic contacts 5 years and older who are able to produce sputum and send for Xpert MTB/RIF test; refer those under 5 years for further investigation 4. Refer those with signs and symptoms of TB to the nearest facility for chest radiograph 5. Offer HIV counselling and testing and provider-initiated testing and counselling 6. Collect GPS coordinates
Follow up visits	<p>When:</p> <ul style="list-style-type: none"> • At 6, 12, and 18 months following the initial evaluation • Exception is when contacts are children under 5 years or HIV+ where first follow-up visit is 3 months from the initial evaluation <p>Activities:</p> <ol style="list-style-type: none"> 1. Complete the DR-TB Contact Tracing form for each contact evaluating for presence of TB symptoms 2. Collect sputum only from those with signs and symptoms of TB and send for Xpert MTB/RIF test 3. Refer those with signs and symptoms for chest radiograph

If the contact remains symptomatic:

- Repeat physical examination. **Smears and cultures** should be performed **monthly** with **repeat chest radiograph** to detect infiltrates, intrathoracic adenopathy, or pleural effusion as indicated.
- Refer to a chest specialist for evaluation, opinion, and diagnosis.
- A trial of a broad-spectrum antibiotic, one that is not active against TB (e.g., trimethoprim/sulfamethoxazole), may be considered for signs and symptoms of pneumonia. However, this should be done very cautiously in seriously ill patients or those with known or suspected HIV infection who are less likely to have positive sputum smears and are more likely to progress rapidly without appropriate TB treatment. Pleural effusion in this setting without clear indication of bacterial pneumonia is more likely due to TB than other causes.
- Bronchoscopy with bronchial airway samples for smear and culture and/or pleural fluid or pleural biopsy for smear and culture should be considered in specific cases and when indicated by an expert on DR-TB. It is important to keep in mind that delay in the diagnosis of DR-TB and start of appropriate treatment can lead to increased morbidity and mortality, as well as unchecked amplification and transmission of drug- resistant strains of TB.

Paediatric contacts

Children who live with MDR-TB patients, particularly young children, have a high risk of infection with MDR-TB and of developing active MDR-TB. **DR-TB should be suspected in a child who is:**

- A close contact of a DR-TB patient
- A contact of a TB patient who died while on treatment when there are reasons to suspect that the disease was DR-TB (i.e., the deceased patient had been a contact of another DR-TB case, had poor adherence to treatment, or had received more than two courses of anti-TB treatment)

- A bacteriologically confirmed TB case who is not responding to first-line drugs given under direct observation

The diagnostic workup of child contacts of DR-TB patients should include the following:

- History and physical exam by a physician or clinician
- Chest radiograph (posteroanterior and lateral views for children under five years of age)
- Tuberculin skin test (Mantoux) with purified protein derivative
- Sputum investigations for symptomatic pediatric contacts (ideally a rapid diagnostic method such as Xpert MTB/RIF or, if not available, sputum smear microscopy, culture, and DST); if the child is under five years of age or cannot expectorate sputum, induced sputum or gastric aspiration for smear, Xpert MTB/RIF, culture, and DST should be considered.
 - NOTE: Referral should be made to a specialist trained in sputum induction or gastric aspiration to ensure a good specimen is collected.
- HIV counseling and testing for parent(s) known or suspected to be HIV-infected, as well as testing for the exposed child.

According to *Guidance for national tuberculosis programs on the management of tuberculosis in children (WHO 2014)*, the presence of three or more of the following should strongly suggest a diagnosis of TB in a child contact:

- Chronic symptoms suggestive of TB
- Physical signs highly suggestive of TB
- A positive tuberculin skin test
- Chest radiograph suggestive of TB including infiltrates, adenopathy, and/or pleural effusion.

Management of TB infection in close contacts of DR-TB patients

The goal of treating TB infection is to prevent infected persons from developing active TB disease. WHO has recommended TPT for contacts of MDR/RR-TB since 2017. This recommendation was conditional, based on evidence of very low certainty and is not specific to use of any particular drug regimen. Its implementation has thus been poor.

TB preventive treatment for contacts of MDR-TB

A regimen of **6 months of daily Levofloxacin** should now be used as TPT for contacts of MDR/RR-TB considering new evidence from two well-conducted randomized controlled trials in South Africa and Viet Nam supporting the use of Levofloxacin of this regimen in people of all ages. WHO is yet to provide guidance on implementation.

Chapter 16:

Drug resistance and infection control

This chapter briefly reviews the recommendations that have a specific focus on DR-TB. For additional information see *Uganda National Guidelines for Tuberculosis Infection Control in Health Care Facilities, Congregate Settings, and Households*.

Definition TB infection prevention and control

A combination of measures aimed at minimizing the risk of TB transmission within populations.

Rationale for TB infection prevention and control

Tuberculosis (TB) continues to be a major public health concern and one of the leading causes of death from a single infectious microorganism at the global level (1). The TB notification rate among healthcare workers was 441/100,000 compared with that in the general population (217/100,000) in 2022. This signifies ongoing TB transmission in healthcare settings. Additionally, there is a much higher transmission rate in congregate settings such as prisons with a notification rate of 1,865/100,000, and in households with a notification rate of 2,370/100,000 among contacts in 2022 (2).

Key recommendations of this chapter:

- Infection control, including administrative and engineering controls and personal protection, shall be made a high priority in the DR-TB program.
- XDR-TB patients should be placed in isolation until no longer infectious.
- DR-TB patients co-infected with HIV should receive routine care outside of normal HIV care settings.

DR-TB infection control

- 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 and in institutional settings. Since every transmission averted represents one less potential DR-TB case, infection control is a leading programmatic priority. It is equally important to protect health workers in the care settings of DR-TB.
- The management of DR-TB does not significantly alter the basic TB infection control strategies. However, every site (hospital, outpatient department clinics, primary health care facilities, prisons, etc.) attempting to treat DR-TB should also undertake a systematic review of current practices and ensure that everything possible is being done to prevent transmission between patients, inmates, and staff.
 - Patients suspected or known to have infectious TB, whether known to have DR-TB or not, should be isolated until determined not to have infectious TB.
 - Patients should be considered non-infectious when:
- The diagnosis of TB is excluded OR
- The patient has documented culture conversion with two consecutive negative cultures, continues on effective therapy, and adheres to periodic sputum monitoring

The priorities of infection control

- Infection control, including administrative and environmental controls and personal protection, should be made a high priority in all DR-TB control.

Recommendations for infection control to prevent DR-TB are essentially the same as those to prevent the spread of drug-susceptible TB, with only minor differences in emphasis. Of note, **XDR-TB patients should be placed in isolation until no longer infectious.** Additionally, DR-TB patients should receive routine care outside of normal HIV care settings.

Role of rapid tests in infection control

- The use of a rapid DST for Rifampicin or other anti-TB drugs is an excellent method of distinguishing those who may have DR-TB from others. Patients who are identified by rapid *Uganda National Guidelines for the Programmatic Management of Drug-resistant Tuberculosis, 2nd edition*
- tests can be properly separated or isolated immediately, in addition to starting proper empirical regimens.

TB infection control has the following three components listed by order of importance:

- Administrative controls
- Environmental or engineering controls
- 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.

16.2.1 Administrative control measures in various settings

- Administrative control measures (work practices) include policies and procedures intended to reduce the amount of TB germs generated into room air by a TB patient when he or she coughs. Therefore, these measures reduce the exposure of healthcare workers and patients, and visitors to TB germs. They are the first and most important control measures.
- Administrative control measures are a vital part of sound infection control practices, which require people with TB symptoms to be promptly identified, separated (most desirable would be to have separate isolation rooms), and treated. In facilities where isolation rooms are not yet available, the following important administrative infection control practices should be followed:

Patient triage and screening at outpatient clinics

- Patients should be screened for cough as they enter the health care facility and should receive basic education about TB respiratory hygiene.
- Patients with a cough lasting over two weeks should be sent to a separate, well-ventilated waiting area and fast-tracked to sputum examination.
- All coughing patients should receive tissues or face masks and should be asked to cover their mouth and nose when they cough.
- HIV-positive clients are vulnerable and are at a higher risk of contracting TB; therefore, avoid placing presumed or known DR-TB patients in the same waiting area as patients coming for routine HIV care services. DR-TB clients with HIV should receive their ART through the TB clinic or TB ward, and TB status should be clearly indicated on the patient's ART card/file.

Inpatient settings

- The circulation of visitors, patients, and their attendants in the hospital should be strictly controlled.
- Patients should be encouraged to spend as much time as possible outdoors.
- Visiting areas should be well marked. Restricted High-risk areas should have signage forbidding/ restricting visitors entry
- Encourage visits outside the building, in open air, especially for contagious patients.
- If visits outside are not possible and the patient is deemed infectious:
 - Limit the duration of the visit and age of the visitor (avoid exposing children)
 - Provide information on transmission risk to the visitor and instruction on use of respirator during visits; patient should wear a surgical mask
- TB wards must be well-ventilated and lit and separated from the other wards in the health structure facility compound.
- Ideally, patients may be placed in single rooms.
- If single rooms are not possible, **cohort isolation** must be implemented. In this approach, patients are separated by degree of contagiousness (smear/culture status), as well as risk of resistance (DR-TB status if known) and HIV status.

Example of cohort isolation

- Sputum smear-positive patients may be separated from less or noncontagious forms of TB (smear-negative pulmonary TB, extrapulmonary TB, patients who have converted)
- Known or suspected MDR-TB patients may be separated from drug-susceptible TB patients
- XDR-TB patients may be separated from MDR-TB patients without XDR-TB
- Immunosuppressed patients (such as HIV-positive patients) should be separated from contagious TB patients.
- Infectious patients with XDR-TB, whether infected with HIV or not, should not be placed on general wards. Given the high mortality rates associated with XDR-TB, such patients should be isolated until they are no longer infectious. Forced isolation and human rights are discussed further in Chapter 19.
- Decongesting health facilities
- A key factor for transmission of TB in health care and congregate settings is overcrowding. Therefore, decongestion practices reduce the risk of TB transmission in those setting. Such practices include;
- initiating MDR-TB treatment in the community (ambulatory care)
- limiting the duration of hospital stay
- multi-month medicine dispensing for patients attending chronic care clinics e.g. HIV

Community/home settings

- Patients and families with infectious TB should be taught to adhere to home isolation restrictions until determined to no longer have infectious TB. During the period of home isolation, the patient should be advised to refrain from routine locations like work, school, places of worship, etc.
- The patient should wear a surgical mask when in contact with others in poorly ventilated areas until such time that smears and/or culture become negative and patient shows response to second-line treatment (ideally until culture conversion for patients in high-risk settings [e.g., HIV clinic, nursery]).

- Children under five years of age, persons with HIV, and pregnant women should spend as little time as possible in the same living space as the DR-TB patient during the patient's period of infectiousness.
- Health care workers visiting a smear-positive DR-TB patient in the patient's home, and anyone tending to the DR-TB patient, should wear properly fitted personal protective (N95/FFP2) respirators until the patient is deemed non-infectious.
- Whenever possible, conduct visits outside the home, in the open air, especially during the period the DR-TB patient may still be infectious.
- Provide education to the patient and patient's family on TB transmission, airborne precautions (cough etiquette), visitor restriction, use of masks, and waste management of sputum containers and tissues.

Prison/ Correctional settings

- To address the burden of TB and DR-TB in prisons, a comprehensive package of measures is required. These include:
 - **Early diagnosis** to reduce exposure to other inmates and staff using systematic screening and rapid diagnostics
 - Use a combination of screening methods (screening on entry, mass screening at regular intervals, daily passive screening, contact screening) based on clinical questionnaires and self-referrals.
 - Use molecular WHO rapid recommended diagnostics (mWRD), such as Xpert MTB/RIF, for all inmates with HIV and those with TB symptoms.

Proper infection control

- Sputum of persons with TB symptoms *must* be collected in well-ventilated areas. Exposing staff and other inmates to aerosols containing TB bacilli coughed into the air during this procedure should be avoided.
 - Keep presumed infectious TB and DR-TB inmates separate from other inmates (particularly those with HIV). **MDR-TB cases must be separated from other TB patients.**
- Prison health and security staff should educate and counsel patients who are put in these isolation rooms about the reason for separation. They should emphasize that it is a preventive measure and not a punishment.
- **Adequate living conditions and nutrition**

-Individual cells for segregating prisoners, should be a minimum of 6 square meters¹.

¹ European Committee for the Prevention of Torture and Inhuman or Degrading Treatment or Punishment (CPT)

The CPT's minimum standard for personal living space in prison establishments is:

- 6m² of living space for a single-occupancy cell
 - + sanitary facility
- 4m² of living space per prisoner in a multiple-occupancy cell
 - + fully-partitioned sanitary facility
- at least 2m between the walls of the cell
- at least 2.5m between the floor and the ceiling of the cell

- -[Mandela Rule 14: In all places where prisoners are required to live or work:
 - (a) The windows
- shall be large enough to enable the prisoners to read or work by natural light and shall be so
- constructed that they can allow the entrance of fresh air whether or not there is an artificial
- ventilation; (b) Artificial light shall be provided sufficient for the prisoners to read or work
- without injury to eyesight].
- -[Mandela Rule 22: 1-Every prisoner shall be provided by the prison administration at the usual
- hours with food of nutritional value adequate for health and strength, of wholesome quality,
- and well prepared and served. 2-Drinking water shall be available to every prisoner whenever

he or she needs it.

- **Supervised and complete treatment of TB** and DR-TB with appropriate drug regimens and assured drugs/medicines
- **Treatment of comorbidities** including HIV, diabetes, hepatitis, and substance use disorders
- **Continual educational activities to** raise TB awareness among prisoners and medical and non-medical prison staff
- **Continuity of care** for released prisoners who are on treatment for TB or DR-TB and for individuals who are on TB treatment before entering prison services. Physically, handover DR-TB patients to the nearest MDR-TB treatment hospital for continuity of care.

Administrative control measures – ending isolation

Criteria for discontinuing isolation: Patient no longer required to wear a mask and may return to daily activities

- Patient is determined not to have infectious TB as defined above and is not considered to be experiencing treatment failure or relapse
- Patient is remaining adherent to treatment as prescribed and adherent to routine sputum monitoring
- Due to high rate of relapse, XDR-TB should be individually assessed and decision on when to discontinue isolation determined by the DR-TB Expert Panel

Environmental (or engineering) control measures

- Environmental controls are the second line of defense for prevention of TB transmission to health care workers and other persons in the health care facility. These controls assume that unsuspected, undiagnosed, untreated TB patients will enter hospitals despite all efforts to identify them before entry.
- Environmental control measures include methods to reduce the concentration of infectious TB germs in the air as well as methods that control the direction of infectious air. The choice of environmental control options factor into building design, construction, local climatic, and socioeconomic conditions. Environmental controls include natural and/or mechanical
- ventilation, use of negative air pressure, directional airflow, installation of air purifiers², ultraviolet germicidal irradiation, and high-efficiency particulate air filtration. Environmental methods should never replace administrative controls; in fact, they complement each other in their order of hierarchy.
- In Uganda, the climate is normally warm; hence, infection control is largely dependent on natural ventilation.
 - Clinics should be designed with large, permanently open windows (even at night and in rainy seasons) without interior corridors (hallways) walls, which tend to trap air inside.
 - Waiting areas should be open on at least three sides.
 - Extraction fans can be used to improve ventilation in closed rooms through wall vents.
 - Where mechanical ventilation systems are in place, they should be well maintained and checked (air movement measurements) to ensure that they function correctly.
- Laboratories that process specimens that may be DR-TB require particularly strict environmental controls. Laboratory aspects are discussed in Chapter 5 of these guidelines.

Personal respiratory protection

- Because administrative and engineering controls cannot provide complete protection, the third and final infection control measure against nosocomial TB transmission is the use of personal particulate respirators.
- “Particulate respirators” or simply “respirators” are designed to protect the wearer from inhaling tiny particles (1–5 µm), including infectious TB droplets, in areas where the concentration of TB germs in the air cannot be adequately reduced by administrative and environmental controls. In situations where there is an increased risk of TB transmission, respirators should be used together with administrative and environmental controls. The use of respirators requires training, fit-testing, and supervision.

Respirators should be worn when:

- In contact with contagious patients
- Collecting sputum samples
- Collecting or disposing of sputum containers
- Entering areas where droplet nuclei could be present (e.g., when entering a room occupied by a known or presumed infectious patient with DR-TB)

- Processing sputum samples
- Cleaning DR-TB wards
- Surgical masks are designed to protect the operating field from relatively large respiratory droplets generated by surgeons and surgical nurses. These masks are usually made of cloth or paper and are loose fitting. Surgical masks are provided to the known or presumed DR-TB patient to wear in order to limit the amount of droplets coughed or expelled into the air.
 5. Surgical masks should be worn by known or presumed contagious DR-TB patients when they leave their room to go to another department or any other enclosed area.
 6. It can be uncomfortable for a patient to have to wear a mask for a long time; therefore, their use is limited to when the patient leaves the MDR-TB ward.
 7. Wearing a mask in public areas could be stigmatizing. Instead, DR-TB patients could use a scarf or handkerchief to achieve the same purpose. Once culture conversion has been documented, the patient is considered not to be infectious and can discontinue use of the mask.

Essential actions for effective TB infection control

1. **Safety without stigma.** Include patients and community in advocacy campaigns. The community needs to be well educated about TB infection, prevention, and control. Additionally, all patients should be counselled to ensure that they understand:
 - Their right to rapid TB diagnosis and treatment.
 - The benefit of knowing their HIV status to take advantage of available services.
 - TB can be spread by coughing, and to expect health settings and community services to require people who are coughing to cover their mouths.
 - Health workers may wear personal protection equipment sometimes, or that patients may be asked to wear a mask to protect others.
 - Safety without stigma should be the goal. A request to wear a mask or to provide sputum outside the health facility or in a well-ventilated room means a safer clinic for everyone. It's important that such requests be made, showing respect to the patient, and that questions the patient may have regarding the request are fully answered.
 - Respirators (also known as high-filtration masks, or N95 masks, or FFP2 standard masks) provide a bacterial filtration efficiency of greater than 95% if challenged with 0.3-micron particles. MTB is trapped in the filter of a mask, which will not be released with shaking or other physical movements of the mask. MTB eventually dies once outside the human body. These masks should be worn when in contact with contagious patients (either suspected or confirmed cases).
 - Patient and health care worker safety may include receiving health care in the community to avoid unnecessary admissions to health care facilities. Information, education, and communication campaigns need to include themes such as, "Our community is TB-safe," or "Our health facilities are stopping TB."
2. **Develop or adapt an infection control plan.** Each health care facility should have an infection control plan, with a staff person or team responsible for it. The plan should identify high-risk areas for TB transmission and should provide information on TB and HIV rates for health workers and patients. The plan should provide area-specific infection control recommendations for the health care facility, including special standard safety procedures for its laboratory.
3. **Ensure safe sputum collection.** Sputum collection can be potentially hazardous for health workers and other patients; workers need to explain to patients that safety without stigma is

the goal of good TB infection control, and stress that sputum needs to be collected outdoors, if feasible.

4. **Promote cough etiquette and cough hygiene.** The waiting area of every health center should have a poster on TB infection control and cough etiquette.
 - When coughing, patients need to be instructed to cover their mouths and nose with a cloth such as a handkerchief, clean rag, tissue, or paper mask. All staff are responsible for safety and are advised to work together to help patients adhere to this practice.
 - When tissues, cloths, or face masks are not available, patients need to be instructed to lift their arm up and cover their nose and mouth with the inner surface of the arm or forearm when they cough or sneeze.
 - Non-touch receptacles for disposal of used tissues and masks should be available in the waiting areas.
5. **Triage TB suspects for “fast-track,” or separation.** Screen all patients on arrival for chronic cough (i.e., two or more weeks), fever, weight loss, night sweats, hemoptysis, or contact with a person with TB.
 - Explain to all health care facility visitors that safety without stigma is the goal, and that the screening is part of quality care.
 - Patients need to understand that they have a right to rapid TB diagnostic services and treatment.
 - Individuals suspected of having TB should be fast-tracked for rapid diagnosis and care services, or should be asked to wait near an open window or in a comfortable area separate from the general waiting room (outdoors when possible).
 - Use community-based treatment whenever possible.
 - Patients with known or suspected DR-TB should be separated from other TB suspects.
6. **Ensure rapid diagnosis and treatment initiation.** Patients suspected of having TB should move to the front of the queue for all services for prompt evaluation for TB. (This preference does not put them before patients with emergency problems such as difficulty breathing or bleeding.)
 - Sputum collection should be done away from other people, and specimens sent to laboratory for AFB smear. Turnaround time for sputum AFB smear results should be no more than 24 hours if testing is done onsite.
 - A patient-tracking system ensures that TB suspects who are AFB smear-negative receive additional procedures (e.g., CXR and referral visits), or treatment as quickly as possible.
 - DOT for TB should begin immediately when TB is diagnosed, and a plan for ensuring adherence to treatment needs to be developed.
7. **Improve room air ventilation.** Patient waiting areas should be open and well ventilated well-ventilated. Leave windows and doors open when possible to maximize cross-ventilation.
 - Appropriately placed simple fans can assist ventilation.
 - When weather permits, open-air shelters with a roof to protect patients from sun and rain are recommended.
 - Patients should not wait for services in narrow, poorly ventilated corridors.
 - When health centre renovations are being carried out, the management team should consider TB infection control as an integral part to building plans.
8. **Protect health workers.** Health workers should know the symptoms of TB and be given a health assessment, including screening for TB and HIV, at least every year. All workers are encouraged

to know their HIV status, and those with HIV infection should be given the opportunity to minimize exposure to persons with TB (e.g., offered a change of duties). HIV-infected workers should be screened for active TB and offered Isoniazid preventive therapy as part of basic HIV care and treatment if no active TB is found.

9. **Capacity building.** All health workers should receive TB infection control training, and be engaged in improving their own and patient safety. This training may be combined with other infection control training.
10. **Monitor infection control practices.** Overseeing infection control practices should be a part of every supervisory visit. This should include:
 - Facility tour to check that infection control is being implemented and that all essential supplies are available. At the very least, facilities should have an infection control plan.
 - Examining medical records of a sample of TB patients, looking at the time interval from admission to suspicion of TB, time to ordering sputum for AFB, time from ordering to collection of sputum, collection of sputum to reporting of results, and to initiation of TB treatment.
 - Interviewing patients to discuss their understanding of infection control, safety, and stigma.
 - When feasible, monitoring annual TB cases among health workers can also provide useful information on transmission of TB in facilities.
 - **How to promptly identify TB suspects in the waiting areas.** Before patients enter an enclosed part of the facility, a designated staff person should ask each adult and any child capable of coughing forcefully (usually age 14 or older) about symptoms or recent history of TB. The questioning should occur before patients wait in line for long periods to register or obtain services. Attention should be paid to the patient's right to privacy, and screening should be conducted in a manner that is sensitive to the issues of stigma that may surround TB.
 - Simple screening questions are: "Do you have a cough?" If patient answers "yes," ask: "For how long have you been coughing?" An adult who has coughed for two weeks or more, or for any duration in PLHIV, may be considered a person with presumed pulmonary TB. To determine whether a patient may be under investigation, or is a diagnosed case of TB who may still be infectious, the staff member needs to ask: "Are you being investigated or treated for TB?" If the answer to either is "yes," the screen classifies the patient as a person with presumed or active TB.

Waste management

- Standard infectious health care waste treatment related to sharp and soft waste should be respected. There are no specific measures for TB services.
- Used containers for MDR samples should be collected in a leak-proof trash bag and incinerated. Do not reuse containers. Do not fill the containers with chlorine solution before incineration (this can produce toxic gases).

Chapter 17:

Human resources: training and staffing

This chapter considers the development of human resources for DR-TB control and addresses a broad agenda that includes the overall management of training and issues related to staffing.

General considerations

Ensuring competent and sufficient human resources for the implementation of a DR-TB control program of high quality requires ongoing management. In many instances, additional staff with appropriate expertise have to be recruited to manage the activities of the program at the central and other levels. Central management should estimate staff requirements for the implementation of all aspects of the program. Realistic projections, based on task analysis, revision of job descriptions, and estimation of workloads for concerned staff, form the basis of a plan for human resource development (HRD) to support the program.

Human resource development plan for DR-TB control program in Uganda

There are numerous constraints to the effective performance of the health workforce, as indicated in table 17.1.

In line with MOH's HRD plan, the DR-TB HRD plan should describe the training required for all staff involved in the diagnosis and treatment of TB, DR-TB patients, as well as the national authorities responsible for overseeing the program. The plan should also include or reference the proper regulatory documents.

HRD plan goal and objectives

The overall goal of the plan is to improve the quality of the services delivered to DR-TB patients through improvement of the skills of health workers at the various levels. A secondary goal is to improve the efficiency and cost-effectiveness of TB control program management.

The objectives of the HRD component of the DR-TB control program are two-fold:

- To ensure the availability of sufficient staff (clinical and managerial) at all levels to implement the plan
- To ensure that all staff involved in the program (at all service levels, and both public or private) are competent (have the required knowledge, skills, and attitudes) and motivated for implementation

The plan includes the following areas of intervention (or methods) related to capacity building:

1. Development of a training plan with standardized training material and curricula.
2. Establish a national resource group ("master trainers") for strengthening management capacity.
3. Establish regional DR-TB management and training teams.
4. Training hospital staff involved in DR-TB management.
5. Training follow-up facility staff in DR-TB treatment and management.

Table 17.1 Human resource constraints to program implementation

Training/Competence	Staffing/Motivation
Inadequate skills of existing staff:	Imbalances in human resources for TB control:
<p>Many staff involved in TB control are, in general, not trained</p> <p>Suboptimal training (in-service training): lack of specific measurable learning objectives, lack of training materials, inadequate length of training, poor use of adequate training methodologies, lack of learning evaluation</p> <p>An assumption by trainers and control managers that everything taught is learned and will lead to competent performance</p> <p>Lack of attention to other factors influencing behavior change in health care providers</p> <p>Training seen as a time-limited activity that is no longer needed when the treatment strategy has reached 100% coverage ("all have been trained")</p> <p>Inadequate pre-service training</p>	<p>Imbalances in overall numbers</p> <p>Imbalances in distribution</p> <p>Urban/rural imbalance</p> <p>Imbalances in skills or skill mix (a mismatch between the type or level of training and the skills required by the health system)</p> <ul style="list-style-type: none"> - Shortages of human resources for TB control - Increased demand on existing staff (not only by national TB control programs) <p>Impact of AIDS</p> <p>Low staff retention</p> <p>Low staff motivation</p> <ul style="list-style-type: none"> - Under-skilled (inadequate/infrequent training, unsupported, lack of supervision) - Poor work environment - Poor career structure - Underpaid/overburdened - Morale problems - Sick or caring for sick family members <p>Insufficient number of posts</p> <p>Increased "brain drain"</p> <p>High staff turnover</p> <p>Staff rotation between wards</p> <p>Staff stigma</p>

Implementation steps for human resource development plan

To prepare the HRD plan for implementation by the DR-TB control program, the following steps are recommended:

At the national level, the DR-TB Coordinator will be the focal person for DR-TB HRD and will undertake the following:

1. Lead the assessment of human resource requirements of the DR-TB control program and their implications for the existing workforce (clinical, managerial, laboratory, pharmaceutical):
- Define tasks to be performed at each level of the system to implement the DR-TB control program
- Assign tasks to specific categories of health workers
- Assess the time needed to implement those tasks, particularly at peripheral level
- (where changes in the number and type of cases diagnosed and treated have the most impact on the workload)
- Assess how many staff within the respective categories are needed to maintain the current service delivery level, including treatment of DR-TB

2. Assess the current human resources situation of the national TB control program and the health system, and determine the number of staff from the relevant categories available at each program level.
3. Identify the gaps in human resources in terms of both the quantity and quality of staff required to implement the DR-TB program.
4. Prepare short- and medium-term plans, including how to ensure adequate staffing and preparation of training programs based on the task learning needs analysis. The following options can be considered:
 - In-service training (clinical and managerial)
 - Initial training in basic implementation of treatment for DR-TB
 - Retraining (major performance problems need more time than a supervisory visit to solve, e.g., a formal training course)
 - On-the-job training (refresher: small performance problems that can be addressed during a supervisory visit)
 - Continuing training (to gain more skills and knowledge without repeating previous training)

Integrating continuous quality improvement into DR-TB care

Continuous Quality Improvement training (This training will provide Work improvement teams (WITs) with basic knowledge on quality improvement hence supporting the WITs DR-TB teams to routinely collect data on quality of DR-TB care and monitor quality on an ongoing basis)

Incorporating QI approaches to improve DR-TB care involves generating of evidence of best practices for scale up. WITs can use the PDSA cycle approach to improve process indicators like Percentage of DR-TB contacts tracked, find patients earlier, evaluate them quickly, and provide effective treatment resulting in a cure.

Step	Description
Establish the health facility Quality improvement team	<ul style="list-style-type: none"> • The team should have a leader to supervise the work of the DR-TB WITs for different care processes.
Set up DR-TB Work improvement team (WITS)	<ul style="list-style-type: none"> • WIT set up for the different care processes along the DR-TB continuum of care • Dedicate time to understand current process for providing DR-TB services, identify gaps and bottlenecks. • Use the CQI approach through applying the principles of the PDSA cycle (Plan, /Do/Study/Act). •
Identify gaps	<ul style="list-style-type: none"> • WITs meet regularly to review performance and DR_TB indicators. • WITs analyse their data and identify performance gaps by comparing current performance to the set targets/ standards.
Gap analysis to get root causes	<ul style="list-style-type: none"> • Use QI tools like brainstorming, Patient flow charts, five whys, cause and effect analysis to identify the root causes of performance.
Develop feasible solutions	<ul style="list-style-type: none"> • Use QI tools like driver diagram to develop possible solutions to address performance gaps.

Prioritise solutions to address performance gaps		<ul style="list-style-type: none"> • Use a prioritization matrix to prioritize the solutions to be tested/ implemented. • Look for solutions that give maximum benefit at a low cost.
Develop improvement projects using the documentation journal	WITs will	<ul style="list-style-type: none"> • Develop improvement aims from the prioritized gaps. • List all the activities in a particular process targeted for improvement. • Use the activities to develop a flow chart for the process. • Use the flow chart to identify the individuals who will perform the different activities and include them in the WIT for the process. • Develop an improvement objective from the prioritized performance gap with the aid of the DR-TB indicators guidance. • Document the data in the graph template of the documentation journal. • Develop an action plan indicating the changes that the team agreed to test or redesigning the service delivery model.
<ul style="list-style-type: none"> • Coordination with other in-service training programs/training institutions and departments (in particular, measures to retain trained staff, interventions to stop unnecessary rotation of staff, and support for career paths) • Pre-service training (basic training in skills needed before entering in-service training) <p>1. Develop training programs to ensure that:</p> <ul style="list-style-type: none"> • Job descriptions are based on task analysis • Training courses/programs have learning objectives based on the task analysis and the job descriptions • Training courses/programs use methods and time allocation that allow participants to meet the learning objectives • The participant-to-facilitator ratio in each course allows participants to meet learning objectives • Learning objectives have been met <p>2. Consider the following issues in planning and implementing evaluation:</p> <ul style="list-style-type: none"> • Evaluation during training courses <ul style="list-style-type: none"> • By participants to determine whether the course met their needs • Of participants to determine whether their skills met the learning objective(s) • Evaluation in the field • Supervision (post-training evaluation) to identify performance problems and determine the cause of the problems • Specific follow-up immediately after training <p>3. Ensure monitoring and supervision to:</p> <ul style="list-style-type: none"> • Detect performance deficiencies in newly trained staff • Identify new staff in need of training (additional staff needs, staff vacancies) <p>4. Carry out timely implementation of the HRD plan with regular monitoring of the program implementation.</p>		

5. Carry out periodic internal and external evaluation of the implementation of the HRD plan (see figure 17.1), with revision as necessary.

Table YY: Methods for training evaluation

MODEL/ EVALUATION	TYPE OF EVALUATION	DURING TRAINING	POST TRAINING	PERFORMANCE EVALUATION <small>Impact evaluation on target achievements of the program</small>
		REACTION EVALUATION	PERFORMANCE EVALUATION	
BY WHOM	PARTICIPANT FACILITATOR TRAINING TEAM/COMMITTEE	SUPERVISOR	RESEARCHER	
TIME	DURING TRAINING	3–6 MONTHS POST TRAINING Integrated into supervision activities	AS NEEDED	
IMPLEMENTATION COORDINATOR			TRAINING COORDINATOR	

Chapter 18:

Management of second-line anti-tuberculosis medicines

This chapter provides information on management of the second-line anti-TB drugs used in the treatment of DR-TB and the procedures for procurement of these medications.

List of Essential Medicines: Second-line anti-TB drugs

Essential medicines are those that satisfy the health care needs of the majority of the population. The medicine selection is based on the development of treatment guidelines and on the evidence underlying the development of those treatment guidelines. The current List of Essential Medicines includes 23 second-line anti-TB drugs (see table 18.1). This list does not imply that no other medications could be useful in the management of DR-TB, but rather, that these are the basic medications, which, when used in accordance with appropriate therapeutic guidelines, cost-effectively meet the needs of a large proportion of the population with DR-TB.

Table 18.1 Second-line anti-TB drugs included in the Essential Medicines and Health Supplies List for Uganda

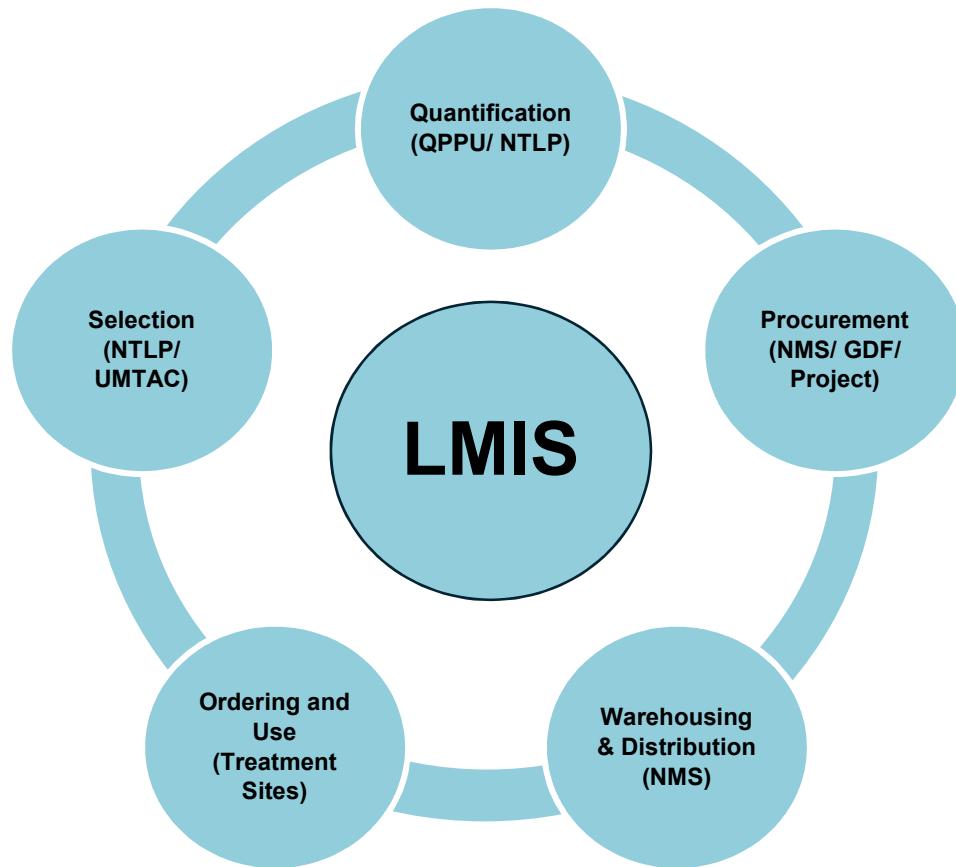
Anti-TB drug	Unit dose
Bedaquiline	100mg and 20mg tablet
Pretomanid	200mg tablet
Linezolid	600mg and 125mg tablet
Moxifloxacin	400 mg tablet
Levofloxacin	250 mg and 100mg tablet
Amikacin	1 g vial
Clofazimine	100mg and 50mg tablet
Cycloserine	250 mg and 125mg tablet
Ethionamide	250 mg and 125mg tablet
Clofazimine	50 & 100 mg capsules
Delamanid	50mg and 25mg tablet
Pyrazinamide	400mg or 500mg tablet
Ethambutol	400mg tablet
High dose Isoniazid	300mg tablet

Medicines that are not included in the Essential Medicines and Health Supplies List for Uganda may be procured upon request from DR-TB treatment initiation facilities with approval from the NTLP Program Manager.

Management cycle of second-line anti-TB medicines

The management cycle of medicines comprises six elements (figure 18.1): medication selection, quantitative assessment of medication requirements, management requirements, of management of procurement, warehousing and distribution, quality assurance, and ensuring rational medication use.

Figure 18.1 Medicine management cycle



Note: *GDF=Global Drug Facility, QPPU=Quantification Procurement Planning Unit, LMIS=Logistics Management Information System*

- Selection of medicines for DR-TB:** Several factors shall be considered when selecting second-line anti-TB drugs, including the efficacy of the medicines, treatment strategy, possible adverse effects, and cost of the treatment (see Chapters 6 and 9).
- Quantification:** Accurate demand forecasting for second-line anti-TB drugs (i.e., correct quantification of the medication needs for a specific period of time) is one of the elements that guarantees an uninterrupted medication supply.

The National Quantification, Planning, and Procurement Unit (QPPU) under the Department of Pharmaceuticals and Natural Medicines (DPNM) of MOH is responsible for national-level quantification and supply planning of DR-TB medicines. The NTLP supply chain advisor will collaborate closely with the QPPU to ensure that commodities for DR TB management are accurately quantified and fully funded. The QPPU will use a combination of morbidity-based and consumption-based approaches to arrive at the most suitable quantities under the circumstances.

Each DR-TB treatment initiation facility will be responsible for quantification and supply planning at the health-facility level ensuring that all items required by patients are obtained in a timely manner to avoid treatment interruption. The quantification approaches used by

QPPU will also apply at the health-facility level. DPNM/QPPU and the NTLP supply chain advisor shall provide technical support to treatment sites especially to ensure timely delivery of supplies from the warehouses.

3. **Procurement of DR-TB anti-TB drugs:** At the national level, DR-TB medicines will be procured by different procurement entities, depending on the source of funding. The National Medical Stores will handle government of Uganda procurements. Other procurements will depend on the conditions of the grant and or project agreements.
4. **Warehousing & Distribution:** All DR-TB medicines procured by the different funders will be received, warehoused, and distributed by the NMS/JMS. DR-TB treatment initiation facilities will place their orders with the NMS/JMS, which will serve and deliver accordingly. The medicines orders will be placed using the electronic ordering system (NMS CSSP or eLMIS/DHIS2).

Inventory Management System: Stock will be held at two levels: 1). NMS and 2) DR-TB treatment initiation facilities. NMS will hold a minimum stock of six months and maximum stock of eight months. Each treatment initiation facility will hold a minimum of two months of stock and maximum of four months of stock. This will allow the country a total minimum stock level of 8 months and maximum stock level of 12 months at any one time.

5. **Logistics Management Information System (LMIS):**

National level stock data; The NMS shall generate, process, and share information on all receipts and distributions of DR-TB medicines. Such information shall be provided routinely (monthly) and on demand. The information shall include receipts, issues, and stock on hand including expiry date and batch numbers, among others. This information shall be submitted to the QPPU and NTLP to facilitate procurement, supply planning and monitoring.

Facility level stock data; Each DR-TB treatment initiation facility shall generate, process, and share information on all DR-TB medicines received and dispensed. Such information shall be provided to NTLP/NMS routinely (every two months) and on demand. The information shall include receipts, issues, and stock on hand including expiry date and batch numbers, among others. By copy of the electronic ordering system, this information shall be submitted to the NTLP to facilitate planning and monitoring.

6. **Quality assurance (QA) and rational use of DR-TB medicines:** To preserve quality, medicines should be stored and transported by the supplier and the NMS following “Good Storage Practices” and the recommendations of the manufacturer regarding temperature and humidity, as detailed in the management of medicines and health supplies manual for Uganda.

The QA component of a medicine supply system makes certain that each medication used by a patient is safe, efficacious, and of appropriate quality. All medicines used in a regimen for DR-TB should meet WHO-recommended standards for safety, efficacy, and quality. QA of the medicines will be maintained under the National Drug Authority regulatory framework.

Access to second-line medicines must be accompanied by measures to ensure rational medication use. 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 medications. NTLP conducts an annual green light committee (GLC) assessment to ensure rational anti-TB drug use, in addition the DPNM performs quarterly stock reconciliation activities to verify if stocks delivered to the treatment sites reached the intended patients.

Although DR TB medicines can be used for other disease conditions as per the Uganda Clinical Guidelines, note that the stocks delivered through the TB program should only be reserved for use by DR TB patients

Ordering and delivery of medicines and supplies

Ordering and delivery of DR-TB medicines shall be based on a pull logistics management system, in which each treatment initiation facility makes a bimonthly order specifying the quantity of each commodity to be supplied by NMS.

There are two steps in making an anti-TB drug request at the treatment centre:

STEP 1: Determine the total consumption for each anti-TB drug (daily, monthly, and bimonthly).

- a) Based on the MDR-TB Treatment Card of the patients in the treatment initiation facility, record the medications to be taken per patient per day.
- b) Calculate the DAILY consumption per anti-TB drug for all patients receiving it.
- c) Calculate the MONTHLY consumption by multiplying the daily consumption by 30 days for oral anti-TB drugs and 26 days for injectables (as one day each weekend is a medication holiday for the injectable).
- d) Calculate order quantity.

EXAMPLE: You want to know the total consumption of Ethionamide in a DR-TB treatment initiation facility. You currently have 200 tablets as the balance on hand. If you have 4 patients taking three 250 mg tablets of Ethionamide a day, and 1 patient taking two tablets of the same medication per day, the calculations for daily, monthly, and order quantity would be:

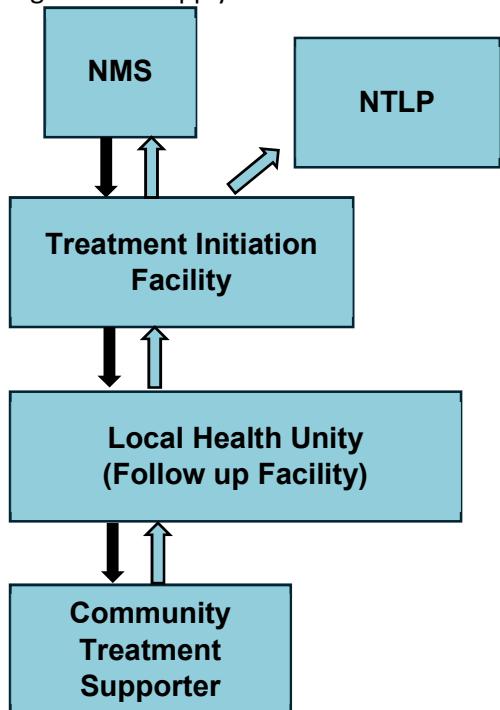
- DAILY consumption = 14 tablets (4 patients x 3 tablets each + 1 patient x 2 tablets)
 - MONTHLY consumption = 420 tablets (daily consumption x 30)
 - 4 months need (maximum stock quantity) = 1,680 tabs (monthly consumption x 4)
 - Ethionamide stock to order = 1,480 tablets (monthly consumption x 4 – the current balance on hand [1,680 tablets – 200 tablets])
- e) Repeat this procedure for all patients and medicines.
 - f) The quantity requested is four months' consumption (maximum stock level) minus the stock on hand. Always double-check calculations.

STEP 2: Fill out the DR-TB Second-line Drug Requisition Form (Form 15) based on the total consumption.

- a) Write the name of the DR-TB treatment initiation facility and the period for which the request is made.
- b) In the first column of the TB Drug Requisition Form, write the medications being requested. These are already pre-printed.
- c) In column A, fill in the daily consumption as explained above. In column B, calculate the monthly consumption ($A \times 30$; multiply by 30 for orals and 26 days for injectables); in column C, calculate the quantity needed by multiplying column B by 4 (4 months' consumption).
- d) In column D, fill in the current stock on hand at the facility. Current stock on hand is determined by doing an actual physical count or is recorded from an updated stock card.
- e) The quantity requested is four months' consumption minus the stock on hand ($C - D$). Always double-check your calculations.

NOTE: The last two columns of the form will be completed by the authorizing staff when the order is filled and sent to the NMS.

Figure 18.2 Supply chain



The DR-TB treatment initiation facility will order all anti-TB drugs for patients under its care, including those sent to follow-up facilities for ambulatory care. Medicines will be sent to follow-up facilities using two medication delivery boxes for two months per patient. The initiation facility must ensure that medicines are delivered to the follow-up facility. The DTLS will pick up empty delivery boxes from follow-up facilities and deliver them to treatment initiation site through RTLFPs.

Returning unused second-line drug stock

In situations where anti-TB drugs are left over (e.g., patient death or lost to follow-up), anti-TB drugs should be returned as early as possible to the treatment initiation facility using the same process noted above and accompanied by a completed Drug Return Form (Form 16).

Chapter 19:

Recording and reporting system for DR-TB

This chapter elaborates on the instruments and minimum variables necessary to register, monitor, and report outcomes for DR-TB patients who require second-line anti-TB medication, integrating Electronic case-based surveillance and pharmacovigilance monitoring systems. The Cohort Review process and indicators for tracking program performance related to detection, enrolment, interim, and final treatment outcomes are also described within this framework.

Key recommendations of this chapter:

- Use updated HMIS Tools and systems which incorporate new diagnostic tests, new WHO definitions, and new data inputs for monitoring program performance indicators
- Use updated reports to report on revised indicators for PMDT

Aims of the information system and performance indicators

The aims of the information system are two-fold:

- To allow managers at different levels to monitor overall program performance (DR- TB patients identified, patients started on treatment, and treatment results), to follow trends in number of cases notified, to plan anti-TB drug supply, and to provide the basis for program and policy developments
- To aid clinical providers in management of individual patients. The performance indicators track:
 - Number of patients detected with RR-/MDR-TB eligible for second-line TB treatment
 - Number of RR-/MDR-TB patients registered and started on second-line TB treatment
 - Interim results of RR-/MDR-TB patients on second-line TB treatment at month 6 and 12 of treatment
 - Final treatment outcomes of confirmed RR-/MDR-TB patients on second-line TB Regimens
 - Post treatment outcomes at 36 Months

Scope of the recording and reporting (R&R information) system

The recording and reporting (R&R) system for DR-TB is based upon, and is an extension of, the basic DOT R&R system. The forms are similar to the standard forms used in DOT programs.

R&R is designed to be consistent across the country to permit comparison. R&R does not include all of the detailed information that treatment units may need to manage individual patients (e.g., information contained in clinical records and other special forms used in the wards or clinics).

Main forms, registers, and flow of information

The forms, registers and systems include the following:

- HMIS TB 002 - REQUEST FORM FOR TB SPECIMEN EXAMINATION
- HMIS TB 004 - DRUG RESISTANT TB TREATMENT PATIENT CONSENT FORM
- DR TB ENROLMENT FORM
- NTLP CULTURE AND DST REQUEST FORM
- DR-TB TREATMENT PANEL APPROVAL FORM
- HMIS TB 001 - SECOND-LINE TB TREATMENT CARD
- HMIS TB 014 - DRUG RESISTANT (DR) TB REGISTER
- HMIS TB 10
- HMIS TB008
- Pharmacy & Logistic forms
- Electronic Case Based Surveillance System (eCBSS)
- Pharmacovigilance Monitoring System-PViMs
- TB Laboratory Information System (TBLIS)
- DAT-Digital Adherence System/V-DOT system

Updated reports include:

- DRTB Section of HMIS 106a Report
- HMIS 033b
- Monthly HMIS 105

Second-line TB Treatment Card (Form 01)

When the Review Panel decides that a patient should start a second-line treatment regimen for RR-TB, the health staff from the DR-TB treatment initiation facility should enter the patient in the Second-line TB Treatment Register (section 19.3.2) and open a Second-line TB Treatment Card for the patient. This card is a key instrument for the clinician/physician who is overseeing the treatment and management of the patient, as well as for the DOT worker(s) who administer anti-TB drugs to the patient daily. The card should be updated daily by checking off the supervised administration of anti-TB drugs. The card represents the primary source of information to complete and periodically update the Second-line TB Treatment Register, eCBSS, and PViMs. The original card is retained at the DR-TB treatment initiation facility and a copy goes with the patient to an ambulatory facility where the patient continues treatment.

The Second-line TB Treatment Card contains the following sections:

Page 1 entails the;

- **REGISTRATION DETAILS**

This describes the patient's prior and present details; Unit-TB No, DR-TB No, NIN, Date, Treatment Initiation Facility, Date of registration, Follow-up health facility 1, Date transferred to this facility, Follow-up health facility 2, and Date transferred to this facility.

- **DR-TB PATIENT BIO-DATA**

This has Patient basic demographic information; Patient Names, Age, Date of birth, Sex, Client category, risk group, marital status, Occupation, and Tel No.

- **PATIENT CONTACT INFORMATION**

The section has the current address for the patient (District, Sub-county/ Division, Parish, and Village / Zone (LC 1)), GIS Coordinates (Eastings and Northings), Contact / Next of Kin (Name, Relationship,

Telephone, District of residence, Sub-county/ Division, Parish, and Village / Zone (LC 1), and Treatment Supporter (Name, Telephone, District, Sub-county/ Division, Parish, and Village / Zone (LC 1).

- **DRUG ABBREVIATIONS**

The summary lists the first-line and second-line drugs used in the treatment of tuberculosis. First-line drugs include Isoniazid (H), Rifampicin (R), pyrazinamide (Z), Ethambutol (E), and others. Second-line drugs comprise Amikacin (Am), Linezolid (Lzd), Levofloxacin (Lfx), Moxifloxacin (Mfx), Bedaquiline (Bdq), Clofazimine (Cfz), Cycloserine (Cs), prothionamide (Pa), high-dose Isoniazid (HHD), Ethionamide (Eto), Delamanid (Dlm), prothionamide (Pto), imipenem (Ipm), and others. This summary provides a concise overview of the various drugs categorized into first and second-line treatments for tuberculosis management.

Page 2:This has the Patient's

BASELINE INFORMATION

The data collection process outlined is extensive and covers various essential aspects of a patient's medical history and current status in managing drug-resistant tuberculosis (DR-TB). It begins with capturing basic information such as the **patient's full name** and the **date of initiation of DR TB treatment**. This foundational data serves as a cornerstone for tracking the patient's progress throughout their treatment journey. Additionally, details regarding the **date of prior TB registration** and any **transfer-in information** from other DR TB treatment facilities provide insights into the patient's prior medical history and potential exposures, aiding in comprehensive care planning.

Furthermore, the inclusion of diagnostic test results such as **GeneXpert and drug susceptibility testing dates** ensures that clinicians have access to timely and accurate information for making informed treatment decisions. **The reasons for entering the 2nd line treatment register** and the registration group based on treatment history offer additional context into the patient's specific needs and circumstances. By documenting known **MDR-TB contact information** and the **completion date of the initial home assessment**, healthcare providers can further tailor treatment strategies to suit individual patient requirements, thus optimising the chances of successful outcomes.

The data collection extends beyond medical factors to encompass social and **demographic information**, such as **HIV status and previous TB treatment episodes** as well as Directly observed Therapy (**DOTS**) Modals:i.e Community, Facility Digital Video, Smart Pill Box etc. This holistic approach enables healthcare teams to address not only the clinical aspects of DR-TB management but also the broader contextual factors that may impact treatment adherence and effectiveness. By systematically documenting these details, healthcare providers can develop more personalised and effective treatment plans, ultimately improving patient outcomes and contributing to the overall success of DR-TB control programs.

Page 3

The Meetings of the DR-TB Review Panel entail recording crucial details such as **dates and decisions related to treatment initiation**, continuation, changes, or cessation, with a focus on treatment regimens. This documentation encompasses the outcomes of drug susceptibility testing (DST), including the date of sputum collection and results of rapid DST tests like Xpert MTB/RIF. Monitoring of smear and culture involves noting sputum collection dates, laboratory sample numbers, and test results, distinguishing between "prior" samples indicating RR-/MDR-TB and baseline samples collected at the start of the second-line treatment regimen.

Within the treatment initiation period, decisions may involve commencing treatment, continuing ongoing treatment, or requiring further evaluation, with various regimen options, including **BPaL**

(Bedaquiline, Pretomanid, Linezolid) /BPALM (Bedaquiline, Pretomanid, Linezolid, and Moxifloxacin), mSTR (9-month all oral) denoting a Modified Short Course Treatment Regimen, and Longer IND referring to Longer **Individualised** regimens. Other periods may involve decisions such as continuing current treatment, adjusting regimens or dosages, or discontinuing treatment. The end of the intensive phase could necessitate transitioning to the continuation phase, continuing intensive treatment, or other considerations. Ultimately, decisions at the end of treatment may confirm the scheduled conclusion or make adjustments based on patient response and clinical evaluation.

Page 4 (Visit Page 1)

The monitoring framework includes weight and nutrition status assessment, X-ray examination, and evaluation of smear microscopy and TB culture. Monthly assessments track weight, height, mid-upper arm circumference (MUAC), and body mass index (BMI), alongside the presence of cavitary disease and primary findings. Progress is noted, including the resolution of TB symptoms, while additional medical parameters such as QTc reading and visual acuity are monitored. The protocol involves documenting whether smears and cultures were conducted, recording their results, and integrating this information into the overall assessment of the patient's condition and treatment progress.

The monthly assessments of weight and MUAC, with height measurements for children, alongside the calculation of body mass index (BMI) at baseline and every six months for adults and every two months for children. Additional evaluations encompass effusion and miliary disease, with options to track progress categorised as improved, stable/unchanged, or worsened. QTc reading, record here the exact figure the patient has. Electrocardiogram (ECG) readings are classified as normal (N) or abnormal (A), with severity grades indicated if abnormal. Smear microscopy results are recorded using a notation method denoting the presence of acid-fast bacilli (AFB) per high-power field (HPF), ranging from 'scanty' to '+++', and culture results are recorded using the number of colonies seen <10 colonies to +++.

Page 5 (Visit Page 2)

Drug susceptibility testing (DST) results are recorded using a notation system: R for resistant, S for susceptible, C for contaminated, I for indeterminate, and Unk for unknown. The data includes the date of specimen collection (in DD/MM/YYYY format), along with results for both second-line line probe assay (SL LPA) and full DST. Results for various drugs are documented monthly, including Amikacin (Am), kanamycin (Km), capreomycin (Cm), ofloxacin (Ofx), Levofloxacin (Lfx), Moxifloxacin (Mfx), and others. Additionally, susceptibility results for key first-line drugs such as Isoniazid (H), Rifampicin (R), Ethambutol (E), streptomycin (S), and pyrazinamide (Z) are recorded, as well as results for other second-line drugs including para-aminosalicylic acid (PAS), Ethionamide (Eto), Cycloserine (Cs), Bedaquiline (Bdq), Delamanid (Dlm), Clofazimine (Cfz), Linezolid (Lzd), Pretomanid (Pa), and any others tested.

TB. SL LPA and Full DST should be conducted at baseline and whenever two consecutive positive cultures are received. This protocol ensures comprehensive monitoring of drug susceptibility patterns, aiding in the timely adjustment of treatment regimens as needed to address emerging resistance.

Page 6 (Visit Page 3)

Laboratory monitoring involves regular assessments of various parameters with specific units for numerical values to ensure comprehensive oversight of the patient's health status. This monitoring is done on a monthly basis for all patients on Treatment. Record the date of test, and month of treatment. These assessments include liver function tests such as ALT/SGPT and AST/SGOT, total bilirubin levels, and albumin concentration, alongside evaluations of renal function through creatinine levels and blood urea nitrogen (BUN). Additionally, measurements of uric acid, potassium, calcium, and magnesium levels are conducted. Blood sugar levels are monitored through assessments of random blood sugar (RBS) or glycated haemoglobin (HbA1c). Haematological parameters such as

haemoglobin (Hbg), hematocrit (Hct), white blood cell (WB) count, and platelet count are also evaluated, along with thyroid function tests (TSH) and assessments of pancreatic enzymes like lipase and amylase. Tests for HIV, CD4 count, cryptococcal antigen (CRAG), viral load, cholesterol levels, hepatitis serology, and pregnancy, are also performed as part of routine monitoring. Additionally, other relevant tests may be conducted based on individual patient needs and clinical indications. All results help the Clinical team to make decisions and interventions accordingly. The decision can even be to change the patient's regimen or substitute certain drugs.

Page 7 (Visit Page 4)

Adverse Effects. Patients are actively assessed for adverse events as long as they are on treatment using

the Adverse Effect screening form. These are graded, recorded, and the date our occurrence is also noted.

Clinicians are supposed to take decisions, and act accordingly using the Clinical Management of Adverse

Events guidelines. The adverse Effects table has the following; Gastrointestinal, Hepatotoxicity, Musculoskeletal, Renal toxicity, Vestibular / Ototoxicity, Vision changes, Neuropathy, Psychiatric, Hypothyroid, Dysglycemia, Dermatologic, Cardiovascular, Hematological, New onset Seizure, Electrolyte

Abnormality, Testicular Changes, Libido, and only add any other new adverse effects if not covered in the

table. If patient is assessed for AEs, enter grade code for side effect as indicated - 0=No side effects 1=grade1 (mild), 2= grade 2 (moderate), 3= grade 3 (severe), 4= grade 4 (life threatening).

Any abnormalities detected are documented in progress notes, in Adverse Effects table, and reported via the Suspected Adverse Drug Reaction Form and Serious Adverse Event (SAE) reporting form

Page 8 (Visit Page 5)

Second-line treatment regimen. Indicate the date treatment is started, changed, or stopped, along with the dosage (mg) of each medication is recorded in this table. One line is used for each date on which a medication(s) is changed. There are added rows to this table to enable recording of drug ramping (e.g., Ethionamide or Cycloserine starting at 250 mg daily and increasing by 250 mg over two to three days until the full dose is reached). There is no need to record drug ramping in a separate part of the medical record or treatment card. The name and signature of the clinician/physician starting or changing the anti-TB drug regimen should be reflected in the column on the right.

Page 9 (Visit Page 6)

Record of daily-observed administration of anti-TB drugs. This is constructed with one line per month to facilitate assessment of adherence. One box is marked for each day the entire treatment is administered. The symbols at the bottom of the table indicate how the dose was given, if the dose was incomplete (not the full regimen), or if the dose was not given. A missed dose (anti-TB drugs not taken) should prompt follow-up action. Missed doses should be tallied at the end of each month and recorded in the column to the far right.

- If all oral medications are given and observed, the dose can be recorded as directly observed (X) or observed by treatment supporter (v).
- Incomplete dose (I) should be indicated in situations when a patient vomits some portion of their medication after taking it, if there is an anti-TB drug stock out resulting in some anti-TB drug(s) missing from the daily prescribed dose, or if the patient refuses some of the medication.

- In order to protect against further acquisition of drug resistance, the policy in Uganda is that the **second-line anti-TB drugs are only to be directly given, and observed**. In rare circumstances, the patient's clinician/physician may determine that it is in the patient's best interest to allow a dose to be self-administered. In such a case, the dose should be recorded as not supervised (**N**). Unsupervised doses should be rare events and the reason should be noted in the comments section on page 7.

– For Drugs not taken indicate (**Ø**)

As long as the patient is on treatment, continue recording on a daily basis as described above.

Page 10 (Visit Page 7)

Monthly Clinical Review notes

The reviewing clinician notes the date of patient review, key findings (TB Symptoms, Adverse events, Adherence (including adjunct and concomitants drugs), co-treatments, General findings (BP, temperature, mucus pallor, skin changes, SPO₂, RR and PR).), plan of action, the Clinician then writes his/her name, and signs off. The months of review run from month 1 to month 20 of treatment.

Final Outcome and Post treatment Monitoring

Treatment outcome.

A final outcome should be assigned to all patients at the end of 24 months of treatment. The outcomes are 1= Cured, 2= Completed, Treatment Failed, 4= Died, and 5 = Lost to follow up. These are explained under other notes, the Outcome definition section. This provides definitions for determining final treatment outcomes. The final outcome is recorded with the date on which the outcome was met.

If the patient was transferred out to another country indicate (a)Yes or (b) No accordingly.

Reviewing physician. The physician or clinician responsible for the patient's second-line TB treatment and reporting of outcomes will write the name, sign and put the date on the Second- line TB Treatment Card once the final outcome has been determined.

Post treatment Monitoring

It is very important to know how the patients are fairing after treatment completion. This is done at 3, 6, and 12 of posttreatment. Record the date sample was collected, post treatment month, Specimen No, Sputum, and Culture result, then finally the outcome whether a Relapse (If culture returns positive with the same initial strain) or Not.

Second-line TB Treatment Register

The NTLP recommends mainly two Registers for longitudinal monitoring of patients; i.e-

a). Unit Tuberculosis Register for all TB patients registered at the facility.

This is the initial register; in which all TB patients eligible for treatment are first registered, including those detected with drug resistance, regardless of whether treatment is actually started or not.

A patient who initiates drug susceptible TB treatment and switches to a second-line anti-TB drug regimen because of RR-TB or MDR-TB should have a comment of "Transferred to Second Line" documented in the outcomes column in the Unit TB Register record and reported as such during the calculation of final outcomes. This patient will now be fully accounted for in the DR TB register.

b). DR TB Register for the DR-TB patients who start treatment using a second-line anti-TB regimen. This register is only located at the DR treatment initiation facility. When a DR- patient is referred to a peripheral facility for follow-up, the documentation will be done in DR Treatment Card (HMIS TB 001)

The Second-line TB Treatment Register. This register will primarily keep records of all DR TB patients starting with personal demographics, laboratory investigations at baseline, patient categorisation, treatment initiation, contact investigation, TB/HIV and monitor Smear and culture follow ups. The register also captures adverse drug reactions monitoring monthly and routine follow up visits, treatment details at baseline and change of regimen along the continuum of care if applicable. The Second-line TB Treatment Register (HMIS 001) shall be updated regularly from individual Second-line TB Treatment Cards and Laboratory Registers. Patients are recorded in the register chronologically by their date of registration.

A copy of the Second-line TB Treatment Card (Form 01) will be kept at the follow-up (peripheral) facility.

Those mono- and poly-resistance TB patients (H, HS, HE, and HZ) whose regimens do not require, or require only one, second-line anti-TB drug should be maintained in the Unit TB Register where adjustment of their regimen should be recorded, including any second-line agents used (see Chapter 7).

Some patients started on second-line treatment regimens may be found to have rifampin- susceptible disease.

- Patients in this situation are removed from second-line TB treatment and placed on appropriate first-line therapy.
- The patient's name is then crossed out of the Second-line TB Treatment Register (but the name left legible) and a comment noted in the last column that he/she has drug-susceptible disease.
- All patients who are switched should be re-registered in the Unit Tuberculosis Register (if they are already registered in the Unit TB Register, the final outcome should be documented in the original line of registration; if possible, do not create a new registration). These patients should not be counted in the DR-TB reports (Form 05 and Form 06/HMIS 106a) as they do not have RR-TB.

Any patient with Rifampicin-resistance (mono- or poly-resistance) should be registered in the Second-line TB Treatment Register and treated on the standard MDR-TB regimen (see Chapter 6). Whether the patient continues on the same second-line treatment regimen or gets an individualized regimen based on DST can be documented on the treatment card, and the final outcome reported in the Second-line TB Treatment Register.

The following information is recorded in the Second-line TB Treatment Register:

- DR-TB registration number. Record the serial number (three digits) followed by the initials of the treatment site and the year of registration (e.g., 001/MLG/2014 for patient number one in Mulago registered in 2014). The numbers change after every calendar year.
- Date of registration. The date of registration should be the day when the treatment initiation facility health staff enters the patient into the Second-line TB Treatment Register.

- Names, phone numbers, sex, age, address. Entered from the Second-line TB Treatment Card, page 1.
- Drug-susceptible/Unit TB registration number. All patients should have been entered in a Unit TB Register. A patient who for any reason has never been registered in the Unit TB Register should be registered there and the number transferred to the Second-line TB Treatment Register.
- Nucleic acid amplification test (e.g., Xpert MTB/RIF results and date). The Xpert MTB/RIF result taken at month 0 (start of treatment) should be recorded here, including the date the sample was taken. If more than one Xpert test was done prior to treatment start, the most recent positive result is registered.
- Second-line anti-TB drugs received for more than one month prior to registration. Information comes from DR-TB Treatment Card, page 2.
- DST (from Second-line TB Treatment Card, page 3). Under this section, include the specimen lab number, date the sample was collected, results of DST, and date DST result is reported. Enter the DST that resulted in the patient being registered for second-line TB treatment. If the DST is performed in a staged manner (e.g., Rifampicin and Isoniazid first, followed by second-line anti-TB drugs in case the patient is RR-/MDR-TB), the results can be completed as they become available, as long as the sample is the one taken before the start of treatment, which is used for registration. Any follow-up DST results are recorded in the Treatment Card, but not in the register.
- Date of DR-TB panel approval
- Reason for entering second-line treatment register. The patient may be a laboratory confirmed or a presumptive case of RR-/MDR-TB. In the case of a patient with poly-resistance without RR-TB who is registered on treatment, a note “not applicable” may be entered to ensure the case is not enumerated in cohort outcome monitoring.
- Type of case (from Second-line TB Treatment Card, page 2). In this section, record the site of disease (pulmonary or extrapulmonary) and the registration category. Patients with both pulmonary and extrapulmonary TB should be classified as a case of pulmonary TB.
- Transfer in facility and date
- Date start second-line treatment. Record the date second-line treatment was started (first DOT dose taken).
- Standard, empirical, individualised. Record whether the regimen started was a standard regimen, empirical regimen, or individualised regimen.
- Second-line treatment regimen (from Second-line TB Treatment Card, page 3).
- Record the initial second-line treatment regimen using the anti-TB drug abbreviations.
- Modality of DOT. Record the date second-line treatment started as either facility-based DOT (FB DOT) or community-based DOT (CB DOT). Note that patients may start as facility-based DOT but are later transferred to the community for treatment continuation.
- DR-TB contacts. Record the total number of contacts identified for each index patient in row 1, the number fully evaluated in row 2, and the number found to have active TB in row 3.
- Initial weight (from Second-line TB Treatment Card, page 2). Record the patient’s weight at baseline (month 0).

- TB/HIV section (from Second-line TB Treatment Card, page 2). Record the baseline HIV status of the patient at the time of registration. For patients who are HIV-positive, record baseline CD4 count and date, as well as date CPT and ART treatment started.
- Monitoring smear and cultures (from Second-line TB Treatment Card, page 3).
- Record all smear and culture results, even if conducted more often than recommended frequency.
- M6 interim treatment outcome. Insert M6 interim outcome from the Cohort Review
- Follow-up facility. Record the name of the follow-up facility delivering treatment, the district, the follow-up facility phone number, and date patient was transferred to the follow-up facility.
- Final outcome (from Second-line TB Treatment Card, page 7). See Chapter 2, section 2.3 for definitions.
- Post-treatment follow-up cultures. Enter results of sputum smears and cultures obtained every six months post treatment completion.
- Comments/remarks. This column may be used to record any notes on the patient, such as if they move or if their place of treatment or intermediate outcomes change. Also, indicate here if a patient is found not to need second-line TB treatment and is transferred back to the Unit TB register.

NTLP DR-TB Laboratory Register for Culture and DST (Form 04)

Laboratories will have separate registers for sputum smear microscopy and culture, while reference laboratories carrying out DST should have additional space in the culture register for DST results. The NTLP DR-TB Laboratory Register for Culture and DST should contain samples from all MDR-TB suspects, indicating the registration group (including if positive smear at three or four months), and be filled in from the request form.

The MDR-TB focal person should regularly/monthly compare MDR-TB cases identified and registered in the Laboratory Register to those in the Second-line TB Treatment Register to ensure that all confirmed MDR-TB cases are entered in the Second-line TB Treatment Register. He/she should proactively look for those missing.

Updated PMDT reports and indicators

There are now four sets of indicators for PMDT reporting. The indicators cover detection, enrolment, interim results, and final outcomes, and have been standardized to form the basis for annual reporting on DR-TB by countries to WHO. To streamline and ensure timely reporting, three of the reports have been combined into one—the Quarterly Report on Drug- resistant TB Cases Registered (Form 06/ HMIS 106a). The remaining indicator on detection will be captured in the Quarterly Report on Detection of TB Cases with RR-TB and MDR-TB (Form 05). The key indicators that are tracked by WHO are defined below.

Report on detection of TB cases with RR-TB and MDR-TB

The NTLP will report on these revised WHO detection indicators for RR-/MDR-TB every six months from information collected on the Quarterly Report on Detection of TB Cases with RR-TB and MDR-TB (Form 05). Reporting periods are January–June and July–December.

DETECTION INDICATORS AND CALCULATIONS

1. TB patients with result for Isoniazid and Rifampicin DST (High priority)

Numerator: Number of TB cases with DST result for **both** Isoniazid and Rifampicin by each risk category specified in the national policy during the period of assessment.

Denominator: Number of TB cases identified in each respective risk category during the period of assessment.

Data source: Numerator data are available from the Laboratory Register; denominator data from the Unit TB Register and Second-line TB Treatment Card. For some risk categories (e.g., contacts of MDR-TB), the information may not be in the Treatment Card and has to be traced from elsewhere in their medical records. See Case Finding Chapter 4 (table 4.1) for list of target groups for DST (national risk groups).

2. Confirmed MDR-TB cases detected among TB patients tested for susceptibility to Isoniazid and Rifampicin⁷

Numerator: Number of confirmed MDR-TB cases by each risk category specified in the national policy during the period of assessment.

Denominator: Number of TB cases in each risk category with DST result for **both** Isoniazid and Rifampicin during the period of assessment.

Data source: Numerator data are available from the Laboratory Register; the denominator is identical to the numerator of Detection indicator 1. The risk groups are described in Chapter 4 on case finding (see table 4.1 for list of target groups for DST, which will represent the national risk groups).

3. Confirmed MDR-TB cases tested for susceptibility to any fluoroquinolone and any second-line injectable anti-TB drug (High priority)

Numerator: 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.

Denominator: Number of confirmed MDR-TB cases during the period of assessment.

Data source: Numerator data are available from the Laboratory Register; the denominator is identical to (non-disaggregated) numerator of Detection indicator 2.

4. Confirmed XDR-TB cases detected among MDR-TB patients tested for susceptibility to any fluoroquinolone and any second-line injectable anti-TB drug

Numerator: Number of confirmed XDR-TB cases detected during the period of assessment.

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.

Data source: Numerator data are available from the Laboratory Register; the denominator is identical to the numerator of Detection indicator 3.

5. Interval between presumption of RR-/MDR-TB and DST results

Definition: The duration in days between the date when the TB patient was identified as being in a risk category as per the national policy and the dates of the DST results for Isoniazid and Rifampicin as recorded in the Laboratory Register. The first date is determined by type of risk category. This date may correspond to when TB is diagnosed if universal DST is practised, or when a laboratory result indicates treatment failure or persistent sputum smear positivity during the course of TB treatment, or when HIV-associated TB is detected. In the case of a contact with TB, this would be when the laboratory confirms MDR in the source case, which may precede or occur after the diagnosis of TB in the contact (information as in the Laboratory Register). In sites testing with Xpert MTB/RIF alone, the indicator can be modified to include all cases with a Rifampicin test result and the date of the first result showing Rifampicin resistance is used, regardless of whether the same patient was confirmed to be MDR-TB or not subsequently.

The calculation is done on all cases with DST results for Isoniazid and Rifampicin (sensitive or resistant) entered in the Laboratory Register during the six-month period of assessment. The difference in days between the two dates is summed for all patients and divided by the number of cases with test results. The indicator is expressed as the arithmetic mean number of days with the minimum and maximum ranges for the episodes included in the calculation. The number of episodes included in the calculation should be indicated.

The five indicators for detection measure the progress toward universal access of TB patients to diagnosis of drug resistance, a key indicator for PMDT.

The first two indicators are calculated for all cases tested and for each risk category.

- These include all TB patients previously treated for TB, patients failing a new or retreatment first-line regimen (Cat 1 or 2 regimen), contacts of a confirmed MDR-TB case, or other individuals considered to be at risk of drug resistance (see Chapter 4).
- The delay in testing and the frequency of MDR-TB among individuals in different risk categories are also evaluated. These parameters are important to evaluate how the targeting and timeliness of DST, as well as the yield of MDR-TB cases, vary by risk category.
- In sites testing with Xpert MTB/RIF alone, in particular, the *Detection indicators* 1, 2, and 5 should include all cases with a Rifampicin test result and the main object for detection changed to a case with RR-TB rather than MDR-TB.

Report on enrolment of TB cases with RR-TB and MDR-TB on second-line TB treatment

The Program Manager is responsible to ensure that all patients in whom MDR-TB is detected are placed on appropriate treatment in the shortest time possible. This may also apply to patients at risk of drug resistance but who are not confirmed (presumptive). The data to report on enrolment indicators is captured in the Quarterly Report on Drug-resistant

TB Cases Registered (Form 06/HMIS 106a), section A. This revised form will enable the NTLP to track timeliness from diagnosis to treatment start in patients that qualify for second- line TB treatment.

In Uganda, patients with RR-TB detected by Xpert MTB/RIF alone will be treated as if MDR- TB and, therefore, will be included in the enrolment calculations as if MDR-TB, given they will receive an MDR-TB regimen. Four minimum indicators are included to assess the coverage of enrolment of TB patients

on second-line TB treatment, with separate stratifications for children and females, who may encounter differential access to care in certain settings. An additional sub-grouping for HIV-positive, RR-/MDR-TB patients assesses the proportion of them placed on ART.

ENROLMENT INDICATORS AND CALCULATIONS

1. RR-/MDR-TB cases (presumptive or confirmed) enrolled on MDR-TB treatment

(High priority)

Definition: 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 second-line anti-TB drugs treatment during the period of assessment.

Data source: *The number of RR-/MDR-TB cases (presumptive or confirmed) is obtained from the Second-line TB Treatment Register; the comparator data are sourced from the Basic TB Register and Laboratory Register for Culture, Xpert MTB/RIF, and DST. For confirmed cases, the date of DST result is used; other cases are defined by the date when they are presumed to have RR-/MDR-TB (e.g., patients whose treatment failed are defined when sputum smear remains positive). This indicator is computed for (i) all cases, (ii) cases aged <15 years, and (iii) females.*

2. Confirmed RR-/MDR-TB cases enrolled on MDR-TB treatment regimen⁸ (High priority)

Definition: Number of confirmed MDR-TB cases registered and started on a prescribed MDR-TB treatment regimen during the period of assessment.

Comparator: Number of confirmed MDR-TB cases detected during the period of assessment.

Data source: *The number of confirmed MDR-TB cases on treatment is obtained from the Second-line TB Treatment Register; the comparator data are sourced from the Laboratory Register for Culture, Xpert MTB/RIF, and DST (using the date of DST result).*

This indicator is computed for (i) all cases, (ii) cases with HIV on ART, and (iii) cases with HIV but not known to be on ART.

3. 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.

Comparator: Number of confirmed XDR-TB cases detected during the period of assessment.

Data source: *The number of confirmed XDR-TB cases on treatment is obtained from the Second-line TB Treatment Register; the comparator data are sourced from the*

8 In sites testing with Xpert MTB/RIF alone, the indicators can be modified to also enumerate RR-TB cases started on a second-line TB treatment and compare them to RR-TB cases, presumptive or confirmed

Laboratory Register for Culture, Xpert MTB/RIF, and DST (using the date of DST result).

4. Interval between RR-/MDR-TB diagnosis and start of MDR-TB treatment

Definition: The duration in days between the date of RR-/MDR-TB confirmation (DST results showing resistance to both Isoniazid and Rifampicin in the Laboratory Register) and the date when the patient started a prescribed second-line anti-TB drug regimen as per the Second-line TB Treatment Register; in sites testing with Xpert MTB/RIF alone, the indicator is modified to include all confirmed RR-TB cases and the date of the first result showing Rifampicin resistance is used regardless of whether the same patient was confirmed with MDR-TB or not subsequently (i.e., the date when the patient was first found to be eligible for an MDR-TB regimen).

The calculation is done on all confirmed RR-/MDR-TB cases recorded on the Second-line TB Treatment Register during the six-month period of assessment. The difference in days between the date of confirmation and start of treatment is summed for all patients and divided by the number of treatment episodes. The indicator is expressed as the arithmetic mean number of days with the minimum and maximum ranges for all episodes included in the calculation. If treatment was started before the confirmatory DST was reported, then the interval is marked as zero days. The number of episodes included in the calculation should be indicated.

The enrolment indicators are measured in the month following the end of the six-month period (January–June and July–December). All data can be extracted from the Basic TB Register, the Second-line TB Treatment Register, and the NTLP DR-TB Laboratory Register for Culture, Xpert MTB/RIF, and DST.

Report on interim results of TB cases with RR-TB and MDR-TB on second- line TB treatment

Treatment for MDR-TB typically takes 20 months or more, and final outcomes can thus only be assessed two to three years after enrolment. The program manager often needs an indication of how patients are faring before that. This is particularly important when a DR-TB treatment component of a program is starting.

- Assessing culture conversion to negative (for confirmed pulmonary cases) in month six and death by six months is widely used as an indicator of treatment response.
- Information on loss to follow-up by six months is helpful.
- It is also useful to know how many patients started on second-line anti-TB drugs for MDR-TB turned out not to have MDR-TB (and likewise for XDR-TB). This evaluates the effectiveness of the treatment algorithm in treating patients who really need second-line regimens and avoiding a potentially toxic regimen in patients who do not.

The period of assessment is three calendar months (January–March; April–June; July– September; and October–December). All patients registered and starting treatment during the period of

assessment are included in the calculation. The report is completed on cohorts quarterly, nine months after the closing day of the cohort. Data to complete the six-month interim results for the Quarterly Report on Drug-resistant TB Cases Registered (Form 06/HMIS 106a), section B is reviewed and finalized during the DR-TB Cohort Review, which is held quarterly (see section 18.4.5).

When the NTLP evaluates and reports the program performance on the interim results, **only laboratory confirmed RR-TB, MDR-TB, and XDR-TB cases that have started treatment are counted**. When calculating the proportion of cases with negative culture by six months, all patients started on treatment remain in the denominator, including patients who died or were lost to follow-up before six months. If a patient is lost to follow-up and dies by six months, then the result retained will be *lost to follow-up*, having been the first outcome met. The interim result indicators include:

1. Number of confirmed RR-/MDR-TB cases started on second-line treatment
2. RR-/MDR-TB cases on MDR-TB treatment regimen with negative culture by/at month 6

Numerator: 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. **NOTE:** Applies only to pulmonary bacteriologically confirmed cases.

Denominator: Number of **confirmed RR-/MDR-TB** cases registered and started on treatment for MDR-TB during the period of assessment. Confirmed RR-/MDR-TB is defined as one in which there is laboratory confirmation of RR or MDR (includes pre- XDR and XDR).

3. RR-/MDR-TB cases on MDR-TB treatment regimen who died by six months

Numerator: 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.

Denominator: Number of confirmed RR-/MDR-TB cases registered and started on treatment for MDR-TB during the period of assessment.

4. RR-/MDR-TB cases on MDR-TB treatment who were lost to follow-up

(defaulted) by 6 months

Numerator: Number of confirmed RR-/MDR-TB cases registered and started on a prescribed MDR-TB treatment that were lost to follow-up by the end of month 6 of their treatment.

Denominator: Number of confirmed RR-/MDR-TB cases registered and started on treatment for MDR-TB during the period of assessment.

5. Patients on MDR-TB treatment regimen found not to have MDR

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.

6. Patients on XDR-TB treatment regimen found not to have XDR

Number of patients started on a prescribed XDR-TB treatment regimen during the period of assessment and later found not to be XDR-TB.

Report of final outcomes of TB cases with RR-TB, MDR-TB, and XDR-TB on second-line TB treatment

The final outcome is **the most important direct measurement** of the effectiveness of the PMDT control program. Data to complete the Quarterly Report on Drug-resistant TB Cases Registered (Form 06/ HMIS 106a), section C is reviewed, and final outcome designation finalized through the DR-TB Cohort Review which is held quarterly (see section 18.4.5). Outcome definitions were updated by WHO in 2013 (see Chapter 2 for the list and definitions of final outcomes). All confirmed DR-TB patients entered in the Second-line TB Treatment Register should be assigned one of the six mutually exclusive outcomes at the end of their therapy.

- Cases that are not evaluated due to transferring out, treatment still not completed at the time of final assessment, or missing information are grouped together under “Not evaluated for outcome.”
- A patient who “transfers in” does not get enumerated in the cohort of the receiving treatment facility, but only in the outcome cohort of the facility where treatment was started.
- All patients should be assigned the first outcome they experience for the treatment being evaluated.
- The outcome Cured is restricted to bacteriologically confirmed pulmonary TB cases.
- The period of assessment is 12 calendar months, usually counted from January– December and referred to as an annual cohort.
- All patients registered and starting treatment during the annual cohort are included in the calculation.
- Only laboratory confirmed RR-/MDR-/XDR-TB cases are counted for cohort reporting of Final Outcomes.
- Outcome indicators are measured 24 months after the end of the year of assessment.
- Final Outcomes of cases with positive HIV status will also be delineated separately, as the proportion of TB cases with HIV in Uganda exceeds the 5% WHO threshold.

Cohort review

DR-TB Cohort Review is a **systematic process to monitor and evaluate the interim and final outcomes of DR-TB patients**. It is a process that identifies both individual patient and health systems issues, *addresses accountability at all levels of DR-TB care*, and serves as a mechanism for program oversight.

The Cohort reviews are at Regional level (Quarterly), and at National level (yearly). These meetings bring together a multi-disciplinary group of NTLP (central, regional, and/or district-level, including M&E); DR-TB clinical and nursing providers; and laboratory, pharmacy, and social services representatives to analyse interim patient data at 3,6 and 12 months, and final outcome data at 24 and 36 months, for cohorts, based on the quarter of treatment initiation. When possible, other appropriate participants (implementing and community partners, medical specialists, academics, etc.) may also be included, particularly to coordinate linkage of services.

Review of data includes targeted presentations of key indicators and milestones of care for individual patients by provider teams from the responsible treatment initiation facilities using a designated Cohort Review Presentation form.

Meetings have been designed as an “enhanced” Cohort Review process by:

- Linking to quarterly DR-TB Expert Panel Reviews, so that the combined activities provide a strong multi-disciplinary capacity building forum including an organised discussion forum of challenges/action steps to summarise and address active program challenges as they arise, assign action steps, and monitor for resolution as a mechanism for continuous quality improvement.
- SOPs and tools have been developed for this process. The cohort Review presentation form is attached amongst the other other tools.

Assuring the quality of the R&R system

Adequate training and supervision are essential for the effective functioning of the information system for Drug-Resistant Tuberculosis (DR-TB). It is crucial for a central unit to conduct regular supervisory visits to the units utilising the information system to uphold the quality of the data. Additionally, holding regular meetings involving staff from various levels can aid in keeping information up to date. The individual overseeing patients diagnosed with Rifampicin resistance, those linked for second-line TB treatment, and those who have initiated treatment should regularly compare data with that in eCBSS and LabXpert DS systems, preferably on a weekly basis. Quarterly meetings for data harmonisation, periodic assessments of data quality, and cohort review sessions are also recommended. Furthermore, triangulating data among electronic systems such as eCBSS, Labxpert, TBLIS, and DHIS2 is essential. Ensuring timely follow-up to update data from community and peripheral health facilities is crucial for maintaining accurate and current information.

Electronic Patient level data Management systems

Whereas PMDT Data is well captured using the HMIS Manual system of cards and registers, The NTLP noted a need for electronic systems to ensure timely, reliable and quality data is collected to enable analysis and quick decision making. The Program has so far developed electronic case based surveillance Systems (eCBSS), Pharmacovigilance Management System, and worked with partners to have interoperable links with Laboratory Management Information System(LMIS), DAT System and Labxpert DS. The systems components are described below:

1. LabXpert DS:

This is a web-based connectivity solution that streamlines the collection of diagnosis information from Genexpert, Truenat, Digital Xray and Afinion machines, minimising the need for manual data entry. It utilises multiplexing technology to efficiently gather data from multiple machines. The system features a dashboard for easy monitoring and management, with modules for various functionalities such as Total Tests conducted, along with breakdowns for MTB+ (Mycobacterium tuberculosis positive), RIF+ (Rifampicin-resistant), Negative results, and Indeterminate results, error tracking, utilisation analysis, trend identification, and statistical reporting. It caters to different facilities and users, enhancing efficiency and accuracy in data management and analysis.

Specifically for Rifampicin Resistant patients, the system allows for capture of patient details for diagnostic and follow up purposes.e.g full name, age, contact information, and residential details including village, parish, sub-county, and district. Additionally, it records the patient's assigned laboratory number, next of kin details, and relevant medical information such as HIV status and reason

for the diagnostic request. The system also documents sample-related information such as sample type, date of collection, appearance, volume, and any additional comments. Furthermore, it allows results dispatch via SMS to both the requester and the patient directly.

Currently an interoperability function is underway to link the details of MTB+ patients identified directly to eCBSS for continuous enrolment and treatment.

2. eCBSS

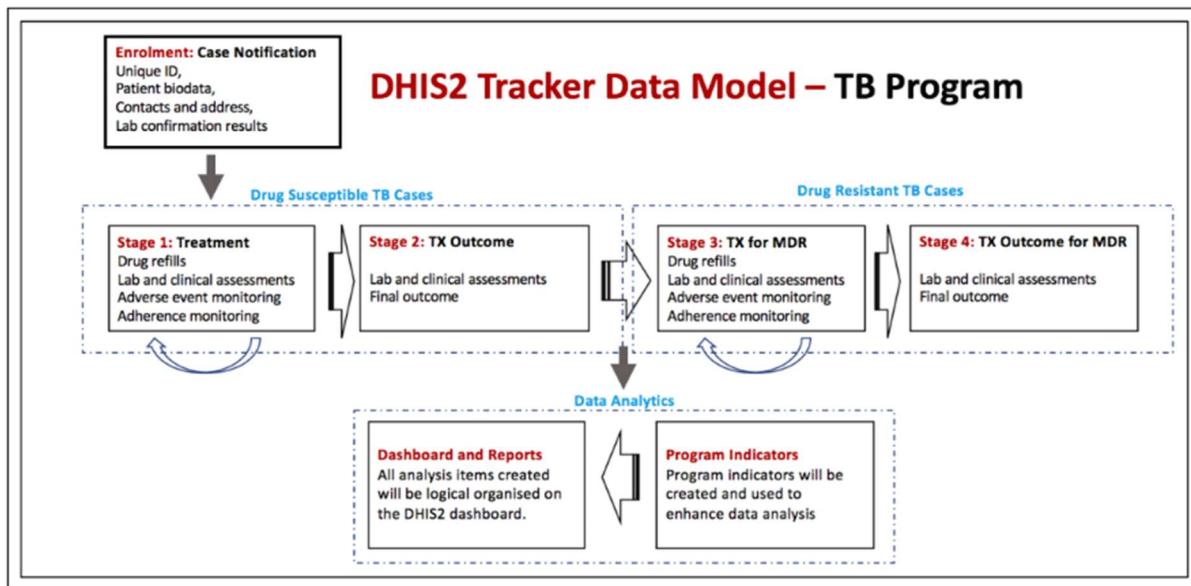
The eCBSS is a web-based system that is built on a customised instance of District Health Software (DHIS2), an open source software platform for reporting, analysis, presentation and dissemination of data for several programs. The system also takes advantage of the offline reporting features with the DHIS2 platform to enable reporting using the android features on Tablets and Smartphones. The system is also built around the following goals and objectives;

The overall objective of the national electronic case-based surveillance systems (eCBSS) for TB and Leprosy program is to provide an efficient system of monitoring patient management, reporting and surveillance of TB and Leprosy at all levels of service delivery.

Specific objectives of the TB/leprosy eCBSS are:

- To improve TB/leprosy treatment outcomes of individual patients through case-based monitoring for the treatment duration. For instance, improving day-to-day management and monitoring of patients at facility level, monitoring of patient transfers and or self- referrals across accredited and non-accredited TB and leprosy treatment units.
- To improve surveillance and public health reporting. For instance, improving the coverage, quality and timeliness of data available to decision-makers on disease control including case notification, treatment outcomes, improving monitoring of trends in TB and TB/HIV disease burden or enabling rapid responses to emerging problems such as DR-TB.
- To improve TB/leprosy medicines and logistics management at the community, health-care facilities, district, regional up to national level. For instance, management of stock levels for TB medicines and free more time for health care workers for patient care.
- The eCBSS workflow considers the step-by-step process of gathering TB and Leprosy data using the current existing national structures. The workflow also follows the standard DHIS2 data models to ensure the system meets user needs as specified in the user documentation.

DHIS2 tracker data model - TB program



eCBSS captures data on Laboratory, Drug Susceptible TB, Multidrug Resistant TB, Leprosy and Contact Tracing as described below:

i) Laboratory Program:

This programme simulates the TB laboratory registration, which the system captures. (Laboratory) Report date, investigations, sample referral from community? Yes/No, Name of Facility/Unit if sample is referred from outside the Facility. Patient information includes examination type, months of follow-up, examination results (smear, GeneXpert, LAM, lab tests), and TB care status.

Yes or No, Health Facility and Level of Care, The system is updated whenever a new patient is tested and the laboratory returns results confirming them as a Bacteriologically confirmed TB Patient documented in the TB Laboratory Register.

ii) Drug Susceptible TB Program:

This programme copies the patient's treatment card, capturing information about the patient such as baseline, Treatment, lab tests, contact screening, transfer, community follow-up, DOT, and treatment outcomes.

Baseline Visit Date, Type and Classification, Disease Classification, Patient Type, Referral Date, Referral Source, Name of Referring Facility/Community, Referral District, Phone Number of Referring CHW

Treatment started with first-line treatment. DS-TB regimen: e.g 2RHZE/ 4RH, whether diagnosed with DR-TB, date of diagnosis, Date began DR-TB treatment, DRTB number, HIV status date, ART status, ART number, CPT/Dapson number, risk group. Health Care Worker, TB Contact, Prisoner, Pregnant, Refugee, Uniformed/Armed Personnel, Fisher People, Diabetic, Miner, Tobacco User, Mentally Ill, Others, GeneXpert Results Diabetes Status.

iii) Drug resistant TB Program:

This Program is similar to the DRTB Treatment card, outlining the information to be captured. E.g Baseline Information, History, Vitals, HIV/ART information, Previous TB Treatment, and Admission details. Each section contains specific fields such as dates, treatment history, medical diagnoses, vital

measurements, and HIV testing status. The card aims to comprehensively document patient information relevant to DR-TB treatment and management,

It also captures Treatment Information such as; Weight & Nutrition Monitoring." This section includes fields such as Treatment month (from 0 to 24), Weight, Height, BMI, MUAC (Mid-Upper Arm Circumference), X-Ray and ECG findings, TB symptom resolution status, DR-TB ECG results, drug administration details including date of drug pickup and regimen initiation, and a section for documenting adverse events with their respective dates. This part of the card focuses on monitoring the patient's progress throughout the DR-TB treatment regimen, including nutritional status, radiological findings, drug administration, and any adverse reactions.

Other essential sections crucial for monitoring and managing patients with drug-resistant tuberculosis. DR TB Panel Review and relevant panelist information. The Laboratory Information section covers prior TB registration, diagnostic tests, treatment initiation details, and other medical diagnoses. Vitals are meticulously recorded, including weight, height, BMI, and MUAC, while HIV/ART status and previous TB treatment history are also documented. Admission status is noted, alongside **treatment outcomes** and post-treatment sputum monitoring details. This comprehensive card serves as a vital tool for healthcare providers to track patient progress, evaluate treatment efficacy, and ensure effective management of DR TB cases.

iv) Contact Tracing Program:

The contact tracing program focuses on screening and testing individuals for tuberculosis (TB) exposure. It starts with the Screening Date and Event point coordinates (Latitude and Longitude). The Screening section involves assessing symptoms such as cough, fever, weight loss/poor weight gain, and excessive night sweats, along with an option to specify other symptoms. Additionally, there's a determination of whether the contact is a presumptive TB case. The Test and Results section includes evaluating HIV status and sending samples for Xpert and microscopy testing, as well as referring the client for further evaluation if necessary. There's also an option to specify other tests if applicable. This structured approach aids in identifying potential TB cases among contacts and facilitating appropriate testing and referral for evaluation, contributing to the control and prevention of TB transmission

It also has a **Test Results section which** encompasses the outcomes of tests and evaluations conducted. It allows for selection or specification of test results and final contact tracing outcomes. Additionally, it includes details regarding TPT (TB Preventive Treatment), indicating whether the contact was referred for TPT and if they started on it. The "Linkage for Treatment" aspect records the date of TB treatment initiation, the health facility and its level of care, TB identification number, and the date of ART (Antiretroviral Therapy) initiation if the individual is HIV positive. This section serves to monitor and document the follow-up actions and treatment linkage for contacts identified through the tracing program, ensuring comprehensive care and management for those potentially exposed to tuberculosis.

1. The Pharmacovigilance Management Information System (PVMIS)

The Pharmacovigilance Management Information System (PVMIS) is a database designed by NTLP to facilitate the monitoring, reporting, and analysis of adverse drug reactions (ADRs) and other safety-related information associated with pharmaceutical products. It serves as a central repository for collecting data from various sources such as healthcare professionals, patients, regulatory authorities, and pharmaceutical companies. PVMIS plays a crucial role in drug safety surveillance by enabling the

systematic evaluation of reported adverse events, identification of potential safety concerns, and the implementation of risk management strategies. Additionally, it supports regulatory compliance by providing tools for signal detection, risk assessment, and regulatory reporting. PVMIS contributes to enhancing patient safety and the overall quality of healthcare by ensuring the timely detection and mitigation of drug-related risks.

2. Laboratory Management Information System (LMIS)

The Laboratory Management Information System (LMIS) designed for Multidrug-Resistant Tuberculosis (MDR-TB) aims to optimise laboratory operations related to MDR-TB diagnosis and treatment. This system facilitates efficient sample tracking, inventory management, quality control, and result reporting tailored to MDR-TB testing procedures. It enables prompt and accurate delivery of MDR-TB test results to healthcare providers and patients while ensuring compliance with relevant regulations and standards. By analysing MDR-TB test data, monitoring treatment outcomes, and supporting communication and collaboration among stakeholders, this specialised LMIS enhances the effectiveness of MDR-TB control and management efforts, ultimately contributing to improved patient care and public health. The facilities are able to see data in real time

3. Video DOT System/DATs

A Video Directly Observed Therapy (DOT) System for Tuberculosis (TB) patients is a technology-enabled solution designed to enhance the monitoring and management of TB treatment remotely. This system utilises video communication platforms to enable healthcare providers to observe patients taking their medication doses in real-time, thereby ensuring treatment adherence and efficacy. Patients can use their smartphones or other devices to connect with healthcare professionals during their medication-taking sessions, eliminating the need for in-person visits to healthcare facilities. Video DOT systems offer convenience for patients, especially those in remote or hard-to-reach areas, while allowing healthcare providers to monitor treatment progress closely and intervene if necessary. By improving treatment adherence and reducing the risk of TB transmission, video DOT systems play a crucial role in achieving successful TB treatment outcomes and controlling the spread of the disease. Currently an interoperability Link is underway to ensure the system syncs the data into eCBSS

PMDT data flow

Uganda's recording and reporting system for PMDT and information flow through the health organisation levels is described below, as well as in figure 19.1.

PMDT DATA FLOW

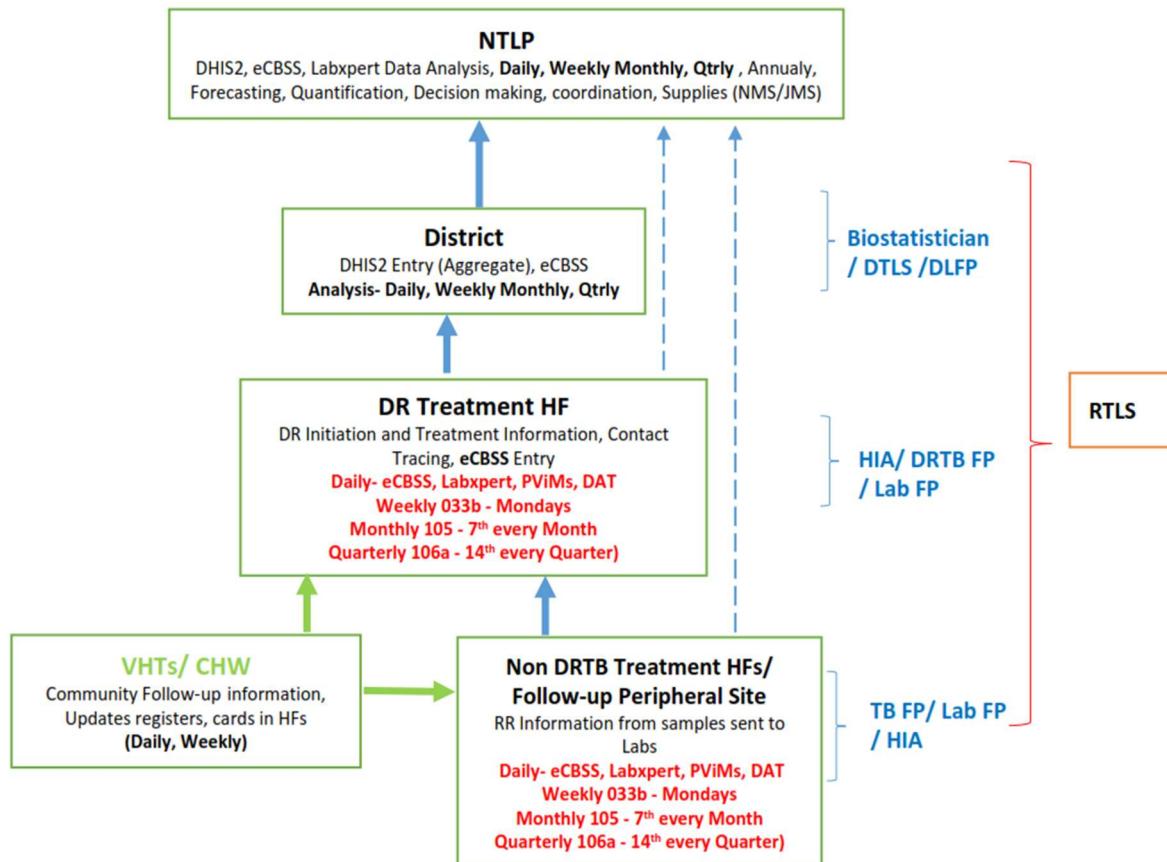


Figure 19.1: PMDT Data Flow Diagram

1. **Non DRTB Treatment Site Peripheral/follow up health facility:** Site where the patient receives DOT for second-lineTB treatment.
 - a) **Forms and instruments to be used:**
 - HMIS TB 004 - REQUEST FORM FOR TB SPECIMEN EXAMINATION
 - Copy of HMIS TB 001 - SECOND-LINE TB TREATMENT CARD
 - Household Assessment (Form 13a) and Contact Investigation forms
 - HMIS TB 010 - TB Client Held Card
 - TB Contact Tracing Form
 - Video DOT System
 - b) **Update:**
 - Update Second-line TB Treatment Card daily
 - Receive patient progress notes/reports and update the Second-line TB Treatment Card
 - In each monthly patient visit to the treatment initiation facility, the DOT provider/treatment supporter will take the copy of the Second-line TB Treatment Card from the follow-up facility with them in order to update records at the treatment initiation facility or check the Video DOT System and update.

- Record DOT transactions and any comments on the Second-line TB Treatment Card
 - Conduct the Household Assessment and Contact Investigation as per the guidelines.
 - Provide original Household Assessment and Contact Investigation forms to the treatment initiation facility and keep a copy onsite.
2. **DR-TB Treatment Initiation Facilities** (Sites where patients' requiring second-line TB treatment will be enrolled, started on treatment, monitored and side effects managed)
- a. **Forms and instruments:**
- Second-line TB Treatment Card (Form 01)
 - Second-line TB Treatment Register (Form 02/HMIS 096b)
 - Culture and DST Request form (Form 03a)
 - NTLP NTRL GeneXpert Request and Report form (Form 03b)
 - Quarterly Report Section on Drug-Resistant TB Cases Registered (Form 06/HMIS 106a)
 - HMIS DR TB enrolment form
 - NTLP DR-TB Treatment Approval form (Form 09)
 - TB008 Patient Referral and Transfer form (Form 10)
 - DR-TB Treatment Patient Consent Form (Form 11)
 - TB10-TB client held card (Form 12)
 - Household Assessment (Form 13a) and Contact Investigation forms (Form 13b)
 - HMIS PHAR 001 STOCK CARD (Form 14)
 - HMIS PHAR 027 DR-TB MEDICINES SECOND LINE DRUG REQUISITION FORM (Form 15)
 - Suspected Adverse Drug Reaction Reporting Form (Form 17)
 - Cohort Review Case Presentation form (Form 18)
 - eCBSS
 - VDOT System
 - Pharmacovigilance Information system
 - Labxpert DS
 - Laboratory MIS

b. Update:

- Open a Second-line TB Treatment Card upon enrolling patient on DR-TB treatment
- Register patient in the Second-line TB Treatment Register upon enrolment
- Complete the DR-TB client held card (Form 12) upon enrolment on second-line treatment and provide the card to the patient to take with them once transferred for follow-up at follow-up facility.
- Prepare the Second-line TB Treatment Card (Form 01) and send a copy of the card to the Local Health facility (follow up facility) whenever the patient is sent to the community in order to continue the ambulatory treatment.
- Receive laboratory reports and update the Second-line TB Treatment Card, Register and database
- Update the Second-line TB Treatment Card and database in each monthly monitoring visit by the patient at the Treatment Initiation facility.

c. Prepare forms and reports and send them to next level:

- Send list of patients enrolled on second-line TB treatment weekly to the MoH/NTLP
- Send the actualized database to MoH/NTLP every quarter
- Send quarterly report on DR-TB patient enrolment to MoH (Form 06/HMIS 106a)
- Prepare case presentations for cohort review, assist in updating Cohort Review tracking tool, and generate quarterly reports on detection, and interim and final outcomes to send to the MoH.

3. Regional TB/District

a. Forms and instruments:

- Daily Linelist of RR-TB and MDR-TB detected from Labxpert DS
- Weekly Surveillance 033b report, Number of RR-TB and MDR-TB detected
- Weekly Linelist of RR-TB and MDR-TB started on DR / MDR Treatment from eCBSS
- HMIS 106a Quarterly Report on Detection of TB Cases with RR-TB and MDR-TB or Linelist from Labxpert DS
- Compare line lists from eCBSS and Labxpert with District Register
- Patient Referral and Transfer forms for patients transferring among districts and sites

b. Update:

- Record all patients who have accessed DST in the district TB register
- Receive laboratory reports of new RR/MDR-TB patients and update the district TB register and District RR/MDR-TB Line List
- Keep a line list of all DR-TB patients in the district (Form 07)
- Update line list of DR-TB patients; referral, treatment status, follow up facility, and outcome
- Complete DR-TB case finding/detection report every quarter (Form 05)

- Assist in completing the Household Assessment form (Form 13a) and initiation and updating of the DR-TB Contact Investigation form (Form 13b)

4. NTLP

a. Forms and instruments:

- Cohort Review patient Level Data
- eCBSS Line Lists
- VDOT System Lists
- Pharmacovigilance Information system Lists
- Labxpert DS Lists of RR Patients

b. Update:

- Update the data using Periodic Cohort review reports (Annual, Bi-Annual, Quarterly)
- Receive laboratory reports of new MDR-TB cases and update the MDR-TB list.
- Extract quarterly and annual reports from the electronic systems

c. Prepare and disseminate reports:

- Global TB Report annually
- Performance updates to Global Fund, WHO, PEPFAR and other stakeholders
- Annual report of final outcomes of TB cases with RR-TB, MDR-TB and XDR-TB on second-line treatment and any other reports required by the Ministry of Health
- Annual Health sector performance report
- Quarterly Report for program performance tracking
- To Regional and District PMDT Team.
-

Annexes:

Annex: Weight-based dosing of medicines used in multidrug-resistant TB regimens, adults and children^a

Group A medicines	Formulation (tablets, diluted in 10 mL of water, as applicable)	3– <5 kg	5– <7 kg	7– 10 kg	10– <16 kg	16– <24 kg	24– 30 kg	30– <36 kg	36– 46 kg	46– <56 kg	56– <70 kg	≥70 kg	Comments
Levofloxacin (Lfx)	100 mg dt (10 mg/mL)	5 mL (0.5 dt)	1	1.5	2	3	–	–	–	–	–	–	
	250 mg tab (25 mg/mL)	2 mL ^b	5 mL (0.5 tab) ^b	1	1.5	2	3	3	4	–	–	–	
	500 mg tab	–	–	–	–	–	1	1.5	2	–	–	–	
	750 mg tab	–	–	–	–	–	1	1	1.5	–	–	–	
Moxifloxacin (Mfx)	100 mg dt (10 mg/mL)	4 mL	8 mL	1.5	2	3	4	4	–	–	–	–	
	400 mg tab (40 mg/mL) Standard dose	1 mL ^b	2 mL ^b	3 mL ^b	5 mL (0.5 tab) ^b	7.5 mL (0.75 tab) ^b	1	1	–	–	–	–	
	400 mg tab high dose ^c	–	–	–	–	–	1 or 1.5	1.5 or 2	1.5 or 2	–	–	–	

Group A medicines	Formulation (tablets, dilute d in 10 mL of water, as applicable)	3 —<5 kg	5 —<7 kg	7– 0 kg	10 — 6 kg	16– <24 kg	24– <30 kg	30– <36 kg	36 — 6 kg	46– <56 kg	56 — 70 kg	≥ 70 kg	Comments
Bedaquiline (Bdq)	20 mg dt	0 to <3 mon ths: 1.5 od (2 wee ks); the n 0.5 od M/ W/F (22 wee ks) ≥ 3 mon ths: 3 od for 2 wee ks; the n 1 od M/ W/F for 22 wee ks	0 to <3 mon ths: 1.5 od for 2 wee ks; the n 0.5 od M/ W/F (22 wee ks) ≥ 3 mon ths: 3 od for 2 wee ks; the n 1 od M/ W/F for 22 wee ks;	3 to <6 months: 3 od for 2 weeks; then 1 od M/W/F ≥ 6 months: 6 od for 2 weeks; then 3 od M/W/F	10 od for 2 weeks; then 5 od M/W/F	20 od for 2 weeks; then 10 od M/W/F	—						

		the n 2 od M/ W/F				
100 mg tab (10 mg/m L) ^d	0 to <3 mon ths: 3 mL od for 2 wee ks; the n 1 mL od M/ W/F ^b	0 to <3 mon ths: 3 mL od for 2 wee ks; the n 1 mL od M/ W/F ^b	3 to <6 months : 6 mL od for 2 weeks; then 2 mL od M/W/F ^b the n 1 mL od M/ W/F ^b	2 od for 2 we eks; the n 1 od M/ W/ F	od for 2 weeks; then 2 od M/W/F	

			ks; the n 4 mL od M/ W/F b								
	100 mg tab (10 mg/m L)	–	200 mg dail y (od) for 8 wee ks; the n 100 mg dos e dail y (od)	Dosing scheme is for BPaLM/ BPaL regime n (>14 years).							
Linezo lid (Lzd)	20 mg /mL susp	2 mL	4 mL	6 mL	8 mL	11 mL	14 mL	15 mL	20 m L	–	
	150 mg dt (15 mg/m L)	2. 5 mL	5 mL (0.5 dt)	1	2e	2	3	–			
	600 mg tab (60 mg/m L)	–	1. 25 mL ^b	.5 mL ^b	5 mL (0.5 tab) ^{b, e}	5 mL (0.5 tab) ^b	7.5 mL (0.75 tab) ^b	1	1		

Group B medicines	Formulation	3–<5 kg	5–<7 kg	7–<10 kg	10–<16 kg	16– 4 kg	24– 0 kg	30– 6 kg	36– 6 kg	46– 6 kg	56– 0 kg	≥70 kg	Comments
Clofazimine (Cfz)	50 mg cap or tab ^f	1 M/F	M/W/F	1 1	2	2							For children <24 kg, the use of the 50 mg tab is preferred.
	100 mg cap or tab ^f	–	1 M/F	M/W/F	1 1	1							
Cycloserine or Terizidone (Cs/Tz)	125 mg mini cap (Cs) (12.5 mg/mL)	2 mL ^b , g	4 mL ^b	1	2	3	4	4	–				
	250 mg cap (25 mg/mL)	1 mL ^b , g	2 mL ^b	5 mL ^b	1	2	2	2	3				
Group C medicines	Formulation	3–<5 kg ^a	5–<7 kg ^a	7–<10 kg	10–<16 kg	16– 4 kg	24– 0 kg	30– 6 kg	36– 6 kg	46– 6 kg	56– 0 kg	≥70 kg	Comments
Ethambutol (E or EMB)	100 mg dt (10 mg/mL)	5 mL (0.5 dt)	1	2	3	4	–	–					–
	400 mg tab (40 mg/mL)	1.5 mL ^b	3 mL ^b	4 mL ^b	6 mL	1	1.5	2	3	4			
Delamandid (Dlm)	25 mg dt	1 od	<3 months: 1 od		1 bd	2 morning 1 evening		2 bd	–				
	50 mg tab ^h (5 mg/ mL)	5 mL (0.5 tab) od ^b	<3 months: 5 mL (0.5 tab) od ^b		5 mL (0.5 tab) bd ^b	10 mL (1 tab) morning 5 mL (0.5 tab) evening		1 bd	2 bd				

Group C medicines	Formulation	3–<5 kg ^a	5–<7 kg ^a	7–<10 kg	10–<16 kg	16–<24 kg	24–<30 kg	30–<36 kg	36–<46 kg	46–<56 kg	56–>70 kg	Comments
Pyrazinamide (Z or PZA)	150 mg dt (15 mg/mL)	5 mL (0.5 dt)	1	2	3	5	—	—	—	—	—	—
	400 mg tab (40 mg/mL)	.5 mL ^b	5 mL (0.5 tab) ^b	7.5 mL (0.75 tab) ^b	1	2	2.5	3	4	5	5	
	500 mg tab (50 mg/mL)	2 mL ^b	mL (5 mL) ^b	5 (5 mL) ^b	1	1.5	2	2.5	3	4	4	
Imipenem – cilastatin (Ipmp/Cln)	500 mg + 500 mg powder for injection, vial (10 mL)	Not used in patients aged <15 years (use meropenem)						2 vials (1 g + 1 g) bd				Only to be used with clavulanic acid.
Meropenem (Mpm)	1 g powder for injection, vial (20 mL)	1 mL tid	2 mL tid	4 mL tid	6 mL tid	9 mL tid	11 mL tid	1 vial tid or 2 vials bd				Only to be used with clavulanic acid.
Amikacin (Am)	500 mg/2 mL solution for injection, ampoule	-i							3–4 mL	4 mL	4 mL	Recommended only in adults aged >18 years.
Streptomycin (Sm)	1 g powder for injection, vial	-i							Calculate according to the dilution used			Recommended only in adults aged >18 years.
Ethionamide or Prothionamide (Eto/ Pto)	125 mg dt (Eto) (12.5 mg/mL)	3 mL ^b	7 mL ^b	1	2	3	4	4	—			Although once daily dose advised, two divided doses can be also
	250 mg tab (25 mg/mL)	—	3 mL ^b	5 mL (0.5	1	2	2	2	3	4	4	

				tab) ^b									given to improve tolerance.
P- aminosal- icylic acid (PAS)	PAS sodium salt (equivale- nt to 4 g PAS acid) sachet	0 .3 g bd	0.7 5 g bd	1 g bd	2 g bd	3 g bd	.5 g bd	3 4 g bd				4– 6 g bd	Usually given in divided doses.

Other medicine s	Formulat- ion	3– <5 kg	5 – < 7 kg	7– <10 kg	10 – <1 6 kg	16 – <2 4 kg	24 – <3 0 kg	30 – <3 6 kg	36 – <4 6 kg	46 – <5 6 kg	56 – <7 0 kg	≥ 70 kg	Comments
Isoniazid j (INH or H) (high dose)	50 mg/5 mL soln	5 m L	9 m L	1 5 mL	20 m L	–	–	–	–	–	–	–	Pyridoxine is always given with high-dose Isoniazid in children (1–2 mg/kg) and in people at risk of side- effects (e.g. those with HIV or malnutrition). In infants, pyridoxine may be given as part of a multi-vitamin syrup.
	100 mg dt or tab (10 mg/mL)	5 m L (0. 5 dt)	1	1.5	2	3	4	4	4. 5	–	–	–	
	300 mg tab	–	–	–	–	1	1. 5	1.5	2	–	–	–	
Clavulani- c acidⁱ (as amoxicill- in/ clavulanate) (Amx/cla- v)	62.5 mg clavulani- c acid as amoxicilli- n/ clavulana- te (250/62. 5 mg), powder for oral solution, 5 mL	1. 5 m L tid	2 m L tid	3 mL tid	5 m L tid	8 m L tid	10 m L tid	10 mL bd or tid	–	–	–	–	Only available in combination with amoxicillin. To be given with each dose of imipenem/cila- statin (bd) or meropenem (tid).

	125 mg clavulanic acid as amoxicillin/clavulanate (500/125 mg) tab	–	1 tid	1 bd or tid	
Pretomanid (Pa)	200 mg tab	–	1		Currently only used as part of the BPALM/BPAL regimens.

bd: two times a day; BPAL: Bedaquiline, Pretomanid and Linezolid; BPALM: Bedaquiline, Pretomanid, Linezolid and Moxifloxacin; cap: capsule; DR-TB: drug-resistant TB; dt: dispersible tablet; g: gram; GDG: Guideline Development Group; HIV: human immunodeficiency virus; kg: kilogram; MDR-TB: multidrug-resistant TB; MDR/RR-TB: multidrug- or Rifampicin-resistant TB; mg: milligram; mL: millilitre; M/F: Monday and Friday; M/W/F: Monday, Wednesday and Friday; od: once daily; soln: solution; susp: suspension; tab: tablet; TB: tuberculosis; tid: three times a day; WHO: World Health Organization.

a Dosing guidance is based on currently available data and may be revised once additional data are available. Dosages were established by the GDGs for the WHO guidelines on DR-TB treatment (2018 and 2020 updates), the WHO Global Task Force on the Pharmacokinetics and Pharmacodynamics (PK/PD) of TB medicines and the expert consultation on dosing convened by WHO in October 2021, following the GDG meeting on child and adolescent TB in June 2021.

Doses for children and young adolescents weighing <46 kg were revised according to Annex 6 of the 2022 WHO operational handbook on tuberculosis – Module 5: Management of tuberculosis in children and adolescents (153), which was informed by an expert consultation on dosing convened by WHO in October 2021 (154). They are based on the most recent reviews and best practices in the treatment of (paediatric) MDR/RR-TB. For certain medicines the dosages were informed by pharmacokinetic modelling results based on the principle of allometric scaling and maturation (155). Due to the pharmacokinetic properties of certain medicines the doses proposed may exceed the mg/kg/day ranges shown here in order to achieve blood concentrations similar to target levels in an average adult patient. The guidance for the 3–<5 kg weight band and for Bedaquiline and Delamanid is based on currently available data and may be revised when new data become available.

b Dissolving of crushed adult tablets or capsule content in 10 mL of water is required for administering this dose. The number of mL in the table reflects the dose to provide. This avoids fractioning solid formulations, although bioavailability of the dissolved, crushed adult tablets is uncertain (use of dispersible tablets is preferred).

c The higher dose may be used except when there is risk of toxicity; levels are expected to be lowered because of pharmacokinetic interactions, malabsorption or other reasons; or the strain has low-level drug resistance.

d Bedaquiline adult tablets (100 mg) crushed and suspended in water have been shown to be bioequivalent to tablets swallowed whole. Vigorous stirring/shaking is needed prior to administering the 100 mg tablet crushed and suspended in water.

e When using the 600 mg tab and the 150 mg dt to dose children weighing 16 to <24 kg, the dose in mg/kg will exceed 10–12 mg/kg and clinicians may opt to administer 1.5 dt or 4 mL of the 600 mg tab dispersed in 10 mL water.

f Clofazimine tablets are technically not dispersible but they do slowly (this takes approximately 5 minutes) dissolve in water (5 mL and 10 mL for the 50 mg and 100 mg tablets, respectively). The suspension should be stirred prior to administration. The 100 mg soft gel capsule is difficult to swallow for young children and therefore countries are strongly encouraged to make the 50 mg tablet formulation available.

g In children weighing 3 to <7 kg doses are lower than previously recommended. This is because of relatively high exposures associated with risk of neuropsychiatric adverse events, which is especially concerning when co-administering Cycloserine with Delamanid.

h Delamanid adult tablets (50 mg) crushed and suspended in water have been shown to be bioequivalent to tablets swallowed whole.

i Amikacin and streptomycin may be used in adults aged 18 years or more, in situations where an effective regimen cannot otherwise be designed using oral agents, when susceptibility is demonstrated and when adequate measures are in place to monitor for adverse events. Given the profound impact that hearing loss can have on the acquisition of language and the ability to learn at school, the use of injectable agents in children should be exceptional and limited to salvage therapy, and the treatment needs to be provided under strict monitoring to ensure early detection of ototoxicity. If used, the weight-based daily dose for Amikacin is 15–20 mg/kg and for streptomycin it is 20–40 mg/kg for children aged 2 years and older. To determine the dosing for infants and children aged below 2 years, a paediatric DR-TB expert should be consulted and a lower mg/kg dose used to compensate for immature clearance. Co-administration with lidocaine is advised to reduce pain at the injection site (156).

j These medicines are only recommended as a companion agent (amoxicillin/clavulanic acid) or are not included in Groups A, B and C, because of a lack of data from the latest analysis on longer MDR-TB regimens in adults (Isoniazid).

Specific comments on dosing children with medicines used in second-line MDR-TB regimens:

- For dosing of premature and low birth weight infants weighing <3 kg, advice should be sought from a paediatric DR-TB expert.
- For dosing of infants weighing 3 to <5 kg, a paediatric DR-TB expert should be consulted whenever possible.
- The use of child-friendly, dispersible tablets in infants and young children is preferred over manipulating adult tablets or administering or manipulating capsules. Where applicable, the dosing provided is based on dissolving the dispersible formulation in 10 mL of water and administering the number of mL (aliquots). The number of mL in the table reflects the dose to provide. The dissolved solution should be used immediately and the remainder of the 10 mL should be discarded.
- For some weight bands, dosing is indicated with both child-friendly, dispersible formulations and adult formulations. If adult formulations are used, the table provides the dose using aliquots in mL and tablet fractions where applicable (if the fraction is 0.5 or more). Aliquots refer to the volume to administer after crushing and dissolving the tablet in 10 mL of water.

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