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Foreword

In Uganda, 130 Multidrug resistant TB (MDR TB) cases were notified to the National TB/Leprosy Program (NTLP) during the period of March 2008 and November 2010. The emergence of drug resistant tuberculosis (DR-TB) is a reality in Uganda and it is a major threat to the progress of controlling TB. Drug resistant tuberculosis is said to occur when TB organisms can continue to grow in the presence of one or more anti-TB drugs. Multi drug resistant TB (MDR-TB) is one of the forms of DR-TB. MDR-TB is said to occur when there is resistance to both Isoniazid and Rifampicin. Drug resistant-TB can spread rapidly with high case fatality rates, particularly in areas with high prevalence of HIV infection like Uganda.

In light of the above, the Ministry of Health (MOH) and Partners found it imperative to address DR-TB challenges and associated problems by developing these guidelines. These guidelines serve as a first step towards initiating DR-TB treatment program and controlling DR TB in the country. The implementation of the guidelines will certainly contribute to the achievement of the Millennium Development Goals (MDGs) and Stop TB Partnership targets. These DR-TB guidelines are an addendum to the NTLP TB/Leprosy guidelines. It is envisaged that, these guidelines will be used as a technical reference material by health care workers involved in DR-TB care and for training of health care workers. They should be used together with other guidelines such as the National TB and Leprosy guidelines, the National TB-HIV policy guidelines and the National TB infection control guidelines.

I would like to urge all health care workers and Partners involved in DR-TB care to use these guidelines to implement DR TB control activities in the country. I am hopeful that the appropriate use of these guidelines will lead to successful control of DR-TB in Uganda.

Dr. Nathan Kenya - Mugisha
Ag. Director General Health Services, Ministry of Health
Abbreviations and acronyms

AFB  acid-fast bacilli
ART  antiretroviral therapy
CDC  United States Centers for Disease Control and Prevention
CPT  co-trimoxazole preventive therapy
DOT  directly observed therapy
DOTS  internationally recommended strategy for TB control
DRS  drug resistance surveillance
DST  drug susceptibility testing
FIN  Foundation for Innovative New Diagnostics
GFATM Global Fund to Fight AIDS, Tuberculosis and Malaria
GLC  Green Light Committee
HIV  human immunodeficiency virus
HPF  high-power field
HRD  human resource development
IUATLD  International Union Against Tuberculosis and Lung Disease
LFT  liver function test
MDR-TB  multidrug-resistant tuberculosis
PMDR-TB Programmatic Management of Drug resistant TB
NTM  non-tuberculous mycobacteria
PIH  Partners in Health
PPD  purified protein derivative
PPM  public-private mix
SCC  short-course chemotherapy
TB  tuberculosis
TSH  thyroid-stimulating hormone
UNAIDS Joint United Nations Program on HIV/AIDS
Union International Union Against Tuberculosis and Lung Disease
UVGI  ultraviolet germicidal irradiation
WHO  World Health Organization
# Antituberculosis drug abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Name</th>
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<tr>
<td>Am</td>
<td>Amikacin</td>
</tr>
<tr>
<td>Amx/Clv</td>
<td>Amoxicillin/Clavulanate</td>
</tr>
<tr>
<td>Cfx</td>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td>Cfz</td>
<td>Clofazimine</td>
</tr>
<tr>
<td>Clr</td>
<td>Clarithromycin</td>
</tr>
<tr>
<td>Cm</td>
<td>Capreomycin</td>
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<tr>
<td>Cs</td>
<td>Cycloserine</td>
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<tr>
<td>E</td>
<td>Ethambutol</td>
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<tr>
<td>Eto</td>
<td>Ethionamide</td>
</tr>
<tr>
<td>Gfx</td>
<td>Gatifloxacin</td>
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<tr>
<td>H</td>
<td>Isoniazid</td>
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<tr>
<td>Km</td>
<td>Kanamycin</td>
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<tr>
<td>Lfx</td>
<td>Levofloxacin</td>
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<tr>
<td>Lzd</td>
<td>Linezolid</td>
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<tr>
<td>Mfx</td>
<td>Moxifloxacin</td>
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<tr>
<td>Ofx</td>
<td>Ofloxacin</td>
</tr>
<tr>
<td>PAS</td>
<td>P-aminosalicylic acid</td>
</tr>
<tr>
<td>Pto</td>
<td>Prothionamide</td>
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<tr>
<td>R</td>
<td>Rifampicin</td>
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<tr>
<td>S</td>
<td>Streptomycin</td>
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<tr>
<td>TH</td>
<td>Thioacetazone</td>
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<tr>
<td>Trd</td>
<td>Terizidone</td>
</tr>
<tr>
<td>Vi</td>
<td>Viomycin</td>
</tr>
<tr>
<td>Z</td>
<td>Pyrazinamide</td>
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CHAPTER 1

1.0 Introduction to Drug Resistant Tuberculosis:
This chapter defines DRTB, describes its magnitude and impact, describes the causes of DRTB and how to address these, and gives the role of the Green Light Committee.

1.1 Definition of Drug Resistant TB (DRTB)
Drug resistant tuberculosis is said to occur when TB organisms can continue to grow in the presence of one or more anti-TB drugs.

Four different types of DRTB are known:
1. Mono-resistance: resistance to one first line anti-tuberculosis drug.
2. Poly-resistance: resistance to more than one first line anti-tuberculosis drug, other than both isoniazid and rifampicin.
3. Multidrug resistance: resistance to both Isoniazid and Rifampicin.
4. Extensively drug-resistance: resistance to any fluoroquinolones and to at least one of three injectable second-line drugs (amikacin, capreomycin or kanamycin).

Drug resistant TB is diagnostically classified as
- Confirmed MDR-TB. These are patients in whom MDR-TB is confirmed by drug susceptibility test (DST).
- Suspected MDR-TB. These are patients in whom MDR-TB is suspected and the Review Panel recommends Category 4 treatment.

1.2 Magnitude of Drug Resistant TB:
Globally, the incidence of drug resistance has increased since the first drug treatment for TB was introduced in 1943. The emergence of MDR-TB following the widespread use of rifampicin beginning in the 1970s led to the use of second-line drugs. Improper use of these drugs has fueled the generation and subsequent transmission of highly resistant strains of TB termed extensively DR-TB. Despite the association with previous treatment, drug-resistant strains including XDR-TB are readily transmissible and outbreaks have been reported, often in populations with high HIV prevalence.

Globally, 490,000 cases of multidrug-resistant TB (MDR-TB) were estimated in 2006, 500,000 in 2007, and 440,000 in 2008 with 150,000 estimated MDR TB deaths in 2008. Only 4.8% in 2006, 5.4% in 2007, 7% in 2008 of the incident MDR-TB cases were notified respectively. Only 22 out of 46 countries in Africa have data (WHO March 2010 up date).

By March 2010, 58 countries and territories (8 in Africa) had reported at least one case of extensively drug-resistant TB (XDR-TB).

In Uganda, the exact magnitude of DR-TB is not known but a national drug resistance survey was ongoing at the time of writing these guideline. Several sub national drug resistance surveys (DRS) have been conducted, and have shown low MDRTB levels of:
0.5% among new cases and 4.4% among retreatment cases in the 1996-97 GLRA study; 4.5% among new cases and 11.5% among retreatment patients in Mulago 2006. MSF found MDRTB levels of 0% and 13.6% among new and retreatment cases in Kitgum in 2007 and European Union funded study in Kampala in 2009 found rates of 1.1% (5) among 472 new patients and 11.5%.

1.3 DR TB causal factors.

Although its causes are microbial, clinical and programmatic, drug resistant 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 mutant bacilli. From a clinical and programmatic perspective, it is an inadequate or poorly administered treatment regimen that allows a drug-resistant strain to become the dominant strain in a patient infected with TB. Ongoing transmission of established drug-resistant strains in a population is also a significant source of new drug-resistant cases.

Table 1.1 summarizes DR-TB causal factor:

<table>
<thead>
<tr>
<th>Healthcare providers: inadequate regimens</th>
<th>Drugs: inadequate supply/quality</th>
<th>Patients: inadequate drug intake</th>
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<tr>
<td>▪ Non monitoring of treatment</td>
<td>▪ Stock-outs (At all levels)</td>
<td>▪ Poor adherence or poor DOT</td>
</tr>
<tr>
<td>▪ Inadequately organized and underfunded TB control programmes</td>
<td>▪ Interrupted supply of drugs (delivery disruptions)</td>
<td>▪ Poor patient health education on TB</td>
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<tr>
<td>▪ Wrong dose by prescribers</td>
<td>▪ Poor storage conditions at peripheral facilities</td>
<td>▪ Lack of transport / long distances to facilities.</td>
</tr>
<tr>
<td>▪ Non compliance with guideline</td>
<td></td>
<td>▪ Side effects</td>
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<td>▪ Social barriers</td>
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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 drug-resistant TB. It is important to prevent the development of resistance since mortality for patients infected with resistant strains is high.

The factors that contribute to the development of new drug-resistant cases should be reviewed (see Table 1.1 above for a list of possible factors). Well-administered first-line treatment for susceptible cases is the best way to prevent acquisition of resistance. Timely identification of DR-TB and adequate DR-TB treatment regimens (Category 4) administered early in the course of the disease
are essential to stop primary transmission.

Integration of DOTS with treatment of DR-TB works synergistically to eliminate all the potential sources of TB transmission.

1.4 The role of Green Light Committee and the Global Response to DR-TB.

The WHO Working Group on DOTS-Plus for MDR-TB was established in 1999 to lead the global effort to control MDR-TB. This working group, part of the Stop TB Partnership, formed the Green Light Committee (GLC) in 2000 to provide technical assistance to DR-TB programmes, promote rational use of second-line drugs worldwide and improve access to concessionally-priced quality-assured second-line drugs.

Uganda met the DR-TB framework requirements and has a plan to manage DR-TB, and benefits from quality-assured second-line drugs at reduced prices. The GLC has offered technical assistance before implementation of programme for control of DR-TB and will continue to monitor the approved project.
CHAPTER 2

2.0 Framework for effective control of drug-resistant tuberculosis

This chapter describes the five essential components of the DOTS framework as they apply to the management of DR-TB. It also describes the integration of the management of DR-TB into the National TB/Leprosy programme management of drug susceptible TB

2.1 DOTS framework as applied to the management of DR-tuberculosis

The framework for DR-TB is organized around the five components of the DOTS strategy because the underlying principles are the same.

a. Sustained political commitment
b. A rational case-finding strategy including accurate, timely diagnosis through quality-assured culture and DST
c. Appropriate treatment strategies that use second-line drugs under proper case management conditions
d. Uninterrupted supply of quality-assured Anti-tuberculosis drugs
e. Standardized recording and reporting system

Each of these components involves more complex and costly operations than those for controlling drug-susceptible TB. However, addressing DR-TB will strengthen the national TB/Leprosy programme.

2.1.1 Sustained political commitment

Sustained political commitment is essential to establish and maintain the other four components. It requires both long-term investment and leadership to ensure an appropriate environment for integrating the management of DR-TB into National TB/Leprosy Programme. An appropriate environment includes adequate infrastructure, development and retention of human resources, partnerships, enactment of necessary legislation, TB control policies enabling rational implementation of the programme and dedicated budget line for procurement of quality-assured second-line drugs. In addition, the NTP must be strengthened to prevent the emergence of more MDR-TB and XDR-TB cases.

2.1.2 A rational case-finding strategy including accurate, timely diagnosis through quality-assured culture and DST

Accurate, timely diagnosis is the backbone of a sound national TB/Leprosy programme. DR-TB must be diagnosed correctly before it can be treated effectively. Based on the epidemiological situation and capacity prevailing in Uganda, case-finding strategy, is limited to only patients with an increased risk of DR-TB namely; failure of Category 1, patients who remain sputum smear-positive at month 2 or 3 of Short Course Chemotherapy, failure of re-treatment regimens, chronic TB cases, relapse, smear positive defaulters,
contacts of MDR-TB and patients with exposure to institutions that have DR-TB or with a high DR-TB prevalence

2.1.3 Appropriate treatment strategies that use second-line drugs under proper case management conditions

An appropriate treatment strategy consists of a rational method for designing the optimal treatment regimen, a patient-centered approach for delivering this regimen with direct observation, and a plan for monitoring and managing adverse drug reactions.

Treatment strategies and Drug regimen
The selection of drug regimen is based on the history of drugs taken by the patient, drugs and regimens commonly used in the country, DST results, and options for DOT throughout the treatment.

The following treatment strategies or combinations should be used:
- Standardized regimen
- Empirical regimen
- Individualized treatment

These strategies are explained in detail in chapter 7.

All patients with MDR-TB will have MDR-TB treatment initiated in an accredited DR-TB reference hospital. Once discharged, patients will continue the treatment in the follow up health facilities nearest to their homes however; health workers from these facilities would have been trained in advance.

Regional / District Hospitals OPD clinics should conduct quarterly clinical evaluations of the patients during continuation phase as a measure to recognize, manage and prevent, SLD side effects.
Health workers in these follow up facilities should help with the selection and training of DR-TB community treatment supporters who should administer treatment under DOT for the ambulatory patients.

DR-TB control activities in a given TB Zone will be under the responsibility of a ZTLS while DTLS will closely monitor these activities in their districts with support supervision of the ZTLSs. The DHOs will head District DR-TB teams that oversee DR-TB suspects/cases in their districts.

2.1.4 Uninterrupted supply of quality-assured anti-tuberculosis drugs

Management of second-line drugs is complex, especially when individualized treatment regimens are used. Drugs are frequently changed as a result of adverse effects, delayed DST results and poor response to treatment. In addition, most second-line drugs have a short shelf-life, global production of quality-assured drugs is limited and drug registration may be a lengthy and costly process that is not always attractive to drug manufacturers.
Steps to ensure uninterrupted drug supply must begin six months or more in advance of the anticipated need, and drug needs must be estimated as accurately as possible.

### 2.1.5 Standardized recording and reporting system

The standardized DR-TB recording system captures defined categories for patient registration, culture and DST results, and monitoring of treatment. Cohort analysis includes interim indicators and treatment outcomes after 2 years or more.

### 2.2 Establishment of management of DR-TB within the National TB/Leprosy programme

DR-TB should be managed as an integral part of the National TB/Leprosy programme. This calls for political commitment to invest in infrastructure, train and retain human resources, quality assured bacteriology and quality assured second line drugs. The design and implementation of a DR-TB control programme hinges on the availability of essential requirements such as quality-assured laboratories for diagnosis and monitoring of treatment response, quality-assured second-line drugs and systems for delivering SLD under DOT throughout the treatment. These requirements are critical in ensuring proper case management and prevention of the emergence of resistance to second-line drugs.

#### 2.2.1 Integration of diagnostic and treatment services to control tuberculosis

For control of DR-TB; Uganda will integrate DR-TB management into services for TB control and expand treatment for DR-TB rapidly to accredited centres as human, financial and technical resources allow.

**Note:** Untreated or improperly treated DR-TB patients are a source of ongoing transmission of resistant strains, resulting in future added costs and mortality.
CHAPTER 3

3.0 Coordination and regulatory framework

3.1 Coordination
National TB/Leprosy control program (NTLP) shall be the central body coordinating all the key stakeholders, organizations and partners involved in DR-TB care and management. Coordination among the different components of public and private healthcare programs and organizations is essential for successful program implementation. The program shall work with both public and private health workers within selected health facilities including those in prison health service.

Initially DR-TB cases diagnosed from prison shall be managed at accredited DR-TB facilities. Later, Uganda prisons health service may directly manage its own cases within prison health services. A memorandum of understanding shall be written delineating responsibilities and funding where different ministries such as Internal Affairs and Defense for the prison system or the military health service system or departments are involved.

The DR-TB program shall involve the community during planning and implementation to foster advocacy and ownership. The community shall also be involved in the selection of treatment supporters to offer DOT service. NTLP shall harness external support as well as complying with international standards of care. DR-TB control program shall be tailored to fit the local infrastructure; it should also target health-care providers in both public and private health facilities.

- National TB/Leprosy programme.
The national TB control programme is the central coordinating body for the activities described in the strategic framework. 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 programme. As needed, the NTLP national programme will build partnerships with all relevant health-care providers.

- Peripheral health system.
DR-TB control programmes will be tailored to fit the local infrastructure. Transfer from hospitals to outpatient settings or between DOT centres will require care, advance planning and good communication. Given the type of care required during the treatment of DR-TB, a team of health workers including physicians, nurses and social workers will often be used.
- **Community level.**
Community involvement and communication with community leaders can greatly facilitate implementation of treatment and respond to needs that cannot be met by medical services alone. Community health education, involvement and organization around TB issues can encourage a feeling of community ownership of control programmes and reduce stigma. This may also help to address the interim needs of patients, including the provision of DOT, food and/or housing. Community health workers often play a critical role in ambulatory care of DR-TB patients.

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

- **All health-care providers (both public and private)**
In our setting, it is important to involve the private sector in the technical aspects of the programme. If involved, private practitioners may provide clinic- or community-based DOT as well as registering patients and their treatment outcomes. The public health system may also get involved in training on national guidelines for DR-TB.

- **International level.**
NTLP continues to enjoy International technical support through WHO, the GLC, supranational TB reference laboratories and other technical agencies. From the earliest planning phase, a full range of issues encompassed in political commitment that need to be addressed include adequate financial support, an enabling regulatory environment, sufficient human resources, physical infrastructure and coordination. In addition, a communication strategy to ensure that information is disseminated effectively from the central level to the periphery and that reports from the peripheral level are received centrally need to be in place. Box 3.2 provides a checklist summarizing the key aspects of a DR-TB control programme.

- **3.1 Policy, Regulatory and operational documents**
NTLP shall lead the development of DR-TB policies as a foundation for any subsequent legal, administrative and technical support necessary for the initiation, implementation and monitoring of the programme. Regulatory and operational issues that shall be considered include:

- Legislation to ensure proper registration, availability, quality, safety and distribution of second-line drugs. (Often, strict control of second-line drugs is possible only after establishment of the programme to provide quality-assured drugs free of charge to patients.)
DR-TB guidelines shall be a vehicle for disseminating operational and clinical protocols to ensure consistency. They describe treatment protocols, define responsibilities for different health-care providers and delineate the human resources that will be needed. It specifically defines how patients will be diagnosed, registered, reported, treated and followed up, in addition to programme monitoring and evaluation.
CHAPTER 4

4.0 Definitions: Case registration, Bacteriology and Treatment outcomes

This chapter presents case definitions, patient registration categories, bacteriological terms, treatment outcome definitions and cohort analysis procedures for DR-TB patients who meet DR-TB diagnostic criteria.

The purpose of a case definition is to ensure:
- Standardized patient registration and case notification,
- Assignment to appropriate treatment regimens,
- Case evaluation according to disease site, bacteriology and history of treatment,
- Cohort analysis of registered Category 4 patients and Category 4 treatment outcomes.

4.1 Definitions of drug resistance and diagnostic Category 4

The diagnosis of DR-TB is confirmed through laboratory tests that show that the infecting isolates of M. tuberculosis grow in vitro in the presence of one or more anti-tuberculosis drugs. The four different categories of drug resistance are:

1. Mono-resistance: resistance to one first line anti-tuberculosis drug.
2. Poly-resistance: resistance to more than one first line anti-tuberculosis drug, other than both isoniazid and rifampicin.
4. Extensively drug-resistance: resistance to any fluoroquinolones and to at least one of three injectable second-line drugs (amikacin, capreomycin or kanamycin).

Diagnostic Category 4 includes patients with:
- **Confirmed MDR-TB**: Tuberculosis patients in whom MDRTB has been confirmed in the lab.
- **Suspected MDR-TB**: These are patients in whom MDR-TB is suspected and the Review Panel recommends Category 4 treatment. Patients may be entered into the Category 4 register and started on Category 4 treatment before MDR-TB confirmation only if representative DST surveys or other epidemiologic data indicate a very high probability of MDR-TB.
- **Poly-resistant TB**: Some cases of poly-resistant TB require Category 4 treatment while others require prolonged treatment with first line drugs combined with two or more second line drugs and are therefore entered into Category 4 Register at DR-TB accredited centre.

Mono- and poly-resistance cases that do not require or require only one second-line drugs should be maintained in the regular district TB register.
4.2.1 Classification by Site of drug-resistant tuberculosis disease
(pulmonary and extra-pulmonary)

DR-TB is further classified according to organ affected. However, the regimens for drug-resistant forms of TB are similar, irrespective of site affected. Defining site is primarily for recording and reporting purposes.

- **Pulmonary tuberculosis.** Tuberculosis involving only the lung parenchyma.

- **Extra-pulmonary tuberculosis:** Tuberculosis involving organs other than the lung parenchyma, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges. Tuberculous intrathoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, therefore constitute a case of extra-pulmonary TB. The definition of an extra-pulmonary case with several sites affected depends on the site representing the most severe form of disease.

**NB:** Patients with both pulmonary and extra pulmonary TB are classified as a case of pulmonary TB.

4.2.2 Category 4 patient registration group based on previous anti-tuberculosis treatment

Category 4 patients are assigned a registration group in two different ways:

- **According previous treatment history (TB drug used).** This is useful in assessing risk for MDR-TB

- **According to the outcome of their previous TB treatment**

A-Classification according to history of previously drug used:

Is useful to assign the appropriate treatment regimen

1- **New Category 4 patients:**
Who have never received anti-tuberculosis treatment or who have received anti-tuberculosis treatment for less than one month.

(Note: include patients who had DST at the start of a Category 1 regimen and are then switched to a Category 4 regimen because of resistance are placed in this group, even if they received more than one month of Category 1 treatment.)

2- **Patients previously treated with first-line drugs (FLD) only.** (For one month or more)

3- **Patients previously treated with second-line drugs.** (For one month or more with one or more second-line drugs, with or without first-line drugs)

- **B-Classification** according to the history of their previous treatment = “Patients
register group”

- **New Category 4 patients:** who have never received anti-tuberculosis treatment or who have received anti-tuberculosis treatment for less than one month.

(Note: include patients who had DST at the start of a Category 1 regimen and are then switched to a Category 4 regimen because of resistance are placed in this group, even if they received more than one month of Category 1 treatment.)

- **Relapse:** A patient whose most recent treatment outcome was “cured” or “treatment completed” and who is subsequently diagnosed with bacteriologically positive TB by sputum smear microscopy or culture

- **Treatment after default:** A patient who returns to treatment, bacteriologically positive TB by sputum smear microscopy or culture following interruption of treatment for two or more consecutive months

- **Treatment after failure of CAT I:** Patient who has received CAT I treatment and in whom treatment has failed. Failure is defined as sputum smear positive at five months or later during treatment. Or if a smear negative at the start of treatment turned smear positive or culture positive at end of 2 months of treatment.

- **Treatment after failure of CAT II:** Patient who has received CAT II treatment and in whom treatment has failed. Failure is defined as sputum smear positive at five months or later during treatment.

- **Transfer in:** patients who have been transferred in from another register for treatment of drug-resistant TB to continue Category 4 treatment.

- **Other Patients** who do not fit the above definitions. This group includes Category 4 patients who were treated outside DOTS programs and/or we do not know the previously drugs used or outcome. Patients who has received several unsuccessful treatments. Previously treated patients with TB extra-pulmonary.

HIV status is also recorded at the start of treatment, and if unknown, provider initiated counselling and testing should be done.

### 4.3 Bacteriology and sputum conversion

Bacteriological examinations in patients with DR-TB include sputum smear microscopy and culture; performed and results reported according to international standards. These examinations should be done at the start of treatment to confirm TB disease and to group the patients according to infectiousness, sputum smear-positive being most infectious.

Sputum sample for smear and culture should always be taken at the time of Category 4 treatment start. In order for a patient to be considered culture- or sputum smear-positive at the start of Category 4 treatment, the following criteria must be met: at least one pre-treatment culture or smear was positive; the collection date of the sample on which the culture or smear was performed was less than 30 days before, or 7 days after, initiation of Category 4 treatment.

**Sputum conversion**

Sputum conversion is said to have occurred when two sets of consecutive smears and cultures, from samples collected at least 30 days apart are negative. The date of the first set of negative smears and cultures is taken as the date of conversion (and this date to
determine length of the intensive phase and treatment). Both bacteriological (smear and culture) methods are used simultaneously to monitor patients throughout therapy.

The recording and reporting system allows for assessing the smear- and culture-status 6 months after the start of treatment as an interim outcome. In addition, smear and culture conversion rate at 6 months is used to assess programme performance.

### 4.4 Treatment outcome definitions (operative concept) for Category 4 treatment

The following are mutually exclusive Category 4 outcome definitions based on the use of laboratory smear and culture as a monitoring tool and are reported in Forms 01, 02 and 07 (see Chapter 18). They are parallel to the six DOTS outcomes for drug-susceptible TB. All patients are assigned the first outcome they experience for the treatment being evaluated for recording and reporting purposes.

1. **Cured.** A Category 4 patient who has completed treatment according to the program protocol and has at least:
   a. **Five consecutive** negative cultures from samples collected at least 30 days apart in the final 12 months of treatment.
   b. If only **one positive** culture is reported during that time, and there is no concomitant clinical evidence of deterioration, a patient may still be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative cultures taken at least 30 days apart.

2. **Treatment completed.** A Category 4 patient who has completed treatment according to the program protocol but does not meet the definition for cure because of lack of bacteriological results (i.e. fewer than five cultures were performed in the final 12 months of treatment).

3. **Died.** A Category 4 patient who dies for any reason during the course of MDR-TB treatment.

4. **Failed.** Treatment will be considered to have failed if:
   - Two or more of the five cultures recorded in the final 12 months of treatment are positive, or
   - Any one of the final three cultures is positive or
   - A clinical decision has been made to terminate treatment early because of poor clinical or radiological response or adverse events. (These latter failures should be indicated separately for the purposes of sub-analysis.)

5. **Defaulted.** A Category 4 patient whose treatment was interrupted for two or more consecutive months for any reason without medical approval.

6. **Transferred out.** A Category 4 patient who has been transferred to another reporting and recording unit and for whom the treatment outcome is unknown.

Note: patients who have transferred in should have their outcome reported back to the
treatment center from which they originally where registered

**BOX 4.1 Helpful hints on registrations and definitions**

**Assigning the first outcome:**
All patients should be assigned the first outcome they experience for recording and reporting purposes. For example a patient defaults on a Category 1V regimen and returns 14 months later to be re-registered and is **cured** with a second Category 1V treatment. This patient should receive a **final outcome of “defaulted”** in the cohort in which he or she was first registered and **“cured”** in the second cohort.

**Transfer Out:** A patient who is”transferred out” must be transferred out to another DR-TB treatment center. For example, a patient in a district with a good access to DR-TB treatment has completed 8 months of a Category 1V regimen and is doing well and has converted his sputum in month two. He informs the DR-TB staff that he is going back to his home district that is 500 km away, and the district does not have access to DR-TB treatment. His uncle is going to purchase the medicines and he will take them under the supervision of a district Medical officer. There are no culture facilities in the district he is moving. This patient should be counted as a default, because he is leaving a district with access to DR-TB care and the DR-TB treatment centre will not be able to track him. A patient must go to another district with access to DR-TB treatment program that can report back the final result to be considered as transferred-out.

**Transferred In:** A patient who transfers-in does not get counted in the cohort of the center in which he completes his treatment. The receiving centre must report back the final outcome of the patient to the original treatment centre. The original centre should be communicating with the receiving centre on both that the patient was received and what the final outcome is.
CHAPTER 5

5.0 Case-finding strategies

This chapter describes strategies for case-finding and diagnosing patients with either suspected or confirmed DR-TB. It suggests, testing only high risk groups of patients as compared to testing all TB patients, as the strategy NTLP has adopted. Furthermore, the chapter covers:
- Risk factors for drug resistance;
- Strategies for case-finding;
- Information on DST collection;
- The use of rapid DST methods to identify drug resistance;
- The use of DST to second-line drugs and case detection of XDR-TB;
- Important issues in case-finding of drug resistance in the HIV-infected patient.

Key recommendations of this chapter:
- Screen patients at risk of DR-TB for drug resistance;
- Use of rapid DST methods for the initial screening of DR-TB facilitates speedy initiation of treatment;
- Screen patients at increased risk of having XDR-TB for resistance with DST to H, R, second-line injectable agents and a fluoroquinolone.

5.1 Background and general considerations

Timely identification and prompt initiation of adequate treatment for drug-resistant cases minimizes mortality among these patients, prevents the patient from spreading the disease to others, and acquiring further resistance and progressing to a state of permanent lung damage.

Availability of representative DRS data for new patients, the different re-treatment categories (failure of Category 1, failure of re-treatment, default and relapse) and other high-risk groups is important for two reasons. DRS data can be used to design an effective case-finding strategy and treatment regimens. DRS data can also be used to estimate the number of patients to be enrolled, drug needs and drug procurement.

5.2 Target groups for DST

NTLP recommends targeting DST to specific groups of patients at increased risk of drug resistance. Patients at increased risk include all: failures of Category 1, retreatment cases, contacts of MDR-TB and TB/HIV patients with CD4+ cell count ≥ 350 cells. Specific elements of the history that suggest an increased risk of drug resistance are listed in Table 5.1. Stronger risk factors are placed higher in the table. Risk factors for XDR-TB are discussed in section 5.10.

1 Rapid DST methods (results in 2-3 days) in these guidelines refer to molecular techniques that detect the genetic determinants of resistance. However, liquid, agar and other validated DST media that determine the presence of resistance within two to three weeks often can be substituted as rapid DST method when molecular methods are not available.
<table>
<thead>
<tr>
<th>Target Group for DST</th>
<th>Reason for inclusion as a target group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure of re-treatment regimens and chronic TB cases</td>
<td>Chronic TB cases are defined as patients who remains sputum smear-positive at end of a supervised retreatment regimen. These patients have the highest MDR-TB rates of any group, often exceeding 80%.</td>
</tr>
<tr>
<td>Exposure to a known MDR-TB/XDR case</td>
<td>Close contacts of MDR-TB/XDR-TB patients tend to have very high rates of MDR-TB/XDR-TB.</td>
</tr>
<tr>
<td>Failure of Category 1</td>
<td>Failures of Category 1 are patients who while on treatment are sputum smear-positive at month 5 or later during the course of treatment. Category 1 failures where Rifampicin was used in the continuation phase and DOT was not used throughout treatment are likely to have DR-TB.</td>
</tr>
<tr>
<td>Patients who remain sputum smear-positive at month 2 or 3 of Short Course Chemotherapy</td>
<td>This group of patients is at risk for DR-TB, rates can vary considerably.</td>
</tr>
<tr>
<td>Relapse and return after default without recent treatment failure</td>
<td>Relapse and return after default cases with a history of erratic anti-TB drug use are strongly associated with DR-TB. Early relapses are also associated with DR-TB.</td>
</tr>
<tr>
<td>Exposure in institutions that have DR-TB outbreaks or a high DR-TB prevalence</td>
<td>Prisoners and health-care workers in clinics, laboratories and hospitals can have high rates of DR-TB.</td>
</tr>
<tr>
<td>TB/HIV patient with CD4+ cell count ≥ 350 cells</td>
<td>There is some association between TB and HIV in some settings though this is not well established in Uganda.</td>
</tr>
</tbody>
</table>
5.3 Strategies for DR-TB case finding.
NTLP recommends using DST for DR-TB case-finding. This involves obtaining two sputum specimens for culture and performing DST with the specimen that yields the best culture. However, at the beginning, when NTLP is just introducing program management of DR-TB there shall be a backlog of patients who had DST in the past but the results may no longer reflect the resistance pattern of the strain they have at the time of enrolment in the DR-TB control programme. This necessitates repeating DST in all patients before enrolling them on DR-TB regimen (see Chapter 7).

Initial evaluation of the DR-TB patients will involve: social evaluation, liver function tests (total serum Bilirubin, SGPT & SGOT, total serum albumin, total serum protein and A/G ratio), serum Creatinine, blood urea, complete urine analysis with estimation of total urine protein content. Serum uric acid, blood sugar, sodium and potassium, HIV test, pregnancy test, full blood count, audiometry or hearing evaluation, visual acuity and color vision evaluation and Magnesium and Calcium levels. If Serum potassium is low. This should also include an assessment for Psychiatric disorders, allergic reactions and hematological disorders before the start of treatment. (see Chapter 11)

5.4 DST Specimen Collection
It is recommended that two sputum specimens be obtained for culture and that DST be performed with the specimen that produces the best culture. DST does not routinely need to be carried out in duplicate. Procedures for collecting and managing specimens for culture and DST are described in chapter 6.
Previously treated patients may have had DST in the past but it may no longer reflect the resistance pattern of the strain they had at the time of enrolment in the DR-TB program. DST should therefore be repeated before enrolment on treatment.

5.5 Case-finding in paediatric patients
The diagnosis of TB is more difficult in children than in adults; similarly DR-TB case finding in paediatric cases is difficult. Pediatric cases therefore require adjustments in diagnostic criteria and indications for treatment. Younger children especially less than 5 years may not be able to produce sputum specimens on demand. Measures such taking a careful history, enlisting important physical signs and performing investigations such as chest x-ray, sputum induction/nasal gastric aspiration for zn, tuberculin skin test may be considered if this service is available.

However, children should not be excluded from treatment solely because sputum specimen is not available. Children with active TB who are close contacts of patients with DR-TB can be started on DR-TB regimen (See Chapter 14).

5.6 Case-finding in HIV-infected patients
Unrecognized MDR-TB and XDR-TB are associated with high mortality in HIV-infected patients, culture and DST testing should be performed on all HIV-infected patients with active TB who are not improving on treatment. Where CD4 levels are known, DST should be targeted for patients with low CD4 (less than 350 cell/mm$^3$) as these are at increased risk of DR-TB. Rapid DST techniques targeting HIV patients with active TB
are very useful to promptly identify and initiate treatment in those with DR-TB.

5.7 Case-finding of patients with mono- and poly-drug resistance
Mono- and poly-drug resistant strains are strains that are resistant to anti-tuberculosis drugs but not to both isoniazid and rifampicin. DST will also identify cases of mono- and Poly-drug resistance, in addition to MDR-TB cases. Patients with mono- or poly-drug resistance may require modifications to their short-course chemotherapy regimens or to be moved to DR-TB regimen (see Chapter 8).

5.8 Rapid DST
Case-finding strategies can be greatly enhanced with rapid 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-tuberculosis drug of the first-line regimen, and rifampicin resistance most commonly occurs with concomitant isoniazid resistance. A positive rapid 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 5.1 is an algorithm on the use of rapid DST for identification and initial management of patients suspected of TB who are at increased risk of DR-TB, and is applicable to situations of both high and low HIV prevalence.
FIGURE 5.1  Algorithm for the use of rapid drug-resistance testing

1. **SMEAR POSITIVE**
   - HIV test (or confirm result)
   - Smear microscopy
   - Ensure infection control measures

2. **PATIENT DETERMINED TO BE AT INCREASED RISK for DR-TB (see Table 5.1)**
   - OR **PATIENT WITH HIV**
     - Follow NTP guidelines for treatment
     - Perform DST of first-line drugs
     - Begin SCC treatment as per NTLP guidelines
     - Determine if ART is indicated
     - If DR-TB identified, treat according to Chapters 7, 8, and 10.

3. **SMEAR NEGATIVE**
   - Smear microscopy
   - HIV test (or confirm result)
   - Ensure infection control measures

4. **Rapid rifampicin test**
   - HIV +
   - Rapid rifampicin test +
   - HIV –
   - Rapid rifampicin test –

5. **Rapid resistance testing**
   - Perform DST of H, R, Km (or AMK), Cm and a fluoroquinolone
   - Treat according to Chapters 7 and 8.

6. **Culture from the culture**
   - May require Category 17 therapy if highly likely to have DR-TB
   - Smear negative and those negative for smear
   - Perform NTP guidelines for treatment
   - Perform DST of first-line drugs
   - Begin SCC treatment as per NTLP guidelines
   - Determine if ART is indicated
   - If DR-TB identified, treat according to Chapters 7, 8, and 10.
5.9 Use of second-line DST in case-finding and diagnosing XDR-TB

The National TB Reference Laboratory (NTRL) currently has the capacity to perform DST on some second-line drugs. The NTRL will continue increasing its capacity and proficiency to test the second-line injectable agents (kanamycin, amikacin, and capreomycin), and a fluoroquinolone. This will enhance case-finding for XDR-TB and to assure proper treatment.

The two strongest risk factors for XDR-TB are:
1. Failure of a TB treatment which contains second-line drugs including an injectable agent and a fluoroquinolone.
2. Close contact with an individual with documented XDR-TB or with an individual for whom treatment with a regimen including second-line drugs is failing or has failed.

All suspects of XDR-TB should have DST to H, R, the second-line injectable agents and a fluoroquinolone. For HIV-infected individuals with risk factors for XDR-TB, because of the high and rapid risk of death with co-infection, liquid or other validated rapid techniques for DST of first- and second-line drugs is recommended.
CHAPTER 6

6.0 Laboratory Aspects

6.1 Background
Definitive diagnosis of drug-resistant TB requires that Mycobacterium tuberculosis to be isolated on culture, identified, and drug susceptibility testing (DST) completed. Major laboratory challenges remain infrastructure, equipment, quality assurance, reliable reproducible methodologies especially for second-line DST and biosafety.

6.2 Chapter objectives
This chapter describes standards for laboratory services needed to diagnose and treat DR-TB.

Key recommendations of this chapter:
- All patients suspected of DR-TB need access to laboratory services for adequate and timely diagnosis of DR-TB;
- DST Laboratories should develop proficiency to isoniazid and rifampicin as a minimum and then consider DST for other drugs.
- Laboratories should develop DST to the fluoroquinolones and second-line injectable agents where adequate capacity and expertise exists;
- Transportation of DR-TB strains across international borders should follow international procedures and guidelines.(Section 6.6);
- Culture and DST Laboratories should follow all standardized protocols for infection control and biosafety;
- Strengthen Quality control and quality assurance for microscopy, culture and DST as well as links with supra-national reference laboratories (SRLs).

6.3 General definitions for the laboratory and DST

- **Critical drug concentration:** The lowest concentration of drug that will inhibit 95% (90% for Pyrazinamide) of wild strains of M. tuberculosis that have never been exposed to drugs, while at the same time not inhibiting clinical strains of M. tuberculosis that are considered to be resistant (e.g. from patients who are not responding to therapy).

- **Minimum inhibitory drug concentration (MIC):** The lowest concentration of drug that will inhibit growth of the M. tuberculosis isolate in vitro.

- **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/technologists.

- **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.

- **Cross-resistance:** Resistance mutations to one anti-tuberculosis drug may confer resistance to some or all of the members of the drug family and, less commonly, to members of different drug families.

### 6.4 General considerations

Procedures for microscopy, culture and DST of first-line anti-tuberculosis drugs have been standardized internationally.

### 6.5 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 culture, confirmation of *M. tuberculosis* and DST to isoniazid and Rifampicin while Clinical laboratory services include basic haematology, biochemistry, serology and urine analysis for adequate evaluation and monitoring of patients (see Chapter 11).

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

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

Transmission of TB – including MDR- and XDR-TB - is a well-recognized risk for laboratory workers. *M. tuberculosis* is classified as a Risk Group 3 laboratory pathogen by WHO, requiring specific laboratory containment measures (see Section 6.10). Appropriate engineering controls, maintenance of essential laboratory safety equipment, and laboratory staff training are equally important.

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

### 6.6 Organization of the laboratory network

TB laboratory networks have a pyramidal structure based on an appropriately large number of peripheral (Level I) laboratories accessible to all TB suspects and patients, a moderate number of intermediate (Level II) laboratories located in mid-sized population centres and health facilities and a single (or more than one) central (Level III) laboratories at the national level. This chapter concentrates on the activities of Level III laboratories as outlined below.
The NTRL shall maintain a sustained link with the Supra National Reference Laboratory (SNL) for DR-TB programme in order to maintain external quality assurance and validation of DST results. In the initial phase of treatment implementation for DR-TB, DST of second-line drugs shall be left to NTRL and supranational reference laboratories with documented capacity, expertise and proficiency. Implementation of laboratory services for culture and DST requires a reasonable balance between cost and turn-around time.
Table 6.1 Functions and responsibilities of the different levels of laboratory services

<table>
<thead>
<tr>
<th>Level I</th>
<th>The peripheral (HC 111s, HCIVs, District hospitals) laboratories</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>• Receipt of specimens</td>
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<tr>
<td></td>
<td>• Preparation and staining of smears</td>
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<tr>
<td></td>
<td>• Ziehl-Neelsen microscopy and recording of results</td>
</tr>
<tr>
<td></td>
<td>• Dispatch of results</td>
</tr>
<tr>
<td></td>
<td>• Maintenance of laboratory register</td>
</tr>
<tr>
<td></td>
<td>• Cleaning and maintenance of equipment</td>
</tr>
<tr>
<td></td>
<td>• Management of reagents and laboratory supplies</td>
</tr>
<tr>
<td></td>
<td>• Internal quality control</td>
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<tr>
<td></td>
<td>• Proper waste management</td>
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<table>
<thead>
<tr>
<th>Level II</th>
<th>The intermediate (Regional Referral Hospital) laboratory</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>• All the functions of a Level I laboratory</td>
</tr>
<tr>
<td></td>
<td>• Fluorescence microscopy (optional)</td>
</tr>
<tr>
<td></td>
<td>• Digestion and decontamination of specimens</td>
</tr>
<tr>
<td></td>
<td>• Culture and identification of M. tuberculosis</td>
</tr>
<tr>
<td></td>
<td>• Training of microscopists</td>
</tr>
<tr>
<td></td>
<td>• Support to and supervision of peripheral-level staff with respect to microscopy</td>
</tr>
<tr>
<td></td>
<td>• Preparation and distribution of reagents for microscopy in peripheral laboratories</td>
</tr>
<tr>
<td></td>
<td>• Quality improvement and proficiency testing of microscopy at peripheral laboratories</td>
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<table>
<thead>
<tr>
<th>Level III</th>
<th>• Proper waste management</th>
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<tbody>
<tr>
<td></td>
<td><strong>The central (National TB Reference) laboratory</strong></td>
</tr>
<tr>
<td></td>
<td>• All the functions of Level I and II laboratories</td>
</tr>
<tr>
<td></td>
<td>• DST of M. tuberculosis isolates</td>
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<tr>
<td></td>
<td>• Identification of mycobacteria other than M. tuberculosis</td>
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<tr>
<td></td>
<td>• Technical control of and repair services for laboratory equipment</td>
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<td></td>
<td>• Updating and dissemination of laboratory manuals, including guidelines on diagnostic methods, on care and maintenance of equipment and on quality assurance</td>
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</tbody>
</table>
- Close collaboration with the central level of the national TB control programme
- Supervision of intermediate laboratories regarding bacteriological methods and their support (particularly training and supervision) to the peripheral laboratories
- Quality assurance of microscopy and culture performed at intermediate laboratories
- Training of intermediate-level laboratory staff
- Organization of anti-tuberculosis drug resistance surveillance
- Operational and applied research relating to the laboratory network, coordinated with the requirements and needs of national TB control programmes
- Proper waste management

6.7 Collection and Transport of infectious substances

For any TB suspect with pulmonary disease, an adequate amount of sputum not less than 3-5ml will be collected. The patient must be educated on the need to prevent spread of TB infection.

The laboratory staff must educate the patient on the need to provide an adequate amount of sputum in a provided standard sterile plastic wide mouthed screw-capped container. One sample should be produced on spot (spot sample) and the second sample on early morning of day two (early morning sample) when a patient wakes up 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 people after:

- Inhaling deeply 2-3 times.
- Coughing out deep from the chest (should avoid producing saliva)
- Opening the container and then s/he spits sputum into it.

Then he closes the container and immediately delivers the sample to the lab for processing. In the laboratory, the sample container is labeled appropriately.

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.

**Packaging:**

The Triple packaging system is recommended. In this system, the sample is physically contained in 3 receptacles i.e. primary receptacle (sputum in falcon tube wrapped in absorbent material e.g. cotton wool), secondary receptacle (a zip lock bag) and a tertiary receptacle (safety box). For details see TSRS (TB specimen referral system) training manual.

**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 to a specific UN number: UN 3373. From 1 January 2007, the shipping name labeled on containers with such specimens is “BIOLOGICAL SUBSTANCE CATEGORY B”. This name is already labeled on all the safety boxes as shown below.

Transportation:
Currently, for Kampala TB zone once specimen packages are ready, Posta Uganda will be called on 0800-11-11-22 (Toll-free number) to collect the sample. For other zones, the package should be delivered to the local post office repository by 3.00 pm. Depending on the distance, use the motorcycle or vehicle for the health facility or public transport to take the package to the post office. The specimen will be registered at the post office and the health facility focal person given written proof of delivery, which must be filed securely in the TSRS box file at the health facility.

Note: If transport to the post office is to be delayed for more than 2 hours, keep the specimen in a refrigerator at 2 – 8 °C for not more than 48 hours.
Posta Uganda will transport the specimen packages from the local post office to the NTRL.

What to do in Case of Damaged/Leaking Packages in Transit
When the leakage is noticed 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. However inform the sending health facility and NTRL for action.

NOTE: Leaking specimens will not be processed at the NTRL.
Feed back on sample results is provided to requesting facility, DTLS and ZTLS through
e-mails, supervisors and post Uganda.

6.8 Microscopy, culture and identification of M. tuberculosis in DR-TB programmes

NTLP, standard operating procedures (SOPs) provide information on sputum smear examination and culture.

6.8.1 Microscopy

Microscopy for acid-fast bacilli (AFB) cannot distinguish viable from non-viable organisms, drug-susceptible and drug-resistant M. tuberculosis 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.

6.8.2 Culture

Quality of laboratory processing is of crucial importance. Quality may be compromised by delays in specimen transport, excessively harsh or insufficient decontamination, poor-quality culture media or incorrect incubation temperature can adversely affect the culture yield. Laboratory errors, such as mislabeling 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. Low positive culture results on solid medium (< 10 colonies) are not well correlated with clinical prognosis and should be interpreted with caution, especially if a single culture with low colony counts is reported. However, persistent positive cultures or any positive culture in the setting of clinical deterioration should be regarded as significant.

6.8.3 Identification of M. tuberculosis

Since Uganda is a high TB, burden country, the majority of mycobacterial isolates will be M. tuberculosis. However, the prevalence of non-tuberculous mycobacteria (NTM) can be more common in patients infected with the human immunodeficiency virus (HIV). Unless the species is confirmed as M. tuberculosis, mycobacterial isolates appearing phenotypically resistant to first-line drugs may represent infection with NTM and not DR-TB. Treatment of NTM is entirely different from treatment of DR-TB. As a minimum, laboratories supporting DR-TB control programmes should be able to identify M. tuberculosis by conventional biochemical identification tests or at least two other methods that follow international guidelines.

6.8.4 Drug susceptibility testing

Identification of DR-TB is based on DST on targeted risk groups and treatment of the identified DR-TB patients on recommended strategies. (See Chapter 5 and 7).

These guidelines recommend that any patient, in whom resistance is considered likely, should have a DST done. This is consistent with the international standards of
There are a number of DST methods that include: solid (LJ), liquid (Bactec, MGIT) and Molecular tests (HAIN).

No rapid molecular tests for detection of XDR-TB are currently available; as a result, conventional and the newer liquid DST techniques are considered the most reliable methods for determining XDR-TB. Some of the newer liquid and agar techniques can determine the presence of XDR-TB within to 7-14 days.

6.8.5 Limitations of DST
The accuracy of DST (performed under optimal circumstances) varies with the drug tested: For first-line anti-tuberculosis drugs, DST is most accurate for rifampicin and isoniazid and less reliable and reproducible for streptomycin, ethambutol and Pyrazinamide.

Testing of in vitro susceptibility of second-line anti-tuberculosis drugs is much more problematic. However, DST results on aminoglycosides, polypeptides, and fluoroquinolones have shown to be relatively reliable and reproducible. Data on the reproducibility and reliability of DST for the other second-line drugs are much more limited have not been established, or the methodology for testing does not exist.

Cross-resistance between the older generation fluoroquinolones (ciprofloxacin and ofloxacin) is almost complete.

Cross-resistance between the aminoglycosides and/or the polypeptides is complex and data very limited. The aminoglycosides kanamycin and amikacin have very high cross-resistance. Cross-resistance between other aminoglycosides and polypeptides appears relatively low.

6.9 Rational use of DST in DR-TB.
Laboratory capacity to reliably detect MDR-TB through quality assured DST of Isoniazid and Rifampicin resistance following a systematic approach is a minimum prerequisite for DR-TB control program
Figure 6.1 Systematic approach to implementation of DST under routine programmatic conditions

**Step 1:**
Isoniazid
Rifampicin

High proficiency in DST to isoniazid and rifampicin should be established first as DST to these drugs are the most reliable and reproducible. As a minimum performance indicator, proficiency testing should correctly identify resistance to isoniazid and rifampicin in more than 90% in two out of three recent rounds of proficiency testing.

**Step 2:**
Ethambutol
Streptomycin
Pyrazinamide

Steps 1 and 2 may be merged if indicated by epidemiological considerations and/or treatment modalities (e.g. standardized or individualized MDR-TB regimens still involving fist-line drugs) and if resources allow extended DST capacity.

**Step 3:**
Amikacin, Kanamycin, Capreomycin, Ofloxacin (or fluoroquinolone of choice in treatment strategy)

Steps 1 and 3 may be merged in settings where XDR is a concern in order to rapidly allow the identification of XDR-TB patients. Given the variability in cross-resistance reported for the aminoglycosides and polypeptides, it is recommended that all aminoglycosides (including streptomycin) as well as capreomycin be tested for resistance where possible. Selection of the most appropriate fluoroquinolone for use is based on treatment strategy.

Sbfresistance to the fluoroquinolone(s) used in DR-TB treatment strategy. Because cross-resistance is not complete between older and newer generation fluoroquinolones it cannot be assumed that resistance to one confers resistance to all fluoroquinolones.

**6.9 Time for testing and reporting: turnaround time**
The turn around time for solid methods is longer (6-10 weeks), liquid shorter (6 weeks) and molecular tests (2 days).

**6.10 Infection control and biosafety in the laboratory**
The relative hazards of infective micro-organisms handled in the laboratory are classified by WHO according to their risk of causing human disease, the potential for laboratory spread and whether effective treatment and prevention measures are available. Related biosafety levels for laboratories have been defined, taking into account the pathogenic
agent, the facilities available, and the equipment, practices and procedures required to ensure a safe laboratory working environment.

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

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

Guidelines on biosafety level 3 precautions should be rigorously followed 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 mycobacteriological 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 should disclose their status to their bosses as HIV-infected should be offered safer work responsibilities and should be discouraged from working with DR-TB specimens. Pregnant women working in the laboratory should be reassigned other duties until after childbirth and lactation.

The use of infection control measures is discussed in more detail in Chapter 15.

### 6.11 Quality control and quality assurance

A diagnosis of DR-TB has profound implications to 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 90% in two out of three recent rounds of panels.

NTRL shall maintain a formal link with one Supranational Reference Laboratory (SRL) Tropical Medicine Antwerp to ensure the quality of laboratory services and the validation of DST results.
CHAPTER 7

7.0 Treatment strategies for MDR-TB and XDR-TB

This chapter describes the treatment regimens (standardized, empirical, and individualized) for the treatment of MDR-TB as well as the more highly resistant strains such as XDR-TB. Any patient treated with second-line drugs falls under Category 4 treatment regimen. For a complete description and weight-based dosing of drugs used in these guidelines, see Annex 1.

Key recommendations of this chapter:

- Design treatment regimens based on the hierarchy of the 5 groups of anti-tuberculosis drugs;
- Promptly diagnose DR-TB and initiate appropriate therapy;
- Use at least four drugs with either certain, or almost certain, effectiveness;
- Use DST to guide therapy; however do not depend on DST in individual regimen design for E, Z, Group 4 and 5 drugs;
- Do not use ciprofloxacin as an anti-tuberculosis drug;
- Treat for 18 months from date of culture conversion;
- Use appropriate adjunctive measures including nutritional/social support and surgery;
- Aggressively treat XDR-TB;
- Treat side effects immediately and adequately.

7.1 Essential assessments prior to designing a treatment strategy

The design of the treatment strategies was guided by DRS data and the frequency of use of TB drugs including SLDs anti-tuberculosis drugs in the country. These guidelines are based on, available evidence/data on the prevalence of drug resistance in new patients as well as in different groups of retreatment cases (failures, relapse, return after default, and chronic cases). They are based on the knowledge that second line drugs except Ofloxacin and amikacin are rarely used in the country. Since Ofloxacin and amikacin have been used for other conditions, there is a high probability of it being ineffective in patients with resistant strains.

At the time of writing these guidelines, representative national data on anti-TB drug resistance in Uganda were not available and actual prevalence of DRTB was yet to be established by the National DRS. However, a number of sub-national studies have shown MDR-TB prevalence ranging from 0.5-1.1% among new cases and 4.4-13.6% among retreatment ones.
In a Kampala- European union funded study done in 2009, MDR-TB prevalence was 1.1 % (5) among 472 new patients and 11.5 % (7) among 61 retreatments. Of the 61 retreatment patients, 48 had relapsed, 7 were returning after default and 2 had failed their prior treatment, 4 others. 415 out of 472 (87.9%) were Susceptible to all drugs, while mono resistance among new cases was 1.5% (7) for rifampicin, 5.7% (27) for Isoniazid, 0.64% (3) for Ethambutol, 8.7% (41) for streptomycin. Mono resistance among retreatment was 13.1% (8) for rifampicin, 19.3% (12) for Isoniazid, 9.8% (6) for Ethambutol, 14.8% (9) for streptomycin.

7.2 Definition of terms used to define DR-TB treatment strategies

There are three DR-TB treatment strategies, namely:

- **Standardized treatment:** This is when DR-TB regimens are designed based on DRS 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 individualized DST and may be changed once individual results come (see Table 7.2 below for recommended MDR/XDR-TB Standard regimens).

- **Empirical treatment:** Is when each regimen is individually designed based on the patient’s past history of TB treatment and DRS data from the representative patient population. Commonly, an empirical regimen is adjusted when DST on the individual patient becomes available.

- **Individualized Treatment:** Is when each regimen is designed based on the patient’s past history of TB treatment and individual DST results. Practically, each regimen is designed based on the patient’s previous history of anti-tuberculosis treatment and individual index case’s DST results.

All MDR/XDR-TB patients shall be on Standardized treatment regimens that are already designed as shown in Table 7.2 below with exception of a few cases that may require Individualized regimen as a result of adverse side effects, poor response to treatment secondary to amplified SLD resistance and Empirical regimen for the MDR/XDR-TB contacts.

7.3 Classes and Groups of anti-tuberculosis drugs

Anti-TB drugs are traditionally divided into first and second line drugs with rifampicin, isoniazid, pyrazinamide, ethambutol and streptomycin being the primary first-line drugs. Anti-tuberculosis drugs are also grouped into 5 groups based on efficacy, experience of use, and drug class; see Table 7.1 below. The group system is very useful for designing cat IV treatment regimens. Not all drugs in the same group have the same efficacy or safety.
Table 7.1 Groups of anti-tuberculosis Drugs.

<table>
<thead>
<tr>
<th>Grouping</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1:</strong> First-line oral drugs</td>
<td>Isoniazid (H); Rifampicin (R); Ethambutol (E); Pyrazinamide (Z); Rifabutin (Rfb)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Group 2:</strong> Injectable drugs</td>
<td>Kanamycin (Km); Amikacin (Am); Capreomycin (Cm); Viomycin (Vm); Streptomycin (S)</td>
</tr>
<tr>
<td><strong>Group 3:</strong> Fluoroquinolones</td>
<td>Moxifloxacin (Mfx); Levofloxacin (Lfx); Ofloxacin (Ofx)</td>
</tr>
<tr>
<td><strong>Group 4:</strong> Oral bacteriostatic second-line drugs</td>
<td>Ethionamide (Eto); Prothionamide (Pto); Cycloserine (Cs); Terizidone (Trd); para-aminosalicylic acid (PAS)</td>
</tr>
<tr>
<td><strong>Group 5:</strong> Drugs with unclear efficacy DR-TB treatment</td>
<td>Clofazimine (Cfz); Linezolid (Lzd); Amoxicillin/clavulanate (Amx/Clv); Thioacetazone (Thz); Imipenem/cilastatin (Ipm/Cln); High-dose isoniazid (High-dose H) &lt;sup&gt;b&lt;/sup&gt;; Clarithromycin (Clr)</td>
</tr>
</tbody>
</table>

<sup>b</sup> High-dose H is defined as 16-20 mg/kg/day.

**General remarks:**

**Group 1:**

All first line drugs to which isolates are sensitive should be used. First line drugs should be used whenever possible, since they are potent and better tolerated than SLDs. If a Group 1 drug was used in a previous regimen that failed, its efficacy should be questioned even if the DST result suggests susceptibility. For patients with strains resistant to low concentrations of isoniazid but susceptible to higher concentrations, the use of high-dose isoniazid may have some benefit (when isoniazid is used in this manner it is considered a Group 5 drug; see below). FLDs should be used at maximal doses (25mg/kg for Ethambutol and 40mg/kg for Pyrazinamide).

**Group 2 (injectable agents).**

All patients should receive a group 2 injectable agent if susceptibility is documented or suspected. Kanamycin or amikacin is the first choice injectable drug. Kanamycin and...
amikacin are very similar and have a high frequency of cross-resistance. If an isolate is resistant to both streptomycin and Kanamycin or if DRS data show high rates of resistance to kanamycin and amikacin, then capreomycin should be used. Viomycin is very similar and shares a high frequency of cross-resistance to capreomycin.

**Group 3.**
All patients should receive a Group 3 medication if the strain is susceptible or if the drug is thought to have efficacy. The most potent fluoroquinolones in descending order are: moxifloxacin = gatifloxacin > levofloxacin > ofloxacin. Moxifloxacin or levofloxacin are the fluoroquinolones of choice.

While Ofloxacin is commonly used because of cost, the higher generation fluoroquinolones, moxifloxacin and Levofloxacin, are more effective and have similar adverse effects. Gatifloxacin is similar to moxifloxacin in efficacy against TB, but it is associated with serious cases of hypoglycemia, hyperglycemia, and new onset diabetes. Gatifloxacin should be used when there is no other option of a higher generation fluoroquinolone and close monitoring is assured.
A higher generation fluoroquinolone is recommended for treatment of XDR-TB

**Group 4.**
Group 4 drugs include ethionamide or prothionamide, PAS and cycloserine. Ethionamide or prothionamide is often added because of low cost. PAS is associated with gastrointestinal side effects but the enteric-coated formulations are better tolerated although are more expensive. When two drugs are needed, from this group, cycloserine is used often in conjunction with ethionamide/prothionamide or PAS.

Since the combination of ethionamide/prothionamide and PAS often causes a high incidence of gastrointestinal side effects and hypothyroidism, these drugs are usually used together only when three Group 4 drugs are needed: ethionamide/prothionamide, cycloserine and PAS. Terizidone contains two molecules of cycloserine. It can be used instead of cycloserine and is assumed to be as efficacious. The drugs in Group 4 may be started at a low dose and stepped up over two weeks (for more on drug ramping, see Section 7.7.3).

**Group 5.**
Group 5 drugs include Clofazimine (Cfz); Linezolid (Lzd); Amoxicillin/clavulanate (Amx/Clv); Thioacetazone (Thz); Imipenem/cilastatin (Ipm/Cln); High-dose isoniazid (High-dose H); Clarithromycin (Clr). Group 5 drugs are not recommended for routine use in DR-TB treatment because their contribution to the efficacy of multidrug regimens is unclear. If a situation requires the use of Group 5 drugs, it is recommended to use at least two drugs from this group given the limited knowledge of efficacy.

There is well-known cross-resistance between some of the antibiotics used in treating tuberculosis. Cross-resistance between specific anti-tuberculosis drugs is summarized in Table 7.3. **Box 7.1 Known cross-resistance between anti-tuberculosis drugs.**
Example 7.1: 6Km₆ (or Cm₆)-Lfx₆ -Eto₆-Cs₆ -Z₆ /18Lfx₆ -Eto₆-Cs₆ -Z₆

The initial phase consists of five drugs and lasts for at least six months or six months past conversion. In this example, the phase without the injectable continues all the oral agents for a minimum of 18 months, for a total minimum treatment of at least 24 months. The injectable is kanamycin, but there is an option for capreomycin. Sometimes only the initial treatment is written and the assumption is that the regimen will be adjusted with DST. This type of notation is used without a coefficient, i.e., KM-Ofx-Eto-Cs-Z

<table>
<thead>
<tr>
<th>Box 7.1 Known cross-resistance between anti-tuberculosis drugs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ All rifamycins have high levels of cross-resistance.</td>
</tr>
<tr>
<td>▪ Fluoroquinolones are believed to have variable cross-resistance between each other, with in vitro data showing that some higher generation fluoroquinolones remain susceptible when lower generation fluoroquinolones are resistant. In these cases, it is unknown if the higher generation fluoroquinolones remain effective clinically.</td>
</tr>
<tr>
<td>▪ Amikacin and Kanamycin have very high cross-resistance. Capreomycin and Viomycin have high cross-resistance. Other aminoglycosides and polypeptides have low cross-resistance.</td>
</tr>
<tr>
<td>▪ Prothionamide and Ethionamide have 100% cross-resistance. Ethionamide can have cross-resistance to isoniazid if the inhA mutation is present. Thioacetazone cross-resistance to isoniazid, ethionamide, and PAS have all been reported but is generally considered low.</td>
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</tbody>
</table>

7.4 Standard code for TB treatment regimens

A DR-TB regimen consists of two phases: the first phase is the period in which the injectable drug is used and the second is after it has been stopped. The number shown before each phase stands for phase duration in months and is the minimum amount of time that phase should last. The number in subscript (e.g., 6) after a letter is the number of drug doses per week. If there is no number in subscript, treatment is daily. An alternative drug(s) appears as a letter(s) in parentheses. The drugs in the higher groups are written first followed by the others in descending order of potency. Examples are given in Box 7.2.
Box 7.2 Examples of standard drug code used to describe drug regimens

Example 7.1: 6Km6(or Cm6)-Lfx6-Eto6-Cs6-Z6/18Lfx6-Eto6-Cs6-Z6

The initial phase consists of five drugs and lasts for at least six months or six months past conversion. In this example, the phase without the injectable continues all the oral agents for a minimum of 18 months, for a total minimum treatment of at least 24 months. The injectable is kanamycin, but there is an option for capreomycin. Sometimes only the initial treatment is written and the assumption is that the regimen will be adjusted with DST. This type of notation is used without a coefficient, i.e., KM-Ofx-Eto-Cs-Z

7.5 Role of drug susceptibility testing in DR-TB treatment.

- To design treatment regimen (standardized, empirical and individualized)
- To adjust treatment regimen

The inability to do routine DST in all patients should not be a barrier for patients that need Category 4 treatment. Fully standardized regimens using second-line anti-tuberculosis drugs have been shown to be feasible and cost-effective in DR-TB treatment. Even when reliable DST is available, standardized regimens can still be chosen as a strategy over individualized regimens for the following reasons:

- Interpretation of DST to some of the first- and second-line drugs is difficult and could mislead regimen design. It is not recommend to use DST to E, Z, and the drugs in Groups 4 and 5 to base individual regimen design.
- Turnaround time for many culture-based DST methods is long.
- The laboratory may not perform DST for certain drugs, or may perform them at different times.

7.6 Designing a treatment regimen

This section describes the methods for designing a treatment regimen. It applies to standardized, empirical and individualized regimens.

7.6.1 General Regimen design and treatment principles applied in Uganda:

The following are the basic principles involved in any regimen design:
1. The history of drugs taken by the patient.
2. Drugs commonly used in the country.
4. At least four drugs with either certain, or almost certain, effectiveness. Often, more than four drugs may be started if the susceptibility pattern is unknown, effectiveness is questionable for an drugs(s), or if extensive, bilateral pulmonary disease is present.
5. Once-a-day dosing is preferred. In event of patient intolerance split doses during the day. For example; ethionamide/prothionamide, cycloserine and PAS have traditionally been given in split doses during the day to reduce side effects.

6. The drug dosage is to be determined by body weight.

7. Treatment of side effects of drugs should be immediate and adequate to minimize the risk of treatment interruptions and prevent increased morbidity and mortality.

8. An injectable drugs (an aminoglycoside or capreomycin) is used for a minimum of six months and at least four months after culture conversion.

9. The minimum length of treatment is 18 months after culture conversion. Each dose is given as directly observed therapy (DOT) throughout the treatment. A treatment card is ticked for each observed dose.

10. DST for drugs should be used to guide therapy.

11. Pyrazinamide can be used for the entire treatment if it is judged to be effective. Many DR-TB patients have chronically inflamed lungs, which theoretically produce the acidic environment in which pyrazinamide is active. Alternatively, in patients doing well, pyrazinamide can be stopped with the injectable phase if the patient can continue with at least three certain, or almost certain, effective drugs.

12. Early DR-TB detection and prompt initiation of treatment are recommended to ensure successful outcomes.

Early DR-TB detection and prompt initiation of treatment are important factors in determining successful outcomes. An injectable agent (Kanamycin or capreomycin) will be used for a minimum of 6 months, (and at least 4 months after sputum conversion). Treatment will be for a minimum duration of 18 months beyond sputum conversion.

Figure 7.2 describes the steps to build a regimen for DR-TB treatment.

**7.6.2 Dosing of drugs**
Dosing of anti-tuberculosis drugs is based on the weight of the patient. Dosing is described in Annexes 1. Dosing for pediatrics is described in Chapter 9.

**7.6.3 Stepping up Dose (drug ramping)**
Most drugs should be started at full dose, except cycloserine, ethionamide, and PAS, in which case the dose of the drug can be increased over a 2-week period. For cycloserine and ethionamide start at 15 mg/kg daily and when the drug is tolerated, step dose to 20 mg/kg daily. For PAS start at 100mg before increasing to 150 mg/kg daily. The approach of slowly stepping up drug dosage is referred to as “drug ramping.”

**7.7 Designing a DR-TB treatment Regimen**
There are a number of principles in Table 7.2 below that need explanation. First is that DST surveillance data for different groups of patients (new, failures of Category 1, failures of Category 2, relapse and default, and failures of Category 4) will greatly help determine the rates of MDR-TB and of resistance to other anti-tuberculosis drugs. This is essential for developing appropriate treatment strategies and for evaluating the impact of control programme interventions.
For a standardized regimen that will treat the vast majority of patients with four effective drugs, it is often necessary to use five or six drugs to cover all possible resistance patterns. As Table 7.2 illustrates, for most cases, an injectable drug and a fluoroquinolone make the core of the regimen.

In using a standardized regimen, it is recommended to order other drugs that are not included in the standard regimen.

**Figure 7.2 How to build a treatment regimen for MDR-TB**

<table>
<thead>
<tr>
<th>STEP 1</th>
<th>Use any available</th>
<th>Begin with any first-line agents that have certain, or almost certain, efficacy. If a first-line agent has a high likelihood of resistance do not use it. (For example, most Category 4 regimens used in treatment failures of Category 2 do not include ethambutol because it is likely to be resistant based on treatment history.)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Group 1: First-line oral agents</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide Ethambutol</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>STEP 2</th>
<th>Plus one of these</th>
<th>Add an injectable agent based on DST and treatment history. Avoid streptomycin even if DST suggests susceptibility because of high rates of resistance with DR-TB strains and higher incidence of ototoxicity.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 2: Injectable agents</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kanamycin (or Amikacin)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Capreomycin (or Viomycin)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Streptomycin</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>STEP 3</th>
<th>Plus one of these</th>
<th>Add a fluoroquinolone based on DST and treatment history. In cases where resistance to ofloxacin or XDR-TB is suspected use a higher generation fluoroquinolone, but do not rely upon it as one of the core four drugs.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 3: Fluoroquinolones</td>
<td></td>
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<tr>
<td></td>
<td>Levofloxacin</td>
<td></td>
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<tr>
<td></td>
<td>Moxifloxacin</td>
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</tr>
<tr>
<td></td>
<td>Ofloxacin</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>STEP 4</th>
<th>Pick one or more of these</th>
<th>Add Group 4 drugs until you have at least 4 drugs likely to be effective. Base choice on treatment history, side-effect profile, and cost. DST is not standardized for the drugs in this group.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1: First-line oral agents</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide Ethambutol</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>STEP 5</th>
<th>Consider use of these</th>
<th>Consider adding Group 5 drugs in consultation with an MDR-TB expert if there are no 4 drugs that are likely to be effective from Groups 1-4. If drugs are needed from this group, it is recommended to add at least two. DST is not standardized for the drugs in this group.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1: First-line oral agents</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide Ethambutol</td>
<td></td>
</tr>
</tbody>
</table>

.b Thioacetazone is contraindicated in HIV-infected individuals due to a serious risk of life threatening drug reaction.
See Box 7.3 for an example of how to design a standardized regimen.
NOTE: The recommended MDR/XDR-TB Standard regimens are already designed as shown in Table 7.2 below

**Box 7.4 Examples of how to design an individualized regimen**

**Example 1.** A patient in whom Category 1 and 2 treatments failed. DST results reveal that the infecting strain is resistant to H-R-S and susceptible to all other medications including E-Km-Cm-Ofx; resistance to Z is unknown. The patient has received HRE for 3 months since the date of the DST. What individualized regimen is recommended?

Answer: Since the patient received two courses containing E and Z, and was on functional monotherapy with E for at least 3 months, the utility of these drugs must be questioned despite the DST results. The same drugs can be included in the regimen but they should not be relied on as one of the four core drugs. The injectable choice may depend on the prevalence of resistance in the community, but since this patient never received Km, Km is low in cost, and the DST is reported to be susceptible it may be the first choice in this case:

6Km (Cm)-Ofx-Eto(Pto)-Cs/18 Ofx-Eto(Pto)-Cs

(Many clinicians will add Z to this regimen; others may use PAS instead of Eto or Pto.)

**Example 2.** A patient in whom Category 1 and 2 treatments failed. A review of DST results reveals that the infecting strain is resistant to H-R-Z-E-S-Km and susceptible to the medications Cm-Ofx. The patient has not received any antituberculosis drugs since the date of the DST. What individualized regimen is recommended?

Answer: Below are two possible options in this case:

1. 6Cm-Ofx-Pto (Eto)-Cs/18Ofx-Pto(Eto)-Cs

Regimen 1 may have the advantage of increased compliance since it requires the minimum number of drugs and avoids the adverse effects of the combination of PAS and Pto (Eto). However, if one or more of the DST results is wrong (and the reliability of DST of second-line drugs even to Cm and Ofx are only moderately reliable) the patient may be effectively on a regimen of only two or three drugs. Prevalence of resistance to second-line drugs and their availability can help in the decision.

2. 6Cm-Ofx-Pto-Cs-PAS/18Ofx-Pto-Cs-PAS

Regimen 2 takes into consideration the uncertainty of DST of second-line drugs. It places the patient on an additional drug as a precaution in case one of the DST results does not reflect the efficacy of any of the drugs tested. Pto and PAS, while difficult to take together, are frequently tolerated by many patients especially with good patient support. A regimen with these five drugs is also preferred if there is extensive damage to the lungs or if susceptibility to any of these drugs is uncertain given a patient’s history.
<table>
<thead>
<tr>
<th>Patient group</th>
<th>Background susceptibility data</th>
<th>Recommended strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>New patient with active TB</strong></td>
<td>Low to moderate rate of DR-TB among new cases</td>
<td>▪ Start Category 1 treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Perform DST to at least H and R in patients who remain smear positive at the end of 2nd or 3rd month of treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Rapid DST techniques are preferable</td>
</tr>
<tr>
<td><strong>Patient in whom Category 1 failed</strong></td>
<td>Low percentage of failures of Category 1 have MDR-TB</td>
<td>▪ Perform DST to H and R at a minimum in all DR-TB suspects prior to treatment start</td>
</tr>
<tr>
<td></td>
<td>Second-line drug resistance is rare</td>
<td>▪ Rapid DST is preferable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Start Category 4 treatment while awaiting DST</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Maintain Category 4 regimen if DST reveals MDR-TB</td>
</tr>
<tr>
<td><strong>Patient in whom Category 2 failed</strong></td>
<td>Low to moderate percentage of failures of Category 1I have MDR-TB</td>
<td>▪ Perform DST to H and R at a minimum in all patients prior to treatment start</td>
</tr>
<tr>
<td></td>
<td>Second-line drug resistance is rare</td>
<td>▪ Continue Category 2 while waiting for the DST results</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Change to Category 4 individualized regimen if DST show MDR-TB or continue Cat II if no MDR-TB</td>
</tr>
<tr>
<td><strong>Patient with history of relapse or patient returning after Default</strong></td>
<td>Low to moderate rate of MDR-TB in this group of patients is common</td>
<td>▪ Perform DST to H and R at a minimum in all patients prior to treatment start</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Start Category 4 treatment while awaiting DST</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Adjust regimen to a Category 4 regimen if DST returns DR-TB</td>
</tr>
<tr>
<td>Patient group</td>
<td>Background susceptibility data</td>
<td>Recommended strategy</td>
</tr>
<tr>
<td>---------------</td>
<td>--------------------------------</td>
<td>-----------------------</td>
</tr>
</tbody>
</table>
| **Contact of MDR-TB patient now with active TB disease** | Close contact with high risk of having the same strain | - Perform rapid diagnosis and DST to H and R at a minimum in all patients prior to treatment start  
- Start Category 4 empirical treatment based on the DST pattern of index case and treatment history of the contact (see Chapter 14) while awaiting DST  
- Adjust regimen according to DST results |
| **Casual contact with low risk of having the same strain** | | - Perform rapid diagnosis and DST to H and R at a minimum in all patients prior to treatment start  
- Start Category 1 treatment while awaiting DST  
- Adjust regimen according to DST results |
| **Patient with documented MDR-TB** | Documented, or almost certain, susceptibility to a FQ and IA | - Start Category 4 treatment: IA-FQ- two Group 4 drugs- +/- Z  
6Km+Lfx+Eto+Cs+Z/18Lfx+Eto+Cs+Z under DOT (Standard regimen) |
| | Documented, or almost certain, susceptibility to FQ  
Documented, or almost certain, resistance to an IA | - Start Category 4 treatment: IA-FQ- three Group 4 drugs- +/- Z  
Use an IA with documented susceptibility  
6Cm+Lfx+Eto+Cs+PAS(+Z)/18 Lfx+Eto+Cs+PAS(+Z) (Standard regimen)  
- If the strain is resistant to all IAs, use one for which resistance is relatively rare |
| | Documented, or almost certain, resistance to a FQ  
Documented, or almost certain, susceptibility to IA | - Start Category 4 treatment: IA-FQ-three Group 4 drugs- +/- Z  
Use a higher generation FQ  
6Km+Mfx+Eto+Cs+PAS(+Z)/18 Mfx+Eto+Cs+PAS(+Z) (Standard regimen) |
| | Documented, or almost certain, resistance to a FQ and IA | - Start Category 4 treatment for XDR-TB (see section 7.14) |
Patient in whom Category 4 failed or Patient with documented MDR-TB and history of extensive second-line drug use

| When XDR-TB is suspected | • Perform DST to IA and FQ (and H and R if not already done) prior to treatment start
  • Start Category 4 treatment - 12Cm-Mfx-Cs-PAS-Cfz-Amx/Clv/12 Mfx-Cs-PAS-Cfz-Amx/Clv (Standard regimen) for XDR-TB (see section 7.14) while awaiting DST
  • Adjust regimen according to DST results |

Patient with documented XDR-TB

| Documented resistance to H, R, IA, and FQ | • Start Category 4 treatment for XDR-TB - 6 Cm-Mfx-Cs-PAS-Cfz-Amx/Clv/18 Mfx-Cs-PAS-Cfz-Amx/Clv (Standard regimen) (see section 7.14) (Cm may be given longer than 6 months) |

7.8 Completion of the injectable drugs (initial phase)

The duration of administration of the injectable drugs, or the initial phase, is guided by culture conversion. The injectable drugs should be continued for at least four months after the patient first becomes and remains smear- or culture-negative.

The use of an individualized approach which reviews the cultures, smears, x-rays, and the patient’s clinical status may also aid in deciding whether or not to continue an injectable drug longer than the above recommendation, particularly in the case of patients for whom the susceptibility pattern is unknown, effectiveness is questionable for the drug(s), or extensive or bilateral pulmonary disease is present.

Intermittent therapy with the injectable drugs (three times a week) can ONLY be considered in patients who have been on the injectable for a prolonged period of time (longer than 6-8 months) and when toxicity becomes a greater risk to the patient. If the patient was on an empirical regimen of five or six drugs, drugs other than the injectable can be considered for suspension ONLY once the supportive DST results are available and the patient continues with at least three of the most potent drugs.

7.9 Length of treatment

The duration of treatment is guided by culture conversion. Continue therapy for a minimum of 18 months after culture conversion. Extension of continuation phase to 24 months may be indicated in chronic cases with extensive pulmonary damage.

7.10 Extra pulmonary DR-TB

Extra pulmonary DR-TB is treated with the same strategy and length of time as pulmonary DR-TB. If the patient has symptoms suggestive of central nervous system involvement and is infected with DR-TB, the regimen should use drugs which have adequate penetration.
into the central nervous system. Rifampicin, isoniazid, pyrazinamide, prothionamide/ethionamide and cycloserine have good penetration into the cerebrospinal fluid (CSF); kanamycin, amikacin, and capreomycin do so only in the presence of meningeal inflammation; PAS and ethambutol have poor or no penetration. For fluoroquinolones use the higher generations because they have better CSF penetration.

### 7.11 Surgery in Category 4 treatment

The most common operative procedure in patients with pulmonary DR-TB is resection surgery (taking out part or all of a lung). Large case series analysis has proven resection surgery to be effective and safe under appropriate surgical conditions. It is considered an adjunct to chemotherapy and appears to be beneficial for patients when skilled thoracic surgeons and excellent postoperative care are available. It is not indicated in patients with extensive bilateral disease.

Resection surgery should be timed so as to offer the patient the best possible chances of cure with the least morbidity. 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, for example, when the disease is still localized to one lung or one lobe. In other words, surgery should not be considered a last resort. Generally, at least two months of therapy should be given prior to resection surgery in order to decrease the bacterial infection in the surrounding lung tissue. Even with successful resection, an additional 18-24 months of chemotherapy should be given.

Specialized surgical facilities should include stringent infection control measures since infectious substances and aerosols are generated in large quantities during surgery and during mechanical ventilation and post-operative pulmonary hygiene maneuvers.

**General indications for surgery in MDR-TB:**

- Persistence of sputum culture positive MDR-TB after 3-6 months of planned chemotherapy in fibro cavitory or destroyed lung lesions;
- Resistance to a large number of drugs, or high risk failure/relapse;
- Localized pulmonary disease;
- Life threatening hemoptysis;
- Destroyed lung
- Drug allergy/intolerance to medications

Operative procedures may include but not limited to lobectomy, Pneumonectomy and segmentectomy.

Computerized tomography, pulmonary function testing, and quantitative lung perfusion/ventilation is recommended as part of the preoperative work-up. In case of sub-optimal surgical facilities and no trained thoracic surgeons, refrain from resection surgery as the result may be an increase in morbidity or mortality.
7.12 Adjuvant therapies in DR-TB treatment

A number of other modalities are used to lessen adverse effects and morbidity, as well as improve DR-TB treatment outcomes.

7.12.1 Nutritional support

In addition to causing malnutrition, DR-TB can be exacerbated by poor nutritional status. Without nutritional support, patients, especially those already suffering from baseline hunger, can become trapped in a vicious cycle of malnutrition and disease. The second-line anti-tuberculosis medications can also further decrease appetite, making adequate nutrition a greater challenge.

Vitamin B6 (pyridoxine) should also be given to all patients receiving cycloserine or terizidone to prevent neurological side effects (see Chapter 11 for dosing and more information). Vitamin (especially vitamin A) and mineral supplements can be given in areas where a high proportion of the patients have these deficiencies. If minerals are given (zinc, iron, calcium, etc.) they should be dosed apart from the fluoroquinolones, as they can interfere with the absorption of these drugs.

7.12.2 Corticosteroids

In DR-TB patients, the adjuvant use of corticosteroids has been shown to reduce mortality and can be beneficial in conditions such as severe respiratory insufficiency, and central nervous system or pericardial involvement. Prednisone is commonly used, starting at approximately 1-2 mg/kg/per day in divided doses and gradually decreasing the dose to 10 mg per week when a long course is indicated. Corticosteroids may also alleviate symptoms in patients with an exacerbation of obstructive pulmonary disease. In these cases, prednisone may be given in a short taper over one to two weeks, starting at approximately 1 mg/kg and decreasing the dose by 5–10 mg per day. Injectable corticosteroids are often used initially when a more immediate response is needed.

7.13 Treatment of extensively drug-resistant TB (XDR-TB)

XDR-TB is more difficult to treat than MDR-TB and extremely difficult in HIV-infected patients. Figure 7.3 summarizes the latest expert consensus on how to manage XDR-TB. There is very limited data on different clinical approaches to XDR-TB.
Figure 7.3 – Treatment strategies for a patient with documented, or almost certain, XDR-TB

13. Use any Group 1 agents that may be effective;
14. Use an injectable agent to which the strain is susceptible and consider an extended duration of use (12 months or possibly the whole treatment). If resistant to all injectable agents it is recommended to use one the patient has never used before;
15. Use a higher generation fluoroquinolone such as moxifloxacin;
16. Use all Group 4 agents that have not been used extensively in a previous regimen or any that are likely to be effective;
17. Use two or more agents from Group 5;
18. Consider high-dose H treatment if low-level resistance is documented.
19. Consider adjuvant surgery if there is localized disease;
20. Ensure strong infection control measures;
21. Treat HIV as per Chapter 10;
22. Provide comprehensive monitoring (see Chapter 11) and full adherence support (see Chapter 12).

*This recommendation is made because while the reproducibility and reliability of DST to injectables is good, there is little data on clinical efficacy of the test. Options with XDR-TB are very limited and some strains may be affected in vivo by an injectable drug even though they are testing resistant in vitro.

Box 7.5 Example of XDR-TB treatment

**Example 1.** A patient in whom a standardized regimen of Km-Ofx-Eto-Z failed and remains sputum smear-positive after 8 months of treatment. The DST done from a specimen taken 4 months ago reveals resistance to HRZE-Km-Cm and susceptibility to Ofx.

**What treatment regimen is recommended?**

**Answer:** This patient may now be resistant to Ofx. Eto and Ofx cannot be relied upon in a new regimen and treatment options are thus limited. A higher generation fluoroquinolone may have some effect. The recommended regimen is: Cm-Mfx-Cs-PAS plus two Group 5 drugs (Cfz and Amx/Clv are perhaps the two most common Group 5 drugs used in this circumstance) i.e.

6. Cm-Mfx-Cs-PAS- Cfz-Amx/Clv/18 Mfx-Cs-PAS- Cfz-Amx/Clv (Cm may be given longer than 6 months)

7.14 Conclusion

DR-TB treatment is a complex health intervention and no one strategy will fit all situations
and thus there is need to consider the epidemiological, financial, and operational factors when deciding which strategy to use.

Table 7.3 Provides a summary of the basic principles for designing treatment regimens

<table>
<thead>
<tr>
<th>Basic Principles</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Use at least 4 drugs certain to be effective If at least 4 drugs are not certain to be effective, use 5 – 7 drugs depending on the specific drugs and level of uncertainty.</td>
<td>Effectiveness is supported by a number of factors (the more factors present the more likely the drug will be effective in the patient): DST results show susceptibility (for drugs in which there is good laboratory reliability). No prior history of treatment failure with the drug. No known close contacts with DR-TB patient who is resistant to the drug. Drug resistance survey shows resistance is rare in similar patients. The drug is not commonly used in the area.</td>
</tr>
<tr>
<td>2. Do not use drugs for which there is the possibility of cross-resistance</td>
<td>Many -tuberculosis drugs exhibit cross-resistance both within and across drug classes. Knowledge of these relationships is essential in designing regimens for DR-TB (see Box 7.1).</td>
</tr>
<tr>
<td>3. Eliminate drugs that are not safe in the patient</td>
<td>Known severe allergy or unmanageable intolerance. High risk of severe adverse drug effects such as renal failure, deafness, hepatitis, depression and/or psychosis. Quality of the drug unknown.</td>
</tr>
<tr>
<td>4. Include drugs from Groups 1 to 5 in a hierarchal order based on potency</td>
<td>Use any of the first-line oral drugs (Group 1) that are likely to be effective (see the first section in this table as to what predicts effectiveness). Use an effective aminoglycoside or polypeptide by injection (Group 2). Use a fluoroquinolone (Group 3). Use the remaining Group 4 drugs to complete a regimen of at least 4 effective drugs. For regimens with fewer than 4 effective drugs, consider adding Group 5 drugs. The total number of drugs will depend on the degree of uncertainty, and regimens often contain 5-7 drugs.</td>
</tr>
</tbody>
</table>
MDR-TB panels and their roles in DR-TB management.

The DR-TB Review Panel is a case management committee composed of health care workers with expertise on MDR-TB management. This committee will meet regularly (monthly) to confirm the diagnosis, determine treatment regimens, assess response to treatment, and determine final outcome through a consensus using standards based on the NTLP Guidelines for Programmatic Management of Drug-resistant TB. The Panel will consider the availability and cost of drugs to make decisions on individual treatment regimens.

For the treatment of MDR-TB, the DR-TB Review Panel will:

- Review the presentation of MDR-TB cases for enrollment;
- Approve the proposed enrollment regimen, regimen change, decentralization, treatment outcome or any action point relevant to the case presented;
- Arrive at a consensus on decisions when management of an MDR-TB patient is unclear and complicated.

The National DR-TB panel shall double as Mulago DR-TB panel and when new DR-TB treatment centers are opened, separate panels will be established but will be overseen by the national panel.

The site panels will be composed of; DR-TB trained Clinicians, lab personnel, a social worker, a nurse and a radiologist if available (or Clinician trained on CXR reading)

These sub national panels shall recommend to the National MDR-TB panel MDR TB patients or suspects for approval of treatment. Once treatment is approved by the National DR-TB panel then accredited DR-TB treatment centre will have the treatment initiated.

DR-TB Core team and Review panels shall meet periodically to discuss individual patients and to address programmatic problems.
CHAPTER 8

8.0 Mono- and poly-resistant strains (Drug-resistant tuberculosis other than MDR-TB)

This chapter describes the recommended treatment strategies for patients with DR-TB other than MDR-TB. These include patients with mono-resistant TB and patients with poly-resistant TB other than MDR-TB. Mono-resistance refers to resistance to a single first-line drug, and poly-resistance refers to resistance to two or more first-line drugs but not to both isoniazid and rifampicin.

8.1 General considerations

Cases with mono- or poly-resistance will be identified during the course of case-finding for MDR-TB. Treatment of patients infected with mono or poly-resistant strains using standardized SCC has been associated with increased risk of treatment failure and further acquired resistance, including the development of MDR-TB. The likelihood of poor outcomes is relatively low with many types of mono- and poly-resistance and the majority of these patients will be cured with SCC) using regimens constructed based on the DST patterns.

8.2 Consequences for reporting

Some mono and poly-resistance TB patients may require prolonged treatment regimens of first line drugs combined with one or two second line TB drugs. These regimens are considered “modifications” of Category 1 or Category 1I treatment. They are not classified as Category 4 treatments, which are regimens designed to treat MDR-TB neither are they classified under Category 1. The adjustment should be noted in the remarks section of the Register and the adjusted treatment continued for the indicated length of time (see table 8.1 below for suggested regimens for mono and poly resistant TB).

Those mono and poly-resistance TB patients whose regimens do not require or require only one second-line drug should be maintained in the regular district TB register.

For poly-resistant TB cases that require two or more second line drugs are entered into Category 4 Register at DR-TB accredited centre but their treatment outcome should be reported back to the health facility/district where they were diagnosed and it is these facilities that will report them to NTLP where they will be analyzed as a separate cohort of patients.

8.3 Treatment of patients with mono- and poly-resistant strains

Definitive randomized or controlled studies have not been performed to determine the best treatment for various patterns of drug resistance, except for streptomycin resistance. The current recommendations are based on evidence from the pre-rifampicin era, observational studies, general principles of microbiology and therapeutics in TB, extrapolations from established evidence and expert opinion. The design of regimens for mono- and poly-resistant cases of TB requires experience. Therefore, the decision to
modify standard short-course chemotherapy and to treat mono and poly resistant cases with, the most effective regimen shall be by specialists and approved by Review panels in the DR-TB reference centre only in order to maximize the likelihood of cure. The Review panel shall meet periodically to review the treatment history, DST patterns and the possibility of strains of M. tuberculosis having acquired new resistance, and then approve the regimen proposed by the specialist in the reference centre.

The regimens in Table 8.1 are based on the assumption that the pattern of drug resistance has not changed from the time of diagnosis to the time a patient starts treatment. Table 8.1 should therefore not be used if further resistance to any of the agents in the suggested regimen is suspected. It is also important to note that a high level of confidence in the laboratory is needed for effective use of Table 8.1. As mentioned in Chapters 6 and 7, DST to ethambutol and pyrazinamide is not highly reproducible.
### Suggested regimens for mono- and poly-drug resistance\(^a\)
(When further acquired resistance is not a factor and laboratory results are highly reliable)

<table>
<thead>
<tr>
<th>Pattern of Drug resistance</th>
<th>Suggested regimen</th>
<th>Minimum duration of treatment (months)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>H (± S)</td>
<td>R, Z, E and Lfx</td>
<td>9</td>
<td>A fluoroquinolone strengthens the regimen for patients with extensive disease.</td>
</tr>
<tr>
<td>H and Z</td>
<td>R, E and Lfx</td>
<td>12</td>
<td>Any other fluoroquinolone with demonstrated susceptibility may be used.</td>
</tr>
<tr>
<td>H and E</td>
<td>R, Z and Lfx</td>
<td>12</td>
<td>Any other fluoroquinolone with demonstrated susceptibility may be used.</td>
</tr>
<tr>
<td>R</td>
<td>Km for 3 months, H, E, Lfx,</td>
<td>18</td>
<td>An injectable agent strengthens the regimen plus at least 2 months of Z.</td>
</tr>
<tr>
<td>R and E (± S)</td>
<td>H, Z, Lfx and Km</td>
<td>18</td>
<td>A longer course (6 months) of the for at least 3 months injectable agent strengthens the regimen for patients with extensive disease.</td>
</tr>
<tr>
<td>R and Z (± S)</td>
<td>H, E, Lfx and Km</td>
<td>18</td>
<td>A longer course (6 months) of the an injectable agent injectable agent strengthens the for at least the first for regimen for patients with extensive 3 months disease.</td>
</tr>
<tr>
<td>H, E, Z (± S)</td>
<td>R, Lfx, Cs</td>
<td>18</td>
<td>A longer course (6 months) of the injectable plus Km an injectable agent may strengthen the regimen for agent for the first 3 months patients with extensive disease.</td>
</tr>
</tbody>
</table>

H = isoniazid; R = rifampicin; E = ethambutol; Z = pyrazinamide; S = streptomycin, Cs = Cycloserine, Lfx = Levofloxacin, and Km = Kanamycin.

\(^a\) Adapted from Drug-resistant tuberculosis: a survival guide for clinicians
BOX 8.1 Example of regimen design for mono- and poly-resistant strains

DRS data indicate that 85% of failures of Category 1 have MDR-TB. A patient who has received a Category 1 regimen of HRZE has a culture sent for DST at month 2 of treatment because of a positive smear. The intensive phase is continued for an additional month, at which time the smear is negative, and the patient is placed on the continuation phase of treatment with HR. The DST returns in month 4 of treatment with resistance to HE and susceptibility to S. DST is not known for Z. The patient is sputum smear-positive at month 4. What regimen should be used?

**Answer:**
The patient has been on at least one month of functional monotherapy with R, and if resistant to Z he or she may have been on monotherapy with R for four months. In this case, do not use Table 8.1 to design the regimen; instead, assume the patient may have now developed resistance to R, and design a Category 4 regimen based on the principles for MDR-TB regimen design described in Chapter 7.
CHAPTER 9

9.0 Treatment of drug-resistant tuberculosis in special conditions and situations

This chapter describes the management of DR-TB in the following special conditions and situations like pregnancy, breastfeeding, contraception, children, diabetes mellitus, renal insufficiency, liver disorders, seizure disorders, psychiatric disorders, substance dependence, HIV infection and XDR-TB.

9.1 Pregnancy

All female patients of childbearing age should be tested for pregnancy during initial evaluation. Pregnancy is not a contraindication for treatment of active DR-TB, which poses great risks to the lives of both mother and fetus. However, birth control is strongly recommended for all non-pregnant women receiving therapy for DR-TB because of the potential consequences for both mother and fetus resulting from frequent and severe adverse drug reactions.

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

• Start treatment of drug resistance in second trimester or sooner if condition of patient is severe. Since the majority of teratogenic effects occur in the first trimester, therapy may be delayed until the second trimester. The decision to postpone the start of treatment should be agreed by both patient and doctor after analysis of the risks and benefits and communicated to the Review Panel. It is based primarily on the clinical judgment resulting from the analysis of life-threatening signs/symptoms and severity/aggressiveness of the disease (usually reflected in extent of weight loss and lung affection during the previous weeks).

• Avoid injectable agents. For the most part, aminoglycosides should not be used in pregnant patients as they can be particularly toxic to the developing fetal ear. However, if an injectable agent must be used then capreomycin is the injectable drug of choice though it may also carry a risk of ototoxicity.

• Avoid ethionamide. Ethionamide should be avoided in pregnant patients as it can increase the risk of nausea and vomiting associated with pregnancy, and teratogenic effects have been observed in animal studies.

9.2 Breastfeeding

A breastfeeding mother with active DR-TB should receive a full course of antituberculosis 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 antituberculosis 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. However, any effects on infants of such exposure during the full course of DR-TB treatment have not been established. Therefore, when resources and training are available, it is recommended to provide infant formula options as an alternative to breastfeeding. When infant formula is provided, fuel for boiling water and the necessary apparatus (stove, heating pans and bottles) must also be provided, as well as training on how to prepare and use the infant formula. All this should be free of charge to poor patients, and should therefore be budgeted in advance for the estimated number of patients who might need this support.

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. In some settings, the mother may be offered the option of using a surgical mask (see Chapter 15) until she becomes sputum smear-negative.

9.3 Contraception

There is no contraindication to the use of oral contraceptives with the 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. Such patients should be advised to continue taking their contraceptives except when they experience vomiting caused by the antituberculosis treatment. Patients who vomit at any time directly after, or within the first two hours after, taking the 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 the contraceptive drugs resulting in decreased efficacy of protection against pregnancy. A woman on oral contraception while receiving rifampicin treatment should be advised to either: use of an oral contraceptive pill containing a higher dose of estrogen (50 µg); or use of another form of contraception; or use a dual method. Consult trained family planning provider

9.4 Children

Children with DR-TB generally have primary resistance transmitted from an index case with DR-TB. Evaluation of children who are contacts of DR-TB is discussed in Chapter 14. When DST is available it should be used to guide therapy, although children with paucibacillary TB are often culture-negative. Nevertheless, every effort should be made to confirm DR-TB bacteriologically by the use of DST and to avoid exposing children unnecessarily to toxic drugs.

The treatment of culture-negative children with clinical evidence of active TB disease and contact with a documented case of DR-TB should be guided by the results of DST and the history of the contact’s exposure to antituberculosis drugs (also see Chapter 14). There is only limited reported experience with the use of second-line drugs for extended
periods in children. The risks and benefits of each drug should be carefully considered in designing a regimen. Frank discussion with family members is critical, especially at the outset of therapy. DR-TB is life-threatening, and no antituberculosis drugs are absolutely contraindicated in children. Children who have received treatment for DR-TB have generally tolerated the second-line drugs well.

Although fluoroquinolones have been shown to retard cartilage development in beagle puppies (6), experience with the use of fluoroquinolones has not demonstrated similar effects in humans (7–8). The benefit of fluoroquinolones in treating DR-TB in children outweighs any risk. Additionally, ethionamide, PAS and cycloserine have been used effectively in children and are well tolerated.

In general, antituberculosis drugs should be dosed according to body weight (see Table 9.1). Monthly monitoring of body weight is therefore especially important in paediatric cases, with adjustment of doses as children gain weight.

All drugs, including the fluoroquinolones, should be dosed at the higher end of the recommended ranges whenever possible, except ethambutol. Ethambutol should be dosed at 15 mg/kg, and not at 25 mg/kg as sometimes used in adults with DR-TB, as it is more difficult to monitor for optic neuritis in children.

In children who are not culture-positive initially, treatment failure is difficult to assess. Persistent abnormalities on chest radiograph do not necessarily signify a lack of improvement. In children, weight loss or, more commonly, failure to gain weight adequately, is of particular concern and often one of the first (or only) signs of treatment failure. This is another key reason to monitor weight carefully in children.

Table 9.1 Paediatric dosing of second-line antituberculosis drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily dose (mg/kg)</th>
<th>Frequency</th>
<th>Maximum daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptomycin</td>
<td>20–40</td>
<td>Once daily</td>
<td>1 g</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>15–30</td>
<td>Once daily</td>
<td>1 g</td>
</tr>
<tr>
<td>Amikacin</td>
<td>15–22.5</td>
<td>Once daily</td>
<td>1 g</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>15–30</td>
<td>Once daily</td>
<td>1 g</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>15–20</td>
<td>Twice daily</td>
<td>800 mg</td>
</tr>
<tr>
<td>Levofoxacin</td>
<td>7.5–10</td>
<td>Once daily</td>
<td>750 mg</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>7.5–10</td>
<td>Once daily</td>
<td>400 mg</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>15–20</td>
<td>Twice daily</td>
<td>1 g</td>
</tr>
<tr>
<td>Protionamide</td>
<td>15–20</td>
<td>Twice daily</td>
<td>1 g</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>10–20</td>
<td>Once or twice daily</td>
<td>1 g</td>
</tr>
<tr>
<td>P-aminosalicylic acid</td>
<td>150</td>
<td>Twice or thrice daily</td>
<td>12 g</td>
</tr>
</tbody>
</table>

Anecdotal evidence suggests that adolescents are at high risk for poor treatment outcomes. Early diagnosis, strong social support, individual and family counseling and a
close relationship with the medical provider may help to improve outcomes in this group.

9.5 Diabetes mellitus
Diabetic patients with MDR-TB are at risk of poor outcomes. In addition, the presence of diabetes mellitus may potentiate the adverse effects of antituberculosis drugs, especially renal dysfunction and peripheral neuropathy. Diabetes must be managed closely throughout the treatment of DR-TB. The health-care provider should be in close communication with the physician who manages the patient’s diabetes. Oral hypoglycemic agents are not contraindicated during the treatment of DR-TB but may require the patient to increase the dosage. Use of ethionamide or prothionamide may make it more difficult to control insulin levels. Creatinine and potassium levels should be monitored more frequently, often weekly for the first month and then at least monthly thereafter.

BOX 9.1 Example of regimen design for paediatric cases
A mother who has been on treatment for MDR-TB for 9 months has been smear- and culture-negative for 6 months. She brings her child to the health centre for evaluation. The child is 14 months old and weighs 6.9 kg. She had BCG at birth and now presents with 4 months of failure to thrive, poor appetite and intermittent low grade fever for 3 months. Tuberculin (PPD) skin testing is 16 mm, and chest radiography reveals hilar adenopathy but no infiltrates. There are no other known TB contacts. TB was first diagnosed in the mother shortly after giving birth to the child; she is a patient who had both Category 1 and II treatment failure. Her resistance pattern from the start of treatment for DR-TB is:

Resistance to H,R,Z,E,S

Susceptible to Am-Cm-Ofx

DST to PAS, Eto and Cs were not done because the laboratory could not guarantee reproducibility of these agents.

What advice and regimen do you prescribe for the child?

Answer: It should be well explained to the mother that the child is very likely to have TB, most probably MDR-TB. If available, DST should be attempted (see Chapter 14). While waiting for the DST results, or if the diagnostic procedure is not available, the child should be started on an empirical regimen based on the DST pattern of the mother. The following regimen is indicated:

injectable agent-fluoroquinolone-Eto(Pto)-Cs

Or

injectable agent-fluoroquinolone-PAS-Cs
The injectable agent can be any drug except S, in this case Km, Cm or Amk.

To illustrate dose calculation, the example for the regimen of Km-Ofx-Pto-Cs is given below. Both the low and high doses for the child’s weight are calculated; a convenient dosing is then chosen between the two numbers (if necessary a pharmacist can mix the exact dose so that any milligram amount can be selected, and dosing is not limited to 1/4 or 1/2 tablets):

Kanamycin: (15 mg x 6.9 kg = 103 and 30 mg x 6.9 kg = 207). Select a dose between the two numbers e.g. 200 mg per day, single dose.

Ofloxacin: (15 mg x 6.9 kg = 103 and 20 mg x 6.9 kg = 138). A convenient dosing is 100 mg/day; this is the full daily dose. Table 9.1 indicates that the daily dose is given in divided doses, so the patient would receive 50 mg (1/4 tablet) in the morning and 50 mg (1/4 tablet) in the evening.

Prothionamide: (15 mg x 6.9 kg = 103 and 20 mg x 6.9 kg = 138). A convenient dosing is 125 mg/day; this is the full daily dose. Table 9.1 indicates that the daily dose is given in divided doses, so the patient would receive 62.5 mg (1/4 tablet) in the morning and 62.5 mg (1/4 tablet) in the evening.

Cycloserine: (15 mg x 6.9 kg = 103 and 20 mg x 6.9 kg = 138). A convenient dosing is 125 mg/day. This is the full daily dose. Table 9.1 indicates that the daily dose is given in divided doses, so the patient would receive 62.5 mg (1/4 capsule) in the morning and 62.5 mg (1/4 capsule) in the evening.

**AS THE CHILD GAINS WEIGHT THE DOSES WILL HAVE TO BE ADJUSTED (CHECK WEIGHT EVERY MONTH)**

9.6 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 the interval between dosing should be adjusted according to Table 9.2.

9.7 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 chemotherapy regimens provided there is no clinical evidence of severe chronic liver disease, hepatitis virus carrier, and recent history of acute hepatitis or excessive alcohol consumption. However, hepatotoxic reactions to antituberculosis 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 antituberculosis treatment. In this case, clinical judgment is necessary. In some cases, it is possible to defer antituberculosis 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.

9.8 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.

Table 9.2 Adjustment of antituberculosis medication in renal insufficiency

<table>
<thead>
<tr>
<th>Drug</th>
<th>Change in frequency?</th>
<th>Recommended dose and frequency for patients with creatinine clearance &lt;30 ml/min or for patients receiving haemodialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>No change</td>
<td>300 mg once daily, or 900 mg three times per week</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>No change</td>
<td>600 mg once daily, or 600 mg three times per week</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Yes</td>
<td>25–35 mg/kg per dose three times per week (not daily)</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Yes</td>
<td>15–25 mg/kg per dose three times per week (not daily)</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>Yes</td>
<td>600–800 mg per dose three times per week (not daily)</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>Yes</td>
<td>750–1000 mg per dose three times per week (not daily)</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>No change</td>
<td>400 mg once daily</td>
</tr>
<tr>
<td>Drug</td>
<td>Change in frequency?</td>
<td>Recommended dose and frequency for patients with creatinine clearance &lt;30 ml/min or for patients receiving haemodialysis</td>
</tr>
<tr>
<td>----------------------</td>
<td>----------------------</td>
<td>------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>Yes</td>
<td>250 mg once daily, or 500 mg/dose three times per week</td>
</tr>
<tr>
<td>Terizidone</td>
<td>–</td>
<td>Recommendations not available</td>
</tr>
<tr>
<td>Prothionamide</td>
<td>No change</td>
<td>250–500 mg per dose daily</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>No change</td>
<td>250–500 mg per dose daily</td>
</tr>
<tr>
<td>P-aminosalicylic acid</td>
<td>No change</td>
<td>4 g/dose, twice daily</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Yes</td>
<td>12–15 mg/kg per dose two or three times per week (not daily)</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>Yes</td>
<td>12–15 mg/kg per dose two or three times per week (not daily)</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>Yes</td>
<td>12–15 mg/kg per dose two or three times per week (not daily)</td>
</tr>
<tr>
<td>Amikacin</td>
<td>Yes</td>
<td>12–15 mg/kg per dose two or three times per week (not daily)</td>
</tr>
</tbody>
</table>

a. For Group 5 drugs see manufacturers’ recommendations on adjustment in renal insufficiency.
b. To take advantage of the concentration-dependent bactericidal effect of many antituberculosis drugs, standard doses are given unless there is intolerance.
c. The 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).
d. Sodium salt formulations of PAS may result in an excessive sodium load and should be avoided in patients with renal insufficiency. Formulations of PAS that do not use the sodium salt can be used without the hazard of sodium retention.
e. Caution should be used with the injectable agents in patients with renal function impairment because of the increased risk of both ototoxicity and nephrotoxicity.

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. The risks and benefits of using cycloserine should be discussed with the patient and the decision on whether to use cycloserine made together with the patient.

In mono- and poly-resistant cases, the use of isoniazid and rifampicin may interfere with many of the anti-seizure medications. Drug interactions should be checked before their
Seizures that present for the first time during antituberculosis therapy are likely to be the result of an adverse effect of one of the antituberculosis drugs. More information on the specific strategies and protocols to address adverse effects is provided in Chapter 11.

9.9 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.

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’s being a danger to him or herself or others. Additional information on psychiatric adverse effects is provided in Chapter 11, Table 11.3.

9.10 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 antituberculosis 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. Good 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.

9.11 HIV-infected patients

Given the important interaction between HIV infection and drug-susceptible and DR-TB, a full chapter (Chapter 10) is devoted to this subject.

Treatment outcomes in XDR-TB cases have been significantly worse than MDR-TB outcomes, and outbreaks in populations with high HIV prevalence have been reported with alarming mortality rates.
CHAPTER 10

10.0 Drug-resistant tuberculosis and HIV

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

**Key recommendations of this chapter:**

- Perform provider-initiated HIV testing and counseling in all TB suspects;
- Use standard algorithms to diagnose pulmonary and extra pulmonary tuberculosis;
- Use mycobacterial cultures and, where available, newer more rapid methods of diagnosis;
- Perform DST at the start of TB therapy to avoid mortality due to unrecognized DR-TB in HIV-infected individuals;
- Determine the extent (or prevalence) of TB drug resistance in patients with HIV;
- Introduce antiretroviral therapy (ART) promptly in DR-TB/HIV patients.
- Consider empirical therapy with second-line antituberculosis drugs;
- Provide co-trimoxazole preventive therapy (CPT) as part of a comprehensive package of HIV care to patients with active TB and HIV;
- Arrange treatment follow-up by a specialized team.
- Where possible, provide nutritional and socioeconomic support.
- Ensure effective infection control
- Involve key stakeholders in DR-TB/HIV activities.
- Watch for overlying toxicity with ART and DR-TB therapy.

10.1 General considerations

Uganda has a high prevalence of HIV 6.4% (Uganda sero behavioral survey 2006) among the general population and about 54% among the 2009 TB cohort. HIV co-infection is a significant challenge for the prevention, diagnosis, and treatment of drug-resistant tuberculosis, especially in the case of MDR-TB and XDR-TB. Recent global drug resistance surveillance suggests an association between HIV and MDR-TB in some parts of the world, although specific factors involved in this association have not been determined. HIV is a powerful risk factor for all forms of TB and DR-TB outbreaks; including XDR-TB outbreaks in HIV-infected patients do appear common.

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 the non-infected. 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 HIV persons. Use of ART in addition to treatment of DR-TB improves outcomes of DR-TB in the HIV infected.

10.2 Recommended collaborative TB/HIV activities

The National TB/HIV policy recommends that TB-HIV collaborative activities are carried out to decrease the joint burden of tuberculosis and HIV (see Table 10.1)

Table 10.1 WHO-recommended TB/HIV collaborative activities*

<table>
<thead>
<tr>
<th>A. Establish the mechanisms for collaboration</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.1 Set up a coordinating body for TB/HIV activities effective at all levels</td>
</tr>
<tr>
<td>A.2 Conduct surveillance of HIV prevalence among tuberculosis patients</td>
</tr>
<tr>
<td>A.3 Carry out joint TB/HIV planning</td>
</tr>
<tr>
<td>A.4 Conduct monitoring and evaluation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Decrease the burden of tuberculosis in people living with HIV/AIDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.1 Establish intensified tuberculosis case-finding and contact tracing</td>
</tr>
<tr>
<td>B.2 Introduce isoniazid preventive therapy</td>
</tr>
<tr>
<td>B.3 Ensure tuberculosis infection control in health care and congregate settings</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C. Decrease the burden of HIV in tuberculosis patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.1 Provide HIV testing and counseling</td>
</tr>
<tr>
<td>C.2 Introduce HIV prevention methods</td>
</tr>
<tr>
<td>C.3 Introduce co-trimoxazole preventive therapy</td>
</tr>
<tr>
<td>C.4 Ensure HIV/AIDS care and support</td>
</tr>
<tr>
<td>C.5 Introduce antiretroviral therapy</td>
</tr>
</tbody>
</table>

*A detailed description of each of the activities listed in Table 10.1 can be found in the WHO document Interim Policy on Collaborative TB/HIV Activities

These activities are the backbone of the TB/HIV collaborative strategy, and along with the implementation of effective DOTS programme will strengthen and increase the success of DR-TB/HIV control and treatment activities.

The activities proposed below are based on the TB/HIV activities listed in Table 10.1 adapted specifically to DR-TB:

- **Perform provider-initiated HIV testing and counseling in all TB suspects.**

  Given the high levels of HIV and TB co-infection in Uganda, provider initiated HIV counseling and testing is recommended for all TB suspects at the same time the sputum is sent for smear microscopy (or culture). This is more efficient and more likely to be successful than referring patients elsewhere for HIV testing and counseling which serves as an entry point to life saving prevention, care and treatment interventions.
- Use standard algorithms to diagnose pulmonary and extra pulmonary tuberculosis.
  
  New recommendations for improving the diagnosis and treatment of smear-negative pulmonary and extra pulmonary TB have been put forth by the NTLP. **Also see Section 10.4 below.**

- **Use mycobacterial cultures and, where available, newer more rapid diagnostic methods.** Mycobacterial cultures of sputum or other fluids and tissues are recommended to help in the diagnosis of sputum smear negative and extra pulmonary TB. Sputum smear microscopy has significant limitations and is insufficient to reliably diagnose a significant proportion of HIV co-infected patients, especially as the degree of immunosuppression advances. Rapid methods such as liquid culture or molecular techniques are therefore recommended. **See Chapter 6 for more information on culture methods.**

- **Perform DST at the start of TB therapy.** Unrecognized DR-TB carries a high risk of mortality in patients with HIV. Prompt initiation of appropriate antituberculosis treatment (and subsequent initiation of anti-retroviral therapy) can reduce mortality among HIV-infected patients infected with DR-TB. Because unrecognized MDR- and XDR-TB are associated with such high mortality in HIV-infected patients, the health worker should order for DST and/or rapid drug-resistance testing for all HIV-infected patients with established active TB more especially if their CD4+ cell count is less than 350 cells/mm³. (See Chapter 5 and Section 10.4 below for detailed discussion on rapid tests and diagnosing DR-TB in HIV patients.) While performing DST for all TB/HIV co-infected patients is the standard of care, these guidelines recognize this may be difficult or impossible due to resource limitations. Alternative strategies in this regard are provided in section 10.4; however universal access to DST should be the long term goal.

- **Determine the extent (or prevalence) of TB drug resistance in patients with HIV.** The extent of the overlap between the DR-TB and HIV epidemics should be determined. This can be done in two ways:
  1. Data from population-based TB drug resistance surveillance (DRS) can be linked with HIV testing of those TB patients included; and/or
  2. When implementing HIV surveillance among TB patients (or provider initiated testing and counseling for all TB patients).

- **Introduce antiretroviral therapy (ART) promptly in DR-TB/HIV patients.** These guidelines recommend the prompt initiation of ART in HIV-infected patients with DR-TB (see section 10.5 below and Table 10.2 on when to initiate HIV treatment in DR-TB). Where indicated, protocols to manage immune reconstitution inflammatory syndrome (IRIS) should be followed (see section 10.5.6 below for more information on IRIS).

- **Consider empirical therapy with second-line antituberculosis drugs.** Patients with a very high risk of DR-TB can be empirically started on Category 4 regimens. This strategy can be applied to all patients regardless of HIV status, but is especially important in those with HIV. **See Chapter 5 for more information on the use of empiric Category 4.**

- **Provide co-trimoxazole preventive therapy (CPT) for patients with active TB and HIV.** Provide co-trimoxazole to all patients with HIV according to WHO recommendations. CPT is not known to interact significantly with any of
the second-line antituberculosis agents. There are overlapping toxicities between ART, TB therapy, and co-trimoxazole, and vigilance in terms of monitoring side-effects is required (see Table 10.3 below and Chapter 11).

- **Arrange treatment follow-up by a specialized team.** The team of care providers should be familiar with the treatment of both DR-TB and HIV, with close monitoring of potential additive side-effects and nutritional status, and periodic assessments of therapeutic response for both infections.

- **Implement additional nutritional and socioeconomic support.** Patients with DR-TB and HIV may suffer from severe wasting, diarrheal diseases, and malabsorption syndromes. Co-infected patients often come from socially marginalized groups or from families with low economic resources. Additionally, DR-TB therapy with second-line antituberculosis medications may result in adverse effects that affect treatment adherence and require more frequent visits to health facilities. Wherever possible, patients with DR-TB/HIV should be offered socioeconomic and nutritional support.

- **Ensure effective infection control.** Infection control procedures can reduce the risk of M. tuberculosis transmission in HIV/AIDS care facilities. For detailed discussion of Infection prevention and control for DR-TB and HIV care setting refer to Chapter 15 of these guidelines and stand alone NTLP TB Infection control guidelines.

- **Involve key stakeholders in DR-TB/HIV activities at the various levels.** At the national and regional/zonal level engage the Partners in funding and Technical Assistance, while at the districts and operational levels engage the Partners in implementations, funding and technical assistance accordingly.

### 10.3 Clinical features and diagnosis of DR-TB in HIV-infected patients

The diagnosis of tuberculosis (including MDR-TB and XDR-TB) in HIV-infected people is more difficult and may be confused with other pulmonary or systemic infections. The presentation is more likely to be extra pulmonary 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 initiation of treatment, and in turn, higher morbidity and mortality. To make a diagnosis of smear negative pulmonary and extra-pulmonary TB, use clinical criteria, laboratory investigations (culture, Rapid DST technique for prompt diagnosis of MDR-TB) and radiography to diagnose TB. For patients with advanced HIV disease, mycobacterial culture of other tissue 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.

This helps in decreasing the delays in accessing the most appropriate treatment regimen for the disease and eventually reducing the chances of transmitting DR-TB.

NTLP shall adopt the following approaches; Targeted DST for patients with increased risk of DR-TB (such as those in whom treatment has failed or who are contacts of DR-TB cases (see Chapter 5), HIV patients with lower CD4 counts (e.g., less than 350 cells/mm3) since these patients are at a very high risk of death due to unrecognized DR-TB.
10.4 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 7, with the following exceptions:

- ART plays a crucial role, as mortality in MDR-TB/HIV without the use of ART is extremely high (91% to 100% as reported in one analysis of MDR-TB outbreaks in 9 different institutions).
- Side effects are more common in patients with HIV. The multiple medicines involved in DR-TB with recognized high toxicity risks, often combined with ART, results in a high incidence of side effects. Some toxicities are common to both antituberculosis treatment and ART, which may result in added rates of adverse events.
- Monitoring needs to be more intense for both response to therapy and adverse effects.
- The use of thioacetazone is not recommended for patients with HIV or for routine use in populations with high rates of HIV.
- Immune reconstitution inflammatory syndrome (IRIS) may complicate therapy.

10.4.1 Initiating ART treatment in patients with DR-TB

The optimal timing for the introduction of ART in patients receiving TB treatment is unknown however, antiretroviral therapy in HIV-infected patients with TB improves survival for both drug-resistant and drug-susceptible disease. Cohorts of patients treated for DR-TB without the benefit of ART have experienced mortality rates often greater than 90%. On the other hand, undue delay in starting of ART could result in significant risk of HIV-related death among patients with advanced disease. Table 10.2, based on the current recommendations for the treatment of HIV infection in adults and adolescents with DR-TB.

Table 10.2: Timing of ART in the ART naive patient starting antituberculosis therapy for DR-TB

<table>
<thead>
<tr>
<th>ART Recommendations</th>
<th>Timing of ART in relation to start of DR-TB treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommend ART</td>
<td>At two weeks or as soon as DR-TB treatment is tolerated irrespective of the CD4 cell count</td>
</tr>
</tbody>
</table>

In an HIV/DR-TB co-infected patient, there is needed to start ART as soon as possible.

10.4.2 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 below.
2. Whether the presentation of active DR-TB in a patient on ART constitutes 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.

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

Currently, little is known about drug-drug interactions between second-line antituberculosis drugs (SLDs) and antiretroviral therapy (ART). There are several known interactions between drugs used to treat HIV and TB, they are summarized below:

- **Rifamycin derivatives.** While rifamycin derivatives are not routinely used in DR-TB treatment, they are used in the treatment of rifampicin-sensitive poly- and mono-resistant TB.
- **Quinolones and didanosine.** Buffered didanosine contains an aluminum/magnesium-based antacid and if given jointly with fluoroquinolones may result in decreased fluoroquinolones absorption; it should be avoided, but if it is necessary it should be given six hours before or two hours after fluoroquinolone administration. The enteric coated (EC) formulation of didanosine can be used concomitantly without this precaution.
- **Ethionamide/prothionamide.** Based on limited existing information of the metabolism of the thiamides (ethionamide and prothionamide), this drug class may have interactions with antiretroviral drugs since thiamides are thought to be metabolized by the CYP450 system (liver enzyme)
- **Clarithromycin.** Clarithromycin is a substrate and inhibitor of Liver enzyme CYP3A and has multiple drug interactions with protease inhibitors (PIs) and NNRTIs.

10.4.4 Potential drug toxicity 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-tuberculosis therapy (SLDs). In general, HIV patients have a higher rate of side effects to both TB and non-TB medications, and the risk of drug side effect increases with the degree of immunosuppression. Identifying the source of side effects in patients receiving concomitant therapy for DR-TB and HIV is difficult. Many of the SLDs and ARVs have overlapping, or in some cases additive, toxicities. Often it may not be possible to link side effects to a single drug, as the risk of resistance for ART therapy precludes the typical medical challenge of stopping all medications and starting them one by one (Desensitization). When possible, avoid the use of agents with shared side-effect profiles. Often, however, the benefit of using drugs that have overlapping toxicities outweighs the risk. Therefore, if two drugs with overlapping toxicities are determined to be essential in a patient’s regimen, these guidelines recommend increased monitoring of side effects rather than disallowing a certain combination. See Chapter 11 and Section 10.5.5 for monitoring side-effects in HIV-infected patients

Side effects that are common to both antiretroviral and anti-tuberculosis drugs are listed in Table 10.3 below. Table 10.3 is meant to alert the clinician to potentially overlapping and additive toxicities.
### Table 10.3 - Potential overlapping and additive toxicities of ART and antituberculosis therapy

Drugs that are more strongly associated with the side effects appear in bold.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Antiretroviral agent</th>
<th>Antituberculosis agent</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral neuropathy</td>
<td>D4T, ddI, ddc</td>
<td>Lzd, Cs, H, Aminoglycosides, Eto/Pto, E</td>
<td>Avoid use of D4T, ddI and ddC in combination with Cs or Lzd because of theoretically increased peripheral neuropathy. If these agents must be used and peripheral neuropathy develops, replace the ARV agent with a less neurotoxic agent and treat according to recommendations in Chapter 11.</td>
</tr>
<tr>
<td>Central nervous system (CNS) toxicity</td>
<td>EFV</td>
<td>Cs, H, Eto/Pto, Fluoroquinolones</td>
<td>Efavirenz has a high rate of CNS side-effects (confusion, impaired concentration, depersonalization, abnormal dreams, insomnia, and dizziness) in the first 2-3 weeks, which typically resolve on their own. If the CNS side-effects do not resolve on their own consider substitution of the agent. At present, there are limited data on the use of EFV with Cs; concurrent use is accepted practice with frequent monitoring for CNS toxicity. Frank psychosis is rare with EFZ alone.</td>
</tr>
<tr>
<td>Depression</td>
<td>EFV</td>
<td>Cs, Fluoroquinolones, H, Eto/Pto</td>
<td>Severe depression can be seen in 2.4% of patients receiving EFV. Consider substituting for EFV if severe depression develops. The severe socioeconomic circumstances of many patients with chronic disease can also contribute to depression. Therefore other possible causes of severe depression have to be ruled out before substitution of EFZ.</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Antiretroviral agent</td>
<td>Antituberculosis agent</td>
<td>Comments</td>
</tr>
<tr>
<td>---------------</td>
<td>----------------------</td>
<td>------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Headache</td>
<td>AZT, EFV</td>
<td>Cs</td>
<td>Rule out more serious causes of headache such as bacterial meningitis, cryptococcal meningitis, CNS toxoplasmosis, etc. Use of analgesics (ibuprofen, paracetamol) and good hydration may help. Headache secondary to AZT, EFV and Cs is usually self-limited.</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>RTV, D4T, NVP, and most others</td>
<td>Eto/Pto, PAS, H, E, Z and others</td>
<td>Nausea and vomiting are common side effects and can be managed with modalities described in Chapter 11. Persistent vomiting and abdominal pain may be a result of developing lactic acidosis and/or hepatitis secondary to medications. Rule out lactic acidosis in persistent Nausea and vomiting before substituting any of the culpable agents.</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>All ART treatment has been associated with abdominal pain</td>
<td>Eto/Pto, PAS</td>
<td>Abdominal pain is a common adverse effect and often benign; however, it may be an early symptom of severe side effects such as pancreatitis, hepatitis, or lactic acidosis. Look out for these events when monitoring treatment.</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>D4T, ddI, ddC</td>
<td>Lzd</td>
<td>Avoid use of these agents together. If an agent causes pancreatitis suspend it permanently and do not use any of the pancreatitis producing anti-HIV medications (D4T, ddI, or ddC) in the future. Therefore rule out gallstones or alcohol as a potential cause of pancreatitis.</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Antiretroviral agent</td>
<td>Antituberculosis agent</td>
<td>Comments</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------------------------</td>
<td>------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>All protease inhibitors, ddI (buffered formula)</td>
<td>Eto/Pto, PAS, Fluoroquinolones</td>
<td>Diarrhea is a common adverse event. Also consider opportunistic infections as a cause of diarrhea, or clostridium difficile (a cause of pseudo membranous colitis).</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>NVP, EFV, all protease inhibitors (RTV &gt; other protease inhibitors), all NRTIs</td>
<td>H, R, E, Z, PAS, Eto/ Pto, fluoroquinolones</td>
<td>Follow hepatotoxicity treatment recommendations in Chapter 11. Also consider TMP/SMX as a cause of hepatotoxicity if the patient is receiving this medication. Also rule out viral etiologies as cause of hepatitis (Hepatitis A, B, C, and CMV).</td>
</tr>
<tr>
<td>Skin rash</td>
<td>ABC, NVP, EFV, D4T and others</td>
<td>H,R, Z, PAS, Fluoroquinolones, and others</td>
<td>Do not re-challenge with ABC (can result in life threatening anaphylaxis). Do not re-challenge with an agent that caused Steven-Johnson syndrome. Also consider TMP/SMX as a cause of skin rash if the patient is receiving this medication. Thioacetazone is contraindicated in HIV because of life-threatening rash.</td>
</tr>
<tr>
<td>Lactic acidosis</td>
<td>D4T, ddI, AZT, 3TC</td>
<td>Lzd</td>
<td>If an agent causes lactic acidosis replace it with an agent less likely to cause lactic acidosis.</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Antiretroviral agent</td>
<td>Antituberculosis agent</td>
<td>Comments</td>
</tr>
<tr>
<td>--------------------------</td>
<td>----------------------</td>
<td>------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Renal toxicity</td>
<td>TDF (rare)</td>
<td>Aminoglycosides, Cm</td>
<td>TDF may cause renal injury with the characteristic features of Fanconi syndrome, hypophosphatemia, hypouricemia, proteinuria, normoglycemic glycosuria and in some cases acute renal failure. There is no data on the concurrent use of TDF with aminoglycosides or Cm. Use TDF with caution in patients receiving aminoglycosides or Cm. 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 every 1 to 3 weeks is recommended (see Chapter 11). Many ARVs and anti-tuberculosis medications need to be dose adjusted for renal insufficiency (Refer to Table 9.2 in Chapter 9.0).</td>
</tr>
<tr>
<td>Nephrolithiasis</td>
<td>IDV</td>
<td>None</td>
<td>No overlapping toxicities regarding nephrolithiasis have been documented between ART and antituberculosis medications. Adequate hydration prevents nephrolithiasis in patients taking IDV. If nephrolithiasis develops while on IDV, substitute with another protease inhibitor if possible.</td>
</tr>
<tr>
<td>Electrolyte disturbances</td>
<td>TDF (rare)</td>
<td>Cm, Aminoglycosides</td>
<td>Diarrhea and/or vomiting can contribute to electrolyte disturbances. Even without the concurrent use of TDF, HIV-infected patients have an increased risk of both renal toxicity and electrolyte disturbances secondary to aminoglycosides and Cm.</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Antiretroviral agent</td>
<td>Antituberculosis agent</td>
<td>Comments</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>----------------------</td>
<td>------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Bone marrow suppression</td>
<td>AZT</td>
<td>Lzd, R, Rfb, H</td>
<td>Monitor blood counts regularly (see Chapter 11). Replace AZT if bone marrow suppression develops. Consider suspension of Lzd. Also consider TMP/SMX as a cause if the patient is receiving this medication. Consider adding folinic acid supplements, especially if receiving TMP/SMX.</td>
</tr>
<tr>
<td>Optic neuritis</td>
<td>ddI</td>
<td>E, Eto/Pto (rare)</td>
<td>Suspend agent responsible for optic neuritis permanently and replace with an agent that does not cause optic neuritis.</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Protease inhibitors, EFV</td>
<td>None</td>
<td>No overlapping toxicities regarding hyperlipidemia have been documented between ART and antituberculosis medications. Follow WHO ART guidelines for management of hyperlipidemia.</td>
</tr>
<tr>
<td>Lipodystrophy</td>
<td>NRTIs (especially D4T and ddI)</td>
<td>None</td>
<td>No overlapping toxicities regarding lipodystrophy have been documented between ART and antituberculosis medications. Follow WHO ART guidelines for management of lipodystrophy.</td>
</tr>
<tr>
<td>Dysglycemia (disturbed blood sugar regulation)</td>
<td>Protease inhibitors</td>
<td>Gfx, Eto/Pto</td>
<td>Protease inhibitors tend to cause insulin resistance and hyperglycemia. Eto/Pto tends to make insulin control in diabetics more difficult, and can result in hypoglycemia and poor glucose regulation. Gatifloxacin is no longer recommended by the GLC for use in treatment of TB due to this side-effect.</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>D4T</td>
<td>Eto/Pto, PAS</td>
<td>There is potential for overlying toxicity, however evidence is mixed. Several studies show subclinical hypothyroidism associated with HAART, particularly stavudine. PAS and Eto/Pto, especially in combination, can commonly cause hypothyroidism.</td>
</tr>
</tbody>
</table>
10.4.5 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 be taken under DOT too to promote adherence (see Chapter 12) which can be compromised due to large pill-burden and numerous potential side-effects that render taking ARVs more difficult.

The complexity of antiretroviral regimens and second-line TB treatment demands rigorous clinical monitoring (see details in Chapter 11, Table 11.1).

If the patient shows signs of TB treatment failure, the same evaluation described in Chapter 13 is warranted. 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 very high, patients with HIV-associated DR-TB may require special socioeconomic, nutritional, and psychosocial support in order to successfully complete treatment.

10.4.6 Immune reconstitution inflammatory syndrome

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. It generally presents within three months of the initiation of ART and is more common with a low CD4 cell count (<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. New opportunistic infections or previously subclinical infections may be unmasked following immune reconstitution and cause clinical worsening. IRIS can also be confused with TB treatment failure, and co-infected patients may be demonstrating progression of TB disease due to drug-resistance.

The management of IRIS is complex and depends on the clinical status of the patient and the site and extent of involvement. Various treatment modalities have been employed, including NSAIDs in mild disease and corticosteroids in moderate-severe disease. Most patients can be treated without interruption of ART.

10.5 XDR-TB and HIV

XDR-TB has been described in a number of countries, including settings with a high prevalence of HIV. An algorithm to help diagnose XDR-TB in HIV-infected individuals is provided in Chapter 5. Treatment strategies for XDR-TB are outlined in Chapter 7.

10.6 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. 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. At community level, home-based measures such as separate living quarters, personal respiratory protection for visitors and adequate ventilation are recommended. See details in Chapter 15.

10.7 Coordination of HIV and TB care: involvement of the TB/HIV Coordination Committee.

Coordination shall be through having a joint strategic plan to collaborate successfully and systematically on 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, 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 programme design from an early stage.

10.8 Summary

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 side-effects, and infection control measures are the essential components of a successful DR-TB /HIV control.
CHAPTER 11

11.0 Initial evaluation, monitoring of treatment and management of adverse effects

This chapter provides information on the identification and management of adverse effects caused by second-line antituberculosis drugs. It addresses the following:

- Monitoring requirements for the treatment of DR-TB;
- Monitoring actions for early detection of side effects;
- Side effects associated with different second-line drugs;
- Strategies for the treatment of side effects;
- Side effects in HIV co-infected patients.

Key recommendations of this chapter (*indicates updated recommendation):

- Standard monitoring should be implemented for all patients on treatment for DR-TB as per Table 11.1 below;
- Both smear and culture should be monitored monthly to evaluate treatment response;*
- Increased monitoring is required in HIV and for patients on ART;*
- The health-care worker of DR-TB control programmes should be familiar with the management of common adverse effects of MDR-TB therapy;
- Ancillary drugs for the management of adverse effects should be available to the patient.

11.1 Pretreatment screening and evaluation

The required initial pretreatment clinical investigation includes a thorough medical history and physical examination. The recommended initial laboratory evaluations are shown in Table 11.1. The initial evaluation serves to establish a baseline and may identify patients who are at increased risk for side effects or poor outcomes. The monitoring of treatment and the management of side effects may have to be more intensive in patients with pre-existing conditions or conditions identified at the initial evaluation (diabetes mellitus, renal insufficiency, acute or chronic liver disease, thyroid disease, mental illness, drug or alcohol dependence, HIV infection, pregnancy, lactation and others). The management of DR-TB when these conditions exist is described in Chapter 9. Methods of avoiding pregnancy during treatment for women of childbearing age should be discussed.

11.2 Monitoring progress of treatment

Patients should be monitored closely for signs of treatment failure. Clinically, the most important way to monitor response to treatment is through regular history-taking and physical examination. The classic symptoms of TB – cough, sputum production, fever
and weight loss – generally improve within the first few months of treatment and should be monitored frequently by health-care providers. The recurrence of TB symptoms after sputum conversion, for example, may be the first sign of treatment failure. For children, height and weight should be measured regularly to ensure that they are growing normally. A normal growth rate should resume after a few months of successful treatment.

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 and is necessary to monitor the progress of treatment. Sputum examinations are also dependent on the quality of the sputum produced, so care should be taken to obtain adequate specimens.

Persistently positive sputums and cultures for acid fast bacilli should be assessed for non-tuberculous mycobacteria (NTM) as overgrowth with NTM in damaged lung secondary to TB is not uncommon. In such cases, though DR-TB may be adequately treated, treatment may need to be directed towards the NTM as well.

Sputum conversion is slower in DR-TB than in drug-susceptible TB. Paucibacillary culture results should not be automatically regarded as negative when treating DR-TB. Acquired drug resistance and treatment failure often begin with the growth of one or two colonies on a sputum culture. Culture conversion should not be considered to be equivalent to cure. A certain proportion of patients may initially convert and later revert to positive sputum culture. The factors associated with this reconversion and its implications are under study.

Sputum smears and cultures should be monitored closely throughout treatment. These guidelines recommend that the tests be performed monthly before smear and culture conversion, with conversion defined as two consecutive negative smears and cultures taken 30 days apart. After conversion, the minimum period recommended for bacteriological monitoring is monthly for smears and bimonthly for cultures (Table 11.1). Specimens for monitoring do not need to be examined in duplicate, but doing so can increase the sensitivity of the monitoring.

For patients who remain smear- and culture-positive during treatment or who are suspects for treatment failure, DST can be repeated. It is usually not necessary to repeat DST within less than three months of completion of treatment. Objective laboratory evidence of improvement often lags behind clinical improvement. The chest radiograph may be unchanged or show only slight improvement, especially in re-treatment patients with chronic pulmonary lesions. Chest radiographs should be taken at least every six months, when a surgical intervention is being considered, or whenever

11.3 Monitoring for side effects during treatment

Close monitoring of patients is necessary to ensure that the side effects of second-line drugs are recognized quickly by health-care personnel. The ability to monitor patients for side effects daily is one of the major advantages of DOT over self-administration of DR-TB treatment.

The majority of side effects are easy to recognize. Commonly, patients will volunteer that
they are experiencing side effects. However, it is important to have a systematic method of patient interviewing since some patients may be reticent about reporting even severe side effects. Other patients may be distracted by one adverse effect and forget to tell the health-care provider about others. DOT workers should be trained to screen patients regularly for symptoms of common side effects: rashes, gastrointestinal symptoms (nausea, vomiting, and diarrhoea), psychiatric symptoms (psychosis, depression, anxiety, and suicidal ideation), jaundice, ototoxicity, peripheral neuropathy and symptoms of electrolyte wasting (muscle cramping, palpitations). DOT workers 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 side effects that are more occult. The recommendations in Table 11.1 are an estimate of the minimal frequency of essential laboratory screening based on the experience of several DOTS-Plus projects. More frequent screening may be advisable, particularly for high-risk patients. Table 11.1 includes monitoring recommendations for HIV-infected patients. Nephrotoxicity is a known complication of the injectable drugs, both of the aminoglycosides and of capreomycin. This adverse effect is occult (not obviously noted by taking the history of the patient or by physical examination) in onset and can be fatal thus need to check serum creatinine at least monthly. In addition, patients with a history of renal disease (including co-morbidities 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 glomerular filtration rate may help to further stratify the risk of nephrotoxicity in these patients (see Chapter 9, section 9.7).

**Patient initial evaluation and monitoring during treatment**

DR-TB health facilities should have capacity to provide the following laboratory investigations free of charge to patients under their care. Besides laboratory investigations, social evaluations will be done before start of treatment and every six months where necessary to ascertain whether the patient has all the necessary social support to foster treatment adherence. This will include an assessment of ability for income, getting food, providing for the family in terms of clothing, education, shelter, medical care etc. Assessment of social habits e.g. alcohol consumption, smoking and other substance abuse which can affect adherence and treatment outcome will be done too.

**Initial evaluation of the patient includes the following investigations:**

- Social evaluation
- Direct smear examination
- DST for first line anti-TB drugs
- Liver functions:
  - Total serum Bilirubin
  - SGPT & SGOT
  - Total serum albumin, total serum protein and A/G ratio.
- Serum Creatinine, blood urea, complete urine analysis with estimation of total urine protein content
- Serum uric acid.
- Blood sugar.
- Sodium and Potassium.
- HIV
- Pregnancy test.
- Initial chest x-ray

**Monitoring of side effects should also include base line and check of:**
- Full blood count
- In highly risk patients (over 50 years, renal insufficiency, DM, HIV, underweight), Creatinine should be evaluated every week or every other week for at least the first month of treatment.
- Creatinine clearance may be needed for high risk group patients.
- Audiometry or hearing evaluation.
- Visual acuity and color vision evaluation
- If Serum potassium is low, check the Magnesium and Calcium levels

Special attention should be paid for:
- Liver toxicity
- Vestibular and hearing toxicity with inject able drugs
- Psychiatric disorders with Cycloserine
- Allergic reactions
- Hematological changes

**Table 11.1 Summary of monitoring parameters during DR-TB treatment.**

<table>
<thead>
<tr>
<th>Monitoring evaluation</th>
<th>Recommended frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluation by clinician</td>
<td>At baseline, then monthly until conversion; then monthly at follow up facilities and quarterly at treatment facilities. In the event of complications or adverse events emerging during treatment, patients should be referred to the next level of DR TB care</td>
</tr>
<tr>
<td>Screening by DOT worker</td>
<td>At every DOT encounter</td>
</tr>
<tr>
<td>Sputum smear and cultures</td>
<td>Monitor monthly until conversion then monthly smear and bimonthly culture in the continuation phase</td>
</tr>
<tr>
<td>Weight</td>
<td>At baseline and then monthly</td>
</tr>
<tr>
<td>Drug susceptibility test (DST)</td>
<td>At baseline to confirm DR-TB and when DR-TB patients remain culture-positive despite treatment. It is not necessary to repeat DST within less than 3 months of treatment</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>At baseline, and then every 6 months</td>
</tr>
<tr>
<td>Monitoring evaluation</td>
<td>Recommended frequency</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>At baseline, then monthly while receiving injectable drugs. Every 1 to 3 weeks in HIV infected patients, diabetics and other high risk patients or when indicated.</td>
</tr>
<tr>
<td>Serum potassium</td>
<td>Monthly while receiving an injectable agent. Every 1 to 3 weeks in HIV infected patients, diabetics and other high risk patients or when indicated.</td>
</tr>
<tr>
<td>Thyroid stimulating Hormone (TSH)</td>
<td>Every 6 months if receiving ethionamide/ prothionamide and/or PAS; and monitor monthly for signs/symptoms of hypothyroidism. TSH is sufficient for screening for hypothyroidism and it is not necessary to measure T3 and T4 levels.</td>
</tr>
<tr>
<td>Liver serum enzymes</td>
<td>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 do monthly monitoring.</td>
</tr>
<tr>
<td>HIV screening</td>
<td>At baseline, and repeat if clinically indicated</td>
</tr>
<tr>
<td>Pregnancy tests</td>
<td>At baseline for women of childbearing age, and repeat when indicated</td>
</tr>
<tr>
<td>Hemoglobin and white blood count</td>
<td>If on linezolid monitor weekly at first, then monthly or as needed based on symptoms; there is little clinical experience with prolonged use. For HIV-infected patients on AZT monitor monthly initially and then as needed based on symptoms</td>
</tr>
<tr>
<td>Lipase</td>
<td>Indicated for work-up of abdominal pain to rule out pancreatitis in patients on linezolid, D4T, ddI, ddc.</td>
</tr>
<tr>
<td>Lactic acidosis</td>
<td>Indicated for work up of lactic acidosis in patients on linezolid or ART.</td>
</tr>
<tr>
<td>Serum Glucose</td>
<td>If receiving gatifloxacin, monitor glucose frequently (weekly) and educate patient on signs and symptoms of hypoglycemia and hyperglycemias.</td>
</tr>
</tbody>
</table>

**Management of side effects, general considerations**

- All anti-tuberculosis drugs are associated with side effects
- Adverse effects are not a contraindication to appropriate treatment
- Poorly managed side effects may lead to non-adherence or inappropriate therapy.
- Minor side effects are common during initial months of treatment
- Serious reactions are rare but require immediately attention.
Community health workers and DOT can help with close surveillance for adverse effects during ambulatory treatment besides, close communication with patient and family members.

- Timely diagnosis and early management are crucial.
- Exploration of alternative etiologies and contributing factors is important.
- Correction of underlying abnormalities.
- Changes to MDR-TB regimen are rarely indicated.
- Ambulatory management is usually adequate.

Summary of important adverse reactions

<table>
<thead>
<tr>
<th>System</th>
<th>Common, mild adverse reaction</th>
<th>Moderate to severe adverse reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological</td>
<td>Dizziness Headaches Fatigue Somnolence Insomnia</td>
<td>Seizure, Peripheral neuropathy, Ototoxicity, Optic neuritis</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>Depression Irritability Anxiety Mood/behavior changes</td>
<td>Psychosis, Suicidal ideation</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Changes in skin color Photosensitivity Dry skin</td>
<td>Anaphylaxis, Stevens-Johnson Syndrome</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Worsened hyperglycemia Menstrual cycle changes</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea Emesis Diarrhea Abdominal bloating Abdominal cramping Gastritis Fat malabsorption Lactose intolerance</td>
<td>Gastric ulcers Hepatitis</td>
</tr>
<tr>
<td>Renal and electrolyte</td>
<td>Arthralgias, Myalgias Muscular cramps Vaginal candidiasis</td>
<td>Renal insufficiency Hypokalemia Hypomagnesaemia</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>Dehydration Initial weight loss</td>
</tr>
</tbody>
</table>

Electrolyte wasting is a known complication of the anti-tuberculosis 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 high-risk patients, and in all those taking capreomycin.

Hypothyroidism is a late effect provoked by PAS and ethionamide. It is suspected by clinical assessment and confirmed by testing the serum level of thyroid stimulating hormone (TSH). The use of these agents together can produce hypothyroidism in up to 10% of patients. Since the symptoms can be subtle, it is recommended that patients are screened for hypothyroidism with a serum TSH at 6–9 months, and then tested again every 6 months or sooner if symptoms arise. The dosing of thyroid replacement therapy
should be guided using serum levels of TSH. Goiters can develop due to the toxic effects of PAS, ethionamide or prothionamide. In areas where iodine deficiency goiters are endemic, treatment with iodine is indicated, in addition to assessment and treatment for hypothyroidism.

11.4 Management of side effects
Second-line drugs have many more side effects than the first-line antituberculosis drugs. Management of side effects is possible even in resource-poor settings. Proper management of side effects begins with patient education. Before starting treatment, the patient should be instructed in detail about the potential side effects that could be produced by the prescribed drug regimen, and if and when to notify a health-care provider.

Table 11.2 reports the number and percentage of patients who had a particular adverse event, observed in the first five GLC-approved projects. The percentage of events may vary depending on the regimens used (for example, among patients using both ethionamide and PAS, a high proportion may develop a rate of hypothyroidism above 3.5%). Nonetheless, Table 11.2 provides an indication of the expected prevalence of side effects. Complete discontinuation of therapy because of side effects is rare and applied to only 2% of the patients in this report. The data presented in 11.2 is for patients not infected with HIV. It is likely that the incidents of side effects is much higher in the HIV-infected, however, data at this time are very limited.

If the side effect is mild and not dangerous, continue the treatment regimen, with the help of ancillary drugs if needed and this is often the best option. In patients with highly resistant TB, a satisfactory replacement drug may not be available, so that suspending a drug will make the treatment regimen less potent. Some side effects may disappear or diminish with time, and patients may be able to continue receiving the drug if sufficiently motivated.

The side effects of a number of second-line drugs are highly dose-dependent.

Table 11.2 Frequency of common side effects among 818 patients in five DR-TB control programme sites (1)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>No. affected (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/vomiting</td>
<td>268 (32.8)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>173 (21.1)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>134 (16.4)</td>
</tr>
<tr>
<td>Dizziness/vertigo</td>
<td>117 (14.3)</td>
</tr>
<tr>
<td>Hearing disturbances</td>
<td>98 (12.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>96 (11.7)</td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td>95 (11.6)</td>
</tr>
<tr>
<td>Electrolyte disturbances</td>
<td>94 (11.5)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>88 (10.8)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>75 (9.2)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>No. affected (%)</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Gastritis</td>
<td>70 (8.6)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>65 (7.9)</td>
</tr>
<tr>
<td>Depression</td>
<td>51 (6.2)</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>42 (5.1)</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>42 (5.1)</td>
</tr>
<tr>
<td>Rash</td>
<td>38 (4.6)</td>
</tr>
<tr>
<td>Visual disturbances</td>
<td>36 (4.4)</td>
</tr>
<tr>
<td>Seizures</td>
<td>33 (4.0)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>29 (3.5)</td>
</tr>
<tr>
<td>Psychosis</td>
<td>28 (3.4)</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>18 (2.2)</td>
</tr>
<tr>
<td>Renal failure/nephrotoxicity</td>
<td>9 (1.1)</td>
</tr>
</tbody>
</table>

Reducing the dosage of the offending drug is another method of managing side effects but only in cases where the reduced dose is still expected to produce adequate serum levels and not compromise the regimen. With cycloserine and ethionamide, for example, a patient may be completely intolerant at one dose and completely tolerant at a slightly lower dose. Unfortunately, given the narrow therapeutic margins of these drugs, lowering the dose may also affect efficacy, so every effort should be made to maintain an adequate dose of the drug according to body weight. Lowering the dose by more than one weight class should be avoided (see Annex 2 for weight classes and dosing).

Pyridoxine (vitamin B6) should be given to all patients receiving cycloserine or terizidone to help prevent neurological side effects. The recommended dose is 50 mg for every 250 mg of cycloserine (or terizidone) prescribed.

Psychosocial support is an important component of the management of side effects. This is one of the most important roles played by DOT workers, who educate patients about their side effects and encourage them to continue treatment. Patient support groups are another means of providing psychosocial support to patients. Table 11.3 summarizes the common side effects, the likely responsible antituberculosis agents and the suggested management strategies. Overlapping toxicities for HIV-infected patients on ART and DR-TB treatment are addressed in Chapter 10.

Management often requires the use of ancillary medications to eliminate or lessen the side effects and a stock of ancillary medications should be available for health-care providers to prescribe to patients free of charge. Table 11.4 is a list of indications and commonly used medications for the management of drug reactions. In addition, it is recommended that all laboratory testing for the monitoring of therapy, pregnancy testing, HIV screening and contraceptive methods be offered free of charge.
11.5 Summary

The timely and intensive monitoring for, and management of side effects caused by second-line drugs are essential components of DR-TB control. Poor management of side effects increases the risk of default or irregular adherence to treatment, and may result in death or permanent morbidity. Patients experiencing side effects should be referred to health-care workers who have experience in treating the side effects. It is rarely necessary to suspend antituberculosis drugs completely. Ancillary drugs for the management of side effects should be available to the patient and without charge.
<table>
<thead>
<tr>
<th>ADVERSE EFFECT</th>
<th>SUSPECTED AGENT(S)</th>
<th>SUGGESTED MANAGEMENT STRATEGIES</th>
<th>COMMENTS</th>
</tr>
</thead>
</table>
| Depression     | Socio-economic circumstances, chronic disease, Cs, fluoroquinolones H, Eto/Pto | 1. Improve socioeconomic conditions.  
2. Group or individual counseling.  
3. Initiate antidepressant therapy.  
4. Lower dose of suspected agent if this can be done without compromising the regimen.  
5. Discontinue suspected agent if this can be done without compromising regimen. | 1. Socioeconomic conditions and chronic illness should not be underestimated as contributing factors to depression.  
2. Depressive symptoms may fluctuate during therapy and may improve as illness is successfully treated.  
3. History of previous depression is not a contraindication to the use of the agents listed but may increase the likelihood of depression developing during treatment. |
| Hypo-thyroidism | PAS, Eto/Pto       | 1. Initiate thyroxine therapy.    | 1. Completely reversible upon discontinuation of PAS or ethionamide/protonamide.  
2. The combination of ethionamide/protonamide with PAS is more frequently associated with hypothyroidism than the individual use of each drug. |
<table>
<thead>
<tr>
<th>ADVERSE EFFECT</th>
<th>SUSPECTED AGENT(S)a</th>
<th>SUGGESTED MANAGEMENT STRATEGIES</th>
<th>COMMENTS</th>
</tr>
</thead>
</table>
| Nausea and vomiting                   | Eto/Pto, PAS, H, E, Z | 1. Assess for dehydration; initiate dehydration if indicated.  
2. Initiate antiemetic therapy.  
3. Lower dose of suspected agent, if this can be done without compromising regimen.  
4. Discontinue suspected agent if this can be done without compromising regimen – rarely necessary. | 1. Nausea and vomiting universal in early weeks of therapy and usually abate with time on treatment and adjunctive therapy.  
2. Electrolytes should be monitored and repleted if vomiting is severe.  
3. Reversible upon discontinuation of suspected agent.  
4. Severe abdominal distress and acute abdomen have been reported with the use of clofazimine. Although these reports are rare, if this effect occurs, clofazimine should be suspended. |
| Electrolyte disturbances              | Cm, Vm, Km, Am, S   | 1. Check potassium.  
2. If potassium is low also check magnesium (and calcium if hypocalcaemia is suspected).  
3. Replace electrolytes as needed. | 1. If severe hypokalaemia is present, consider hospitalization.  
2. Amiloride 5–10 mg QD or spironolactone 25 mg QD may decrease potassium and magnesium wasting and is useful in refractory cases.  
3. Oral potassium replacements can cause significant nausea and vomiting. Oral magnesium may cause diarrhoea. |
<table>
<thead>
<tr>
<th>ADVERSE EFFECT</th>
<th>SUSPECTED AGENT(S)a</th>
<th>SUGGESTED MANAGEMENT STRATEGIES</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optic neuritis</td>
<td>E, Eto/Pto</td>
<td>1. Stop E. 2. Refer patient to an ophthalmologist.</td>
<td>1. Usually reverses with cessation of E. 2. Rare case reports of optic neuritis have been attributed to streptomycin.</td>
</tr>
<tr>
<td>Arthralgias</td>
<td>Z, fluoroquinolones</td>
<td>1. Initiate therapy with non-steroidal anti-inflammatory drugs. 2. Lower dose of suspected agent, if this can be done without compromising regimen. 3. Discontinue suspected agent if this can be done without compromising regimen.</td>
<td>1. Symptoms of arthralgia generally diminish over time, even without intervention. 2. Uric acid levels may be elevated in patients on pyrazinamide. Allopurinol appears not to correct the uric acid levels in such cases.</td>
</tr>
</tbody>
</table>

a See list of drug abbreviations, page 9.

Note: Drugs in bold type are more strongly associated with the adverse effect than drugs not in bold.
<table>
<thead>
<tr>
<th>Indication</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea, vomiting, upset stomach</td>
<td>Metoclopramide, dimenhydrinate, prochlorperazine, promethazine, bismuth subsalicylate</td>
</tr>
<tr>
<td>Heartburn, acid indigestion, sour stomach, ulcer</td>
<td>H2-blockers (ranitidine, cimetidine, famotidine, etc.), proton pump inhibitors (omeprazole, lansoprazole, etc.) Avoid antacids because they can decrease absorption of fluoroquinolone</td>
</tr>
<tr>
<td>Oral candidiasis (non-AIDS patient)</td>
<td>Fluconazole, clotrimazole lozenges</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Loperamide</td>
</tr>
<tr>
<td>Depression</td>
<td>Selective serotonin reuptake inhibitors (fluoxetine, sertraline), tricyclic antidepressants (amitriptyline)</td>
</tr>
<tr>
<td>Severe anxiety</td>
<td>Lorazepam, diazepam, clonazepam</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Dimenhydrinate</td>
</tr>
<tr>
<td>Psychosis</td>
<td>Haloperidol, thorazine, risperidone (consider benztropine or biperiden to prevent extrapyramidal effects)</td>
</tr>
<tr>
<td>Seizures</td>
<td>Phenytoin, carbamazepine, valproic acid, phenobarbital</td>
</tr>
<tr>
<td>Prophylaxis of neurological complications of cycloserine</td>
<td>Pyridoxine (vitamin B6)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Amitriptyline</td>
</tr>
<tr>
<td>Vestibular symptoms</td>
<td>Meclizine, dimenhydrinate, prochlorperazine, promethazine</td>
</tr>
<tr>
<td>Musculoskeletal pain, arthralgia, headaches</td>
<td>Ibuprofen, paracetamol, codeine</td>
</tr>
<tr>
<td>Cutaneous reactions, itching</td>
<td>Hydrocortisone cream, calamine, caladryl lotions</td>
</tr>
<tr>
<td>Systemic hypersensitivity reactions</td>
<td>Antihistamines (diphenhydramine, chlorpheniramine, dimenhydrinate), corticosteroids (prednisone, dexamethasone)</td>
</tr>
<tr>
<td>Indication</td>
<td>Drug</td>
</tr>
<tr>
<td>--------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>Inhaled beta-agonists (albuterol, etc.), inhaled corticosteroids (beclomethasone, etc.), oral steroids (prednisone), injectable steroids (dexamethasone, methylprednisolone)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Levothyroxine</td>
</tr>
<tr>
<td>Electrolyte wasting</td>
<td>Potassium and magnesium replacement</td>
</tr>
</tbody>
</table>
CHAPTER 12

12.0 Treatment delivery and community-based DR-TB support

This chapter outlines the strategies for treatment delivery that will improve adherence among patients receiving treatment for DR-TB. The main adherence promotion strategies include DOT, socioeconomic support, emotional support, and management of drug side effects.

The chapter devotes a section to community-based DR-TB care and support. It illustrates that engaging the community can contribute substantially to mitigating the problem of DR-TB.

Key recommendations of this chapter:

- Use patient education, DOT, socioeconomic support, emotional support, management of side effects and monitoring to improve adherence;
- Incorporate community-based care and support in national plans.

12.1 Treatment delivery modes

DR-TB treatment can be delivered through three modes: community-based care, clinic-based treatment and hospitalization. MoH majorly shall employ hospitalization in intensive phase and community based care in continuation phase.

Regardless of the mode of delivery, the management of DR-TB depends on a steady supply of medicines provided to patients free of charge through a reliable network of educated providers.

- **Community-based care.** Community-based care is provided by trained community treatment supporters (TS). The team of supporters includes clinicians (physicians, medical officers, and clinical officers), nurses, social workers and lay persons. Refer to 12.5 below for a more detailed description of community-based care and support.

- **Clinic-based care.** This involves the patient travelling to a clinic to receive DOT six days a/ per week. This can work well if the patient lives near a facility that offers DOT of DR-TB; there is no travel barrier and waiting time is minimized. The patient should be given an enabler (transport) for travel in situations other than these. To enhance adherence the facility should offer patient-centered, patient-friendly services. For example make special appointments e.g. early morning appointments for patients that need to get to go to work, late afternoon for others. Such patient should be smear-negative if traveling on public transportation or waiting in common waiting rooms. Special attention must be taken to ensure that HIV-infected patients are not exposed to smear-positive patients. It may be necessary to have a separate area with infection control measures for smear-positive patients.

- **Hospitalization.** Early on in the history of DR-TB treatment admission was
considered a must. Admission is no longer considered a strict necessity but is to be reserved for severely sick, those living far away from the facilities, and initially till sputum conversion. Patients should be provided with acceptable living conditions including adequate food, fans or cooling systems during hot climates, and sufficient activities so as to avoid boredom. Proper infection control measures described in Chapter 15 must also be observed. Prisons require specific measures to improve adherence. (WHO guidelines for TB control in prisons)

12.2 Adherence to therapy
Patients with DR-TB are more likely to have had problems with non-adherence in the past. Adherence to DR-TB therapy is particularly difficult because of its prolonged treatment regimens with larger numbers 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 preventing the generation of extremely-drug resistant strains capable of spreading within the community that leave virtually no possibility of cure for the patient.

Thus adequate support measures should be taken. The measures to ensure DOT and adherence to treatment include: patient education, DOT, socioeconomic support, emotional support, management of side effects and close monitoring to improve adherence.

12.2.1 Patient education
Patients and their families should receive education about DR-TB, its treatment, potential drug side effects and the need for adherence to therapy. This should commence at the start of therapy and continue throughout the course of treatment. Education can be provided by clinicians, nurses, lay treatment supporters and other health-care providers. Materials should be appropriate to the literacy levels of the population and should be culturally sensitive as well.

12.2.2 Directly observed therapy (DOT)
Because DR-TB treatment is the last therapeutic option for many patients and because there is a serious public health consequence if therapy fails in a patient with DR-TB; it mandatory that all patients on treatment for DR-TB be on directly observed therapy (DOT). DOT can be provided either in the community, at health centre, or hospital setting. DOT should be provided to a patient in manner that it solves long transportation times and distances, long waiting times. Difficulty in accessing services may all reduce the efficacy of DOT.

Who can deliver DOT? The first choice for and the initiators of DOT are healthcare workers after which treatment supporters in the community take up the role. Community-based support in DOT can be very effective especially if provided by former patients acting as treatment supporters for daily DOT. Former patients are a living proof that adherence to daily DOT pays and there is hope for cure if they persevere in their treatment.

It is recommended that the patient’s DOT treatment supporter should not be
a family member. Family relationships are often complicated for the DR-TB patient, and a family treatment supporter could be subject to subtle manipulation by the patient, relatives, employers, etc.

- **Maintaining confidentiality.** The DOT treatment supporter should maintain strict confidentiality regarding the patient’s disease.

### 12.3.3 Socioeconomic interventions

Socioeconomic problems including hunger, and risk of loosing employment should be addressed to enable patients and their families to adhere to treatment. These problems can be successfully tackled through the provision of “enablers and “incentives”. Enablers are goods or services that make it easier for patients to adhere to treatment, such as the provision of transport refunds. Incentives are goods or services that are used to encourage patients to adhere to therapy, such as the provision of food packages. Professional social workers should be used to assess the need for such socioeconomic interventions and monitor their delivery. Depending on resource envelop, socioeconomic interventions may include:

- Free health care;
- Food parcels to DR-TB patients and their dependents where possible;
- Temporary shelter in a housing facility for DR-TB patients;
- Transportation fees;
- Advice and assistance in administrative matters relating to the treatment;
- Assistance in defending rights and/or reinforcing the responsibilities of patients;
- Advise to employers to ensure DR-TB patients retain their jobs
- School fees for dependent children;
- Providing skills training and livelihood to patients both while on treatment as well as to prepare them with skills that can support them as they reintegrate to the community upon treatment completion.

### 12.2.4 Psychosocial and emotional support

Having DR-TB can be an emotionally devastating experience for patients and their families. 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. This support may be organized in the form of support groups or one-to-one counseling by trained providers. Adherence may be enhanced by using informal support from a multidisciplinary “support to adherence” team (social worker, nurse, health educator, companion and doctor).

### 12.2.5 Early and effective management of drug side effects

Although rarely life-threatening, the side effects of second-line drugs can be debilitating. Patients who experience high rates of side effects may be at increased risk of interrupting treatment. Early and effective management of side effects is therefore one of the strategies for promoting adherence to DR-TB treatment. Refer to chapter 11 for details.
of management of side effects.

12.2.6 Monitoring and the 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 18 are designed to assist the care provider in follow-up. When a patient fails to attend a DOT 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 and to ensure that treatment is resumed promptly and effectively. The situation should be addressed in a sympathetic, friendly and non-judgmental manner. Every effort should be made to listen to reasons for the patient missing a dose(s) and to work with patient and family to ensure continuation of treatment. Transportation problems if any should be addressed.

12.3 Community-based care and support

Community-based care and support is any action or help provided by, with or from the community, including situations in which patients are receiving ambulatory treatment. This support contributes to and may even be necessary to patient recovery. Political will from the health and local community authorities is vital to these efforts, it may help to tap organizations that have the expertise in social and community mobilization.

- Community care supporters. There are numerous potential supporters who can be brought into the effort to address programmatic needs at community level. This includes health centre nurses, supported former DR-TB patients (but non HIV), affected families, associations, cooperatives, grassroots organizations, local NGOs, community treatment supporters etc).

Function of the community treatment supporters.
1. Supervise oral doses including escorting the patient(s) for injections at the health centre.
2. Provide injections (in some authorized cases only).
3. Accompany the patient to all medical consultations.
4. Remind & Provide sputum bottles to the patient on monthly basis for sputum collection.
5. Record daily doses on Category 4 treatment card.
6. Collect drugs and supplies in a drug box from follow-up treatment centre every two weeks or monthly. Then return the drug box to follow-up treatment centre at end of two weeks or month.
7. Educate the patient’s family on the importance of screening for HIV and TB.
8. contact tracing, infection control, recording and reporting, training, advocacy, and social support.

The treatment supporter should be someone who:
1. is chosen by or is acceptable to the patient;
2. is committed to support the patient for a long time;
3. has received MDR-TB specific training;
4. is available to observe doses twice a day;
5. is available to accompany patients to clinic and lab appointments;
6. provides support to not more than two MDR-TB patients;
7. should not be immune suppressed.

12.4 Conclusion
Treatment delivery to patients with DR-TB can be accomplished with involvement of a multidisciplinary team of treatment supporters in community-based TB care approach.
CHAPTER 13

13.0 Management of patients after MDR-TB treatment failure

The chapter describes the management of MDR-TB treatment failure

13.1 Assessment of patients at risk for failure

The following are the indicators of treatment failure:
1. Lack of signs of improvement after four months of treatment
2. Clinical, radiographical or bacteriological evidence of progressive active disease

The following steps are recommended in patients with treatment failure:

- The treatment card should be reviewed to confirm that the patient has adhered to treatment.
- The treatment regimen should be reviewed in relation to medical history, contacts and all DST reports. If the regimen is deemed inadequate, a new regimen should be designed.
- The bacteriological data should be reviewed. Often, the smear and culture data are the strongest evidence that a patient is not responding to therapy. One single positive culture in the presence of an otherwise good clinical response can be due to laboratory contamination or error. In this case, subsequent cultures that are negative or in which the number of colonies is decreasing may help prove that the apparently positive result did not reflect treatment failure. Positive smears with negative cultures may be caused by the presence of dead bacilli and therefore may not indicate treatment failure. Repeated culture- and smear-negative results in a patient with clinical and radiographical deterioration may indicate that the patient has a disease other than MDR-TB.
- The health-care worker should confirm that the patient has taken all the prescribed medicines. A non-confrontational interview should be undertaken separately with the patient and the DOT treatment supporter. Questions should being asked to rule out the possible manipulation of the DOT treatment supporter by the patient. Also review of patient’s card, pill count can be done. If manipulation is suspected, the patient should be assigned to a new DOT treatment supporter.
- Other illnesses that may decrease absorption of medicines (e.g. chronic diarrhoea) or may result in immune suppression (e.g. HIV infection) should be excluded.
- If surgical resection is feasible, it should be considered.
- MDR-TB treatment often consists of a treatment cycle; if no response is seen, reassessment of the regimen and treatment plan and formulation of a new plan of action are necessary. Patients who have persistent positive smears or cultures at month 4 but who are doing well clinically and radiographically may not require a regimen change. Whenever a regimen change is indicated because of treatment
failure, a new regimen is started (with at least four effective drugs) and options for adjunctive treatment – most commonly surgery – can be considered. **Adding one or two drugs to a failing regimen should be avoided.** Changes in treatment can be made as early as 4–6 months if conversion is not seen and if there is clinical deterioration.

### 13.2 Indications for suspending treatment

It takes 3–4 months to evaluate whether a change in treatment plan has been effective. If the patient continues to deteriorate despite the measures described in the previous section, treatment failure should be considered. There is no single indicator to determine whether a treatment regimen is failing. Signs indicating treatment failure include:

- Persistent positive smears or cultures past month 8–10 of treatment;
- Progressive extensive and bilateral lung disease on chest X-ray with no option for surgery;
- High-grade resistance (often XDR-TB) with no option to add two additional agents;
- Overall deteriorating clinical condition that usually includes weight loss and respiratory insufficiency.

**NB.** It is not necessary for all of these signs to be present to identify failure of the treatment regimen. However, a cure is highly unlikely when they are all present.

- The epidemiological definition of treatment failure for recording outcomes -Is often different from that used in the process of suspending therapy in a patient where the therapy is failing.
- The epidemiological definition is an outcome to account for the patient in a treatment cohort analysis, while the clinical decision to suspend therapy is made after the clinical search for all other options has been exhausted and cure of the patient is considered to be highly unlikely.

Non-adherent to DRTB treatment patients in whom the “Panel” decides to stop DRTB treatment are for cohort analysis purposed classified as failures.

### 13.3 Suspending therapy

Treatment can be considered to have failed and suspension of therapy is recommended in cases where the medical personnel are confident that all the drugs have been ingested and there is no possibility of adding other drugs or carrying out surgery.

There are two important considerations in suspending therapy or changing it to a supportive care regimen.

1. Patient’s quality of life: the drugs used in MDR-TB treatment have significant adverse effects, and continuing them while the 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, resulting in highly resistant strains such as XDR-TB which may be transmitted to others.

13.4 Approach to suspending therapy

- Should start with discussions among the clinical team but final decision to be made by DR-TB National panel.
- A clear plan should be prepared for approaching the patient and the family. (It is not recommended to suspend therapy before the patient understands and accepts the reasons to do so, and agrees with the supportive care offered)
- Offer supportive care for patient.
- Offer pain control and symptom relief
- Relief of respiratory insufficiency should be offered.
- Nutritional support should be provided.
- Regular medical visits must be made.
- Continuation of ancillary medicines should be ensured.
- Hospitalization, hospice care or nursing home care can be planned.
- Infection control measures must be practiced.

13.5 Supportive care for patients in whom all the possibilities of MDR-TB treatment have failed

A number of supportive measures summarized in Box 13.1 below. It is very important that medical visits continue and that the patient is not abandoned. The supportive measures are:

<table>
<thead>
<tr>
<th>BOX 13.1 End-of-life supportive measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain control and symptom relief. Paracetamol, or codeine with paracetamol, gives 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.</td>
</tr>
<tr>
<td>Relief of respiratory insufficiency. Oxygen can be used to alleviate shortness of breath. Morphine also provides significant relief from respiratory insufficiency and should be offered whenever necessary.</td>
</tr>
<tr>
<td>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.</td>
</tr>
<tr>
<td>Regular medical visits. When therapy stops, regular visits by the treating physician and support team should not be discontinued.</td>
</tr>
<tr>
<td>Continuation of ancillary medicines. All necessary ancillary medications should be continued as needed. Depression and anxiety, if present, should be addressed.</td>
</tr>
</tbody>
</table>
BOX 13.1 End-of-life supportive measures

- **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.

- **Preventive measures.** Oral care, prevention of bedsores, bathing and prevention of muscle contractures are indicated in all patients. Regular scheduled movement of the bedridden patient is very important.

- **Infection control measures.** The patient who is taken off antituberculosis treatment because of failure often remains infectious for long periods of time. Infection control measures should be continued (see Chapter 15).

### 13.6 Conclusion

Suspension of therapy (confirmed by the DRTB Panel) will 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.
CHAPTER 14

14.0 Management of Contacts of MDR-TB patients
- This chapter describes the management of symptomatic adults and children who have or have had a known contact with an MDR-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
- Close contacts of DR-TB patients should receive careful clinical follow-up.

14.1 General considerations
Opportunities to halt the transmission of DR-TB in communities and to treat it (DR-TB) in a timely fashion are often missed due to: lack of investigation of contacts of MDR-TB patients, failure to ask patients presenting with active TB disease about any history of exposure to MDR-TB, and poor access to second line drugs and/or DST.

Close contacts of DR-TB patients are defined as people living in the same household, or spending many hours a day together with the patient in the same indoor living or working space. Close contacts of DR-TB patients who develop active TB most commonly have drug-resistant disease.

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, contact tracing of cases of XDR-TB should be done as an emergency.

14.2 Management of symptomatic adult contacts of a patient with MDR-TB
If the contact appears to have active TB disease, culture and DST should be performed.

While DST results are awaited, seek the approval of DR-TB Panel to start an empirical regimen based on the resistance pattern of the index case may be started.

If a symptomatic adult contact yields no evidence of TB, a trial of a broad-spectrum antibiotic, one that is not active against TB such as trimethoprim/sulfamethoxazole, can be used.

If contact remains symptomatic, repeat physical examinations, smears and cultures should be performed monthly with repeat chest X-ray as needed. Refer to a chest specialist for evaluation for opinion and diagnosis.

Bronchoscopy and bronchial airway samples for smear and culture should be considered in specific cases and when indicated by an expert on DR-TB. Delay in the diagnosis of MDR-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.

14.3 Management of symptomatic paediatric contacts of patients with MDR-TB

MDR-TB should be suspected in a child if the child is:
- A close contact of an MDR-TB patient.
- A contact of a TB patient who died while on treatment when there are reasons to suspect that the disease was MDR-TB (i.e. the deceased patient had been a contact of another MDR-TB case, had poor adherence to treatment or had received more than two courses of antituberculosis treatment).
- A bacteriologically proven TB who is not responding to first-line drugs given under direct observation.

Sputum smear and culture should be done for symptomatic pediatric contacts of DR-TB patients.

If the child is aged less than 5 years or cannot expectorate sputum, induced sputum or gastric aspiration for smear, culture and DST should be considered by the specialist. HIV counseling and testing for parent(s) known, or suspected to be HIV-infected including the exposed child should be done.

14.4 Chemoprophylaxis of contacts of MDR-TB index cases

The only chemoprophylaxis regimens to have been studied are based on isoniazid and, to a lesser extent, rifampicin. Since by definition MDR-TB is resistant to both of these drugs, it is unlikely that use of these drugs to treat latent infection caused by an MDR-TB strain will prevent the development of active TB disease.

Contacts of MDR-TB patients in whom latent infection is diagnosed may not be infected with the same strain; some may be infected with isoniazid-susceptible strains, particularly in high-burden areas where many different strains of TB may circulate in homes, schools, work places, etc. Studies from high-burden TB areas have shown that approximately one-half to two-thirds of household members had the same strain of TB, as determined by genetic testing. (The degree of strain concordance could be higher in contacts who are children aged under 5 years because they have less exposure to strains circulating outside the household.)

Close contacts of DR-TB patients should receive careful clinical follow-up for a period of at least two years. If active disease develops, prompt initiation of treatment with a regimen designed to treat MDR-TB is recommended. On the basis of the currently available evidence, NTLP does not recommend the universal use of second-line drugs for chemoprophylaxis in MDR-TB contacts.

Therefore, all MDR-TB contacts should be screened for TB every six months for two years: those found to have a positive smear should have rapid DST done to confirm MDR-TB or else started on empirical regimen based on DST patterns of the source case as DST results are being processed.
CHAPTER 15

15.0 Drug resistance and infection control

This chapter reviews briefly 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.

Since every transmission averted represents one less potential DR-TB case, infection control shall be a leading programmatic priority. It is equally important to protect health workers in the setting of DR-TB.

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 should receive routine care outside of normal HIV care settings.

15.1 The priorities of 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.

Moreover, DRTB patients may respond to treatment slowly and remain sputum smear positive longer than other TB patients, therefore they may infect more contacts.

The management of DR-TB does not significantly alter the basic TB infection control strategies. However, every site (hospital, OPD clinics, PHC facilities, et cetera) attempting to treat DR-TB should also undertake a systematic review of current practices and ensure that everything possible is done to prevent transmission among patients and to staff.

Infection control, including administrative and environmental controls and personal protection, should be made a high priority in all DR-TB control.

XDR-TB patients should be placed in isolation until no longer infectious.
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 drugs is an excellent method of distinguishing those who may have DR-TB from others. Patients who are identified
by rapid tests can be properly separated or isolated immediately in addition to starting proper empirical regimens.

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.

TB infection control has three components listed by order of importance as: administrative controls, environmental or engineering controls, and personal respiratory protection. The administrative controls (work practices) are the most effective and least expensive and therefore take the highest priority. Environmental controls and personal protective equipment will not work in the absence of solid administrative control measures.

15.1.1 Administrative control measures (work practices)

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. They therefore reduce the exposure of health care workers and patients to TB germs. They are the first and most important control measures. If the risk of exposure can be eliminated, then no further controls are needed. However, in practice it is never possible to eliminate the risk of exposure.

Administrative control measures (work practices) 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. The physical separation of TB patients or people suspected of having TB requires rational design, construction or renovation, and use of buildings.

Placing HIV-infected patients on wards with known or suspected TB together with other TB or MDR-TB patients should always be avoided.

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 more in Chapter 19.

In general, no attendants should be allowed into DR-TB wards. Health-care workers visiting TB patients at home as well as relatives visiting admitted patients before treatment is well established should wear properly fitted personal protective respirators while the patient wears a face mask.

Attention should also be paid to outpatient clinical settings because of the risk of severe morbidity and mortality by HIV-infected persons from DR-TB. Hence persons with known DR-TB should receive routine care outside of normal HIV care settings for of spreading DR-TB to the HIV infected patients.
15.1.2 Environmental (or engineering) controls

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, 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, and methods that control the direction of infectious air. The choice of environmental controls is related to building design, construction, and must be tailored to local climatic and socioeconomic conditions. They include natural and/or mechanical ventilation, ultraviolet germicidal irradiation (UVGI) 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. As such clinics should be designed with large permanently open windows (even at night and in rainy seasons); without interior corridors (hallways) that tend to trap air inside. The waiting areas should be open on at least three sides.

Extraction fans can be used to improve ventilation in closed rooms through wall vents. Mechanical ventilation systems 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. These aspects are addressed in Chapter 6 of these guidelines.

15.1.3 Personal respiratory protection

This is the third and last line recommended control measure. This involves the use of personal protective equipment (particulate respirators; hereby referred to as respirators). Because administrative and engineering controls cannot provide complete protection, the third line of defense against nosocomial TB transmission is the use of personal respirators.

Wearing respirators prevents health care workers from inhaling TB germs 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.

“Particulate respirators” or simply “respirators” are designed to protect the wearer from tiny particles (1–5 µm) airborne including infectious droplets.

Surgical masks are designed to protect the operating field from relatively large respiratory droplets generated by surgeons and surgical nurses.
**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. Patients need to understand that they have a right to rapid TB diagnosis and treatment. In addition, patients need to appreciate that they are better off if they know their HIV status in order to benefit from the available services. They need to know that TB can be spread by coughing, and to expect health settings and community services to require people who are coughing to cover their mouths when doing so. They need to understand that health workers may wear personal protection equipment sometimes, or that patients may be asked to wear a mask in order to protect others. Safety without stigma should be the goal. A request to wear a mask or provide sputum outside the health facility or in a well-ventilated room should not be stigmatizing, but is part of a safer clinic for everyone.

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 (IEC) 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 (IC) plan and a staff person or team responsible for IC. The plan should identify high-risk areas for TB transmission. It should provide information on TB and HIV rates for health workers and patients. The plan provides 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 centre 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, a clean rag, tissues, or paper masks. 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, haemoptysis, 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). When possible, use community-based treatment.

Patients with known or suspected drug-resistant TB should be separated from other TB suspects.

6. **Assure 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 (acid-fast bacillus) smear.

Turn-around time for sputum AFB smear results should be no more than 24 hours if testing is done on-site. A patient-tracking system assures that TB suspects who are AFB smear-negative receive additional procedures (e.g. chest x-ray and referral visits), or treatment as quickly as possible.

DOTS treatment for TB should begin immediately when TB is diagnosed, and a plan for assuring adherence to treatment need to be developed.

7. **Improve room air ventilation.**

Patient waiting areas should be open and well-ventilated. This includes leaving 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 a facility tour to check that IC is being implemented and that all essential IC supplies are available. At the very least, facilities should have an IC plan. When feasible, monitoring annual TB cases among health workers can also provide useful information on transmission of TB in facilities. Surveillance of TB disease among health workers is another means of evaluation.

Additional on-site measures include 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, to initiation of TB treatment and interviewing patients to discuss their understanding of infection control, safety and stigma.

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 may be considered a ‘TB suspect’ for 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 TB suspect or case.
CHAPTER 16

16.0 Human resources: training and staffing

This chapter considers the development of human resources for DR-TB control and addressing a broad agenda that includes the overall management of training and issues related to staffing.

16.1 General considerations

Ensuring competent and sufficient human resources for the implementation of a DR-TB control program of high quality requires ongoing management. Usually there are numerous constraints to the effective performance of the health workforce.

In many instances, additional staffs 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 plan) to support the program.

The objectives of the human resource development component of the DRTB control program are twofold:

- To ensure the availability of sufficient staff (clinical and managerial) at all levels to implement the plan without detriment to other areas of work of the NTLP.
- To ensure that all staff involved in the program (at all service levels) are competent (have the required knowledge, skills and attitudes) and motivated for implementation.

16.2 Human resources development plan for DR-TB control programmes

There are numerous constraints to the effective performance of the health workforce, as indicated in Table 16.1.

The HRD plan for the DR-TB control programme should be part of the national HRD plan. The plan should include all staff involved in the diagnosis and treatment of TB including DR-TB, patients and national authorities responsible for overseeing the programme, and include the proper regulatory documents.

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 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. Development of a national resource group (‘master trainers’) for the strengthening of management capacity.
3. Development of regional/district DR-TB management and training teams.
4. Training of health service units.
5. Training of hospital staff involved in DR-TB management.

The objectives of the human resource development component of the
DR-TB control programme are twofold:

- To ensure the availability of sufficient staff (clinical and managerial) at all levels to implement the plan without detriment to other areas of work of the national TB control programme.
- To ensure that all staff involved in the programme (at all service levels, and both public or private) are competent (have the required knowledge, skills and attitudes) and motivated for implementation.

### Table 16.1 Human resource constraints to programme implementation

<table>
<thead>
<tr>
<th>TRAINING/COMPETENCE</th>
<th>STAFFING/MOTIVATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate skills of existing staff:</td>
<td>Imbalances in human resources for TB control:</td>
</tr>
<tr>
<td>- Many staff involved in TB control in general are not trained</td>
<td>- Imbalances in overall numbers</td>
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<tr>
<td>- Suboptimal training (in-service training): lack of specific measurable learning</td>
<td>- Imbalances in distribution</td>
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<tr>
<td>objectives, lack of training materials, inadequate length of training, poor use</td>
<td>- Urban/rural imbalance</td>
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<tr>
<td>of adequate training methodologies, lack of learning evaluation</td>
<td>- Imbalances in skills or skill-mix (a mismatch between the type or level of</td>
</tr>
<tr>
<td>- An assumption by trainers and control managers that everything taught is learnt</td>
<td>training and the skills required by the health system)</td>
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<tr>
<td>and will lead to competent performance</td>
<td>- Shortages of human resources for TB control</td>
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<td>- Lack of attention to other factors influencing behavior change of health-care</td>
<td>- Increased demand on existing staff – not only by national TB control programmes:</td>
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<tr>
<td>providers</td>
<td>- Impact of AIDS</td>
</tr>
<tr>
<td>- Training is seen as a time-limited activity that is no longer needed when the</td>
<td>- Low staff retention</td>
</tr>
<tr>
<td>treatment strategy has reached 100% coverage – “all have been trained”</td>
<td>- Low staff motivation</td>
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<tr>
<td>- Inadequate pre-service training</td>
<td>- Under-skilled (inadequate /infrequent training</td>
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<tr>
<td></td>
<td>unsupported/lack of supervision</td>
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<tr>
<td></td>
<td>- Poor work environment</td>
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<td></td>
<td>- Poor career structure</td>
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<td></td>
<td>- Underpaid</td>
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<td></td>
<td>- Overburden</td>
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<td></td>
<td>- Morale problems</td>
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<tr>
<td></td>
<td>- Sick or caring for sick family members</td>
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<td></td>
<td>- Insufficient number of posts</td>
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<td></td>
<td>- Increased “brain drain”</td>
</tr>
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<td>- High staff turnover</td>
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</tbody>
</table>
16.3 Planning for DR-TB Control:

To prepare the HRD plan for implementation by the DR-TB control, the following 10 steps are recommended:

1. Assign a focal point for human resources development for the DR-TB control programme within the national TB control programme.

2. Assess the human resource requirements of the DR-TB control programme 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 programme.
   - 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 of the respective categories are needed to maintain the current service delivery level and include treatment of DR-TB.

1. Assess the current human resources situation of the national TB control programme and the health system and determine the number of staff of the relevant categories available at each programme level.

2. Identify the gaps in human resources in terms of both the numbers and quality of staff required to implement the DR-TB program. Prepare short- and medium-term plans including how to ensure adequate staffing and preparation of training programmes 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).
   - Coordination with other in-service training programmes/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).

1. Develop training programmes to ensure that:
   - Job descriptions are based on task analysis.
   - Training courses/programmes have learning objectives based on the task analysis and the job descriptions.
   - Training courses/programmes use methods and time allocation that allow
participants to meet the learning objectives.
- The participants: Facilitators’ ratio in each course allows participants to meet the learning objectives.
- The learning objectives have been met.

2. Consider the following issues in planning and implementing evaluation:
   - Evaluation during training courses:
     - 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.

3. Ensure monitoring and supervision to:
   - Detect performance deficiencies in newly trained staff.
   - Identify new staff in need of training (additional staff needs, staff vacancies).

4. Carry out timely implementation of the HRD plan with regular monitoring of the program implementation.

5. Carry out periodic internal and external evaluation of the implementation of the HRD plan, with revision as necessary.

Methods for training evaluation

<table>
<thead>
<tr>
<th>MODEL/TYPe OF EVALUATION</th>
<th>DURING TRAINING</th>
<th>POST TRAINING</th>
</tr>
</thead>
<tbody>
<tr>
<td>REACTION EVALUATION</td>
<td></td>
<td>PERFORMANCE EVALUATION</td>
</tr>
<tr>
<td>LEARNING EVALUATION</td>
<td>Pre test and post test evaluation: organisation, participants, facilitator, material, learning method</td>
<td>Evaluation on competency &amp; performance at work place</td>
</tr>
<tr>
<td>BY WHO</td>
<td>PARTICIPANT</td>
<td>SUPERVISOR</td>
</tr>
<tr>
<td>FACILITATOR</td>
<td>TRAINING TEAM / COMMITTEE</td>
<td></td>
</tr>
<tr>
<td>TIME</td>
<td>DURING TRAINING</td>
<td>3 - 6 MONTHS POST TRAINING, INTEGRATED TO SUPERVISION ACTIVITIES</td>
</tr>
<tr>
<td>IMPLEMENTATION COORDINATOR</td>
<td>TRAINING COORDINATOR</td>
<td></td>
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</table>

Impact evaluation on target achievement of program / organization
CHAPTER 17

17.0 Management of second-line antituberculosis drugs

This chapter provides information on management of the second-line drugs used in the treatment of DR-TB and the procedures for procurement of these drugs through the GLC mechanism.

17.1 List of Essential Medicines: second-line antituberculosis drugs

Essential medicines are those that satisfy the health-care needs of the majority of the population. The drug 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 nine second-line drugs (see Box 17.1). This Model List does not imply that no other drugs could be useful for management of DR-TB, but simply that these are the basic drugs, which when used in accordance with appropriate therapeutic guidelines, cost-effectively meet the needs of a big proportion of the population with DR-TB.

BOX 17.1: Second-line antituberculosis drugs included in the Model List of Essential Medicines*

<table>
<thead>
<tr>
<th>Kanamycin</th>
<th>Levofloxacin</th>
<th>Ofloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycloserine</td>
<td>Amikacin</td>
<td>Capreomycin</td>
</tr>
<tr>
<td></td>
<td>Ethionamide</td>
<td>P-aminosalicylic acid</td>
</tr>
</tbody>
</table>

17.2 Drug management cycle of second-line antituberculosis drugs

A number of factors must be considered when selecting second-line drugs, including the efficacy of the drugs, the treatment strategy, possible adverse effects and the cost of the treatment (see Chapter 7).

Accurate demand forecasting for second-line drugs, i.e. correct quantification of the drug needs for a specific period of time, is one of the elements that guarantees an uninterrupted drug supply. There are two main approaches for demand forecasting:

- The morbidity-based approach method is recommended for new projects. In this method, the treatment regimen (standardized, individualized or empirical) and the number of patients to be treated with each regimen is taken into account. Several other key factors must also be considered, including the existing stock, lead time for delivery, safety stock needed and the shelf-lives of the drugs. Shelf-lives of second-line drugs are longer than those of first-line drugs, ranging from 18 to 36 months. It is recommended that stock should be sufficient for a period of 2–3 times the delivery delay. This method was used by NTLP at the start of program.

- The most precise method is usually the consumption-based approach, with projections of future needs based on records of past consumption by patients of individual drugs. This method assumes that the data is complete, accurate, and properly adjusted for stock-outs and expected changes in demand and use. NTLP will use this method for forecasting SLD needs.

An inventory management system needs to be set up to ensure a safety stock is constantly available the program/country maintains optimal stock movement and to provide an accurate source of information for drug demand forecasting.

Effective management of procurement ensures the availability of the drugs selected, in the right quantities, at the right time, at affordable prices and of acceptable standards of quality.

To preserve quality, the drugs should be stored and transported by the supplier and the National Medical Stores/National TB control programme following “Good Storage Practices” and the recommendations of the manufacturer regarding temperature and humidity.

The quality assurance component of a drug supply system makes certain that each drug used by a patient is safe, efficacious and of appropriate quality. All drugs used in a regimen for DR-TB should meet the WHO recommended standards for safety, efficacy and quality.

Access to second-line drugs must be accompanied by measures to ensure rational drug use. Misuse of the drugs will result in loss of susceptibility to the second-line agents, producing circulating strains that will be extremely difficult to cure with currently available medicines. Box 17.2 lists the most important elements to consider when preparing a plan to procure second-line drugs for the management of MDR-TB.
BOX 17.2: Main elements to consider when planning procurement of second-line antituberculosis drugs

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<thead>
<tr>
<th>Drug forecast based on treatment regimen, cohort size and pace of patient enrolment</th>
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</thead>
<tbody>
<tr>
<td>• Drug registration status of products selected</td>
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<tr>
<td>• Drug labeling</td>
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<tr>
<td>• Customs regulations for importing drugs</td>
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<tr>
<td>• Shelf-life of the products</td>
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<tr>
<td>• Lead-time for delivery of the drug request</td>
</tr>
<tr>
<td>• Estimated size of buffer stock (2–3 times the delivery delay)</td>
</tr>
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</table>

Critical Issues in Quantification
1. Developing the medicine list
2. Preparing an action plan for quantification
3. Using centralized quantification
4. Using both manual and computerized methods for quantification
5. Estimating time requirements, including procurement period, stock-outs (manufacturing plants/pharmaceuticals time lag), buffer stock.
6. Preparing the necessary paper work needed for ordering and receiving SLDs (the supply pipeline documents)
7. Considering the impact of lead time at all levels (buffer stock: is 2-3 times the delivery delay)
8. Adjusting for program growth (If more patients are to managed, more DR-TB centres are opened) and damages
9. Cross-checking previous estimates for purposes of improving quantification and forecasting for future years.
10. Estimating total procurement cost
11. Adjusting and reconciling final quantities in accordance with available funds

17.3 The WHO Green Light Committee mechanism

GLC mechanism that was set up in 2000 by WHO and its partners in the Stop TB Working Group on DOTS-Plus.

GLC mechanism is in place to address several obstacles in the area of drug procurement, including the high cost of second-line drugs, the lack of local capacity to apply a stringent quality assessment of drug manufacturers and their products, inconsistent availability and the lack of guidelines on the proper use of second-line drugs.
GLC-approved programs purchase directly from agent(s) contracted by WHO to procure second-line anti TB medicines. By utilizing the GLC mechanism, a NTLP accesses quality-assured second line drugs at concessionary prices.

### Procurement Cycle

<table>
<thead>
<tr>
<th>WHO</th>
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<tr>
<td>• Prequalification project</td>
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<td>• GMP standard</td>
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<tr>
<td>• Preferential prices (negotiated by WHO and partners)</td>
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<tr>
<th>GDF</th>
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<tr>
<td>• Management of procurement orders</td>
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<tr>
<td>• Quality control (with IDA)</td>
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<tr>
<td>• Market review, forecasting</td>
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<tr>
<th>Country/project</th>
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<tbody>
<tr>
<td>• Planning</td>
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<tr>
<td>• Logistics and distribution</td>
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<tr>
<td>• Implementation</td>
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<td>• Reporting</td>
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<th>IDA</th>
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<tbody>
<tr>
<td>• Purchasing</td>
</tr>
<tr>
<td>• Order consolidating</td>
</tr>
<tr>
<td>• Delivery to the country</td>
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</tbody>
</table>

### Tracking of the shipment

The standard approach to tracking the shipment and use of drug supplies, called the consumption method, is to calculate the amount of drugs that enter and leave the warehouse each month. This is typically accomplished with *stock cards* that record the stock level for each type of product and all stock movements.

### Handling and storage conditions:

1. Supplier shipment
2. Port handling
3. Distribution within your health system
4. Storage space

### Distribution:

1. Received at the port of entry
2. Cleared through customs
3. Transported from central warehouse to storage depots and health facilities
The Distribution Cycle

Customs
Customs clearance requirements can be the most challenging part of international shipping. It is imperative that a representative of the recipient be at the port of receipt. This can be an employee or a customs agent hired for the purpose of assisting with customs clearance. Documentation requirements vary but normally a Certificate of Donation Packing List, airway bill or bill of lading and Certificates of Analysis for pharmaceutical products, and a National Drug Authority verification certificate for importation are required before the shipment leaves the port.

Receipt and Inspection
1. Compare the supplier invoice with the original purchase order
2. Verify that the packages contain the correct quantities of medicines
3. Verify that the medicines are in correct dosage form and packaging
4. Pull a sample for quality control in the laboratory if required
5. Verify evidence of damage
6. Are general characteristics of the tablets, capsules and solutions correct (color, consistency, form)
7. Confirm that the expiry dates fit the country requirement for importation of medicines
Storage
1. Storage costs are a significant part of medicine supply budgets
2. Apply good distribution practices
3. Conditions of the store should meet manufacturer requirements
4. Stock rotation (first to expire, first out)
5. Security—limited access to only authorized personnel plus security during and after work hours
6. Storage areas:
   a. Medicines arranged alphabetically or by therapeutic category
   b. Packaging materials protect against environment
   c. Quarantine space for damaged, expired, sample, restricted use and dangerous products
7. Good storage practices by controlling for:
   a. Temperature and humidity
   b. Cleanliness
   c. Pests
8. Proper maintenance and management of Inventory records (Stock cards—computer systems)
9. Samples of the stored medicines pulled for quality control
10. Staging for delivery to other unit and repackaging into individual patient containers for a specified period of time.

17.4 Stock management records to be kept at the store and dispensing points.
1. Maintain a stock card for each strength of drug in the drugs store.
2. Stock cards are important for good accountability of stock movements. The cards should be made of stiff cardboard and be placed near the drug products that they refer to on the shelves. If one drug is available in two different strengths, open separate stock cards for each strength.
3. Stock cards are very useful tools in the management of stores. Follow these procedures:
   a. Maintain a stock card for each drug or strength of a drug in the store where drugs are kept.
   b. Enter quantity of any new stock with the “date, batch number, supplier and expiry date.
   c. Enter balance of stock brought forward in “balance” column with date.
   d. Entries of receipt and issue of drugs are made after the event.
   e. Always have an up to date balance of stock.
   f. Always issue out required amount of drugs from the store and enter the quantity of drug issued in the “out” column.
   g. Physically check the actual balance of stock against current balance in stock card monthly to detect any discrepancy.

Central unit store responsibilities:
- Prepare quarterly consumption and inventory reports for the program (at central level).
- Prevent stock outs by monitoring stock levels and reordering with ample lead time
for delivery.
- Monitor all sites to ensure that inventory is current and complete.
- Oversee physical movement of stock between sites.
- When an electronic stock management system is used, oversee management of electronic stock with help from store manager.
- Verify the physical stock management tools used by pharmacy/TB ward personnel.
- Provide stock cards, dispensing logs or consumption report forms.
- Confirm pharmacy personnel are preparing reports correctly.
- Train pharmacy staff on physical stock procedures.

Site pharmacist(s) at facility
If a pharmacist is not available, this position can be filled by a pharmacy technician, a nurse or other health care worker with pharmacy experience.
- Ensure adequate drug stock of SLD in hospital/clinic ward /outpatients
- Issue monthly supplies of SLDs to treatment supporters
- Compile consumption reports and add up weekly totals
- Enter weekly consumption information into Electronic Medical Record (EMR) or stock management system (when program uses such electronic systems)
- Compile bimonthly drug reports as required by district, Regional or national authorities
- Supervise other facility personnel dealing with drugs
- Maintain stock cards (see section below on stock cards)

Managing Stock
Managing the stock and supply of medications is essential for the provision of health care. This requires an effective system, either paper- or computer-based, for maintaining an accurate inventory of supplies as shipments of medicines arrive at a central storage facility and are then distributed to clinics and pharmacies to be dispensed to patients.

DR-TB health care facilities should have systems to track DR-TB drug supplies that are currently available and to assess the quantities of medications that will be needed.

A stock card is maintained for each product and is updated every time a shipment is received or supplies are dispensed to the pharmacy. A physical count should be conducted on monthly basis to reconcile the daily and monthly records and provide a reliable foundation for projections of orders and budgetary requirements.

Ordering and Delivering of Drugs and Supplies.
This will involve a mixture of the following systems backed by regular supervision to the treatment units by the ZTLSs who must verify requests.
“Push system”: Central level decides how much to deliver to each unit based on past deliveries and number of patients under treatment.
“Pull system”: Each health unit determines quantities needed (Is preferred, but requires
highly competent personnel and sufficient funding to keep the pipeline full).

**There are two steps in making a drug request at the treatment center:**

1. Determining the total consumption for each drug daily, monthly and bimonthly.
   a. Based on the MDR-TB Treatment Card of the patients in the Referral Center, record the drugs to be taken per day per patient.
   b. Calculate the DAILY consumption per drug for all patients receiving it.
   c. Calculate the MONTHLY consumption by multiplying the daily consumption by 26 days.
   d. Calculate the BIMONTHLY consumption by multiplying the monthly consumption by 2.

   For instance, you want to know the total consumption of prothionamide in a Referral Center. If you have 4 patients taking 3 tablets of 250mg prothionamide a day, and 1 patient taking 2 tablets of the same drug per day, the total daily need would be 14 tablets; the monthly need would be 364 tablets (daily consumption X 26); and the bimonthly need would be 728 tabs (monthly consumption X 2). The stock to order would be 1092 tablets (monthly consumption x 3 or 2 months’ supply plus 1 month of buffer). Repeat this procedure for all patients and drugs.

2. Once you calculate the needs, fill out the SLD/ Drug Requisition Form based on the total consumption.
   a. Write the name of the Referral Center and the order period this request is made for.
   b. In the first column of the TB Drug Requisition Form, write the drugs you will request.
   c. Write the projected bimonthly consumption, then the one month buffer, same as quantity in the “Month” column of your calculation.
   d. Follow the formula indicated above in each column.
   e. Always double check your calculations.

Once you determine the needs for each drug for the two months you will add one month’s supply to that sum as a buffer stock to have on hand in case of emergencies. After determining the total bimonthly needs plus one month buffer stock, complete the Requisition Form by subtracting the stock-on-hand from this number. The stock on hand is how much stock of each drug is presently in the facility. The last two columns of the form will be completed by the authorizing staff when the order is filled and sent to the Central stores.
Supply chain

*NB Only SLDs for the number of patients on treatment are managed
CHAPTER 18

18.0 Category 4 recording and reporting system

This chapter describes the information system for Category 4 patients, with the objective of recording information needed to monitor programme performance and treatment outcomes. It presents the instruments and minimum variables necessary to implement and monitor Category 4 treatment. Tools are also introduced to track screening and enrolment efforts. Lastly, the chapter presents additional optional components (see Box 18.1) that programs should use when it is feasible and relevant.

Key recommendations of this chapter:

- Use standardized recording and reporting in DR-TB programs.
- DR-TB treatment cards have a section on HIV
- International Health Regulations should be followed.*

18.1 Aims of the information system and performance indicators

The aims of the information system are twofold:

- To allow managers at different levels to monitor overall programme performance (DRTB patients identified, patients started on treatment and treatment results), to follow trends in number of cases notified, to plan drug supply, and to provide the basis for programme and policy developments;
- To aid clinical providers in management of individual patients.

The performance indicators include:

- The number of patients detected with MDR-TB in the laboratory (Form 05);
- The number of MDR-TB patients started on treatment (Form 05);
- Interim treatment outcome at 6-months of MDR-TB cases (Form 06);
- Final outcome of MDR-TB treatment (Form 07).

18.2 Scope of the Recording and Reporting (R&R information) system

The R&R system for DR-TB is based upon, and is an extension of, the basic DOTS R&R system. The forms are similar to the standard forms used in DOTS programmes.

The R&R is designed to be consistent across the country to permit comparison. The R&R does not include all of the detailed information that treatment units may need to manage individual patients; for example information contained in clinical records and other special forms used in the wards or clinics.

18.3 Main forms and registers and flow of information

The forms and registers include the following:

- Category 4 Treatment Card (Form 01);
- Category 4 Register (Form 02);
- DST request form (Form 03);
- Laboratory Register for culture and DST (Form 04).
Reports include:
- Quarterly report on MDR-TB detection and Category 4 treatment start (Form 05);
- Six-month interim outcome assessment of confirmed MDR-TB cases (Form 06);
- Annual report of treatment result of confirmed MDR-TB patients starting Category 4 treatment (Form 07).

Chapter 4 defines patient registration groups and treatment outcomes useful for the completion of these forms.

18.3.1 Category 4 Treatment Card (Form 01)
When the Review Panel decides that a patient should start Category 4 treatment, the health staff in the treatment unit should enter the patient in the Category 4 Register (Section 18.4.2). The staff should complete the Category 4 Treatment Card when the patient is actually starting treatment.

This card is a key instrument for DOT workers who administer drugs to patients on a daily basis. The card should be updated daily by checking off the supervised administration of drugs. The card represents the primary source of information to complete and periodically update the Category 4 Register. The original card is retained at the specialised hospital and a copy goes with the patient to an ambulatory facility where the patient continues treatment. A copy of the card may be used as a notification form and later also to report the final outcome of treatment.

The Category 4 Treatment Card contains the following sections:

Page 1
- **Basic demographic and clinical information.** Name, address, sex, age, weight, site of disease.
- **Category 4 registration number.** This is a new unique identification number assigned when the patient is entered in the Category 4 register.
- **Date of Category 4 registration.** The registration date in the Category 4 register.
- **Previous district TB registration number and date of registration.**
- **Registration group** according to result of previous anti-tuberculosis treatment. See Chapter 4, Section 4.5 for definitions.
- **Previous TB treatment episodes:** Lists and describes any previous anti-tuberculosis treatment and outcomes. Start with the earliest treatment and label it number 1. Use the abbreviations for TB drugs given on the front of the treatment card. The outcome of any previous treatment is also noted here.
- **Previous use of second-line drugs.** Document use of any of the second-line drugs listed on the front of the chart for the treatment of TB for more than one month.
- **Meetings of DR-TB panel** Periodic meetings between DR-TB Panel and the group of caregivers involved with Category 4 patients. This section provides a space to record major decisions by the panel.
- **HIV testing information.** This section is filled in for all patients. If tested for HIV include date of testing and results. If HIV-infected, indicate whether patient
is on CPT and/or ART.
- **HIV flow sheet.** This section is only filled in for HIV-infected patients.
- **Medical diagnoses other than TB.** Record all other important medical diagnoses here including diabetes, hypertension, cardiomyopathy, HIV, opportunistic infections, etc.

**Page 2**
- **Monitoring of weight.** Weight should be recorded at least monthly.
- **Monitoring of laboratory data** including creatinine, potassium, liver function tests, and thyroid tests. Recommendations regarding the interval for monitoring these indicators can be found in Chapter 11.
- **Monitoring and recording side effects.** Record date, adverse effects, and suspected drug.

**Page 3**
- **Regimen.** The initial Category 4 regimen and later changes are recorded. One line is used for each date on which a drug (or drugs) is changed. If drug dosage is progressively increased (e.g., starting 250 mg of ethionamide daily and increasing by 250 mg over two to three days until the full dose is reached), this is usually not recorded on the treatment card but should be recorded in the patient's medical record.
- **DST results.** Record the date of sputum collection and results of all DST performed.
- **Monitoring of chest X-ray.**
- **Monitoring of smear and culture.** Record date of sputum collection, sample number in the laboratory register and result of smear and culture. “Prior” refers to the sample used to indicate Category 4 registration; include the date and result of that sample. Month “0” is the time of specimen collection at the start of the Category 4 regimen. **Pages 2 and 6 of the treatment card.**

**Page 4**
- **Record of daily observed administration of 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. Additionally, if dosing is twice daily, one slash mark could be made for the A.M. dose and a second, intersecting mark could be made for the P.M. dose; if both are received, the box would contain an “x”. However, if there are inconsistencies in administration among drugs then a more detailed system containing one box for each drug prescribed daily is used.

**Page 5**
- **Outcome of treatment.** Chapter 4, Section 4.4 provides definitions. The outcome should be recorded when the final bacteriology results become available.

**18.3.2 Category 4 Register (Form 02)**
The NTLP has two basic TB registers: a District Tuberculosis Register for drug susceptible TB and a Category 4 Register for DR-TB. The Category 4 Register is the record of all patients who start Category 4 treatment (see Chapter 4, section 4.1 for a general definition of Category 4 patients). This register allows quick assessment of the implementation of Category 4, facilitates quarterly reporting and analysis of treatment start and outcomes.
The District Tuberculosis Register is the traditional DOTS register in which all TB patients are first registered. In order to integrate the treatment of Categories new, retreatment and DR-TB (I, II, III and IV), this register will be modified in three ways:

1. To capture information on culture, dates of collection and results for both the initial testing and the follow-up.
2. Capture DST information, date of collection of the sample and the drugs tested.
3. Any patient who is switched to a Category 4 regimen because of resistance (without meeting the formal criteria of failure) should have the outcome category “Change to Category 4” entered in the District Tuberculosis Register.

When a patient is starting Category 4 treatment the health staff in the treatment unit should enter the patient in the Category 4 register and indicate in the district register that the patient has entered Category 4. The date of registration should be the day when the health staff enters the patient in the Category 4 Register. The Category 4 Register should be updated regularly from the Category 4 Treatment Card and from the laboratory registers. Patients should be recorded consecutively by their date of registration. There should be a clear separation (extra line) when a new quarter is started.

Those mono and poly-resistance TB patients (H, HS, HE, and HZ) whose regimens do not require or require only one second-line drug should be maintained in the regular district TB register where adjustment of their regimen should be recorded, including any second-line agents used (see Chapter 8).

For any mono or poly-resistant TB cases (involving rifampicin or HEZ resistance) that require two or more second line drugs are entered into Category 4 Register at DR-TB accredited centre but their treatment outcome should be reported back to the health facility/district where they were diagnosed and it is these facilities that will report them to NTLP where they will be analyzed as a separate cohort of patients.

Some patients started on Category 4 regimens may be found to have drug-susceptible disease. Patient in this situation are removed from Category 4 treatment and placed on appropriate first-line therapy. Then the patient is crossed out of the Category 4 register (but the name left legible) and a comment noted in the last column that s/he has drug-susceptible disease. All patients who are switched should be registered in the District Tuberculosis Register (if they are already registered in the district register the final outcome should be documented in the original line of registration (do not create a new registration). These patients do not need to appear in Forms 05, 06 and 07 of the DR-TB reporting forms as they do not have MDR-TB.

Any patient with mono- or poly resistance treated with SLDs should be registered in Category 4 register and should not be crossed out in the Category 4 Register. Whether the patient continues on the same Category 4 regimen (or gets an individualized regimen based on DST can be documented on the treatment card and the final outcome reported in the Category 4 Register. Such patients do not need to appear in Forms 05, 06 and 07
of the DR-TB reporting forms as they do not have MDR-TB.

The following information is recorded in the Category 4 Register (for explanation see also 18.4.1):

- **Category 4 registration number.**
- **Date of Category 4 registration.**
- **Name, sex, date of birth, address (from treatment card, p. 1).**
- **District TB registration number.** All patients should have been entered in a District Tuberculosis Register. A patient who for any reason has never been registered in the District Tuberculosis Register should be registered there and the number transferred to the Category 4 Register.
- **Site of disease (from treatment card, p. 1).** Pulmonary, extra pulmonary or both. Patients with both pulmonary and extra pulmonary TB should be classified as a case of pulmonary TB.
- **Registration group (from treatment card, p. 1).** Described in Chapter 4, Section 4.5.
- **Second-line drugs received for more than one month prior to registration (from treatment card).**
- **DST (from treatment card p. 4).** Date sample taken, date of DST result and the results. Enter the DST that resulted in the patient being registered as a Category 4 patient. Follow-up DSTs are not recorded in the register. If the patient has more than one DST, results are recorded on the treatment card. If DST is performed in a staged fashion (e.g., to rifampicin and isoniazid first, followed by other first-line drugs, and then by second-line drugs) all results from the same sample should be recorded in the register.
- **Category 4 regimen (from treatment card, p. 5).** Record the initial Category 4 regimen using the drug abbreviations. Include milligram doses and number of tablets.
- **Date of start of Category 4 treatment (from treatment card, p.5).**
- **Smear and culture monitoring results (from treatment card, p.4).** Record all smear and culture results, even if done more often than recommended frequency.
- **Final outcome (from treatment card, p.6).** See Chapter 4, Section 4.6 for definitions.
- **HIV status (from treatment card, p.2)** Testing results, CPT and ART treatment information.
- **Comments/Remarks.**

### 18.3.3 Laboratory Register for culture and DST (Form 04)

Laboratories will have separate registers for sputum smear microscopy and culture (5), while reference laboratories carrying out DST should have additional space in the culture register for DST results (see Form 04). The Laboratory Register for culture and DST should contain samples from all MDR-TB suspects, indicating the registration group (including if positive smear at 3 or 4 months), and be filled in from the request form.

The MDRTB focal person should regularly/monthly compare MDRTB cased identified and registered in the Laboratory Register to those in the Category 4 Register to ensure
that all confirmed MDR-TB cases are entered in the Category 4 Register. He should proactively look for those missing.

18.3.4 Quarterly report on MDR-TB detection and Category 4 treatment start (Form 05)
This report is used to assess the number of MDR-TB cases detected (distribution and trends) and the number of MDR-TB cases who start treatment. The report is made by the unit managing MDR-TB quarterly. The quarterly report includes:

- The number of patients with date of result showing MDR-TB during the relevant quarter, taken from the Laboratory Register (Form 04). The results should be disaggregated by registration group (see Box 18.1).
- The number of MDR-TB patients started on Category 4 treatment during the quarter, taken from the Category 4 Register (Form 02).

Similarly, the number of XDR-TB cases registered (after cross-checking DST results with type of resistance) and the number of XDR-TB cases started on XDR-TB treatment are reported.
Since there may be a considerable delay between Category 4 registration and the start of Category 4 treatment, the patients who start treatment during the quarter may not be the same as the ones detected with DR-TB. The information gives an approximate indication of treatment coverage. It also enables the computation of the average delay between detection of DR-TB and treatment start (see Box 8.1).

18.3.5 Six-month interim outcome assessment of confirmed MDR-TB case (Form 06)
The treatment takes on average two years before final results are known. However, the NTLP can be informed of interim outcomes at 6 months. Form 06 is used to report bacteriological status (negative, positive or no information) of those still on treatment at 6 months, and final outcomes in those who had already defaulted or died, interim outcomes of transferred out patients. Bacteriological results are based on the smear and culture data during months 5 and 6 of treatment. The 6-month outcome assessment considered unknown for a particular patient if a culture or smear results is unknown for either month 5 or 6.

All cases from the Category 4 Register are included in this report.

The form is completed 9 months after the closing day of the cohort. This allows culture information at 6 months of treatment to be included for all patients in the cohort. Interim treatment outcome of TB patients who started treatment during the first quarter of a year (1 January to 31 March), will be filled in 1 January of the following year; those who started during the second quarter are filled in April, while third and fourth quarter patient interim outcomes are compiled in July and October the following year.
18.3.6 Annual report of treatment outcomes of confirmed MDR-TB patients starting Category 4 treatment (Form 07)

This report is made by the central unit and shows the final result of treatment by year of treatment start. All the patients are classified by previous use of tuberculosis drugs (none, only first-line drugs, also second-line drugs). If relevant, results for patients with XDR-TB could be added. All data can be extracted from treatment cards and Category 4 Register. Form 07 is first completed at 24 months after the last patient in the cohort started treatment. Most of the patients will have finished treatment by 24 months and this allows preliminary assessment of cure rates. Since a few patients may be on treatment for longer than 24 months, the form may be completed again at 36 months, which will then be considered the final result. Outcome for patients started in January – March are compiled in April the following two years. Similarly annual reports of outcomes of patients started during second, third and forth quarters are reported in July, October January the following two years.

18.4 Addressing the backlog of patients in whom Category 1II treatment failed in the past

When program management of DRTB is being introduced there is likely to be a backlog of: a) known MDRTB patients and b) patients who are still sputum smear-positive after supervised Category 1II treatment from previous years or who have received several unsuccessful treatments, are considered incurable by health staff, and who have lived with active TB disease with no or inadequate treatment for a period of time. All these are to be subjected to a DST (repeat for known MDRTB cases and to rule out MDRTB for retreatment ones) to confirm MDR-TB and establish resistance patterns before DRTB treatment is initiated.

The number of patients waiting for Category 4 treatment should be estimated in all programmes, as this will facilitate planning of drug and other resource needs. As the Category 4 treatment programme progresses, the list of chronic cases will become smaller and eventually only include cases that have failed Category 4 treatment.

18.5 Assuring the quality of the recording and reporting system

Assuring the quality of the recording and reporting system

In order for the information system for DR-TB to function well, adequate training and supervision are needed.

Regular supervisory visits by a central unit to the units using the information system are fundamental to maintain good quality of the information.

Regular meetings with staff from different levels may also be very helpful in updating information.

The person responsible for CAT IV management should regularly (at least weekly) compare the Category 4 Register with the DST register in the NTRL (and in all certified laboratories performing DST) to ensure that all patients in whom MDR-TB is diagnosed are registered and started on Category 4 treatment.

Patients diagnosed with MDR-TB in laboratories without proper quality assurance should not be included in the Laboratory Register for Culture and DST (Form 04) until their DST has been confirmed in a qualified laboratory.
18.6 Computerized systems

The recording and reporting system can be managed by hand. However, an electronic system is highly desirable since it facilitates better quality of information as well as data analysis; it will also obviate the need for transcription and repeated entry into different forms. Patient data may be entered in a format similar to the Category 4 Treatment Card, and lists similar to the Category 4 Register can then be generated. Print-outs of the list may be compared with the handwritten Category 4 Register to ensure completeness of the system. The corrected database may then be used to generate quarterly and annual reports.

Even if a computerized system is in place, a hand-written Category 4 Register should be kept, since otherwise corrections can not be seen.

BOX 18.1 Other DRTB Recording and Reporting Components/indicators

Other indicators and analysis include:

- **MDR-TB treatment coverage**: the proportion of patients started on Category 1V treatment among the total number patients detected with MDR-TB during a defined period. This indicator is calculated from the Quarterly report on MDR-TB detection and Category 1V treatment start (Form 05). The same analysis is also done for XDR-TB.

- **Delay between MDR-TB detection and Category 1V treatment start.** This indicator is computed separately for each treatment history group and for XDR-TB. This indicator can be calculated using data obtained from the Laboratory Register for culture and DST (Form 04) and the Category 1V Register (Form 02).

- **DST coverage in patient groups targeted for DST.** This assessment requires comparing the number of patients in the target groups for DST to the number in whom DST has been done. Target groups for DST in Uganda include all failures of Category 1 treatment and all retreatment cases. The MDRTB Focal point should therefore regularly (monthly/quarterly) compare the names of all cat I failures and all patients who start retreatment regimens (Category 1I) to the names of patients in the lab register for DST; thereby determine the coverage of obtaining DST in this patient group.

- **The number of failures of Category 1 treatment.** Routinely notified quarterly (challenge is R&R tools only capture numbers not names). Similarly, numbers on retreatment (not names) are notified quarterly

- **The number of failures of Category 1I treatment.** Same as above

- **Percentage of MDR-TB in different patient groups.** This information may be collected from the District TB Registers (if DST data are included), from the Laboratory Register for culture and DST (Form 04) or through surveys. For example, the percentage of MDR-TB in failures of Category 1 vs. failures of Category 1I vs. default vs. relapse.
Recording and reporting system and information flow through the health organization levels

1. **Peripheral Health Services**: Site where the patient receive CAT IV treatment:
   a. Forms and instruments to be used.
      i. Copy of Cat IV treatment card (Form 1)
   b. Update
      i. Update Treatment Card daily
      ii. Receive laboratory reports and update the CAT IV Treatment Card
      iii. In each monthly visit to be done by the patient to the District Hospital (or the nearest health centre with a trained medical officer), the patient and health worker and/or treatment supporter will take the CAT IV Treatment Card with them in order to update them.
   c. Prepare reports
      i. In each quarterly visit to be done by the patient to the Regional DR-TB referral centre, the patient and health worker and/or treatment supporter will take the CAT IV Treatment Card with them in order to facilitate the updating of CAT IV Treatment Card which remained in Regional/National DR-TB Referral Centre where DR-TB treatment was initiated.

2. **Regional DR-TB Referral Centre** (Site where the patients’ treatment will be monitored and side effects managed)
   a. Forms and instruments
      i. Copy of Cat IV treatment card (Form 1)
      ii. Data base (OpenMRS shall be used).
   b. Update
      i. Cat IV Treatment Card (Form 1) and data base in each quarterly monitoring visit by the patient at this Referral Centre.
      ii. Receive laboratory reports and update the CAT IV Treatment Card and data base
   a. Prepare forms and reports and send them to next level.
      i. Send the actualized data base to National DR-TB Referral Centre every quarter

3. **National DR-TB Referral Centre** (Where patients start treatment)
   a. Forms and instruments
      i. Cat IV treatment card (Form 1)
      ii. Cat IV treatment Register
      iii. Data base (Excel, OpenMRS, etc)
      iv. Report on MDR-TB detection and Category 4 treatment start (Form 05)
   b. Update:
      v. CAT IV Treatment Card daily, when the patient remain in the hospital
      vi. Cat IV register monthly, when the patients remain in the hospital.
      vii. Cat IV treatment Register basing on the Data Base received from
Regional Referral Centre (Every quarter) and

viii. Data Base basing on the updated Data Base received from Regional Referral Centre

ix. CAT IV Treatment Card and Data Bank basing on received laboratory reports

c. Prepare forms and reports and send them to NTLP.

- Prepare the Cat IV treatment card (Form 1) and send copies to Regional Referral Centre and Local Health Centre when discharge the patient from the hospital in order to continue the ambulatory treatment.
- Prepare the Cat IV treatment Register and maintain it en the hospital
- Prepare the Quarterly report on MDR-TB detection and Category 4 treatment start (Form 05)
- Sent Quarterly report on MDR-TB detection and Category 4 treatment start (Form 05) and the actualized data base to NTLP in quarterly base.

4. NTLP

b. Forms and instruments

i. Install the Data base when possible (OpenMRS, etc)

ii. Annual report of treatment result of confirmed MDR-TB patients starting Category 4 treatment (Form 07)

c. Update

i. Collect the Quarterly report on MDR-TB detection and Category 4 treatment start (Form 05)

ii. Update the Data Base basing on the updated data base received from National DR-TB Referral Centre.

iii. Receive laboratory reports of new MDR-TB cases and update the MDR-TB list.

d. Prepare reports and send them.

i. Prepare the Annual report of treatment result of confirmed MDR-TB patients starting Category 4 treatment (Form 07) and send it to National Referral Centre and Regional Referral Centre

ii. Prepare periodical reports regarding the Clinical and programmatic management of the MDR-TB cases and send it to National Referral Centre and Regional Referral Centre
CHAPTER 19

19.0 Managing DR-TB through Patient-Centered Care

Any patient in whom DR-TB is suspected or diagnosed should be provided with high-quality patient-centered care, as outlined in both the International Standards for Tuberculosis Care and the Patients’ Charter for Tuberculosis Care. This new approach identifies certain rights and responsibilities of both providers and patients, and facilitates a mutual collaboration to achieve the cure with dignity. This chapter provides guidance on how this ‘partnership’ can be forged, in common cause.

19.1 General considerations

The programmatic management of DR-TB is extremely challenging even in the best of circumstances, and demands substantial efforts from a team of health professionals and from the patient to reach a successful outcome. The long duration of complicated treatment and often difficult adverse effects require a joint commitment to complete the process, and this is best practiced in an environment of mutual respect and consideration. Certain basic steps should be taken to assure this, and some of these are made by changing attitudes, perceptions and behaviors while others may require refining existing management practices and service delivery systems.

19.2 Understanding Patient-Centered Care

An understanding of Patient-Centered Care provides the basis to building better patient-provider relations, and can contribute to improved adherence, reduced stigmatization and better outcomes. It also sends a message to the wider effective community that DR-TB can be successfully treated within a dignified framework of mutual respect, thus facilitating case finding and community participation.

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, ‘Champions’ (expert patients) and trained health workers can offer information sharing sessions to educate patients, and for better detecting risk factors for default (e.g. understanding side effects) and other warning signs that can affect treatment outcome. These discussion sessions should be through two-way communications, mutually deciding on interventions for problems, for example, on how to handle drug side effects.

19.3 Dignity, from Day One

People suspected of having DR-TB should begin what may be a long march towards a cure in a manner to encourage their willful 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.
To sustain this initial expression of respect patients should be educated on TB disease and their rights in their local language at the first consultation and there after. Providing all this information to patients will assist the provider with educating the patient about the disease and treatment as a basis for reaching better final outcomes. It is a key element of the Stop TB Strategy under component five, Empowering People with TB and Communities.

The socioeconomic impact of both the physical aspects of tuberculosis and of the long treatment can be extremely difficult for patients and their families. At the onset of treatment, an assessment of the means and financial resources of the patient should be conducted with a view to supporting those in need of assistance. Although food packages and transport support may be useful to mitigate some of the difficulties, providing a minimum revenue for all patients might be a worthy investment to assure adherence and willful participation.

19.4 Staff as stakeholders, patients supporting peers

Hospitals managing DR-TB patients should identify a member of staff who will serve as the focal point for developing Patient-Centered Care, and to identify a number of patients that could be initiated in ways to encourage their peers to embrace this new approach. This lays the groundwork for the development of a social network within the clinical facility, which can play an essential role in galvanizing adherence and decreasing default. Working together, a health worker and a patient can facilitate a wider participation, foster a spirit of collaboration and take an innovative step to reduce stigma. This dynamic relationship facilitates gaining further support from the community and authorities to raise the standards of care.

The human resource component specifically that of health care workers is an important aspect of the patient-centered approach and an essential factor in achieving a favorable response to treatment. Community health workers (CHW) should be trained appropriately in communicating and interacting ‘positively’ with both patients and families. The attitudes and interpersonal skills of health workers are tools for better outcomes as patients default from treatment if dissatisfied with the way they are treated as human beings, and this echoes throughout the wider affected community. Furthermore, amongst patients, it is commonly understood that stigma, like water, flows downward, not upwards from the bottom. Thus health care workers can play a leading role in diminishing stigma by seeing the patient-provider relationship with an appreciation of the challenges each other faces, and viewing the process to cure DR-TB as a joint-endeavor.

Providing on-site social support for patients and their families through peer counseling has shown itself to be highly effective in TB in a number of communities, and it is a key element of the scaling-up the response to HIV. MDR-Cured patients (“Community Champions”) can be identified and trained to function as a peer supporter. These ‘champion-counselors’ would follow each patient from diagnosis through to cure, and act as both ‘friend’ and educator. From the patient’s perspective, having this companion available greatly reduces the psychological burden of the long treatment.
19.5 Communicating ‘Cure’

Although implementing patient-centered 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 staff that seek to manage DR-TB should appreciate the fundamental human resistance to being ‘controlled’. Although the term TB ‘Control’ is still used by many health professionals, people with the disease are much more responsive, and more responsible if the term TB ‘Care’ is emphasized. 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 for their families and communities, which strengthens their participation in supporting the patients and the program.

Health workers should adopt methods of communicating ‘with’ and not ‘at’ patients and their families, in a manner that builds a ‘positive partnership’ towards successful treatment completion hence cure (communicating cure). 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 focal points for patient-centered care and peer supporters can also play an important role as ‘communicators’.

19.6 Forced isolation and respect for human rights

Management of DR-TB, which can be a threat to public health, must be balanced with a consideration of the human rights and dignity of the patient. Guided by the Siracusa Principles the WHO states that forcibly isolating people with DR-TB must be used only as the last possible resort when all other means have failed, and only as a temporary measure.

Health authorities and providers choosing the extreme measure of involuntary treatment should only do so if they can assure it is done in a transparent and accountable manner. If it can be proven through evidence-based analysis 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 drug sensitivity testing, social support, and be treated with 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 an 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 liberties may be determined to be necessary on a case-by-case basis, but these should not be prescribed unless clinically evidenced, and with the information communicated in a clear and understandable manner to the patient, accompanied by a peer-supporter or family member. In the extreme case of XDR-TB where cure is no
longer a possibility, extra steps should be taken by health providers to assure that palliative care is extremely ‘patient-centered’ and extra measures of social support provided to both the patient and their family. Although infection control remains essential and isolation may be needed, facilitating additional compassionate human contact permits the patients and families the dignity to better deal with the reality. For more information on human and patients’ rights.

19.7 Civil Society
The involvement of civil society, such as patient support groups, NGOs, community or faith-based organizations in various aspects of the programmatic management of DR-TB is strongly recommended. These organizations can assist through diverse but important actions, including providing social support services, case finding, prevention campaigns, and advocating for greater resources for local services. DR-TB is a problem for the affected community, and welcoming the participation and building working relations with civil society organizations not only brings new resources to confront the problem, but can serve as a dynamic link between patient and care provider (also see Chapter 12).

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

### Annex 1: Recommended dosages of TB drugs

<table>
<thead>
<tr>
<th>Medication (drug abbreviation), (common presentation)</th>
<th>Weight class</th>
<th>&lt;33 kg</th>
<th>33-50 kg</th>
<th>51-70 kg</th>
<th>&gt;70 kg (also maximum dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1: First-line oral anti-tuberculosis drugs</strong></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Isoniazid (H) (100, 300 mg)</td>
<td></td>
<td>4-6 mg/kg daily or 8-12 mg 3 x wk</td>
<td>200-300 mg daily 300 mg daily or 450-600 mg 3 x wk</td>
<td>or 600 mg 3 x wk</td>
<td>300 mg daily or 600 mg 3 x wk</td>
</tr>
<tr>
<td>Rifampicin (R) (150, 300 mg)</td>
<td></td>
<td>(R)10-20 mg/kg daily</td>
<td>450-600 mg</td>
<td>600 mg</td>
<td>600 mg</td>
</tr>
<tr>
<td>Ethambutol (E) (100, 400 mg)</td>
<td></td>
<td>25 mg/kg daily</td>
<td>800-1200 mg</td>
<td>1200-1600 mg</td>
<td>1600-2000 mg</td>
</tr>
<tr>
<td>Pyrazinamide (Z) (500 mg)</td>
<td></td>
<td>30-40 mg/kg daily</td>
<td>1000-1750 mg</td>
<td>1750-200 mg</td>
<td>2000-2500 mg</td>
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<tr>
<td><strong>Group 2: Injectable anti-tuberculosis drugs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptomycin (S) (1 g vial)</td>
<td></td>
<td>15-20 mg/kg daily</td>
<td>500-750 mg</td>
<td>1000 mg</td>
<td>1000 mg</td>
</tr>
<tr>
<td>Kanamycin (Km) (1 g vial)</td>
<td></td>
<td>15-20 mg/kg daily</td>
<td>500-750 mg</td>
<td>1000 mg</td>
<td>1000 mg</td>
</tr>
<tr>
<td>Amikacin (Am) (1 g vial)</td>
<td></td>
<td>15-20 mg/kg daily</td>
<td>500-750 mg</td>
<td>1000 mg</td>
<td>1000 mg</td>
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<tr>
<td>Capreomycin (Cm) (1 g vial)</td>
<td></td>
<td>15-20 mg/kg daily</td>
<td>500-750 mg</td>
<td>1000 mg</td>
<td>1000 mg</td>
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<tr>
<td><strong>Group 3: Fluoroquinolones</strong></td>
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<tr>
<td>Ofloxacin (Ofx) (200, 300, 400 mg)</td>
<td></td>
<td>15-20 mg/kg daily</td>
<td>800 mg</td>
<td>800 mg</td>
<td>800-1000 mg</td>
</tr>
<tr>
<td>Levofloxacin (Lfx) (200, 500 mg)</td>
<td></td>
<td>7.5-10 mg/kg daily</td>
<td>750 mg</td>
<td>750 mg</td>
<td>750-1000 mg</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Formula and Dose</td>
<td>Daily Dosing</td>
<td>750 mg</td>
<td>750 mg</td>
<td>750 mg</td>
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</tr>
<tr>
<td>Moxifloxacin (Mfx)</td>
<td>(400 mg)</td>
<td>7.5-10 mg/kg daily</td>
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**Group 4: Oral bacteriostatic second-line antituberculosis drugs**

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Formula and Dose</th>
<th>Daily Dosing</th>
<th>750 mg</th>
<th>750 mg</th>
<th>750 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethionamide (Eto)</td>
<td>(250 mg)</td>
<td>15-20 mg/kg daily</td>
<td>500 mg</td>
<td>750 mg</td>
<td>750-1000 mg</td>
</tr>
<tr>
<td>Protonamide (Pto)</td>
<td>(250 mg)</td>
<td>15-20 mg/kg daily</td>
<td>500 mg</td>
<td>750 mg</td>
<td>750-1000 mg</td>
</tr>
<tr>
<td>Cycloserine (Cs)</td>
<td>(250 mg)</td>
<td>15-20 mg/kg daily</td>
<td>500 mg</td>
<td>750 mg</td>
<td>750-1000 mg</td>
</tr>
<tr>
<td>Terizidone (Trd)</td>
<td>(250 mg)</td>
<td>15-20 mg/kg daily</td>
<td>600 mg</td>
<td>600 mg</td>
<td>900 mg</td>
</tr>
<tr>
<td>P-aminosalicylic acid</td>
<td>(PAS)</td>
<td>150 mg/kg daily</td>
<td>8 g</td>
<td>8 g</td>
<td>8-12 g</td>
</tr>
</tbody>
</table>

Sodium PAS: Dosing can vary with manufacture and preparation: check dose recommended by the manufacturer.

**GROUP 5: AGENTS WITH UNCLEAR ROLE IN DR-TB TREATMENT (NOT RECOMMENDED BY WHO FOR ROUTINE USE IN MDR-TB PATIENTS). OPTIMAL DOSES FOR DR-TB ARE NOT ESTABLISHED**

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Formula and Dose</th>
<th>Daily Dosing</th>
<th>750 mg</th>
<th>750 mg</th>
<th>750 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clofazimine (Cfz)</td>
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<tr>
<td>Linezolid (Lzd)</td>
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<tr>
<td>Amoxicillin / Clavulanate (Amx/Clv)</td>
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<tr>
<td>Thioacetzone (Thz)</td>
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<tr>
<td>Imipenem/cilastatin (Ipm/Cln)</td>
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<tr>
<td>Clarithromycin (Clr)</td>
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</table>

**NB: High-dose isoniazid = 16-20 mg/kg daily (High-dose H)**
Annex 2: FORM 1

NATIONAL TB/LEPROSY PROGRAM / MoH DR-TB

No. ...........

Treatment Health facility: ...........................................

Follow up health facility: ........................................ date: ............

Follow up health facility: ........................................ date: ............

DR-TB PATIENT BIODATA

Name: ........................................ First name: ........................................

Age: ........ Date of birth: ____ / ____ / ____  Sex: M / F

Marital status: ☐ Married ☐ Single ☐ Widowed ☐ Separate ☐ Divorced

Occupation: ........................................ Tel N0: ........................................

Address: ........................................ District: .................... County: ....................

Sub-county: ........................................ LC1 Zone: ........................................

Contact: Name: ........................................ Tel: ........................................

District: ........................................ County: ........................................

Sub-county: ........................................ LC1 Zone: ........................................
Date of registration: _________________

Start date of treatment Cat IV: _________________

- Suspected MDR-TB cases
- Confirmed MDR-TB Case
- Pulmonary
- Extra pulmonary

If extra pulmonary, specify site____________

Date of DST: _______

Laboratory: _____________ N° ______

Result: S=Sensitive=Resistant, C=Contaminated

<table>
<thead>
<tr>
<th>R</th>
<th>H</th>
<th>E</th>
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<th>Z</th>
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<thead>
<tr>
<th>K</th>
<th>Pro</th>
<th>CS</th>
<th>Ofx</th>
<th>PAS</th>
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</table>

### Previous treatment with second line drugs for 1 month or more?

- No ☐ Yes ☑ Drug(s) .................................................... Duration ............

Km = Kanamycin  Cm = Capreomycin Cfx = Ciprofloxacin  Ofx = Ofloxacin

### CO-MORBIDITIES:

HIV test date............ Result ... HIV File No.........CD4: date ............ Result............

CPT: ☐ yes ☐ no  Start Date : .......... ART: ☐ yes ☐ No  Start Date : ..........

ART Regimen: ........................................ ART File No: .................

Others: ☐ Renal insufficiency ☐ Hepatitis ☐ Diabetes ☐ GIT Ulcer ☐ Hearing impairment ☐ Mental disorder ☐ Epilepsy

<table>
<thead>
<tr>
<th>Date</th>
<th>Decision of the DR - TB Panel</th>
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## RESULTS OF TESTING SENSITIVITY

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### Smear

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<th>Result</th>
<th>Date</th>
<th>Lab. No</th>
<th>AFB</th>
<th>Result</th>
<th>Date</th>
<th>Kg</th>
<th>Date</th>
<th>Urea</th>
<th>Creatinine</th>
<th>Clearance</th>
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### Culture

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<th>Kg</th>
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<th>Clearance</th>
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### Weight

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<th>Urea</th>
<th>Creatinine</th>
<th>Clearance</th>
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### Other Reviews

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<th>Date</th>
<th>Urea</th>
<th>Creatinine</th>
<th>Clearance</th>
<th>Other</th>
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</table>
Taking drugs under direct observation per month

Prescription drugs: Indicate date, doses (in milligrams), frequency of injections and the number of tablets (at the beginning and for any change).

<table>
<thead>
<tr>
<th>Date</th>
<th>Km</th>
<th>Lfx</th>
<th>Eto</th>
<th>CS</th>
<th>PAS</th>
<th>Z</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose in mg</td>
<td>No. days/wk</td>
<td>Dose in mg</td>
<td>This morning</td>
<td>This evening</td>
<td>Dose in mg</td>
<td>This morning</td>
</tr>
</tbody>
</table>

Taking drugs under direct observation per month

Mark: x = directly observed, 0 = drugs not taken, I = Incomplete dose (write an “I” in red pen). - Drug Holiday (Under no circumstances will treatment be self administered). X = Change in regimen (Specify reason for regimen change under comments).
Taking drugs under direct observation per month (continued)

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

Mark: \(x\) = directly observed, \(0\) = drugs not taken, \(I\) = Incomplete dose (write an “I” in red pen), - Drug Holiday (Under no circumstances will treatment be self administered) \(\#\) = Change in regimen (Specify reason for regimen change under comments)

Comments:
________________________________________________________________
________________________________________________________________
________________________________________________________________
________________________________________________________________
________________________________________________________________

<table>
<thead>
<tr>
<th>RESULT TREATMENT</th>
<th>TICK ONE BOX</th>
<th>DATE</th>
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</thead>
<tbody>
<tr>
<td>Cured</td>
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<td></td>
</tr>
<tr>
<td>Treatment completed</td>
<td></td>
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<tr>
<td>Died</td>
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<td>Defaulted</td>
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<td>Transferred to...</td>
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<td>Health unit</td>
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(Health unit)
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<tr>
<th>Date</th>
<th>Clinical monitoring / Side Effects</th>
<th>Diagnosis and Action to be taken</th>
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<tr>
<td>Date</td>
<td>Clinical monitoring / Side Effects</td>
<td>Diagnosis and Action to be taken</td>
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</table>
Annex 3

National TB and Leprosy Programme

DST REQUEST FORM

DATE:_____________________

1.0 PATIENT IDENTIFICATION

Name:………………………………………………..SEX……………………..Age (years):……..

Patient ID:……………………..Patient unit TB No:………….Contact Tel No:………………………………………………..

LC1/Village:………………………Parish/ward:…………………………District of Residence:…………………………..

2.0 HEALTHY FACILITY DETAILS:

Name:……………………….District:…………………………..TB Zone:………..

3.0 CLINICAL INFORMATION:

3.1 PATIENT CATEGORY

☐ TB suspect ☐ New Patient ☐ Failure ☐ Defaulter ☐ Relapse ☐ Chronic Case ☐ Other……

3.2 ANTI-TUBERCULOSIS DRUGS EVER BEEN USED:

☐ Isoniazid ☐ Rifampicin ☐ Streptomycin ☐ Ethambutol ☐ Pyrazinamide

☐ Kanamycin ☐ Amikacin ☐ Capreomycin ☐ Ofloxacin ☐ Other specify:………………….

4.0 REASONS FOR REQUEST

☐ Diagnosis ☐ Smear positive at -------- month(s) of treatment ☐ Culture ☐ Initial DST ☐ Follow Up DST at ……….. Months of TB treatment ☐ Other reason (specify):…………………………..

5.0 SPECIMEN INFORMATION

Peripheral Microscopy Results:…………………

5.1 Specimen collected at (Follow-up visit):

☐ 0 months ☐ 2 months ☐ 5 months ☐ 8 months ☐ Other specify:…………………………..

5.2 Date collected:………………………Time:………

6.0 EXAMINATION REQUESTED

☐ MICROSCOPY: ☐ CULTURE: ☐ DRUG SUSCEPTIBILITY TEST:

Requested by: Name:___________________Sign_________________________Phone number:_________________

For National TB Reference Laboratory Use:

Date Received:___________________Time:_____________________

Appearance:________________Volume:____________Received by (Name):________________________

Laboratory Number:________________Reported by: Sign________________________

TSRS

PART IDENTIFICATION

NUMBER

142
### Annex 5: NTLP DR-TB LABORATORY REGISTER FOR CULTURE AND DRUG SUSCEPTIBILITY TESTING (DST)

**FORM 04**

<table>
<thead>
<tr>
<th>Date specimen received</th>
<th>Lab serial number</th>
<th>Type of specimen received</th>
<th>Requesting/Referring facility</th>
<th>Patient’s names in full</th>
<th>Patients’ address</th>
<th>Sex</th>
<th>Age</th>
<th>Registration group;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td>M</td>
<td></td>
<td>TB suspect</td>
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<td></td>
<td>F</td>
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<td>N-New</td>
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<td>R-Relapse</td>
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<td>D-Treatment after default</td>
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<td>F1-Treatment failure of Cat1</td>
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<td>F2-Treatment failure of Cat2</td>
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<td>TI-Transfer in</td>
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<td>O-Other.......................</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>District</th>
<th>S/country</th>
<th>County</th>
<th>LC1 Zone</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>
Annex 6: NTLP DR-TB LABORATORY REGISTER FOR CULTURE AND DRUG SUSCEPTIBILITY TESTING (DST)

**FORM 04**

<table>
<thead>
<tr>
<th>Reason for examination</th>
<th>Culture</th>
<th>Results of confirmatory test for M. tuberculosis (positive or negative)</th>
<th>Name of person reporting Culture results</th>
<th>Sign</th>
<th>Culture sent for DST (Yes or No)</th>
<th>Date DST results reported</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis* Follow-up**</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

---

* New patient or patients starting a retreatment regimen

** Patient on TB treatment, indicate months of treatment at which follow-up examination is performed

*** Outcome of culture reported as follows:

<table>
<thead>
<tr>
<th>Notation method for recording cultures</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No growth reported</td>
<td>0</td>
</tr>
<tr>
<td>Fewer than 10 colonies</td>
<td>Report number of colonies</td>
</tr>
<tr>
<td>10-100 colonies</td>
<td>+</td>
</tr>
<tr>
<td>More than 100 colonies</td>
<td>++</td>
</tr>
<tr>
<td>Innumerable or confluent growth</td>
<td>+++</td>
</tr>
</tbody>
</table>
Annex 6: NTLP DR-TB LABORATORY REGISTER....continued

NTLP DR-TB LABORATORY REGISTER FOR CULTURE AND DRUG SUSCEPTIBILITY TESTING (DST)
FORM 04

<table>
<thead>
<tr>
<th>DST Results</th>
<th>Classification Resistance</th>
<th>Name of person reporting DST results</th>
<th>Signature</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td></td>
<td></td>
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<tr>
<td>H</td>
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<td>Cm</td>
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<td>Fq</td>
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<tr>
<td>Other</td>
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</tbody>
</table>

Record DST results as:  S = Susceptible, r =resistant, C = Contaminated
Annex 7: NTLP QUARTERLY REPORT ON MDR-TB DETECTION AND CATEGORY IV TREATMENT START

FORM 05

Name of area........................................................................................................ Name of area Coordinator..............................................................

Patients identified during.........., quarter of year.............. Date.................................................................

1. Number of patients detected with MDR-TB/XDR-TB in the lab (by date of result of MDR-TB/XDR-TB in Laboratory register) during the quarter:

   MDR-TB   XDR-TB

2. Number of MDR-TB/XDR patients who started Category 4 treatment during the quarter:

<table>
<thead>
<tr>
<th>New case</th>
<th>Previously treated with first line drugs</th>
<th>Previously treated with second line drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDR Confirmed cases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDR Suspected cases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>XDR Confirmed cases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>XDR Suspected cases</td>
<td></td>
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</tbody>
</table>

1\textsuperscript{st} Quarter: 1\textsuperscript{st} January – 31\textsuperscript{st} March
2\textsuperscript{nd} Quarter: 1\textsuperscript{st} April – 30\textsuperscript{th} June
3\textsuperscript{rd} Quarter: 1\textsuperscript{st} July – 30\textsuperscript{th} September
4\textsuperscript{th} Quarter: 1\textsuperscript{st} October – 31\textsuperscript{st} December

Signature: .................................................................
### Annex 8: NTLP SIX MONTH INTERIM OUTCOME ASSESSMENT OF CONFIRMED MDR-TB CASES

**FORM 06**

(To be filled out 9 months after treatment start).

Name of unit:__________________________________________

Date filled in:__________________________________________

Quarter treatment was started:___________________________

Date of the report:______________________________

<table>
<thead>
<tr>
<th>Number started on treatment</th>
<th>Bacteriological results at 6 months of treatment</th>
<th>No longer on treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative (smear and culture negative)</td>
<td>Died</td>
</tr>
<tr>
<td></td>
<td>Positive (smear and culture positive)</td>
<td>Defaulted</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>Transferred out</td>
</tr>
</tbody>
</table>

|                             |                                               |                        |
Annex 9: NTLP ANNUAL REPORT OF TREATMENT RESULT OF CONFIRMED MDR-TB PATIENTS STARTING CATEGORY 4 TREATMENT

FORM 07

(to be filled in 24 and 36 months past the closing date of year of treatment).

Year of treatment start: ______________________

Date of the report: __________________________

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Cured</th>
<th>Treatment Completed</th>
<th>Failed</th>
<th>Defaulted</th>
<th>Died</th>
<th>Transferred out</th>
<th>Still on treatment</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>New</td>
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<tr>
<td>Previously treated with first-line drugs only</td>
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<tr>
<td>Previously treated with second-line drugs</td>
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</table>
**Annex 10: NTLP**

**FORM 08**

**PROPORTION OF CONFIRMED MDR-TB CASES STARTED ON MDR-TB TREATMENT BY QUARTER REGISTERED AS MDR-TB CASES AND REASON FOR NOT YET STARTING MDR-TB TREATMENT**

*Date filled in: ____________________________*

<table>
<thead>
<tr>
<th>Quarter &amp; year of MDR-TB registration</th>
<th>Total MDR-TB Cases registered during the quarter</th>
<th>Total MDR-TB cases started on treatment</th>
<th>Delay from DST result to treatment start (program needs to define short etc.)</th>
<th>Reason for not yet started on MDR-TB treatment</th>
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</table>
### Annex 11: NTLP FORM 09

**INTERIM RESULT OF MDR-TB TREATMENT BY QUARTER OF TREATMENT START IN CONFIRMED MDR-TB CASES.**

Date filled in: __________________________

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
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<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quarter of MDR-TB treatment start</td>
<td>At how many months after treatment start assessment is made</td>
<td>Number started on MDR-TB treatment</td>
<td>Bacteriological Results at time of assessment</td>
<td>No longer on treatment</td>
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<td></td>
<td></td>
<td>Negative (Smear and culture negative)</td>
<td>Positive (Smear and culture positive)</td>
<td>Unknown</td>
<td>Died</td>
<td>Defaulted</td>
<td>Transferred out</td>
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</tbody>
</table>
Annex 12  UGANDA NTLP Patient Identity Card, FORM 10

<table>
<thead>
<tr>
<th>Disease classification</th>
<th>Date treatment started</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>Day</td>
</tr>
<tr>
<td>Extra pulmonary</td>
<td></td>
</tr>
<tr>
<td>Site</td>
<td></td>
</tr>
</tbody>
</table>

| Type of patient
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>New</td>
</tr>
<tr>
<td>Transfer in</td>
</tr>
<tr>
<td>Treatment after</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment Category</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Initial treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in treatment</td>
</tr>
<tr>
<td>Allergies</td>
</tr>
<tr>
<td>Severe adverse reactions</td>
</tr>
</tbody>
</table>

Remember

Take care of your card

You can be cured if you follow your treatment regimen by taking your prescribed drugs regularly.

Tuberculosis can spread to other people if you do not take your medication.
# Annex 13 NTLP DR-TB Notification Form

## (FORM 11)

Notification form to the District/Follow up facilities for MDR-TB Patients

<table>
<thead>
<tr>
<th>Field</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>District</td>
<td>________________</td>
</tr>
<tr>
<td>Referral Center:</td>
<td>________________</td>
</tr>
<tr>
<td>Patient Name:</td>
<td>_________________________</td>
</tr>
<tr>
<td>District TB registration number:</td>
<td>_________________________</td>
</tr>
<tr>
<td>Date of district TB registration:</td>
<td>_________________________</td>
</tr>
<tr>
<td>Address:</td>
<td>__________________________ Sex:  M____F____ Age:_____ Date of Birth:____________</td>
</tr>
<tr>
<td>TB Disease Site:</td>
<td>Pulmonary / Extra-pulmonary / Both (circle appropriately)</td>
</tr>
<tr>
<td>If extra-pulmonary, specific site:</td>
<td>____________________</td>
</tr>
<tr>
<td>Resistance type: (MDR-TB / XDR-TB/ poly resistant)</td>
<td>______________________</td>
</tr>
<tr>
<td>Confirmed or suspected?</td>
<td>______________________</td>
</tr>
<tr>
<td>Date treatment started</td>
<td>______________________</td>
</tr>
<tr>
<td>Registration Group: New , Relapse, Treatment after default, Treatment after failure of new patient treatment regimen, Treatment after failure of retreatment regimen, Transfer in, Other_________ (specify)</td>
<td></td>
</tr>
</tbody>
</table>

**To be completed by the receiving facility and returned**

The following MDR-TB patient has been registered in our follow up facility DR-TB Register

<table>
<thead>
<tr>
<th>Field</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>District:</td>
<td>________________</td>
</tr>
<tr>
<td>Referral Center:</td>
<td>________________</td>
</tr>
<tr>
<td>Patient Name:</td>
<td>_________________________</td>
</tr>
<tr>
<td>MDR-TB registration Number:</td>
<td>_________________________</td>
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<tr>
<td>Date of MDR-TB registration:</td>
<td>_________________________</td>
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<tr>
<td>District TB registration number:</td>
<td>_________________________</td>
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<tr>
<td>Date of district TB registration:</td>
<td>_________________________</td>
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<tr>
<td>Signature and Date</td>
<td>_________________________</td>
</tr>
</tbody>
</table>
Annex 14: DR-TB SECOND LINE DRUG REQUISITION FORM

(FORM12)

Health facility Name: ________________________________

FOR THE MONTHS OF: __________ TO __________ Year __________ Date Request made: __________ Requisition NO: __________

<table>
<thead>
<tr>
<th>Item Number</th>
<th>Item Description</th>
<th>Unit</th>
<th>Daily consumption (all patients)</th>
<th>Monthly consumption</th>
<th>Bimonthly consumption</th>
<th>Quantity needed (plus one month buffer)</th>
<th>Quantity on hand (stock balance)</th>
<th>For Official use only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Kanamycin 1g</td>
<td>vial</td>
<td>A</td>
<td>B=AX26</td>
<td>C=BX2</td>
<td>D=C+B</td>
<td>E</td>
<td>F=D-E</td>
</tr>
<tr>
<td></td>
<td>Capreomycin 1g</td>
<td>vial</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Water for Injection 5ml</td>
<td>ampoule</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Syringes and needles</td>
<td>5ml</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Pyrazinamide 500mg</td>
<td>tab</td>
<td></td>
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<tr>
<td></td>
<td>Levofoxacin 250mg</td>
<td>tab</td>
<td></td>
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<td></td>
<td>Moxifloxacin 400mg</td>
<td>tab</td>
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<tr>
<td></td>
<td>Cycloserine 250mg</td>
<td>tab</td>
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<tr>
<td></td>
<td>PAS sodium granules 60% 4g</td>
<td>sachets</td>
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<td>Ethionamide 250mg</td>
<td>tab</td>
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<td></td>
<td>Pyridoxine 50mg</td>
<td>tab</td>
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<td></td>
<td>Others, Specify</td>
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</tbody>
</table>

Comments:

Name of Unit In-charge .......................................................... Unit In-charge Signature..........................................................

Name and signature of authorizing officer ........................................ Name and signature of issuing officer ........................................
<table>
<thead>
<tr>
<th>S/N</th>
<th>Name of patient</th>
<th>MDR TB Number</th>
<th>Age</th>
<th>Sex</th>
<th>Regimen</th>
<th>Months of completed treatment</th>
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</thead>
<tbody>
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Comments:
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_____________________________________________________________________________________________________________________________
### Annex 15: NTLP DR-TB WAITLIST/ REGISTER

**FORM 13**

<table>
<thead>
<tr>
<th>Serial No.</th>
<th>District Name</th>
<th>District TB No.</th>
<th>Unit TB No.</th>
<th>Patient's NAME</th>
<th>Sex</th>
<th>Age</th>
<th>Address (County, Sub-county, parish, LCI)</th>
<th>Patient Category (N,R,F,D,O)</th>
<th>Type of TB (PTB, EPT)</th>
<th>Current Regimen</th>
<th>HIV status (C, CT, CT)</th>
<th>Date of Diagnosis</th>
<th>Date of Treatment Approval</th>
<th>Alive or Dead</th>
<th>Patients' Phone Contact</th>
</tr>
</thead>
<tbody>
<tr>
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</table>
Annex 16: Stock Card

FORM 14

Program ________________________________
Facility Name ___________________                        Location_____________________

<table>
<thead>
<tr>
<th>Item Description:</th>
<th>Item Code:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unit of Issue:</td>
<td></td>
</tr>
<tr>
<td>Minimum Stock Level:</td>
<td>Maximum Stock Level:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Date</th>
<th>Voucher Number</th>
<th>Received from/ Issued to</th>
<th>Quantity received</th>
<th>Quantity Issued</th>
<th>Losses/ Adjustments</th>
<th>Stock Balance</th>
<th>Initials</th>
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</thead>
<tbody>
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</tbody>
</table>

156
### CONTACT TRACING CARD FOR SMEAR POSITIVE CONTACTS AND DR-TB

**Name of health facility used for screening:** __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __

<table>
<thead>
<tr>
<th>No</th>
<th>Name of contact case</th>
<th>Age</th>
<th>Sex [M/F]</th>
<th>TB symptoms with duration</th>
<th>TB physical signs</th>
<th>smear sputum results (Positive/Negative)</th>
<th>X-ray finding (suggestive/Not suggestive)</th>
<th>Culture results (positive/Negative)</th>
<th>Tuberculin skin test in (Mantoux) unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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</tbody>
</table>

Screening to be repeated: __ /__ /                  Date of repeat: __ /__ /__ /__ /__ /__ /__ /__ /__ /__ /__ /__ /

**Note:** Screen quarterly for 1 year for susceptible TB contacts and for 2 years in case of Drug resistant TB contacts.

**Name of contact tracer:** __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ ____
<table>
<thead>
<tr>
<th>Item Number</th>
<th>Description (Specify preparation of drug)</th>
<th>Unit</th>
<th>Number of units</th>
<th>Reason</th>
<th>Comments</th>
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</thead>
<tbody>
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</tbody>
</table>

Instances when drugs are sent back to Referral Centers or central pharmacy: changes regimen, patient defaults, patient dies, patient finishes treatment, expired drugs, and damaged drugs

Sent by: ________________________________

(Signature and Printed Name/Date)
Annex 19: MDR-TB Screening Form

(FORM 17)

MDR-TB Screening Form (FORM 17)

Referral Centre that patient was screened at: _____________________________ Date: ___________________________ (mm/dd/yy)

I. Demographics

<table>
<thead>
<tr>
<th>Name:</th>
<th>Surname ______________________________________________________</th>
<th>Second Name ____________________________________________________________</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Sex:</th>
<th>Male / Female</th>
<th>Date of birth: ______________________</th>
<th>Age: ______</th>
<th>Place of birth: __________________________</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Marital status:</th>
<th>Single</th>
<th>Married</th>
<th>Living together</th>
<th>Widowed</th>
<th>Divorced/ legally separated</th>
<th>(Circle one)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Patient Phone no.:</th>
<th>_____________________________</th>
<th>NOK Phone no: __________________________</th>
</tr>
</thead>
</table>

Permanent address:

<table>
<thead>
<tr>
<th>District:</th>
<th>_____________________________</th>
<th>County:</th>
<th>Subcounty:</th>
<th>LC1 Zone: _________________</th>
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</thead>
</table>

(give details on how to reach the address e.g. plot No. if applicable)

<table>
<thead>
<tr>
<th>Occupation:</th>
<th>_________________________________________________________________________________________________________</th>
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</table>

<table>
<thead>
<tr>
<th>Spouse name:</th>
<th>_____________________________</th>
<th>Address/ Contact no: __________________________</th>
<th>Relationship:</th>
<th>_____________________________</th>
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</table>

Person to notify in case of emergency: _____________________________ Relationship: _____________________________

<table>
<thead>
<tr>
<th>Address:</th>
<th>_____________________________</th>
<th>Tel. No.: __________________________</th>
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(give details on how to reach the address e.g. Plot No if applicable)

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<tr>
<th>Referred by:</th>
<th>_____________________________________________________________</th>
<th>(Names)</th>
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<table>
<thead>
<tr>
<th>Address:</th>
<th>_____________________________________________________________</th>
<th>Phone no: __________________________</th>
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</thead>
</table>

Number of household contacts: _____________________________ 0 - 5 years old, _____________________________ 6 - 15 yrs old; _____________________________ More than 15 yrs old:

II. History of Present Illness

Chief Complaint/s:

Review of Symptom/s | Duration in month/s | Comments
|-------------------|---------------------|------------------|

| Cough | | |
| Fever | | |
| Back/ chest pain | | |
| Hemoptysis | | |
| Weight loss | | |
| Night sweats | | |

Other symptoms

<table>
<thead>
<tr>
<th>Dyspnea at rest</th>
<th>Duration in month/s</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea on exertion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pedal edema</td>
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</tbody>
</table>
### III. Past Medical History:

**History of Previous TB Treatment:** (from first to last)

<table>
<thead>
<tr>
<th>Start Date (mm/dd/yy yy)</th>
<th>Regimen Initials</th>
<th>Duration (months)</th>
<th>Treatment Facility</th>
<th>DOT (Y/N)</th>
<th>Outcome</th>
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**Exposure to Active TB:**

- No [ ] Ye [ ] If Yes [ ]
- MDR [ ] Non MDR/Unknown [ ]

**Other Diseases**

- Diabetes Mellitus [ ]
  - Duration: ______ year(s)
  - Comments: (drugs)

- Cancer [ ]
  - Duration: ______ year(s)

- HIV infection/AIDS [ ]
  - Duration: ______ year(s)
  - Status: ________________________________

- Kidney disease [ ]
  - Duration: ______ year(s)

- Lung disease [ ]
  - Duration: ______ year(s)

- Epilepsy [ ]
  - Duration: ______ year(s)

- Psychiatric condition [ ]
  - Duration: ______ year(s)

- Others [ ]
  - Duration: ______ year(s)

**Allergy:**

**Drugs:**

1. ________________________________
2. ________________________________

**Type of Reaction:**

**Concomitant treatments/Duration:**

**Previous surgery:**

- None [ ]
- Pneumonectomy/ Lobectomy [ ]
- Others, specify __________________________

**Date of surgery:** ______ /___/___

**Other complications:** __________________________

**Obstetrics and Gynecologic History**

<table>
<thead>
<tr>
<th>Last Pregnant: /<em><strong>/</strong></em> (mm/dd/yyyy)</th>
<th>Gravida ____</th>
<th>Parity ____</th>
<th>Ages (<strong><strong>-</strong></strong>-____)</th>
</tr>
</thead>
</table>

**Contraceptive use (for women only):**

- No [ ] Yes [ ]

**Comments:**

___________________________________________________________________________________
___________________________________________________________________________________
IV. Substance Use:

- Tobacco/Cigarettes: [ ] Current [ ] Past [ ] Never
- Alcohol: [ ] Current [ ] Past [ ] Never
- Drug Abuse: [ ] Current [ ] Past [ ] Never

Number per day x yrs

Amount per day x yrs

V. Physical examination and laboratory procedures:

Vital Signs: PR/HR: _______/min, BP: _______/_____/mmHg,
Temp: _______ Celsius, Weight: _______ Kg,
RR at rest: _______/min, Height: _______ cm

System Examination:

<table>
<thead>
<tr>
<th>0 = Not done</th>
<th>1 = Normal</th>
<th>2 = Abnormal</th>
</tr>
</thead>
</table>

General Health:
Skin:
BCG scar:
Oropharynx:
Cardiovascular:
Thorax & Lungs:
Use of accessory muscles:
Abdomen:
Genito-Urinary:
Extremities:
Neurological:
Lymph Nodes:
Endocrine:

VI. Laboratory procedures:

1. TB Smear, Culture and DST results from other laboratory

<table>
<thead>
<tr>
<th>Type of Sample</th>
<th>Results</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>______________</td>
<td>______________</td>
<td><em><strong>/</strong></em>/___</td>
</tr>
<tr>
<td>______________</td>
<td>______________</td>
<td><em><strong>/</strong></em>/___</td>
</tr>
<tr>
<td>______________</td>
<td>______________</td>
<td><em><strong>/</strong></em>/___</td>
</tr>
</tbody>
</table>

2. Other Laboratory Results:

Liver Function Tests
Renal Function Tests
Pathology_________________________________________________  
Other___________________________________________________

3. Chest X-ray:  Date: _____/_______/_______

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Right Lung</td>
<td>Left Lung</td>
</tr>
</tbody>
</table>

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - Normal</td>
<td>7 - Fibrosis</td>
</tr>
<tr>
<td>1 - Cavitary</td>
<td>8 - Fibrothax</td>
</tr>
<tr>
<td>2 - Infiltrate</td>
<td>9 - Bullae</td>
</tr>
<tr>
<td>3 - Nodule</td>
<td>10 - Pleural effusion</td>
</tr>
<tr>
<td>4 - Military TB</td>
<td>11 - Pneumothorax</td>
</tr>
<tr>
<td>5 - Intrathoracic lymphadenopathy</td>
<td>12 - Bronchiectasis</td>
</tr>
<tr>
<td>6 - Endobronchial spread</td>
<td>13 - Atelectasis</td>
</tr>
<tr>
<td>14 - Consolidation</td>
<td>15 - Mass</td>
</tr>
</tbody>
</table>

VII. Assessment:

☐ Not TB  
☐ MDR-TB suspect  
☐ New  
☐ Retreatment

If new or retreatment, tick any of the following risk factors for MDR-TB

- Category 1 Failure (New Patient Regimen)  
- Category 2 Failure (Retreatment Regimen)  
- Return after Default  
- Relapse  
- Symptomatic contact of MDRTB patient / Suspected MDRTB patient

☐ Disease other than TB, specify ________________________________

VIII. Plan:

☐ Start TB treatment, specify regimen: ________________________________

☐ Prescribe ancillary drugs or drugs for comorbidity, or symptomatic treatment

☐ Others:

Attending MD: ________________________________ Date: ________________________________
| Facility Name: | MDR-TB TREATMENT ATTENDANCE | Months | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | Remarks |
Annex 21: DR-TB PATIENT REFERRAL/TRANSFER FORM

(FORM 19)

<table>
<thead>
<tr>
<th>DR-TB PATIENT REFERRAL/TRANSFER FORM (FORM 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Complete top part in duplicate)</td>
</tr>
</tbody>
</table>

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

- Referred to be registered and begin TB treatment
- Transfer (registered patient is moving) begin TB treatment
- Referral for ____________________

Name/address of referring/transferring facility_________________________________

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

Name of patient __________________________ Age _______ Sex: M ☐ F ☐

Address (if moving, future address) _______________________________________

Name and address of contact person for patient ____________________________________

Diagnosis* _____________________________________________________________

Unit DR-TB No.*  ___________________ Date treatment started* _________________

Treatment Regimen:* _________________________________________________________

Treatment category: ☐ New patient* ☐ Retreatment ☐ MDR-TB

Other drugs patient is receiving _______________________________________________

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

Signature ______________________ Position ______________ Date of Referral / transfer ____________

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

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

Name of facility _____________________________________________________________

District ___________________________ Date __________________________

Name of patient __________________________ DR-TB No. _______________

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

Signature __________________________ Position _________________________

Send this part back to referring/transferring facility as soon as patient has reported.
Annex 22: NTLP DR-TB treatment approval Form

(FORM 20)

DR-TB Panel treatment approval form for MDR-TB Patients

District: ____________________
Referral Center: ____________________
Patient Name: ____________________
District TB registration number: ____________________
Date of district TB registration: ____________________
Address: ____________________ Sex: M____F_____ Age:_____ Date of Birth:___________

TB Disease Site: Pulmonary / Extra-pulmonary / Both (circle appropriately)

If extra-pulmonary, specific site: ____________________
Resistance type: (MDR-TB / XDR-TB/ poly resistant)___________________
Confirmed or suspected? ____________________

Date of DR-TB Panel treatment approval ____________________

Patient registration Group: New , Relapse, Treatment after default, Treatment after failure of new patient treatment regimen, Treatment after failure of retreatment regimen, Transfer in, Other__________ (specify)

Remarks or basis for approval by DR-TB review panel:

______________________________________________________________________________________

The following MDR-TB patient has been approved for DR-TB TREATMENT on the following regimen ____________________

Signature and Date_______________________________ (DR-TB Panel chairperson)

Notify DTLS/ZTLS about the approval and complete section below once patient is enrolled on treatment.

District: ____________________ Referral Center:________________________

Patient Name: ____________________

MDR-TB registration Number: ____________________

Date of MDR-TB registration: ____________________

District TB registration number: ____________________

Date of district TB registration: ____________________

Signature and Date_______________________________ (DR-TB Referral facility staff)