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FOREWORD

The emergence of drug resistance tuberculosis, particularly MDR-TB has become a major public health problem in a number of countries and an obstacle to the global TB control efforts. Nearly half a million cases of MDR-TB emerge every year, but only 3% of them get treatment globally and 110,000 die annually.

Ethiopia is one of the 27 high burden M(X)DR-TB countries ranking 15th with more than 5000 estimated MDR-TB patients annually. The estimated Multi Drug Resistance cases are 1.6% and 12% among all new and previously treated TB cases respectively. How ever the extent of drug resistance TB is not well known and the treatment of patients is not yet started. Currently there are many Drug Susceptibility Test (DST) confirmed back log patients registered by the National Referral Laboratories.

MDR-TB is essentially man made that emerges as a result of poor TB control including poor supply-management and quality of anti TB drugs, improper/inadequate treatment which is further fuelled by high prevalence of human immunodeficiency virus in the country. This rapidly changing terrain requires health officials and providers to respond with novel and effective responses.

Cognizant of the magnitude of DR-TB the Federal Ministry of Health of Ethiopia established MDR-TB TWG and conducted a series of consultative meeting with the support of TBCAP/USAID. Both local experts as well as internationally renowned consultants have contributed their valuable inputs in the preparation of MDR-TB guidelines.

Finally I would like to express my gratitude to all who contributed, in particular TBCAP/USAID for the valuable technical and financial inputs it provided for the development of this document.

Yibeltal Assefa, MD, MSc
Director, Medical Service Directorate, FMoH
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<th>Description</th>
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<td>3TC</td>
<td>Lamivudine</td>
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<tr>
<td>ABC</td>
<td>Abacavir</td>
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<tr>
<td>ACSM</td>
<td>Advocacy, Communication and Social Mobilization</td>
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<tr>
<td>AFASS</td>
<td>Acceptable, Feasible, Affordable, Sustainable and Safe</td>
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<tr>
<td>AIDS</td>
<td>Acquired Immuno-Deficiency Syndrome</td>
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<td>Am</td>
<td>Amikacin</td>
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<td>ART</td>
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<td>DST</td>
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<td>GFATM</td>
<td>Global Fund to fight against AIDS, Tuberculosis and Malaria</td>
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<td>H</td>
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<td>HIV</td>
<td>Human Immuno-Deficiency Virus</td>
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<td>HRD</td>
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<td>HS/DP</td>
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<td>IEC</td>
<td>Information, Education and Communication</td>
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<td>IPT</td>
<td>Isoniazide Preventive Therapy</td>
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<tr>
<td>Km</td>
<td>Kanamycin</td>
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<tr>
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<td>Levofoxacin</td>
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<td>LM IS</td>
<td>Logistics Management Information System</td>
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<td>LPA</td>
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<td>MDR TB TWG</td>
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<td>Mfx</td>
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<td>NNRTI</td>
<td>Non-Nucleoside Reverse Transcriptase Inhibitor</td>
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<td>Nucleoside Reverse Transcriptase Inhibitor</td>
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<td>Para-aminosalicylic acid</td>
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<td>PFSA</td>
<td>Pharmaceuticals Fund and Supply Agency</td>
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<tr>
<td>PI</td>
<td>Protease Inhibitor</td>
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<tr>
<td>PITC</td>
<td>Provider Initiated HIV Testing and Counselling</td>
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<td>PLHIV</td>
<td>People living with HIV</td>
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<td>PTB</td>
<td>Pulmonary Tuberculosis</td>
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<tr>
<td>R</td>
<td>Rifampicin</td>
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<td>Abbr.</td>
<td>Description</td>
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<tr>
<td>RHB</td>
<td>Regional Health Bureau</td>
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<td>RRL</td>
<td>Regional Reference Laboratory</td>
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<td>S</td>
<td>Streptomycin</td>
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<td>SCC</td>
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<tr>
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<td>Supra National Reference Laboratory</td>
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<td>TB</td>
<td>Tuberculosis</td>
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<td>TB/HIV</td>
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<td>TDF</td>
<td>Tenofovir</td>
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<tr>
<td>TLCP</td>
<td>Tuberculosis &amp; Leprosy Control Program of FMoH</td>
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<tr>
<td>TLCT</td>
<td>Tuberculosis &amp; Leprosy Control Team of FMoH</td>
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<tr>
<td>TSH</td>
<td>Thyroid Stimulating Hormone</td>
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<tr>
<td>UVGI</td>
<td>Ultra-Violet Germicidal Irradiation</td>
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<tr>
<td>VCT</td>
<td>Voluntary HIV Counseling and Testing</td>
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<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>XDR-TB</td>
<td>Extensively Drug Resistance TB</td>
</tr>
<tr>
<td>Z</td>
<td>Pyrazinamide</td>
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<tr>
<td>ZDV</td>
<td>Zidovudine</td>
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CHAPTER ONE: BACKGROUND

1.1TB Control Program

The Government of Ethiopia has recognized that ill health of a fast growing population is an impediment to social and economic development. Henceforth it has chosen to strengthen primary health care as a strategic approach to address major gaps in public health.

Tuberculosis has long been recognized as a major public health problem since the 1950s. Since then control efforts have been initiated by establishment of sanatoria and later strengthened by implementation of DOTS Strategy in the 1990s. However tuberculosis still remains a major problem in Ethiopia, and driven by the HIV/AIDS epidemic, has become a formidable threat, calling for concerted efforts by all partners. At present, tuberculosis control strategy in Ethiopia, relies on WHO recommended Stop TB Strategy and it has been implemented in the country since 2006.

According to the 2008 WHO TB report, Ethiopia ranks 7th in the list of the world’s 22 high burden countries for TB with incidence estimated at 379/100,000 for all forms of TB and 168/100,000 for smear positive tuberculosis. The Annual Risk of TB Infection (ARI) is estimated at 2.2%.

According to the Ministry of Health hospital statistics data, tuberculosis is one of the leading causes of morbidity, the fourth cause of hospital admission, and the second cause of hospital death in Ethiopia. Tuberculosis contributes to 4.6% of all Ethiopian Disability Adjusted Life years (DALYs). TB mortality rate is estimated at 84 per 100,000 populations per year. The high rates of chronic malnutrition, widespread poverty, overcrowding, and high sero-prevalence of HIV infection (the adult HIV prevalence is estimated at 2.2 % for 2008) has created an environment which made tuberculosis a formidable threat in Ethiopia.

Of the total cases notified in 2007/2008 (141,589), 138,650 (98%) were new cases (MOH TB Leprosy annual report 2000EC). Out of the 138,650 new cases, 40,744 (29%) are pulmonary smear positive cases. The treatment success rate of smear positive PTB patients has been substantially improving over the years and it was 87% according to WHO annual TB reports of 2008. The case detection rate of new pulmonary positive cases was 34% for 2007/08,. TB affects all age groups and both sexes.

The general framework of TB control is provided by a National Strategic Plan 2007-2010. The strategic plan is in accordance with the main strategies and focus of the WHO’s Stop TB Strategy.

A National TB Control Program is in charge of all TB control activities since 1997, backed by standard implementation guidelines following the DOTS principles. At central level, the tuberculosis control program (NTP) comprises of a Tuberculosis and Leprosy Control Team (TLCT) under the Diseases Prevention and Control Department of the Federal Ministry of Health (FMoH) of Ethiopia. Task and responsibilities at each level of the Federal state and the Regions are clearly defined: At operational levels, tuberculosis control activities are integrated in the general health care delivery system. DOTS has been implemented in almost all districts in Ethiopia, and is being scaled up to nearly 100% of the 143 hospitals and 699 health centres that are providing TB diagnostic and treatment services.
National standardized guidelines (for TB control and care, for TB laboratory, for TB-HIV implementation), HMIS registers and reporting forms for TB and TB-HIV, have been updated in 2008 and are currently in use. Drugs are provided only through the national procurement and distribution system and drug protocols are in accordance with internationally recognized standards. According to the MOH health indicator 1999EC, the primary health service coverage is 86.7%. Gradually, the rapidly expanding private health sector is being involved in TB control activities. Non-for-profit NGO are already participating in the DOTS implementation in many districts and agreements are being developed with private practitioners and clinics willing to provide comprehensive TB diagnosis and treatment. Over one hundred private facilities are already participating in the national TB Control Program and a bold expansion plan intends to enrol nearly 400 additional facilities within three years.

At peripheral level, TB is integrated within the general health care services. The laboratory technicians and OPD health workers are most of the time also in charge of other health activities.

TB control among vulnerable population like prisoners, refugees and other congregated settings are among the priority areas in the national TB program as stated in the present Strategic Plan. TB in prison is integrated in the National TB Prevention and Control Program. However, there is not yet systematic medical screening on admission. And prisoners contagious for tuberculosis may still be put into a crowded cell and the nutritional status of prisoners is quite often unsatisfactory.

**1.2 Drug Resistant and Multi-Drug Resistant TB situation in Ethiopia**

Drug-resistant TB is a man-made problem, largely being the consequence of human error as a result of individual or combination of factors related to management of drug supply, patient management, prescription of chemotherapy, and patient adherence. Poor infection control practice also has been identified as a major contributing factor for the spread of MDR-TB. MDR-TB, like drug susceptible TB, is a droplet infection and is easily transmitted to immunocompromised individuals, especially to the HIV infected. Experiences in other African countries showed that transmission among HIV infected individuals results in MDR-TB micro-epidemics, both nosocomial and societal. More recently the emergence of Extensively Drug-Resistant TB (XDR-TB) has added to the complexity of TB care and treatment.

According to WHO 2008 report, in Ethiopia, 5825 MDR-TB cases (4964 among newly diagnosed and 861 among previously treated TB cases) were estimated to have occurred in 2006. According to the anti-TB drug resistance survey conducted nationwide in 2005 (EHNRI/FMOH), among 804 newly diagnosed TB cases 1.6% were found to be infected with MDR TB. The rate of MDR TB among specimens from 76 previously treated TB cases was 11.8%. The same survey reported that, TB with Isoniazid mono-resistance and Rifampicin mono-resistance, among new TB cases, was 2% and 1%, respectively. Notified prevalence of mono-resistance to INH and Rifampicin among previously treated TB cases was 5.3% and 1.3%, respectively. Based on the prevalence rate from the survey and TB case notification in 2007/08 (2000 EC), the magnitude of MDR TB in Ethiopia was estimated to be 997 cases, which includes 651 and 346 MDR-TB cases among newly diagnosed and re-treatment cases respectively.
The treatment of MDR-TB with second line drugs is long, complex and costly, and has a considerable rate of adverse effects. Recent progress has been made globally in improving policy environment and advances in TB drug development to embark on trials of MDR TB treatment to identify optimal treatment protocol for drug resistant Tuberculosis.

The TB Control Program in Ethiopia has not yet started managing MDR-TB cases with efficient second line protocols. No second line anti-TB drugs are available in Ethiopia, with the exception of fluoroquinolone, and the importation of any drug is as per the regulation of the National Drug Administration and Control Authority (DACA). But there are evidences that a small cohort of patients were treated in some facilities in Addis Ababa.

The Ethiopian Government has identified MDR-TB as one of priority public health problem and it is committed to initiate comprehensive treatment for MDR-TB cases in the country. The FMOH has also clearly endorsed the mechanism of single procurement and controlled use of the second line anti-TB drugs, when they are available, after acceptance from the Green Light Committee (GLC) and stands for this unique channel. Management of MDR TB will be an integral component of the NTP and will be implemented through the existing health care delivery system.

The FMOH has set up a specific group of specialists to provide expert advices on MDR TB issues, and has drafted a Plan of Action for MDR TB control and care. The MDR TB Technical Working Group was established by the FMOH and other partners to support MDR TB activities in the country. It was the decision of the FMOH to develop clinical and program management guideline for DR-TB with the technical support of MDR TB Technical Working Group and technical assistance of well renowned international experts in the area, before launching case management in public institutions under close supervision and follow up of National TB control program.

1.3 Implementation Framework

It is of utmost importance that drug-resistant TB be prevented by rigorous adherence to the principles of the National Tuberculosis Control Programme (the DOTS strategy) and by patiently and consistently building partnerships with patients, their families and communities to cure TB at the first attempt (see components of DOTS strategy below).

The MDR-TB program of the NTP needs to be tailored to the national and regional situation, based on MDR-TB epidemiology, infra-structure and taking into account cultural specifics. Therefore, the programmatic Management of MDR-TB in Ethiopia is introduced in a step-wise manner, starting with a Green Light Committee approved pilot program in Addis Ababa. However, a rapid expansion to the regions is foreseen and preparation is underway.

The framework approach to management of drug-resistant TB, summarized below includes five essential components which form the basis of every national TB control programme that includes detection and treatment of drug-resistant TB. Details of the implementation steps and roles and responsibilities are illustrated in the program design section (see chapter two).

This guideline will serve as a guiding document for both clinical and programmatic management of MDR TB in the country. It can be used as a major national reference for TB program managers, clinicians, laboratory personnel, pharmacists as well as other concerned stakeholders.
Five components of the DOTS Strategy as applied to drug resistant TB

1. Sustained political commitment
   ♦ Addressing the factors leading to the emergence of MDR-TB
   ♦ Long-term investment of staff and resources
   ♦ Coordination of efforts between communities, local governments and international agencies
   ♦ A well-functioning DOTS programme

2. Appropriate case-finding strategy including quality-assured culture and drug susceptibility testing (DST)
   ♦ Rational triage of patients into DST and the DR-TB control programme
   ♦ Relationship with supranational TB reference laboratory

3. Appropriate treatment strategies that use second-line drugs under proper case management conditions
   ♦ Rational treatment design (evidence-based)
   ♦ DOT
   ♦ Monitoring and management of adverse effects
   ♦ Properly trained human resources

4. Uninterrupted supply of quality-assured second-line anti-tuberculosis drugs

5. Recording and reporting system designed for drug resistance-TB control programs that enables performance monitoring and evaluation of treatment outcomes
CHAPTER TWO: PROGRAMATIC DESIGN AND MANAGEMENT OF MDR-TB

This chapter outlines the programmatic and technical components of MDR-TB management and summarizes the general set up of the program at the initial treatment site and subsequent scale up to other sites in the country. Technical details for each programmatic component are described in the respective chapters.

2.1 Pilot Phase

During the initial phase, management of MDR-TB cases will be coordinated by St. Peter TB Specialized Hospital in the city of Addis Ababa. This pilot phase aims at building clinical expertise and experience with managing the second line anti-TB drugs and their side effects. This will enable St. Peter TB Specialized Hospital to function as a national referral centre in case of severe side effects and as a centre of excellence and training during the scaling up to the regions.

St. Peter TB Specialised Hospital was selected for several reasons: It has long history of TB management, at present it is the only Federal hospital specialised in TB care which has given the staff ample experience in TB management, and its setting is spacious enough to accommodate renovation and building of new structures. The staff has also taken the initiative to treat some patients with MDR-medications imported privately. St Peter Hospital also has a good collaborative partnership with the Ethiopian Health and Nutrition Research Institute (EHNRI) housing the National Reference Laboratory (NRL). In the future St. Peter Hospital will rely on its own laboratory, as funding has been secured for installing a first-class TB laboratory with solid and liquid medium culture facilities and Line-Probe Assay capacity. EHNRI will continue to play a crucial role, supporting the establishment of regional laboratories and ensuring periodic external quality control.

Case-finding is based on systematic drug-susceptibility testing for all TB suspects in Addis Ababa, who meet the MDR-TB suspect criteria (see Chapter 3 on case-finding strategies). This means that all health centre staff will be instructed and trained to identify and refer MDR-TB suspects to the designated laboratory for free TB culture and DST.

Decision for starting a patient on MDR treatment will be taken individually by a medical committee set up in St. Peter TB Specialised Hospital using transparent agreed upon criteria.

2.2 Treatment Delivery

The treatment delivery system involves three phases: These will be explained as relevant for Addis Ababa, however during roll-out the same principles should apply to all sites.

2.2.1 Phase I – Intensive phase inpatient
Every patient with confirmed MDR-TB requires initial hospitalization for 4 to 8 weeks at St. Peter TB Specialized Hospital in-patients department. The major criteria for discharge include sputum smear conversion, the patient’s general condition and a satisfactory follow-up plan.

Responsibilities of St Peter Hospital:

- During this phase all responsibilities for patient care lie with St Peter Hospital with the support from NTP.
• To guarantee proper contact tracing St Peter Hospital will ensure it happens during the pilot stage and assist in making the diagnosis in children under five years.
• Submit quarterly reports of MDR-TB enrolment to NTP.

Responsibilities of treatment follow-up centres:
• All sites referring patients for MDR-TB treatment should perform active contact tracing and can refer children to next higher level for definite diagnosis, if sufficient capacity is not available.

2.2.2 Phase II - Intensive phase out-patient
After completion of inpatient treatment the MDR-TB patients will be transferred for ambulatory treatment to be supervised by one of the health centers in Addis Ababa, which are selected as MDR-TB treatment sites. This phase of treatment lasts until completion of the intensive phase of treatment where patient should take daily injections. The number of the treatment sites for this second phase will be decided based on agreed criteria including the distribution of patients in the city, capacity and experience of the health centres in TB treatment and its manageability by the capacity of St Peter Hospital for ongoing support. The major aim of this second phase decentralized treatment is to bring the service as close as possible to patient’s dwelling in order to minimize travel time and loss to follow-up. Among the treatment sites in Addis Ababa, it is recommended to include one site for uniformed services to facilitate access for the army, police and prisons. An out-patient treatment site within St Peter Hospital can serve as model treatment centre.

Responsibilities of St Peter Hospital:
• with NTP and RHB select the appropriate health centres to be designated as MDR-TB treatment sites
• Coordinate training of staff of the selected treatment sites on management of MDR-TB (including clinical management, drug supply management, recording and reporting of MDR-TB data). It is imperative that the orientation should involve the clinicians, nurses, pharmacists/druggists and data managers.
• Together with staff of treatment site, provide orientation to patients to prepare them for ambulatory treatment
• Supply the treatment site with second line anti-TB drugs for the particular patient in collaboration with responsible drug agency
• Conduct regular supportive supervision and mentoring to the treatment sites initially monthly and later on quarterly basis to ensure quality performance.
• Maintain a database of all MDR-TB patients started on treatment and after patients are transferred to treatment sites it should be updated on monthly basis based on the reports from the treatment site.
• Conduct clinical and laboratory assessment of transferred patients on monthly basis in line with the treatment monitoring plan

Responsibility of treatment follow-up centres:
• Appoint the designated TB-person to functions as lead person for conducting treatment follow-up for MDR-TB patients (including daily administration of injectables and DOT).
• Attend training on MDR-TB
• Keep a record of MDR-TB patients on follow up and submit monthly report to St Peter Hospital
- Tracing of non-adherers
- Patient education and counselling

**Responsibility of the patient:**
- Take medications as prescribed under direct observation of the health workers
- Visit St Peter Hospital for monthly clinical and laboratory check-up
- Practice infection control measures at household level
- Supply reliable contact details and update them when changed

2.2.3 Phase III – Continuation Phase
This is the time when the continuation phase of treatment is provided under directed supervision of a family DOT provider. This is done under close supportive supervision of the treatment health centre. The decision to transfer the treatment of patients to household level will be dependent on:
- Patient’s willingness
- Availability of responsible family DOT provider
- Capacity of the family DOT provider
- Patients clinical condition
- Sputum culture conversion which determines duration of the injection phase
- Successful completion of all injections

All family DOT providers will receive a detailed orientation and health education on administration of treatment, early recognition of side effects and how to support the patient. A smooth cross referral system will be established between all three treatment delivery levels, ensuring easy referral in case of side effects and any other related problems.

**Responsibilities of St Peter Hospital:**
- Supply the treatment site with three months dose of second line anti-TB drugs for the particular patient
  - For initial 45 patients it is recommended to also have monthly check-up at St Peter Hospital
- Continue with support to health centre as outlined under intensive phase.
- Submit quarterly report of treatment outcomes to NTP

**Responsibility of health centres:**
- Select appropriate DOT provider at family or community level
- Provide orientation to the DOT provider
- Supply the patient with monthly dose of drugs
- Provide DOT services to patients where no other DOT provider available
- Conduct monthly check-up of patient condition and treatment adherence
- Submit report to St Peter Hospital about follow-up information
- Tracing of non-adherers

**Responsibility of DOT provider:**
- Attend the orientation at treatment site
- Observe when the patient swallows her/his daily dose of second line anti-TB treatment
- Report the patient adherence information to the health centre on monthly basis
• Refer patient to treatment centre in case of recognizing side effects

Responsibility of the patient:
• Take medications as prescribed under direct observation of the family or community DOT provider
• Visit the treatment centre on monthly basis for regular check up

2.3 Prisons and the ‘Difficult to Treat

TB control among vulnerable populations like those in prison is among the priority areas in the national TB program as stated in the present National Strategic Plan. TB management in prisons is integrated in the National TB Prevention and Control Program. There is a TB program and functional comprehensive HIV services within the National Defence Force, Police Force and prison administration sectors (collectively known as the Uniformed Forces), which is working closely with the NTP and NGO partners. These sectors will continue to be priority as far as MDR-TB is concerned, as the risk of TB transmission is believed to be higher in such types of congregate settings. The support includes: training of health care workers in the area of TB and MDR TB, improving case finding of TB through introduction of fluorescent microscopic diagnosis of TB, establishing and strengthening referral linkage of TB patients to HIV related services including ART and improving infection control practices.

Prisoners and military personnel will be priority targets in the treatment of MDR TB through early identification of TB cases, screening for the presence of drug-resistant TB by sending patient/sample to the national referral laboratory for DST and referral of those found to have resistant TB to MDR TB treatment site. Moreover, one uniformed health facility in Addis Ababa will be chosen as one of the centres for MDR TB treatment follow-up site so that military and prisoner patients who started treatment at St Peter Hospital will complete the rest of the treatment at this site.

Priority will also be given to establish linkage to another MDR-facility should a prisoner on MDR-treatment be discharged from prison.

2.4 Treatment Regimens and Follow-up

Treatment regimens are standardized to facilitate training, procurement and allow for rapid scale-up. However, reserve second line drugs will be added to the standardized regimens in case of documented resistance to one of the key second line drugs: kanamycin or levofloxacin and in case of side-effects or pregnancy. See Chapter 4 Management of MDR-TB Cases for detail.

Since there is budget allocated for the purchase of second line drugs through GLC/GDF mechanism, drugs as well as all concomitant medications needed to treat side effects( as stipulated in the guidelines) will be provided to the patients free of charge, as it is the case for all TB patients. Diagnostic services for MDR suspects such as DST and CXR will also be free.

2.5 Infection Control

Infection control is a crucial element of any MDR-TB programme and serves to prevent transmission to both health care workers and patients/visitors in the health facility involved.
Administrative and environmental measures to allow proper ventilation as well as personal protection measures including use of N-95 masks are key interventions. These measures will be ensured in all health facilities involved in MDR-TB care. See Chapter 9 Infection Control of DR-TB for detail.

2.6 MDR-TB Treatment Scale Up Plan

A scale-up of treatment sites has to follow the pilot phase to facilitate access to all regions. The MOH has developed a set of criteria, for selection of sites for treatment of MDR-TB during the scale up, which includes the following items. The initial four are essential, the others are preferable:

- Political commitment as shown by active participation of decision makers
- Professional commitment in the ‘designated’ hospital
- Good record of quality of care, especially on DOTS
- Linkage to a laboratory with required capacity and with external quality assurance (EQA)
- Infra-structure including capacity to hospitalize and infection control
- Adequate pool of well trained human resource
- Burden of MDR-TB cases in the catchment area
- Geographic location
- Linkage to a medical faculty

With the assistance of international partners the EHNRI /MOH is in the process of upgrading five regional laboratories in the country, introducing both solid- and liquid culture, DST and Line Probe Assay. In Addis Ababa a second state of the art laboratory is being established in St Peter Hospital.

In addition, clinicians in the designated sites will be trained to build their capacity during the pilot programme in Addis Ababa. St Peter Hospital will play an important role in transferring knowledge and skill to their regional colleagues.

The MOH/NTP plan a stepwise approach, in which the regional MDR-TB treatment sites first enrol patients from their immediate catchment areas before expanding within the region. Thus, the regional sites will first build experience with systematic MDR-TB case-finding, treatment and case-holding before involving health facilities at far away distance. During the initial phase in regional roll-out, mobile teams composed of doctors/health officers, nurses or druggists from an existing site will visit, mentor and support new sites on a regular basis until the new site can manage independently. The mobile team visiting newly emerging sites should provide on site training and help them with the setting up of appropriate system and even assist with consulting patients for the initial phase.

The scale-up is planned to be implemented stepwise, around a timetable as suggested in Table 2-1.

This scheme helps with planning of scale-up like laboratory services, training and supportive supervisions. However, it might neither reflect the capacity of health services nor the need of patients accurately and may be revised over time. Patients should have the choice to make use of the site closest to their home.
### Table 2-1. National plan to scale up MDR-TB treatment in Ethiopia

<table>
<thead>
<tr>
<th>Phase</th>
<th>Service site</th>
<th>Target population</th>
<th>Timeframe</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Pilot phase – Addis Ababa (St Peter Hospital)</td>
<td>Addis Ababa</td>
<td>2009</td>
<td></td>
</tr>
<tr>
<td>2nd step – Regional hospitals*</td>
<td>Mekelle</td>
<td>Tigray, Afar</td>
<td>2009/11**</td>
</tr>
<tr>
<td></td>
<td>Bahirdar</td>
<td>Amhara, Benishangul-Gumuz</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adama</td>
<td>South Oromia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hawasa</td>
<td>SNNPR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Harrar</td>
<td>Harrar, Diredawa, Somali</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Jimma</td>
<td>West Oromia, Gambella</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Addis Ababa (Alert, Minelik II)</td>
<td>Addis Ababa</td>
<td></td>
</tr>
<tr>
<td>3rd step – Addis Ababa (federal/ regional hospitals (6))</td>
<td>Addis Ababa</td>
<td>2011</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- addition of 2 regional centres</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- expansion within the regions</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>surrounding the regional centres</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Selection of proposed sites was based on the criteria listed above, and final selection will done in consultation with regional health bureaus

** Timeframe could be revised depending on experience during 1st and 2nd phase of implementation

### 2.7 MDR-TB Case Enrolment Plan

A total of 45 patients will be enrolled for the initial program at St. Peter Hospital in 2009; in the second year of implementation, additional 200 patients at St. Peter Hospital and about 50 at each of the eight new sites making a total of approximately 600 patients, will be enrolled for treatment. The actual enrolment of patients at each site will be determined based on local data and caseload of the respective site.

However, experiences in other countries show that the dynamics of MDR-TB case-finding and enrolment are difficult to predict. Depending on the pace of enrolment of newly diagnosed MDR-TB patients and the ability to trace backlog cases, the numbers mentioned above may represent either over- or underestimates. Therefore, the MOH prefers a flexible approach, based on continuous monitoring of MDR-TB case-load dynamics. This stringent monitoring will allow for timely applications for cohort expansion with the Green Light Committee, and thus prevent shortage of drugs when MDR-diagnosis exceeds expectations.

All these treatments will be funded by GFATM. Performance assessment, epidemiological surveillance data, and annual evaluation will be done by NTP and by the Green Light Committee.

### 2.8 MDR support system within the TB control Program

#### 2.8.1 Central level support

To lead the national MDR program, the NTP assigns a fulltime MDR-TB focal person or, resource permitting, organizes a unit within NTP. This will be supported by a technical group of experts, composed of few members of MDR-TB TWG, especially from partner organizations committed to support MDR-TB program. Due to the long list of activities that need to be carried out for the proper implementation of an MDR TB program, it is considered to hire more staff dedicated mainly to facilitate and coordinate MDR TB activities in order to assure the quality and maintain momentum of implementation. The National Reference Laboratory at EHRNI will be in charge of performing second-line drugs DST as needed and provide support to St. Peter TB Specialised Hospital laboratory and other regional laboratories.
The operational MDR TWG is a very important part of the organization, and will be continuously involved in supporting MDR TB activities in the country.

2.8.2 Site level support

A team of trained health care workers composed of Medical Doctors (internist, paediatricians, general practitioners) nurses, pharmacists, laboratory technicians and social worker will be established as MDR team members in each selected MDR hospital. A special data management system will also be organized at hospital level and other support staff will be assigned as per the need. The team will assume full responsibility of DR-TB management at health facility level which includes patient management mainly with the following tasks:

- receiving referred patients,
- suspect investigation,
- confirmation of the diagnosis of DR-TB,
- decision to start treatment,
- determine the treatment follow-up mechanism,
- organizing patient support schemes (nutritional, psychological, social, financial…)
- decide to discharge patients from treatment .

Apart from these clinical responsibilities, the team serve as hospital level wing of the national MDR-TB program unit.

During the initial phase, St. Peter Hospital will be responsible for providing medical care to the MDR-TB patients. All patients will be hospitalized until smear conversion and longer if their clinical status requires so. During intensive and continuation phases the patients will be monitored at least on a monthly basis by the selected group of clinicians responsible for the clinical management of MDR-TB patients. The laboratory at this hospital will be responsible for monthly smear follow up and cultures according to protocol. The medical team of St Peter Hospital will also take charge of patients’ follow up during the continuation phase, check for side effects and retrieve non-adherers.

An important component of the treatment is to assure that nutritional support will be provided to the patients during the course of the in-patient phase of treatment at the hospital level. Existing resources (GFATM) and additional support will be mobilized accordingly.

2.9 Data management system

The national level data management (entry, analysis, dissemination) will be done by the central data management unit at NTP and additional logistic and human resource should be arranged to handle the extra load of data due to MDR. MDR-TB recording and reporting will be linked to the DOTS recording and reporting system and be developed in line with international recommendations.

At time of the initial pilot program, the staff that is currently responsible for collecting and entering TB data at the St Peter Hospital should be responsible for entering data related to MDR-TB. All the relevant data of the cohort of patients recorded at the St Peter Hospital will be sent quarterly to the central unit at NTP. A database must be created in order to allow for appropriate patient follow-up. The template for MDR-TB database will be developed by NTP and circulated to MDR-TB management sites.
Laboratory information (smear, culture and DST results) and cohort-data should be sent to the national reference laboratory and NTP both in hard and electronic copies.

2.10 Referral Network

The referral network involves referral and cross-referral between the five diagnostic and treatment delivery levels involved and therefore requires clear procedures and lines of responsibilities;

1. Health centres identifying and referring MDR-TB suspects to the reference laboratory
2. The reference laboratory (performing culture and DST)
3. The St Peter Hospital (and in future other treatment initiation sites) for initial evaluation, hospitalization and monthly follow up
4. Selected treatment centres in Addis Ababa (health centres and in the prison/military system); conducting treatment follow-up
5. Family DOT providers, supervising treatment

Obviously, a strong cross-referral and communication system amongst these 5 levels is of utmost importance. Therefore, clear Standard Operations Procedures (SOPs) and job-descriptions and standard referral forms are developed and incorporated within targeted training for staff and family members involved. In addition level 4 and 5 will be provided with contact details of experts in St Peter Hospital, so they can easily communicate and refer in case of severe side effects or any other treatment related reason.

During the hospitalization phase, the treatment center in Addis Ababa will be contacted and a family DOT supporter identified. Before discharge of the patient from the hospital, the designated treatment center staff and the family DOT supporter will visit the patient in the hospital and receive instructions by the MDR-TB treating team.

In any case, when patients are transferred back to the peripheral treatment centre, a detailed patient report outlining the complete management and follow-up needs will be sent with the patient (and a copy retained at referral centre) together with a one-month supply of medication. The peripheral site manager will be informed before the transfer takes place.

If considered necessary, a health extension worker or a community health promoter will be involved to assist in DOT and providing health education as well as moral and social support through the rest of the treatment.

During the first year St Peters Hospital will only treat patients from Addis Ababa, in order to facilitate case-holding and supportive supervision of treatment and management of side effects.

2.11 Transporting MDR-TB Suspect

When a person suspected of MDR TB moves from a referring health unit to the MDR treatment site, all the necessary precaution should be applied to minimize the risk of exposing other susceptible individuals. The most important safety measure is ensuring adequate infection prevention measures from the time the person is identified as suspect until he/she is received at the MDR treatment site. The first and perhaps easiest way of minimizing transmission to others is to advice the patient on cough etiquette (cover mouth and nose while
coughing and sneezing, avoid spitting…), and provide the patient with surgical masks or cloth to help him cover mouth and nose. The patient should preferably stay isolated in a ventilated room with windows and doors open as much as possible. The patient should move to the treatment site as immediately as possible.

Logistics permitting, it is advisable the MDR suspect to use a vehicle separate from other susceptible individuals. However, in most cases where separate transportation is a logistical difficulty, the patient can share transportation with other people but with maximum precaution to minimize risk of transmission (seating arrangement, ventilation, cough etiquette…).

After reaching the treatment site the MDR-TB suspect deserves to benefit from fast track mechanism where he/she should not spend long in waiting queue and should get the service as immediately as possible. Staff in the MDR treatment site will be trained to prioritize coughing patients and facilitate immediate services for those referred as MDR suspects.

2.12 Drug Management System

2.12.1 Authority to prescribe and deliver MDR-TB treatment

The recommended approach of prescribing second line anti-TB drugs for treatment of MDR-TB rests on qualified physicians who have special training on management of MDR–TB. The treatment involves a team approach whereby trained nurses will take charge of daily administration of injectables and oral drugs. As Ethiopia is experiencing a severe shortage of trained professional medical staff and yet has to ensure scale-up of quality MDR-TB services, it is crucial to task-shift responsibilities to lower level health care cadres while regulating appropriate use of MDR-TB drugs. At the time of scale up to peripheral health facilities, the appropriate level of health workers who take responsibility of prescribing second line drugs will be identified by the MDR program. A key criterion of certifying health workers will remain to be special training on MDR-TB management. Thus Health Officers should be empowered to initiate MDR-treatment and specifically trained nurses to provide follow-up treatment. Transfer of trained personnel should be limited, as MDR-TB management is complex and expansion of a safe MDR-TB programme may be seriously hampered by rotation of qualified staff.

2.12.2 Drug importation:

The importation of second line anti-TB drugs will follow the similar channel like the first line anti-TB drugs. Which means NTP will coordinate with relevant sections of ministry of health and DACA to hold a facilitation and regulatory role.

2.12.3 Drug distribution

Distribution of second line anti-TB drugs to MDR-TB treatment sites will be the responsibility of NTP in similar pattern with its first line anti-TB drugs distribution channel.

At time of initial phase sufficient quantity of drugs, for treating planned number of MDR TB cases, will be made available at St. Peter Hospital and then after refill will be done on quarterly basis depending on report of utilization. Then for patients who completed in-patient treatment, a one-month supply will be provided to the treatment center earmarked for the particular patient
transferred to that centre. The drug supply from St Peter Hospital to treatment center will be handled by the pharmacy unit of St Peter Hospital that delivers the drugs to the pharmacy unit of the treatment center using its own transportation. Regular refill will follow utilization report.

A strict reporting mechanism will be established in the drug management system which enables track these valuable medications. It will be ensured that treatment sites keep a buffer stock of second line anti-TB drugs and related supplies, which can cover the transition period between successive distributions.

At time of scale up, the experience obtained from St Peter Hospital will be replicated to new sites with the necessary adjustment based on the findings of the pilot assessment. For more detail see Chapter 11 management of second-line Anti-Tuberculosis drugs.
CHAPTER THREE: CASE FINDING STRATEGIES

This chapter describes the risks groups that are more vulnerable to develop MDR-TB, of which it provides special emphasis on high risk groups that are given priority attention in the national case finding strategy. It highlights on the recommended case finding procedures. Besides, it deals with contact tracing and approach to symptomatic paediatric and adult contacts of patients with M(X)DR-TB.

3.1 Risk Groups for MDR-TB

Like most TB control programmes, the NTP does not have the resources to perform culture and drug susceptibility testing (DST) for all TB patients. Also, with the current levels of M(X) DR-TB, testing every patient’s strain is not cost-effective or necessary. DST should therefore be used selectively for patients at risk for MDR-TB based on a careful history. Specific elements of the history that suggest an increased risk for drug resistance are described in Table 3.1. These factors are not necessarily indications for routine culture and DST. The risk categories identified by the National TB control programme are indicated below in Section 3.3.1.

Table 3.1. Risk factors for MDR-TB

<table>
<thead>
<tr>
<th>RISK FACTOR</th>
<th>COMMENTS</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 are sputum positive at the end of a re-treatment regimen. These patients have the highest MDR-TB rates of any other group, often greater than 80%.</td>
</tr>
<tr>
<td>Exposure to a known MDR-TB case</td>
<td>Most studies have shown close contacts of MDR-TB patients to have very high rates of MDR-TB.</td>
</tr>
<tr>
<td>Failure of first-line Short Course Chemotherapy (SCC)</td>
<td>Failures for SCC are patients who, while on treatment, are sputum smear positive at 5 months or later during the course of treatment. Not all patients who fail a regimen have MDR-TB and the percentage may depend on a number of factors, including whether DOT was used throughout the treatment course.</td>
</tr>
<tr>
<td>Relapse or Return after default</td>
<td>Erratic drug intake or early relapse may point to possible MDR-TB. Relapses with in the first six months post-treatment may have similar MDR-TB rates as failures.</td>
</tr>
<tr>
<td>History of using poor or unknown quality TB drugs</td>
<td>The percentage of MDR-TB caused by use of poor quality drugs is unknown but considered significant.</td>
</tr>
<tr>
<td>Treatment in poorly-performing control programmes that operate poorly</td>
<td>These are usually non-DOTS programs or DOTS programs with poor patient adherence or drug management and distribution systems.</td>
</tr>
</tbody>
</table>
Co-morbid conditions associated with malabsorption or rapid transit diarrhoea

Malabsorption may result in selective low serum drug levels and may occur in either HIV-negative or -positive patients.

| HIV | Numerous MDR-TB outbreaks have been documented in HIV+ individuals, and XDR-TB outbreaks in HIV+ individuals have been documented in South Africa |

### 3.2 Case Definition & Classification of DR-TB

Drug resistant 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.

Case definitions for DR-TB are used for the following reasons:
- To allow proper patient registration and epidemiological notification;
- To facilitate case allocation to appropriate treatment categories;
- To facilitate case evaluation according to site, bacteriology and treatment history;
- To evaluate programme performance through cohort analyses.

Four different categories of drug resistance have been established:
- **Mono-resistance**: Resistance to one anti-tuberculosis drug.
- **Poly-resistance**: Resistance to more than one anti-tuberculosis drug, other than both isoniazid and rifampicin.
- **Multidrug-resistance (MDR)**: Resistance to at least isoniazid and rifampicin.
- **Extensive drug-resistance (XDR)**: Resistance to any fluoroquinolone, and at least one of the three injectable second-line drugs (capreomycin, kanamycin, and amikacin), in addition to MDR.

### 3.2.1 Classification based on treatment history

History of previous TB treatment allows categorization of M(X) DR-TB patients into three categories. These categories are essential for epidemiological monitoring of the M(X) DR-TB epidemic and help to identify patients that may be at risk. M(X) DR-TB patient categories are as follows:

- **New category IV**: Patients with no history of previous TB or M(X)DR-TB treatment
- **Category IV previously treated with 1st line**: Patients with a history of previous TB treatment, ie. with first-line TB drugs
- **Category IV previously treated with 2nd line**: Patients with a history of previous M(X) DR-TB treatment, ie. with second-line TB drugs
3.2.2 Classification based on site of disease

This is where the site of disease is used to classify cases according to pulmonary or extra-pulmonary involvement:

- **Pulmonary M(X) DR-TB** refers to disease involving the lung parenchyma.
- **Extra-pulmonary M(X) DR-TB** refers to organs other than the lungs.

A patient with both pulmonary and extra-pulmonary M(X) DR-TB constitutes a case of pulmonary M(X) DR-TB.

The case definition for extra-pulmonary M(X) DR-TB in several sites depends on the site with the most severe form of disease.

### 3.3 Case-finding Strategies and Procedures for MDR-TB

#### 3.3.1 Priority risk groups

DST plays a key role in strategies for case-finding of drug-resistant TB. Procedures for collecting and managing specimens for culture and DST are described in Chapter four. Different techniques, limitations, quality assurance requirements and other issues of culture and DST are also addressed in that Chapter.

Routine culture and DST should be done for the following groups of individuals:

- Failure after re-treatment
- Symptomatic close contacts of confirmed MDR-TB patients
- Symptomatic individuals from known high-risk groups [e.g. health care workers]
- Treatment failure
- New TB patients who remain sputum smear-positive after two months (new cases) or three months (re-treatment cases) of first-line treatment
- Re-treatment TB patients [e.g., return after default, relapse]

High risk group in this manual is to refer mainly health care workers considering their substantial risk of exposure to M(X)DR-TB cases. When the national capacity in diagnosing and managing MDR-TB grows other high-risk groups like prisoners, HIV infected individuals, etc. might be included in the list of high risk group in the future.

Previously treated TB patients may have had DST results in the past that may no longer reflect the resistant pattern of the strain they have at the time of MDR-TB enrolment. DST should therefore be performed again in all patients who have received TB treatment since the date of their last DST result.

The international standard of care is to start MDR-TB treatment only on laboratory confirmation. Patients on first-line anti-TB treatment improving clinically and radiologically, but with a drug-resistant laboratory report, should be considered to have an abnormal laboratory report and investigated again, rather than be changed to MDR-TB treatment.

Paediatric cases require adjustments in diagnostic criteria and treatment. Young children in particular may not be able to produce sputum specimens. More aggressive measures such as
nasal gastric aspiration may be considered. Children should not be excluded from MDR-TB treatment solely because sputum specimens are not available; children with active TB who are close contacts of patients with MDR-TB can be started on regimens designed for MDR-TB treatment. (See chapter seven on more detail on the diagnostic work-up and management of children and MDR-TB contacts).

3.3.2 Case finding procedure

All health care facilities involved in the diagnosis and treatment of tuberculosis will:
- Identify TB patients meeting the MDR suspect criteria
- Advice those patients on the need for culture and DST
- Refer the patients to the designated reference laboratories for free DST
- Ensure that patients are managed in accordance with the national TB Leprosy manual until the result of the DST becomes available
- Collect result of DST from the laboratory
- Arrange for referral of patients to St Peter’s Hospital in case of MDR-TB (during the pilot phase in Addis Ababa). Referrals need to be planned with the MDR-TB focal person at the hospital.

3.3.3 Case finding strategies for XDR-TB

All strains identified as MDR-TB should routinely undergo second-line DST in order to determine whether XDR-TB is present. In specific instances, eg. when screening contacts of known XDR-TB patients, DST of second-line drugs should be requested together with DST of first-line. DST of second-line drugs and how to interpret the results are discussed in Chapter four.

3.4 Contact Tracing and Management

Opportunities to halt the spread of drug resistant mycobacterium in communities and to treat M(X)DR-TB in a timely fashion are often missed. The main reasons are lack of investigation of contacts of M(X)DR-TB patients, failure to ask patients presenting with active TB disease about any history of exposure to M(X)DR-TB, and lack of access by national treatment programmes to second-line regimens and/or access to DST.

3.4.1 Case definition of contacts

Close contacts of M(X)DR-TB patients are defined as people in the same household, or spending many hours a day together with the patient in same indoor living space including a hospital ward.

Persons with recently acquired M. tuberculosis infection are at relatively high risk of developing active disease: in general, 5-10% of infected immune-competent persons will develop active disease in their lifetime. The risk of developing TB is highest during the first two years following infection, after which this risk declines markedly. Child contacts of M(X)DR-TB patients (especially those under two years of age) are therefore at increased risk.

The most potent factors that increases the probability that adults infected with M(X)DR-TB will develop active disease is impaired immunity, such as that seen in HIV infection. It
should be remembered, however, that there are many other medical causes of impaired immunity: Malnutrition, congenital syndromes, certain haematological disease, endocrine diseases, renal diseases, diabetes mellitus, and people on immune-suppressive drugs or radiotherapy.

The available data indicate that close contacts of M(X)DR-TB patients who develop active TB most commonly have drug-resistant disease.

3.4.2 Active contact tracing

Active contact tracing in Ethiopia is presently performed poorly in most settings. However, in the case of M(X)DR-TB special efforts need to be made to trace all household contacts those are:

- All children under five years of age irrespective of developing symptoms
- Adults and children above five years old known to be HIV infected irrespective of developing symptoms
- All symptomatic adults and children above five years old

When an adult in a ward is identified with M(X)DR-TB, patients who have shared the ward should also be screened. All other newly diagnosed TB patients, known HIV patients with cough and other symptomatic patients in the ward should get a rapid and full DST.

If the source patient works in nursery schools, all children need to be screened. If the source patient is in another institution (school, factory, prison, etc) the respective TBL coordinator (regional, zonal, district or facility) should be notified. And a decision needs to be taken on resources and relevant interventions in consultation with the regional M(X)DR-TB focal person.

To simplify follow up of contacts a standard form can be used, see Annex VII.

3.4.2.1 Approach to symptomatic adult contacts of a patient with M(X)DR-TB

All close contacts of M(X)DR-TB cases should be identified through contact tracing and evaluated for active TB by a health-care provider. If the contact appears to have active TB disease, culture with DST on two samples and a rapid DST should be performed. If DST is not available, or while DST results are awaited, an empirical regimen based either on the resistance pattern of the index case or on the most common resistance pattern in the community may be started. If the laboratory result proves non-MDR-TB, the patient should be managed according to national protocol for management of susceptible TB using first line anti-TB drugs. Delay in the diagnosis of M(X)DR-TB and start of appropriate treatment can lead to increased morbidity and mortality as well as unchecked amplification and spread of drug-resistant strains of TB.

When investigation of a symptomatic adult contact yields no conclusive evidence of active TB, a trial of a broad-spectrum antibiotic that is not active against TB such as amoxicillin or doxycycline can be used. If the patient continues to have symptoms, sputum induction or bronchoscopy for smear and culture should be considered if available. Where these diagnostic tools are not available or the results are not conclusive, a diagnosis should be based on the clinical information at hand. If the initial investigation is not suggestive of active
TB but the contact remains symptomatic, repeat physical examinations, smears and cultures should be performed monthly with repeat chest X-ray as needed.

3.4.2.2 Approach to symptomatic paediatric contacts of patients with M(X)DR-TB

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

The diagnosis of TB is more difficult in children than in adults. Symptoms of TB in young children can be non-specific, e.g. chronic cough or wheeze, failure to thrive and recurrent fevers. Bacteriological confirmation may be difficult to obtain because of the inability of children to generate a sputum sample, as well as the paucibacillary nature of paediatric TB and the increased likelihood of extrapulmonary TB in children. While every effort should be made to establish a bacteriological diagnosis (and thus obtain DST) in a child with suspected M(X)DR-TB, in practice paediatric cases are often not confirmed bacteriologically.
3.4.3 Management of adult contacts of a patient with M(X)DR-TB

Identify all close contacts at risk of M(X)DR TB (people with HIV or malnourished or with TB symptoms)

Evaluate at health facility for active TB

TB suspected or confirmed

Send two sputum samples for Line Probe Assay and possibly DST

Line Probe Assay shows resistance to HR, lab immediately processes second sample for full DST

Start MDR regimen based on DST of source patient and re-evaluate patients when DST is available

TB Excluded

Educate about infection control. No chemoprophylaxis indicated. Follow up after one month if still symptomatic.

3.4.4 Symptomatic paediatric household contacts should receive:

- An evaluation by a physician, including history and physical examination.
- Sputum smear and culture: if the child is aged under 5 years or cannot expectorate sputum, induced sputum or gastric aspiration for smear and culture should be considered. Sputum induction may be preferable to gastric aspiration since the yield of one sample from sputum induction with chest percussion has been shown to be equivalent to three gastric aspirates. Another alternative is performing a string test which is better tolerated than a naso-gastric tube.
- A chest X-ray examination (computerized tomography is helpful especially in documenting hilar adenopathy but this is often not available).
- Obtaining sample from an extrapulmonary site e.g. FNA
- DST. If the diagnosis is not conclusive the symptomatic child can be treated with a broad-spectrum antibiotic that is not active against TB, such as amoxicillin. The child should be followed closely, with evaluations including smear test and culture on samples from induced sputum or gastric aspirates, or sputum samples whenever
possible, as well as chest X-rays. If a child’s clinical condition is highly suggestive of TB, or progressively deteriorates, empirical therapy designed according to the DST pattern of the strain from the index case can be started.

Children with M(X)DR-TB who are incorrectly entered in short-course chemotherapy may suffer significant and protracted morbidity as a result of ongoing active disease, with the possibility of lifelong disability or even death. Because children with TB may never become sputum smear-positive, it is reasonable to initiate empirical M(X)DR-TB therapy based on the DST pattern of the contact. If DST of the contact is not available therapy can be started based on standard second line regimen.

3.4.5 Chemoprophylaxis of contacts of M(X)DR-TB index cases

So far, the only chemoprophylaxis regimens studied extensively are isoniazid and, to a lesser extent, rifampicin. M(X)DR-TB by definition is resistant to both of these drugs, hence it is unlikely that use of these drugs to treat latent infection caused by an M(X)DR-TB strain will prevent the development of active TB disease.

Close contacts of M(X)DR-TB patients should have 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 M(X)DR-TB is recommended. On the basis of the currently available evidence, it is not recommend to use second-line drugs for chemoprophylaxis in M(X)DR-TB contacts.
CHAPTER FOUR: LABORATORY ASPECTS OF DR- TB

4.1 Improving Laboratory Infrastructure

Setting up laboratory for M(X) DR-TB is essential for two major reasons: First, to identify M(X) DR-TB isolates early before they spread widely to contacts in health care facilities and the community. This is crucial in our setting because of the high rate of HIV and the high risk of a rapid progression to TB following infection in the immune-compromised. Second is to guide the management of MDR-TB. This can be done determining the susceptibility pattern of TB germs to TB.

Optimal management of drug-resistant TB and establishment of DR-TB programme require:
1. Mycobacterial laboratory service: should provide good quality direct TB smear, TB culture and differentiation of clinically relevant species (M. tuberculosis, M. bovis, a few non tuberculous mycobacteria). Capacity to do or refer for sensitivity testing for at least to the two key drugs isoniazid (H) and rifampicin (R).
2. Molecular laboratory services: should be able to perform line probe assay to identify rapidly drug sensitivity to isoniazid (H) and rifampicin (R).
3. Clinical laboratory services: should provide basic laboratory service including basic hematology, biochemistry, serology and urine analysis, which are required for the proper evaluation and monitoring of patients.
4. A comprehensive routine system of internal quality control and external quality assurance which comprises of
   • Networking and relationship with national/supranational TB reference laboratory
   • Good infection control measures
   • Internal method to document the validity of results

Thus, the Ethiopian Health and Nutritional Research Institute (EHNRI) functioning as national reference laboratory in Ethiopia is in the process of upgrading its regional laboratory capacity with the help of international partners. For the first round, the TB laboratories of EHNRI and St. Peter TB Specialised Hospital in Addis Ababa will be developed to be able to perform line probe assay testing, TB culture and DST and comply with the appropriate safety standards. Almost simultaneously the regional laboratories at Adama, Bahirdar, Harrar, Hawassa and Mekelle will be renovated to ensure bio-safety and equipped to perform line probe assay testing and TB cultures. Once these laboratories are fully functioning it is considered to expand this capacity to further laboratories in the future.

4.2 Laboratory Diagnosis of M(X)DR

4.2.1 Microscopy

Despite recent advances in mycobiology, early laboratory diagnosis of tuberculosis still relies on the examination of stained smears. Microscopy of sputum smears makes a particularly important contribution since the technique is simple, inexpensive and detects those cases of pulmonary tuberculosis and MDR-TB that are most infectious. However AFB sputum smear microscopy cannot also distinguish between viable and non-viable bacilli. For example, even with adequate treatment, specimens from M(X)DR-TB patients may remain smear positive for a short period after they become culture negative suggesting that the bacilli are non-viable. Therefore, its utility for monitoring patient infectiousness and response to treatment is limited.
Direct smear microscopy using acid-fast stains is generally considered to be a relatively insensitive diagnostic procedure, with the reported sensitivity ranging from 25% to 65% when compared to culture. Although direct microscopy is the cornerstone of diagnosis of drug-susceptible pulmonary TB, routine microscopy cannot distinguish between drug-susceptible and drug-resistant *M. tuberculosis*, or between different species of mycobacteria.

The main uses of microscopy for drug-resistant TB are therefore limited to assessing the infectiousness of patients, and confirming that microbes growing on (or in) artificial media are mycobacteria rather than contaminants.

4.2.2 Line Probe Assay

Line Probe Assay is a new test that makes use of molecular technology and can identify the presence or absence of specific mutations on the genes of TB bacilli. As it is known which mutations are responsible for TB bacilli to be resistant to isoniazid (H) and rifampicin (R) this is a rapid and accurate test to identify MDR-TB.

If a patient with TB is smear positive the sputum contains enough bacilli to perform line probe assay directly on the sputum and MDR-TB can be proved on the same day. However if the sputum is smear negative it is recommended to perform TB culture first (preferably in liquid medium) and once growth of TB can be demonstrated this isolate can be used to perform the line probe assay.

The benefits of this test are the high degree of sensitivity (98%) and specificity (99%), the speed of the test and the potential to perform high volumes of test per day. A draw back is that it needs well-trained committed staff with a high level of quality assurance.

If funds and infrastructure allow, the LPA can be used as a screening test in MDR-TB suspects, thus limiting the need for time-consuming and labor intensive conventional culture and DST. However, before switching to this approach the validity of LPA in that specific setting needs to be documented.

4.2.3 Culture

Mycobacterial culture provides definitive diagnosis of tuberculosis but compared with other bacteria, which typically reproduce within minutes, *Mycobacterium tuberculosis* multiplies extremely slowly (generation time 18-24 hours). So results of TB culture may take several weeks. Mycobacteria also require special culture media. A variety of suitable culture media (Loweinstein Jensen, Middle Brook and different liquid media) are available.

Quality of laboratory processing is of crucial importance. Delays in specimen transport, excessively harsh or insufficient decontamination, poor-quality culture media inadequate laboratory technique or incorrect incubation temperature can adversely affect the culture yield. Specimens should also be kept at 4°C during transportation or refrigerated if delays are anticipated. Those good practices assures higher yield and also reduces contamination of samples.

Laboratory results should always be correlated with the patient’s clinical condition, and investigations repeated if necessary. False negative cultures may result from inadequate specimens, delayed transport of the specimens to the laboratory and poor laboratory
techniques, or insufficient incubation period. Incubation should ideally be done for eight weeks, since some tubercle bacilli may require extended periods of incubation. Using liquid media can reduce this time to 40 days, but is more expensive, and increases risk of contamination and nosocomial TB transmission in the laboratory.

Laboratory errors, such as mislabelling or cross-contamination between specimens during aerosol-producing procedures, may also lead to false results.

**Identification of M. tuberculosis**

After culture it is necessary to perform a test for species identification. Several tests are available. In countries with a high burden of TB like Ethiopia, most mycobacterial isolates are *M. tuberculosis*. The prevalence of mycobacteria other than TB (MOTT) varies from country to country and can be more common in patients infected with the HIV. Unless the species is confirmed as *M. tuberculosis*, mycobacterial isolates appearing resistant to Anti-TB drugs on culture may represent not drug-resistant TB but infection with MOTT.

As a minimum, laboratories supporting DR-TB control programme should be able to carry out the basic biochemical tests useful for identifying *M. tuberculosis* like; niacin, catalase and nitrate or have rapid serological test-kits like Cappila.

4.2.4 Culture and Drug Susceptibility Testing

Drug susceptibility testing (DST) is required to make a definitive diagnosis of M(X) DR-TB and guide clinical management. DST can be done by several methods. One molecular method (line probe assay) has already been discussed. These tests provide a genotypic result. Previously the only method was phenotypical testing, where *M. tuberculosis* was cultured and DST performed by mixing specific concentrations of TB drugs with the culture medium and comparing the rates of growth of the TB culture. And is essential in Research has shown that the three most commonly used techniques (proportion, absolute concentration and resistance ratio) are all highly reliable and reproducible, and that the results do not differ according to the method used. The national TB reference laboratory in Ethiopia is proficient at the proportion method and will continue to use this method.

4.2.4.1 Limitations of phenotypic DST

Different anti-TB drugs have different ‘critical concentrations’ (the breakpoint between calling a strain resistant or susceptible), which also depend on the culture medium used for DST. DST for first-line anti-TB drugs has been thoroughly studied and consensus reached on appropriate methodologies, critical drug concentrations, and reliability and reproducibility of testing. The accuracy of DST (performed under optimal circumstances) varies with the drug tested: it is most accurate for rifampicin and isoniazid and less accurate for streptomycin and ethambutol. As DST for pyrazinamide requires a different (acidic) culture medium and lacks accuracy, it is seldom performed.

The clinician needs to understand the limitations of DST and interpret the results accordingly. DST provides an indication of the likelihood of a drug being effective. Drugs for which the DST results show susceptibility are more likely to be effective than drugs for which the DST shows resistance. When discrepant results are obtained, they must be interpreted with care by a clinician experienced in drug-resistant TB.
However the biggest drawback of phenotypic DST is the long time lag between sputum sent until a result is known. This often leads to delay of effective treatment allowing the TB patient to deteriorate, even die and increased the potential for further transmission of MDR-TB. Several techniques are being studied to speed up results but the only one widely approved is using automated equipment with liquid medium that increases the cost significantly.

4.2.4.2 Algorithm for performing DST

The national TB reference laboratory must decide which drugs to test and in what sequence to test them, according to the strategy for designing MDR treatment regimens.

Reliable DST for at least isoniazid and rifampicin is a prerequisite for MDR-TB control programmes. Some programmes may choose to have these tests done at a distant laboratory until a local laboratory is able to do them. In Ethiopia it was decided to use line probe assay at five regional laboratories to rapidly determine rifampicin and isoniazide resistance. This way the standard MDR regimen can be initiated almost immediately. Ideally liquid culture facilities should also be available at regional level to enhance the possibility to test smear negative sputum samples with line probe assay. Once MDR-TB has been established by line probe assay, smear positive sputum samples (or cultured isolates where smear negative) can be sent to a central laboratory (EHNRI or St Peter Hospital) in Addis Ababa for full phenotypic DST.

As resistance to rifampicin and isoniazide is already established it would theoretically not be necessary to repeat phenotypic DST for these two drugs, however for quality control purposes it was decided to initially repeat these. Phenotypic DST for ethambutol (E), kanamycin (Km) and ofloxacin (Ofx) will also be performed to guide the clinician on the presence of further resistance and the need to adapt the MDR regimen. As there is cross resistance between kanamycin (Km) and amikacin (Am), kanamycin can be used during DST testing even if amikacin is used as part of the MDR treatment regimen. The same principle applies to the quinolones where ofloxacin can be used in the laboratory as surrogate marker for quinolone resistance irrespective of which quinolone is used in the MDR treatment regimen. As there is little experience in Ethiopia performing DST test for second-line TB drugs (kanamycin and ofloxacin) initially all samples will also be sent to a supra-national TB laboratory in the Netherlands to confirm the quality of the tests performed in Ethiopia.
4.3 Infection Control and Bio-safety in the Laboratory

Transmission of TB – including drug-resistant forms such as MDR-TB – is a recognized risk for laboratory workers.

A well-maintained, properly functioning Class II B biological safety cabinet is an indispensable piece of laboratory equipment for the performance of culture and DST of specimens from MDR-TB patients. The biological safety cabinet Class II B serves for personnel as well as product protection. However the most expensive and sophisticated biological safety cabinet will not provide protection against MDR-TB infection that result from poor laboratory technique. Respirators designed to protect the wearer from tiny (1–5
µm) airborne infectious droplets should always be used. Instructions on safe handling of specimens should be scrupulously followed. Ultraviolet light is useful for surface contamination and may be applied to radiate the work area when it is not in use.

Training in laboratory procedures and strict adherence to safety measures should be accompanied by a simple surveillance programme whereby the health status of laboratory staff is monitored regularly. Laboratory workers who choose to disclose their HIV-positive status should be offered safer work responsibilities and should be discouraged from working with MDR-TB specimens. Pregnant women should be reassigned until after childbirth and lactation.

### 4.4 Quality Control and Assurance

A comprehensive quality control/quality assurance programme will be developed in each TB laboratory to ensure the accuracy, reliability and reproducibility of the results obtained and to ensure bio-safety. Quality control/quality assurance procedures should be performed regularly as an integral part of laboratory operations.

The procedures for internal quality control must be performed during each test round to verify that the test is working correctly. The external quality control comprises procedures that are carried out by an external organization to test that the results are correct. Quality assurance is control for the entire process of testing, covering all stages from collection of sputum until the result is reported back to the treatment facility.

A manual of standard operating procedures (SOPs) should be available for each of the laboratory operations. Standard operating procedures must be based on precisely how the procedure is carried out in the particular laboratory and incorporate any minor modifications that may have been made when compared with a standard protocol. The manual should also describe a protocol for regular maintenance checks and repairs of equipment.

The network of supranational TB reference laboratories provides quality assurance through validation of drug susceptibility data. For this purpose EHNRI has establish formal links with a supranational TB reference laboratory in The Netherlands to help ensure the quality of laboratory services and validation of DST results. Usually, an external quality assurance programme with a supranational TB reference laboratory consists of:

- An initial assessment visit by the laboratory
- Proficiency testing with a panel of coded isolates and then
- Periodic rechecking of isolates obtained within the programme.

This system has been negotiated by EHNRI with the supranational TB reference laboratory and it was decided to double check all second-line DST results for backlog DSTs performed and for the 45 patients in the initial treatment cohort.

### 4.5 Organization and Development of the Laboratory Network

The laboratory network has a pyramidal structure based on a large number of periphery laboratories (level I) accessible to all TB suspects and patients, a moderate number of regional referral (level II) laboratories located in mid-sized population centers and health facilities and a few (or even a single) apex national referral (level III) laboratories at the
national level. **Table 4.1** describes the different functions and responsibilities of the three different levels of laboratory services.

The TB control programme must have a rapid, reliable means of collecting and transferring specimens, cultures and information from the patient and physician to each level of the laboratory service and for returning the results. There should be no financial barrier between the patient and the TB diagnostic services at any of these three levels. A country or region can control and prevent drug-resistant TB only if infectious patients are detected and cured without delay. Ready access to microscopy for acid-fast bacilli (AFB), line probe assay, culture and DST free of charge to the patient are essential elements of political commitment to control drug-resistant TB.
Table 4.1: Functions and responsibilities of the different levels of laboratory

<table>
<thead>
<tr>
<th>LEVEL I – The peripheral (often health facility) laboratory</th>
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<tbody>
<tr>
<td>■ Receipt of specimens</td>
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<tr>
<td>■ Preparation and staining of smears</td>
</tr>
<tr>
<td>■ Ziehl-Neelsen microscopy and recording of results</td>
</tr>
<tr>
<td>■ Dispatch of results</td>
</tr>
<tr>
<td>■ Maintenance of laboratory register</td>
</tr>
<tr>
<td>■ Cleaning and maintenance of equipment</td>
</tr>
<tr>
<td>■ Management of reagents and laboratory supplies</td>
</tr>
<tr>
<td>■ Internal quality control</td>
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<table>
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<tr>
<th>LEVEL II - The accredited regional laboratory</th>
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<tbody>
<tr>
<td>■ All the functions of Level I laboratory</td>
</tr>
<tr>
<td>■ Fluorescence microscopy (optional)</td>
</tr>
<tr>
<td>■ Line Probe Assay</td>
</tr>
<tr>
<td>■ Digestion and decontamination of specimens</td>
</tr>
<tr>
<td>■ Culture and identification of M. tuberculosis</td>
</tr>
<tr>
<td>■ Training of microscopists</td>
</tr>
<tr>
<td>■ Support to and supervision of peripheral-level staff with respect to microscopy</td>
</tr>
<tr>
<td>■ Preparation and distribution of reagents for microscopy in peripheral laboratories</td>
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<tr>
<td>■ Quality improvement and proficiency testing of microscopy at peripheral laboratories</td>
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<table>
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<tr>
<th>LEVEL III - The central (national reference) laboratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>■ All the functions of Level I and II laboratories</td>
</tr>
<tr>
<td>■ Line Probe Assay</td>
</tr>
<tr>
<td>■ DST of M. tuberculosis isolates</td>
</tr>
<tr>
<td>■ Identification of mycobacteria other than M. tuberculosis</td>
</tr>
<tr>
<td>■ Technical control of and repair services for laboratory equipment</td>
</tr>
<tr>
<td>■ Updating and dissemination of laboratory manuals, including guidelines on diagnostic methods, on care and maintenance of equipment and on quality assurance</td>
</tr>
<tr>
<td>■ Close collaboration with the central level of the national TB control programme</td>
</tr>
<tr>
<td>■ Supervision of intermediate laboratories regarding bacteriological methods and their support (particularly training and supervision) to the peripheral laboratories</td>
</tr>
<tr>
<td>■ Quality assurance of microscopy and culture performed at intermediate laboratories</td>
</tr>
<tr>
<td>■ Training of intermediate-level laboratory staff</td>
</tr>
<tr>
<td>■ Organization of anti-tuberculosis drug resistance surveillance</td>
</tr>
<tr>
<td>■ Operational and applied research relating to the laboratory network, coordinated with the requirements and needs of national TB control programme</td>
</tr>
</tbody>
</table>
CHAPTER FIVE: MANAGEMENT OF M(X)DR-TB CASES

5.1 Preparation of the Patient before Treatment

Each MDR-TB treatment site (e.g. St Peter’s Hospital) will have a multidisciplinary committee. The committee is accountable to review the details of each patient, including previous history, DST results and concurrent illnesses, and make a decision in relation to treatment with Category IV regimen and its individualization. If the committee decides on treatment, the patient is initially admitted to the designated in-patient facilities of the MDR-TB treatment site for minimum of 1 month, usually until smear conversion or longer if the clinical status requires so.

Patients will be registered according to the standardised case definitions. A treatment card will be opened and treatment initiated. Prior to starting therapy all patients should be appropriately informed and understand implications of treatment. They should also receive appropriate health education and answers to their questions need to be provided in detail. Family should be involved since the beginning of the treatment preparation.

### Basic information to be provided for MDR-TB patient:
- Nature of his/her illness (TB and MDR-TB)
- Mechanism of transmission; the need to evaluate contacts, and prevention of further spread.
- Implication if there is concomitant HIV infection, importance of HIV testing
- Medications and duration of treatment; expected follow up visits including necessary laboratory and radiological monitoring.
- Information not to share medications, appropriate storage of medications.
- All services related to the treatment of his/her illness (MDR TB) are free.
- Importance of adherence to treatment until completion.
- Expected drug side effects and their manifestations; availability of treatment to treat side effects, whom to report when such manifestations occur.
- Expectations from the treatment.
- Responsibilities of the patient including providing information on accurate contact details. Rights of the patient in relation to his/her treatment.
- Where to contact for his social problems and any information needed (provide information brochure).
- Implications if there is pregnancy and contraception (for women in child bearing age)

Patients with MDR-TB face the prospect of lengthy and often unpleasant treatment as well as the real possibility of premature death. Therefore, education, counselling and emotional support are particularly important. Proper early counselling will also help to ensure good adherence to the treatment regimen and increase the likelihood of a successful outcome.

HIV counselling and testing will be provided if the HIV status is not already known. HIV treatment will follow the national ART guideline.
Summary of activities in preparation of MDR-TB patients before initiating treatment:

- Classification and registration including details of patient address and contact person.
- Initial clinical evaluation by history taking and physical examination
- Baseline laboratory and radiological investigations
- HIV Testing and Counselling (PITC)
- Patient Education
- Contact tracing

5.2 Initial Patient Evaluation

The required initial pre-treatment investigation includes a thorough medical history and physical examination. The recommended initial laboratory evaluations are shown in the table 5.3. The initial evaluation serves to establish a baseline and may identify patients who are at increased risk of adverse effects or poor outcomes. The treatment monitoring and the management of adverse effects may have to be more intensive in patients with pre-existing 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 MDR-TB when these conditions exist is described in Chapter Six. Methods of avoiding pregnancy during treatment for women of childbearing age should be discussed. Symptoms like nausea and vomiting need to be aggressively treated before the initiation of treatment.

5.3 Definition of Terms Regarding Treatment Strategies in Ethiopia:

- **Standardized treatment**: Drug Resistance Survey (DRS) data from representative patient populations are used to base regimen design in the absence of individual DST. All patients in a defined group or category receive the same regimen.
- **Individualized Treatment**: Each regimen is adopted according to guidelines based on the patient’s past history of TB treatment, individual FL- and SL-DST results and possible side-effects.
- **Empiric Treatment**: Each regimen is individually designed based on the patient’s past history of TB treatment and with consideration of DRS data from the representative patient population. An empirical regimen is adjusted when DST on individual patient becomes available.

5.4 Standard Code for TB Treatment Regimens

There is a standard code for writing out TB treatment regimens. Each antituberculosis drug has an abbreviation (table 5.1). A M(X)DR-TB regimen consists of two phases: the first phase is the period in which the injectable agent 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 stage should last. The number in subscript (e.g., 3) after a letter is the number of drug doses per week. If there is no number in subscript, treatment is daily. An alternative drug appears in parentheses.

For instance in Ethiopia, the standard regimen for MDR-TB is:
6E-Z-Km(Am)–Lfx–Eto–Cs / 12 E-Z-Lfx–Eto–Cs
• The number shown before each phase indicates the duration as a minimum of 6 months of injectables and 12 months after the injectable was stopped.
• (Am) appears in parentheses as it can be used as alternative drug to Km particularly while waiting for Km to be registered in Ethiopia.

Table 5.1: Grouping of anti-tuberculosis agents

<table>
<thead>
<tr>
<th>Grouping</th>
<th>Drugs</th>
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<tbody>
<tr>
<td><strong>Group 1:</strong> First-line oral agents</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 agents</td>
<td>Kanamycin (Km); Amikacin (Am); Capreomycin (Cm); Streptomycin (S)</td>
</tr>
<tr>
<td><strong>Group 3:</strong> Fluoroquinolones</td>
<td>Moxifloxacin (Mfx); Levofloxacin (Lfx)</td>
</tr>
<tr>
<td><strong>Group 4:</strong> Oral bacteriostatic second-line agents</td>
<td>Ethionamide (Eto); Cycloserine (Cs); para-aminosalicylic acid (PAS)</td>
</tr>
<tr>
<td><strong>Group 5:</strong> Agents with unclear role in DR-TB treatment (not recommended by the WHO for routine use in DR-TB patients)</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>a</sup> Rifabutin is not on the WHO List of Essential Medicines, however it has been added here as it is used routinely in patients on protease inhibitors in many settings.

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

5.5 MDR-TB Treatment Strategies in Ethiopia

The Ethiopian treatment strategy combines standardized and individualized treatment based on second line DST (Kanamycin and Ofloxacin) in all confirmed MDR-TB patients. Due to cross-resistance in vitro resistance to Kanamycin can be used as surrogate indicator of resistance to Amikacin as well and resistance to Ofloxacin can be used as indicator of resistance to Levofoxacin and partial Moxifloxacin resistance. All MDR-TB suspects will be referred for line probe assay, followed by full first line – DST (FL-DST) and partial second line DST (SL-DST) once MDR-TB is confirmed. Whereas all known MDR-TB patients will have FL-DST and SL-DST performed simultaneously. Line probe assay will assist in the decision to start the standard second line anti TB treatment. Treatment will be adjusted after receiving FL- and SL-DST result according to regimens shown below or see specific section in case of severe side-effects or other special needs.

A standard regimen will be given to all MDR-confirmed cases under daily DOT (at least one drug intake will be medically supervised per week day). If a second dose per day is needed and on weekends doses will be self administered. The initial phase will be at least six months, and then the continuation phase will be at least 12 months. The total duration may be extended by clinicians according to the findings of culture conversion.

Regimens are designed in order to provide always at least 4 proven effective drugs, with a maximum of 7 drugs. Group 1 drug that might still be effective: Ethambutol or Pyrazinamide will be used in all patients but will not be counted as effective drugs. Additional 2nd line may have to be included in case of 2<sup>nd</sup> line drug resistance as seen by DST.
Because of serious side effects during the course of some patients, some regimen will have to be modified and in these cases, additional 2nd line “reserve” drug will be given in substitution, also on an individualized basis.

Table 5.2 MDR-TB Treatment Regimens in Ethiopia

<table>
<thead>
<tr>
<th>NTP has standardized the regimen distinguishing 5 patient categories:</th>
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</thead>
<tbody>
<tr>
<td>1. Patients with MDR-TB confirmation, but no full DST results available yet</td>
</tr>
<tr>
<td>2. MDR-TB Patients susceptible to both Kanamycin and Quinolone</td>
</tr>
<tr>
<td>3. MDR-TB Patients susceptible to Kanamycin, but resistant to Quinolone</td>
</tr>
<tr>
<td>4. MDR-TB Patients susceptible to Quinolone, but resistant to Kanamycin</td>
</tr>
<tr>
<td>5. XDR-TB Cases (i.e.: MDR-TB and resistance to Quinolone and Kanamycin)</td>
</tr>
</tbody>
</table>

Regimen for Group 1* and 2: E-Z-Km(Am)-Lfx-Eto-Cs
Regimen for Group 3: E-Z-Km(Am)-Mfx-Eto-Cs-PAS
Regimen for Group 4: E-Z-Cm-Lfx-Eto-Cs
Regimen for Group 5 (XDR): E-Z-Cm-Mfx-Eto-Cs-PAS

* Clinical team at M(X)DR-TB treatment referral hospital may adapt the regimen after receiving the result of SL-DST.
Total treatment duration of all regimens will be at least 18 months past culture conversion

With the standardized regimen above, Ethiopia's NTP applies the following principles taking into account the clinical condition of the patients and the medical history:

- Each MDR TB regimen will consist of at least four new drugs with almost certain effectiveness
- As standard all patients will receive Pyrazinamide, Kanamycin/Amikacin, Levofloxacin, Ethionamide, and Cycloserine
- Ethambutol is continued if DST suggests susceptibility to the drug. However, as most patients have already used Ethambutol for prolonged periods and DST for Ethambutol is not fully reliable, this drug will not count as one of the 4 effective drugs 'with certain effectiveness', even if the DST shows susceptibility
- Pyrazinamide will be used throughout in all patients as resistance uncommon and no reliable DST available, but it will also not be counted as an effective drug.
- Kanamycin DST is used as a surrogate marker also for Amikacin. In case of resistance to Kanamycin/Amikacin, Capreomycin can be used as injectable and can be counted as effective drug.
- Ofloxacin DST is used as a surrogate marker for quinolone resistance. However, in case of resistance to Ofloxacin, Levofloxacin, a higher generation of quinolone, will be kept in the regime, unless Moxifloxacin is available which should then be used. In case of quinolone resistance neither Levofloxacin nor Moxifloxacin will count as one of the drugs 'with certain effectiveness'. Thus PAS is added when resistance to quinolones is confirmed.
- The drugs dosages are determined by body weight (See Annex I).
5.6 Duration and Phases of Treatment

- **Intensive phase:** The injectable agent (Kanamycin/Amikacin/Capreomycin) is used for minimum of 6 months and at least 4 months after culture conversion.

  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 agent longer than the above recommendation, particularly in the case of patients for whom the susceptibility pattern is unknown, effectiveness is questionable for an agent(s), or extensive or bilateral pulmonary disease is present.

- **Continuation phase:** The treatment period following the intensive phase.

  The total treatment is for minimum duration of 18 months beyond culture conversion (eg. pediatric patients receiving second line treatment with baseline culture negative result). Thus if the culture is negative at completion of first month of MDR-treatment, intensive phase will be 6 months and continuation phase 13 months. However, if culture conversion is at completion of second months, intensive phase will be 6 months and continuation phase 14 months. If culture conversion is at completion of fourth months, intensive phase will be 8 months and continuation phase will be 14 months.

  Extension of therapy to 24 months may be indicated in chronic cases with extensive pulmonary damage.

  Sputum culture conversion is defined as two consecutive negative cultures, from samples collected at least 30 days apart. Thus one has to await the consecutive months results, however the date of first sputum collection will be used will be used as a reference point for deciding on the duration of treatment.

  The intensive phase can be divided into in-patient phase (until smear conversion takes place, or at least one month) and out-patient phase (where injections are received at designated health centres). Injections are provided 6 times per week during hospitalisation and 5 times per week during ambulatory treatment. Intermittent therapy with the injectable agent (three times a week) can also be considered in patients who have been on the injectable for a prolonged period of time and when toxicity becomes a greater risk to the patient. Oral drugs are provided 7 days a week.

5.7 Management of Extra-pulmonary M(X)DR-TB

Extra-pulmonary DR-TB is treated with the same strategy and length of time as pulmonary M(X)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. Pyrazinamide, 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. The fluoroquinolones have variable CSF penetration, with better penetration seen in the higher generations.
5.8 Adjuvant and Supportive Treatment

5.8.1 Nutritional support

In addition to causing malnutrition, M(X)DR-TB can be exacerbated by poor nutritional status. Without nutritional support, patients, especially those already suffering from malnutrition, 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. All MDR-TB patients should be given appropriate nutritional counselling and linked to nutritional support program whenever possible.

5.8.2 Vitamin B6 (pyridoxine)

Vitamin B6 supplement should always be given to all patients receiving cycloserine to prevent neurological side effects (Daily Dosage; Pyridoxine [Vitamin B6] 50mg for every 250mg of cycloserine)

5.8.3 Other vitamins and minerals

Vitamins (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.

5.8.4 Corticosteroids

In M(X)DR-TB patients, the adjuvant use of corticosteroids has been shown not to increase 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 mg/kg 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.

5.8.5 Psycho Social and emotional support

It is known from the experience of other M(X)DR-TB programs that provision of emotional support to patients may improve chances of adhering with therapy. In the Ethiopian program support will be provided formally in the form of support groups or one-on-one counselling with trained providers. Additional support will be provided by physicians, nurses, community workers or volunteers, and family members. Ideally a multidisciplinary team, comprising of a social community worker, nurse, health educators, companions, and doctors, should be set up to act as a “support to adherence” team to the patient.

Socio-economic problems should, as far as possible, be addressed to enable patients and their families to adhere to the M(X)DR-TB treatment. Based on the experience of other M(X)DR TB project funded by GFATM, similar approach will be used to fund the basic needs of the patients. In many settings, these problems have been successfully tackled
through the provision of “incentives” and “enablers” for the patients and health care workers to adhere to the treatment. Enablers refer to goods or services that make it easier for patients to adhere to treatment; incentives refer to goods or services that are used to encourage HCWs to help patients adhere to therapy. Interventions will be given to patients with the most need, and will be given as per TLCT guidelines and norms. The programme, wherever available, will avail the services of professional social workers that can assess the need for the appropriate socioeconomic interventions, and monitor their delivery.

5.9 Patient Follow up and Monitoring

Patients should be monitored closely for signs of adverse effects and 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.

Objective laboratory evidence of improvement often lags behind clinical improvement. The chest radiograph may be unchanged or show only slight improvement, especially in retreatment patients with chronic pulmonary lesions. Chest radiographs should be taken at least every six months or whenever the patient’s clinical situation has worsened. 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 Mycobacteria Other Than TB (MOTT) as overgrowth with MOTT 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 MOTT 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 quarterly for cultures (Table 5.3). Programmes with adequate culture capacity may choose to do cultures more frequently, every 1–2 months, after conversion. 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 (see below), DST can be repeated. It is usually not necessary to repeat DST within less than three months of change or completion of treatment.

**Table 5.3 Schedule for Follow-up**

<table>
<thead>
<tr>
<th>Month of treatment</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
<th>18</th>
<th>21</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical evaluation (weight)</strong>* (history of contraception and last normal menstruation)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Evaluation on early treatment failure</strong></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sputum smear</strong>*</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>XXX</td>
<td>XXX</td>
<td>XXX</td>
<td>XXX</td>
<td>XXX</td>
<td>XXX</td>
<td>XXX</td>
</tr>
<tr>
<td><strong>Sputum culture</strong></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Chest x-ray</strong></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Liver function test</strong></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Renal function test</strong></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Complete blood count</strong></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Electrolytes (serum potassium, K, Mg, uric acid)</strong></td>
<td>X</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>X</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td><strong>TSH</strong></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

* Monthly
Y: only for patients taking Capreomycin and patients at increased risk of electrolyte wasting

**5.9.1 Clinical evaluation at follow up visit**

Thorough clinical evaluation will be done on each visit based on a standard check list on the treatment card (see Table 5.3).

All physicians and health care workers involved will be trained to systematically interview and screen their patients with the aim to ensure timely and correct identification and management of side effects. This training will enable them to manage common side effects like nausea, vomiting and diarrhoea. The required ancillary drugs will be made available to them through the pilot-project.

However, there will be ample opportunity for cross-referral between treatment follow-up centres and the designated hospital. All treatment centres will receive contact details, including mobile phone numbers, from relevant physicians in the Referral hospitals, in order to ensure easy referral in case of serious side effects.

**5.9.2 Follow-up of the Non-adherent Patient**

When a patient fails to attend a DOT appointment, a system will be put in place that allows prompt patient retrieval. The DOT provider/supporter should visit the patient’s home on the same day to find out why the patient has not appeared for his/her appointment/treatment, and 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 why the patient missed a dose(s) and to work with patient and family to ensure treatment continuation. The NTP should try to ensure means of transport for the active retrieval of non-adherer without delay through the existing locally appropriate system.

5.9.3 Follow up and Management of Drug adverse effect

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

The majority of adverse effects are easy to recognize. Commonly, patients will volunteer that they are experiencing adverse effects. However, it is important to have a systematic method of patient interviewing since some patients may be reserved about reporting even severe adverse 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 adverse effects: rashes, gastrointestinal symptoms (nausea, vomiting, diarrhoea), psychiatric symptoms (psychosis, depression, anxiety, 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 adverse effects that are more occult. The recommendations in Table 4.3 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 such as HIV co-infected DR-TB patients. (See annex III, for management of drug adverse effect in Ethiopia.)

5.10 Management of Mono- and Poly-drug Resistant TB

This section describes the recommended treatment strategies for patients with drug-resistant TB other than M(X)DR-TB. These include patients with mono-resistant TB and patients with poly-resistant TB other than M(X)DR-TB. Mono-resistance refers to resistance to a single first-line drug while poly-resistance refers to resistance to two or more first-line drugs but not resistance to the combination of rifampicin and isoniazide.

5.10.1 General considerations

No specific efforts are recommended to diagnose mono- and poly-resistant strains of TB in routine DOTS programmes. However, cases with mono- or poly-resistance will be identified during the course of case-finding for M(X)DR-TB. Treatment of patients infected with mono- or poly-resistant strains using standardized short-course chemotherapy has been associated with increased risk of treatment failure and further acquired resistance, including the development of M(X)DR-TB. While the likelihood of poor outcomes is relatively low with some types of mono- resistance (i.e. the majority of patients with mono-resistant strains will be cured with short-course chemotherapy), it is recommended to use different regimens based on DST patterns as described below.
5.10.2 Treatment of patients with mono- and poly-resistant strains

Table 5.4 gives suggested regimens for different DST patterns. When using this table, it is essential to consider whether resistance has been acquired to any of the drugs that will be used in the recommended regimen.

Table 5.4: Suggested regimens for mono- and poly-drug resistance

<table>
<thead>
<tr>
<th>Resistance</th>
<th>Abbr</th>
<th>Management at TB facility</th>
<th>MDR-regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptomycin, Ethambutol, Streptomycin + Ethambutol</td>
<td>S, E, ES</td>
<td>2HRZE / 6EH (Cat 1) or 3HRZE / 5RH3 (Cat 2 without S)</td>
<td>NA</td>
</tr>
<tr>
<td>Isoniazid*, Isoniazid + Streptomycin</td>
<td>H, HS</td>
<td>9HRZE or 11HRZE** (modified)</td>
<td>NA</td>
</tr>
<tr>
<td>Isoniazid + Ethambutol***, Isoniazid + Ethambutol + Streptomycin</td>
<td>HE, HES</td>
<td>Refer for MDR-treatment</td>
<td>6Z-Km(Am)-Lfx-Eto-Cs/ 12Z-Lfx-Eto (stop E if resistance)</td>
</tr>
<tr>
<td>Rifampicin****, Rifampicin + Streptomycin, Rifampicin + Ethambutol, Rifampicin + Ethambutol + Streptomycin</td>
<td>R, RS, RE, RES</td>
<td>Refer for MDR-treatment</td>
<td>6Z-E-Km(Am)-Lfx-Eto-Cs/ 12Z-E-Lfx-Eto</td>
</tr>
</tbody>
</table>

*If based on rapid RH-LPA continue HRZE until further decision can be taken with full DST result.
**If there is no culture conversion at 2, 4, 6 or 8 months do another DST and continue to 11HRZE, see monitoring schedule on next page.
*** As Z-resistance is unknown patient could have been on basic R-mono-therapy for extended period and full MDR-treatment is advised.
**** R-mono-resistance uncommon, if based on rapid RH-LPA give empiric MDR treatment, if based on full DST assume further resistance in meantime and give full MDR treatment.

5.10.3 Development of further resistance

Further resistance should be suspected if the patient was on the functional equivalent of only one drug for a significant period of time (usually considered as one month or more). Sometimes resistance develops if the patient was on the functional equivalent of two drugs, depending on the drugs concerned. For example, pyrazinamide is not considered a good companion drug to prevent resistance. If a patient was receiving functionally only rifampicin and pyrazinamide in the initial phase (because of resistance to isoniazid and ethambutol), resistance to rifampicin may develop. Thus, it is crucial to consider which functional drugs the patient received between the time of DST specimen collection and the time of the new regimen design (i.e. consider whether resistance has developed to any of the functional drugs).

5.10.4 DST results

The DST result that prompts a change in treatment may not accurately reflect the bacterial population at the time it is reported since it reflects the bacterial population at the time the
sputum was collected. The regimens in Table 5.4 have considered that possibly the pattern of drug resistance has changed during a two month interval. However Table 5.4 should **not** be used if available DST results are outdated and further resistance to any of the agents in the suggested regimen is suspected in which case Line Probe Assay and DST needs to be repeated.

As DST of pyrazinamide is not being carried out, pyrazinamide cannot be depended upon as being an effective drug in the regimen but should be added for its probable benefit.

As Ethiopia uses mainly FDCs for management of TB regimens separate drugs are often not available. Thus modifications for mono-resistance to isoniazid just extends the active phase for a longer time period and continues using isoniazid although there is known resistance as there is no way to exclude it from the treatment protocol. Most cases of poly-resistance require a referral to a M(X)DR-TB specialist centre for full MDR-treatment. Thus five possible scenarios are suggested:

5.10.5 Consequences for reporting

Patients whose regimens require minor adjustments (with no need for any Cat IV TB drugs) should be recorded in the traditional District Tuberculosis Register. These regimens are considered “modifications” of Category I or Category II treatment and involve prolonging standard treatment with more intensive monitoring (See Figure 5.1). They are not classified as Category IV treatments, which are regimens designed to treat M(X)DR-TB. The adjustment should be noted in the comments section of the Register and the adjusted treatment continued for the indicated length of time. The patients do not require referral to specialised M(X)DR-TB services.
## 5.11 Monitoring of patient on modified Cat 1 or Cat 2 treatment with H or HS resistance:

Once INH-mono-resistance has been established with rapid RH-DST continue prolonged treatment with HREZ and await full DST. If only other resistance is S continue HREZ. If there is also resistance to E or E+S refer to MDR-treatment facility.

### Figure 5.1  Flowchart for monitoring of Mono- or poly-resistant TB

- **H mono-resistance on fast-RH-DST or H or HS resistance on full DST**
  - Give HRZE or SHRZE
  - At month 2 full DST should be available
  - **H or HS resistance only**
    - Continue treatment with HRZE
    - Do smear and TB culture every 2 months
    - If any subsequent culture positive do full DST and prolong treatment for 11 months
    - **Additional resistance to E or ES**
      - Refer for full MDR treatment
    - **Additional resistance acquired**
      - Refer for full MDR treatment
    - Declare cured if no positive smears or culture during last three sputums (e.g. at 2, 4, 6 months – nine months treatment or at 4, 6, 8 months – eleven months treatment)
    - Declare treatment completed at 11 if last months if subsequent smears or cultures positive but no further resistance acquired
    - Declare treatment failure, if two or more of cultures are positive or if one of the last three cultures is positive
5.12 Management of Patients where MDR-TB Treatment Appears to be Failing

5.12.1 Assessment of patients at risk for failure

Patients who do not show signs of improvement after four months of treatment are at risk for treatment failure. In all patients who show clinical, radiological or bacteriological evidence of progressive active disease, or reappearance of disease after the 4th month of treatment should be considered as being at high risk for treatment failure. The most pertinent evidence being continued positive sputum cultures or sputum smear still positive at four months. One single positive culture in the presence of an otherwise good clinical response can be caused by a laboratory contaminant 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. If culture and smear results are repeatedly negative in a patient with clinical and/or radiographical deterioration, it may indicate that the patient has an additional disease other than M(X)DR-TB.

When expecting treatment failure the following questions and steps are recommended:

Is there good adherence?
- review treatment card
- conduct non-confrontational interview with patient about possible adherence problems (side-effects, depression, substance dependence, social, financial, problems with health care worker, drug supply)
- conduct non-confrontational interview with health worker responsible for daily follow-up

Is the treatment regimen correct?
- review previous TB treatment history
- review patient’s full DST reports including second-line drugs
- check known contacts’ DST reports (of family and patients in same ward)
- check treatment regimen

Consider other medical problems?
- HIV status, ART treatment, chronic diarrhoea
- other pulmonary disease

In such situations adjust treatment plan according to findings: improve adherence, manage side-effects, adjust regimen and treat other illnesses. If surgical resection is feasible, it should be considered at this stage

5.12.2 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, clinical treatment failure should be considered. There is no single indicator to determine whether a treatment regimen is failing. Although there is no simple definition for clinical treatment failure, there often comes a point during the treatment when it becomes clear that the patient is not going to improve.

Signs indicating clinical treatment failure include:
• persistent positive smears or cultures past 8-10 month of treatment;
• high-grade resistance with no option to add two additional agents;
• progressive extensive and bilateral lung disease on chest X-ray with no option for surgery;
• overall deteriorating clinical condition that usually includes weight loss and respiratory insufficiency.

It is not necessary for all of these signs to be present to identify clinical 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 different from that used in the process of suspending therapy in a patient when the therapy is clinically failing. The epidemiological definition is an outcome to account for the patient in a treatment cohort analysis, while the clinical decision to suspend therapy in an individual is taken after the search for all other clinical options has been exhausted and cure of the patient is considered to be highly unlikely. (The treatment outcomes definition for recording purposes of treatment failure is: Two or more of the five cultures recorded in the final twelve months are positive, or if any of the final three cultures are positive. If a clinical decision has been taken to terminate therapy early due to poor response or excessive adverse events it is also recorded as failure.)

5.12.3. Suspending Therapy

Treatment can be considered to have failed clinically and suspension of therapy is recommended in cases where the medical personnel involved 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. The first is the patient’s quality of life: the drugs used in M(X)DR-TB treatment have significant adverse effects, and continuing them while the treatment is failing may cause additional suffering. The second is the public health concern: continuing a treatment that is failing can amplify resistance in the patient’s strain, resulting in resistance to all known anti-tuberculosis drugs; the “super-resistant” strain may cause subsequent infection of others. However the counter argument is that by providing even a failing regimen the bacterial load might be kept lower and the risk of transmission might be reduced.

5.12.3.1 Approach to suspending therapy

The approach to suspending therapy should start with discussions among the clinical team, including all physicians, nurses and DOT workers involved in the patient’s care. Once the clinical team decides that treatment should be suspended, a clear plan should be prepared for approaching the patient and the family. This process usually requires a number of visits and takes place over several weeks. However the decision should be communicated clearly and not in ‘may be terms’ creating a false hope. Home visits during the process offer an excellent opportunity to talk with family members and the patient in a familiar environment. 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.
5.12.4 Supportive care for patients in whom all the possibilities of M(X)DR-TB treatment have failed

A number of supportive measures can be used once the therapy has been suspended. It is very important that medical visits continue and that the patient is not abandoned. The supportive measures are described in detail in the Integrated Management of Adolescent and Adult Illness guidelines produced by WHO in a booklet titled *Palliative care: symptom management and end-of life care* available as Ethiopian version and a *National Palliative Care Training Manual*. The supportive measures are summarized below:

- **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.
- **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 if available.
- **Nutritional support.** Small and frequent meals are often best for a person at the end of life. It should be accepted that the intake will reduce as the patient’s condition deteriorates and during end-of-life care. Nausea and vomiting or any other conditions that interfere with nutritional support should be treated.
- **Regular medical visits.** When therapy stops, regular visits by the treating physician and support team should not be discontinued.
- **Continuation of ancillary medicines.** All necessary ancillary medications should be continued as needed. Depression and anxiety, if present, should be addressed.
- **Hospitalization, hospice care or nursing home care, whenever feasible.** 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 anti-tuberculosis treatment because of failure often remains infectious for long periods of time. Infection control measures should be continued both at home or health institutions.(see Chapter Nine)

In conclusion, suspension of therapy should be considered only after all other options for treatment have been explored. Suspending therapy in a patient who has failed M(X)DR-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 SIX : TREATMENT OF DRUG-RESISTANT TUBERCULOSIS IN SPECIAL CONDITIONS AND SITUATIONS

6.1 Pregnancy

All female patients of childbearing age should be tested for pregnancy upon initial evaluation. LMP will be asked routinely during each follow up. Pregnancy is not a contraindication for treatment of active drug-resistant 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 drug-resistant 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 drug-resistant 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. 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). When therapy is started, three or four oral drugs with demonstrated efficacy against the infecting strain should be used and then reinforced with an injectable agent and possibly other drugs immediately postpartum.

• **Avoid injectable agents.** For the most part, aminoglycosides should not be used in the regimens of pregnant patients and can be particularly toxic to the developing fetal ear. Capreomycin may carry the same risk of ototoxicity but is the injectable drug of choice if an injectable agent cannot be avoided.

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

Thus recommended regimen: E-Z-(Cm)-Lfx-Cs-PAS

6.2 Breastfeeding

A woman who is breastfeeding and has active drug-resistant TB should receive a full course of anti-tuberculosis treatment. Timely and properly applied chemotherapy is the best way to prevent transmission of tubercle bacilli to her Baby.

In lactating mothers on treatment, most anti-tuberculosis drugs are found in the breast milk in concentrations that would equal only a small fraction compared to a therapeutic dose used in an infant. However, any effects on infants of such exposure during the full course of MDR-TB treatment have not been established. Therefore, the use of infant formula is a reasonable
way to avoid any unknown adverse effects. However, the use of infant formula will depend on multiple factors, including the patient’s resources, safety of water supply, and bacteriological status of the mother. If infant formula is AFASS:

- **Acceptable**: Mother perceives no problem in replacement feeding.
- **Feasible**: Mother has adequate time, knowledge, skills, resources, and support to correctly mix formula or milk and feed the infant up to 12 times in 24 hours.
- **Affordable**: Mother and family, with community and the MDR-TB programme can pay the cost of replacement feeding without harming the health and nutrition of the family.
- **Sustainable**: Availability of a continuous supply of infant formula and all ingredients needed for safe replacement feeding.
- **Safe**: Replacement foods are correctly and hygienically prepared and stored. The infant can be on formula feeding. If the setting is not appropriate for infant formula, then breast-feeding may be considered.

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 until she becomes sputum smear-negative.

### 6.3 Contraception

There is no contraindication to the use of oral contraceptives with the non-rifampicin containing regimens. Patients who vomit directly after taking an oral contraceptive can be at risk of decreased absorption of the drug and therefore of decreased efficacy. These patients should be advised to take their contraceptives apart from times when they may experience vomiting caused by the anti-tuberculosis 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 may choose between two options: following consultation with a physician, use of an oral contraceptive pill containing a higher dose of estrogen (50 µg); or use of another form of contraception (e.g. non estrogen hormonal contraceptive).

### 6.4 Diabetes Mellitus

Diabetic patients with MDR-TB are at risk for poor outcomes. In addition, the presence of diabetes mellitus may potentiate the adverse effects of anti-tuberculosis drugs, especially renal dysfunction and peripheral neuropathy. Diabetes must be managed closely throughout the treatment of drug-resistant TB. The health-care provider should be in close communication with the physician who manages the patient’s diabetes. Oral hypoglycaemic agents are not contraindicated during the treatment of drug-resistant TB but may require the patient to increase the dosage. Use of ethionamide 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.
6.5 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 6.1.

**Creatinine Clearance** can be calculated using the *Cockroft and Gault formula:*

For men: \( \text{Cr Clearance (ml/min)} = \frac{\text{weight (kg)} \times (140 - \text{age (yrs)}) \times 72}{\text{serum creatinine (mg/dl)}} \)

For women use same formula and multiply by 85/100

**Table 6.1 Adjustment of antituberculosis medication in renal insufficiency**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>CHANGE IN FREQUENCY?</th>
<th>RECOMMENDED DOSEb AND FREQUENCY FOR PATIENTS WITH CREATININE CLEAR. &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 wk (not daily)</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Yes</td>
<td>15–25 mg/kg per dose three times per wk (not daily)</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>Yes</td>
<td>750–1000 mg per dose three times per wk (not daily)</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>No change</td>
<td>400 mg once daily</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>Yes</td>
<td>250 mg once daily, or 500 mg/dose 3 times per wk</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>No change</td>
<td>250–500 mg per dose daily</td>
</tr>
<tr>
<td>PAS</td>
<td>No change</td>
<td>4 g/dose, twice daily</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>Yes</td>
<td>12–15 mg/kg per dose 2 or 3 times per wk (not daily)</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>Yes</td>
<td>12–15 mg/kg per dose 2 or 3 times per wk (not daily)</td>
</tr>
<tr>
<td>Amikacin</td>
<td>Yes</td>
<td>12–15 mg/kg per dose 2 or 3 times per wk (not daily)</td>
</tr>
</tbody>
</table>

a Adapted from *Treatment of tuberculosis (11).*
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.

6.6 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, protonamide and PAS can also be hepatotoxic, although less so than any of the first-line drugs. Hepatitis occurs rarely with the fluoroquinolones. All other drugs can be used, but close monitoring of liver enzymes is advised. If significant aggravation of liver inflammation occurs, the drugs responsible may have to be stopped. Uncommonly, a patient with TB may have concurrent acute hepatitis that is unrelated to TB or anti-tuberculosis treatment. In this case, clinical judgement is necessary. In some cases, it is possible to defer anti-tuberculosis treatment until the acute hepatitis has been resolved. In other cases when it is necessary to treat drug-
resistant TB during acute hepatitis, the combination of four non-hepatotoxic drugs is the safest option.

### 6.7 Seizure Disorders

Some patients requiring treatment for drug-resistant 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 drug-resistant TB therapy. In addition, any other underlying conditions or causes of seizures should be corrected. 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 use (see Annex 1 for drug interactions). Seizures that present for the first time during anti-tuberculosis therapy are likely to be the result of an adverse effect of one of the anti-tuberculosis drugs. More information on the specific strategies and protocols to address adverse effects is provided in Chapter Five.

### 6.8 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 drug-resistant 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 counselling 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 drug-resistant TB should work closely with a mental health specialist and have an organized system for psychiatric emergencies. Psychiatric emergencies include psychosis, suicidal ideation and any situation involving the patient’s being a danger to him or herself or others.

Thus recommended regimen is: E-Z-Km(Am)-Lfx-Eto-PAS
6.9 Substance Dependence

Patients with substance dependence disorders should be offered treatment for their addiction when ever possible. Complete abstinence from alcohol or other substances should be strongly encouraged, although active consumption is not a contraindication for anti-tuberculosis 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.

6.10 HIV-infected Patients

Given the important interaction between HIV infection and drug-susceptible and drug-resistant TB, a full chapter (Chapter Eight) is devoted to this subject.
CHAPTER SEVEN : MDR-TB IN CHILDREN

7.1 Background

Children may be less likely than adults to acquire resistance during the treatment of tuberculosis (TB) due to lower bacillary load. However, there is no reason to expect that children will evade infection by resistant strains of TB. When children have multi-drug-resistant tuberculosis (MDR-TB), it is usually ‘primary resistance’, i.e., they are infected with strains transmitted from adults with MDR-TB. The rate of transmission of strains of MDR-TB has been shown to be the same for children as for adults and also the incidence of primary drug resistance is similar among adults and paediatric cases.

7.2 MDR TB Case Finding in Children

The diagnosis of active tuberculosis among children is difficult because of the lack of a standardized reliable case definition. Clinical presentation is variable and often subtle. Lower bacillary loads, which are common in pediatric tuberculosis, render microbiologic confirmation difficult. Up to 50% of children may remain smear- and culture-negative despite the presence of active disease. As a result, the identification of drug resistance, and thus the definitive diagnosis of MDR-TB, is particularly problematic among children. This is especially problematic for children with a clinical diagnosis of TB who are known to have a household contact with MDR-TB, or for children who live in ‘hot spots’ of MDR-TB transmission. Such children may have been infected with resistant strains of tuberculosis but, despite having active infection, remain smear and culture-negative.

It is essential to consider MDR-TB in children who are experiencing failure of DOTS or known to have household contact with a person known or suspected to have MDR-TB. For treatment of MDR-TB in children mycobacterial cultures from sputum, gastric aspirates, or extrapulmonary sites should be pursued aggressively followed culture and Line Probe Assay and DST. When Line Probe Assay or 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 drug-resistant TB bacteriologically by the use of culture, Line Probe Assay and DST and to avoid exposing children unnecessarily to toxic drugs.

7.3 Treatment of MDR-TB in Children

The treatment of culture-negative children with clinical evidence of active TB disease and contact with a documented case of drug-resistant TB should be guided by the results of Line Probe Assay and DST and the history of the contact's exposure to anti-tuberculosis drugs. However, every effort should be made to diagnose MDR-TB in children as early as possible as delay in diagnosis is highly associated with increased mortality.

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. MDR-TB is life threatening, and none of the anti-tuberculosis drugs are absolutely contraindicated in children. Children who have received treatment for drug resistant TB have generally tolerated the second-line drugs well. Adverse events seem to be less common among children than among adults and rarely compromise treatment when managed appropriately.
Although fluoroquinolones have been shown to retard cartilage development in animal studies, experience with the use of fluoroquinolones has not demonstrated similar effects in humans. It is considered that the benefit of fluoroquinolones in treating MDR-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 6.1). 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 MDR-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. See Annex I for weight based dosage of second line anti-TB drugs.

Anecdotal evidence suggests that adolescents are at high risk for poor treatment outcomes, perhaps due to biologic reasons (more advanced disease due to late diagnosis) and social factors (more problems with adherence, behaviour, drug use, pregnancy, poor acceptance of illness). Early diagnosis, strong social support, individual and family counselling, and a close relationship with the care provider may help improve outcomes.
CHAPTER EIGHT - DRUG-RESISTANT TUBERCULOSIS AND HIV

8.1 General Considerations

HIV co-infection is a significant challenge for the diagnosis, treatment and prevention, of drug-resistant tuberculosis, especially in the case of MDR-TB and XDR-TB. Reports have shown high mortality rates among HIV-infected patients with DR-TB, and alarming mortality rates in patients co-infected with XDR-TB and HIV. 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.

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. DR-TB is often associated with higher mortality rates in the HIV-infected compared to the non-infected, however the use of ART in addition to treatment of DR-TB has been reported to improve outcomes of DR-TB in the HIV infected.

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

WHO Recommendation for Highest Standard of Care:1

- Perform provider-initiated HIV testing and counseling in all TB suspects.
- Use standard algorithms to diagnose pulmonary and extrapulmonary tuberculosis.
- Use mycobacterial cultures and, where available, newer more rapid methods of diagnosis.2
- Perform DST at the start of TB therapy.3
- 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 anti-tuberculosis drugs.4
- Provide co-trimoxazole preventive therapy (CPT) for patients with active TB and HIV.
- Arrange treatment follow-up by a specialized team.
- Implement additional nutritional and socioeconomic support.
- Ensure effective infection control.
- Involve key stakeholders in DR-TB/HIV activities.

8.2 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 extrapulmonary or sputum smear-negative than in HIV-infected patients. The use of ART in addition to treatment of DR-TB has been reported to improve outcomes of DR-TB in the HIV infected.

1 Adapted to be specifically applicable to DR-TB
2 See indications for culture and DST in the specific section
3 See indications for culture and DST in the specific section
4 Empiric use of Category IV is reserved for patients that have an extremely high rate of MDR-TB such as failures of Category II, or very close contacts of DR-TB.
uninfected TB patients, especially as immunosuppression advances. This can result in misdiagnosis or delays in diagnosis, and in turn, higher morbidity and mortality.

8.3 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 Five, 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).
- Adverse effects are more common in patients with HIV. The multiple medicines involved in DR-TB with recognized high toxicity risks, often combined with ART, results in a high incidence of adverse effects. Some toxicities are common to both anti-tuberculosis 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.
- Immune reconstitution inflammatory syndrome (IRIS) may complicate therapy.

8.3.1 Initiating ART treatment in patients with DR-TB

Antiretroviral therapy in HIV-infected patients with TB improves survival for both drug-resistant and susceptible disease. However, the likelihood of adverse effects could compromise the treatment of either HIV or DR-TB if both treatments are started simultaneously. On the other hand, undue delay in the start of ART could result in significant risk of HIV-related death among patients with advanced disease. The optimal timing for the introduction of ART in patients receiving TB treatment is unknown. Table 8.1, based on WHO guidelines for the treatment of HIV infection in adults and adolescents, provides recommendations for initiating ART in relationship to starting therapy for DR-TB.

Table 8.1 Timing of ART in the ART naïve patient starting anti-tuberculosis therapy for DR-TB

<table>
<thead>
<tr>
<th>CD4 cell count</th>
<th>ART Recommendations</th>
<th>Timing of ART in relation to start of DR-TB treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 &lt;200 cells/mm$^3$</td>
<td>Recommend ART</td>
<td>At two weeks or as soon as DR-TB treatment is tolerated</td>
</tr>
<tr>
<td>CD4 between 200 and 350 cells/mm$^3$</td>
<td>Recommend ART</td>
<td>After eight weeks$^a$</td>
</tr>
<tr>
<td>CD4 &gt;350 cells/mm$^3$</td>
<td>Defer ART$^b$</td>
<td>Re-evaluate patient monthly for consideration of ART start. CD4 testing is recommended every 3 months during DR-TB treatment.</td>
</tr>
<tr>
<td>Not available</td>
<td>Recommend ART$^c$</td>
<td>Between two and eight weeks</td>
</tr>
</tbody>
</table>

$^a$ Clinical evaluation may prompt earlier initiation of ART.
$^b$ ART should be started if other non-TB stage 3 or 4 events are present.
$^c$ This recognizes that some patients may be prematurely placed on life-long ART.

8.3.2 DR-TB in patients already receiving ART

There are two issues to consider in patients who are diagnosed with DR-TB while on ART. The first is whether modification of ART is needed due to drug-drug interactions or to decrease the potential of overlapping toxicities. These concerns are discussed below.
The second issue is 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.

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

Currently, little is known about drug-drug interactions between second-line anti-tuberculosis agents and antiretroviral therapy. 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. Guidance on use of rifamycin derivative-based regimens and ART (including with PI-based regimens) is available in WHO and national guidelines.

- **Quinolones and didanosine.** Buffered didanosine contains an aluminum/magnesium-based antacid and if given jointly with fluoroquinolones may result in decreased fluoroquinolone 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. Ethionamide/prothionamide is thought to be metabolized by the CYP450 system, though it is not know which of the CYP enzymes are responsible. Whether doses of ethionamide/prothionamide and/or certain antiretroviral drugs should be modified during the concomitant treatment of DR-TB and HIV is completely unknown.

- **Clarithromycin.** Clarithromycin is a substrate and inhibitor of CYP3A and has multiple drug interactions with protease inhibitors and NNRTIs. If possible avoid the use of clarithromycin in patients co-infected with DR-TB and HIV because of both its weak efficacy against DR-TB and multiple drug interactions.

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

Adverse effects that are common to both antiretroviral and anti-tuberculosis drugs are listed in Annex IV. It should be noted that relatively very little is known about the rates of adverse effects in the concomitant treatment of DR-TB and HIV. When possible, avoid the use of agents with shared side-effect profiles. Often, however, the benefit of using drugs that have
overlying 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 adverse effects rather than disallowing a certain combination. See Chapter Five for monitoring side-effects in HIV-infected patients.

8.3.5 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. DOT is particularly important in the setting of second-line anti-tuberculosis therapy, since it can result in a large pill-burden and numerous side-effects that make taking ARVs more difficult.

The complexity of antiretroviral regimens and second-line TB treatment, each with its own toxicity profiles and some of which may be potentiated by concomitant therapy, demands rigorous clinical monitoring. 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.

8.3.6 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 a previously sub-clinical 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 sub-clinical 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.

8.4 XDR-TB and HIV

XDR-TB has been described in a number of countries, including settings with a high prevalence of HIV. Treatment strategies for XDR-TB are outlined in another section of this document.
8.5 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.
CHAPTER NINE: INFECTION CONTROL IN DR- TB

This chapter addresses special considerations for reducing transmission of M(X)DR-TB through infection control measures. Infection control practices are discussed in more detail in the Ethiopian Infection Control Guidelines and in WHO documents\(^5\). Since every instance of transmission averted represents one less potential MDR-TB case, infection control needs to be a leading programmatic priority. It is equally important to protect health workers in the MDR-TB setting.

Recommendations for infection control to prevent MDR-TB are essentially the same as those to prevent the spread of drug-susceptible TB, with only minor differences in emphasis. This chapter reviews briefly the recommendations that have a specific focus on MDR-TB. Additional care needs to be taken for areas with high HIV prevalence.

TB infection control has three components. By order of importance, they are:
1. Administrative controls,
2. Environmental or engineering controls,
3. Personal respiratory protection.

9.1 Administrative Controls

The administrative controls are the most effective and least expensive and therefore have highest priority in resource-constrained settings.

9.1.1 Prompt identification of MDR-TB cases

Identifications of infectious cases promptly is the single most important aspect of infection prevention as it has two major advantages: a) as effective treatment is the most important factor to reduce infectiousness early diagnosis and treatment can reduce transmission to others, b) as soon as a case has been identified other precautionary measures like cohorting can be implemented.

To ensure early identification of drug resistant TB cases a well-functioning TB service is mandatory. A proactive case-finding strategy should be implemented throughout the TB program (according to the set implementation guideline). In order to ensure rapid diagnosis of MDR-TB, molecular assays such as the Line Probe Assays will aid the fast identification of MDR-TB cases. Furthermore a high level of suspicion at all levels is beneficial.

9.1.2 Coordination of infection control in institution and Infection Control Plan

To ensure proper planning and implementation of infection control measures at an institution, it necessitates the appointment of a focal person of infection control for the institution, and an infection control committee representing key departments of the facility. Alternatively the assurance that the HIV-multi-disciplinary team deals with TB-infection issues adequately. If there is a separate infection control committee it is of utmost importance that both the TB and HIV departments are involved as the highest risk of TB transmission and TB disease is from

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patients with active TB to immune compromised patients (mainly people living with HIV). It is crucial that these activities enjoy the highest form of managerial support.

The initial task of the committee is the formulation of a comprehensive infection control plan for the institution.

The Infection Control Plan should include the following components:

- **Rapid TB and M(X)DR-TB case finding strategy**
- **Coordination and management mechanism of TB infection control strategy**
- **Risk assessment**
  - The number of TB and M(X)DR-TB patients seen per year/month/day
  - The time that infectious TB and M(X)DR-TB patients spend in each area
  - Special procedures that increase infectious particles in the area — e.g. sputum induction, TB culture,
  - Identify settings that pose increased risk of TB transmission (e.g. ART clinic)
  - Purpose: to develop Infection Prevention Guidelines
- **Guidelines for Infection Prevention**
  - Administrative controls
  - Environmental or Engineering controls
  - Personal respiratory protection
- **Evaluation of adherence to Infection Prevention Guidelines**
  - Screening all patients as soon as possible
  - Separation of suspects/TB patients to a well-ventilated waiting area
  - Speed-up management of patients/suspects
  - Ensure rapid diagnostic investigation of TB suspects
  - Minimize the time from suspicion of TB and M(X)DR-TB to effective treatment
  - Isolation of infectious TB patients in the wards
  - Training & education of all staff
  - Use and maintain environmental control measures
  - Instructing patients in respiratory hygiene/cough etiquette

9.1.3 Separation of TB or M(X)DR-TB suspects and patients

An important aspect of administrative control measures is the physical separation of patients known or suspected to have TB or M(X)DR-TB (especially smear-positive cases) from other patients, especially those who are immuno-compromised.

In many resource-limited settings, however, isolation rooms are not available and patients are mixed together in open wards. A second, less satisfactory but practical, solution is to separate rather than isolate patients. In this approach, patients with TB are cohorted and beds allocated accordingly: smear positive TB, smear positive suspected drug resistant TB, smear positive confirmed drug resistant TB, smear negative etc. The presence of a substantial number of HIV-infected patients further complicates separation as they are not only potentially infectious but also highly vulnerable to intercurrent infection and re-infection from others. Placing HIV-infected patients with known or suspected TB together with other TB or M(X)DR-TB patients should always be avoided.

This separation may be difficult as wards should also be separated by sex, which increases the number of different areas required. However, in facilities identified to manage M(X)DR-
TB this should be strictly enforced. Ideally a building or block completely separate from other departments should be identified. A building with many small rooms is better than huge wards and the nurse station should be separate (not inside the ward).

Infectious TB patients especially those with M(X)DR-TB should be encouraged to spend time outdoors (in the sun) but should be restricted from freely wandering around in the hospital corridors and grounds. If possible number of visitors should be limited and visitation hours should be held in designated area outdoors. Additional precautions should be taken for visitors known to be infected with HIV or for children. Surgical masks should be placed on infectious TB patients whenever they move through other areas in the hospital (e.g. referral to X-ray) or have visitors indoors. Patients’ willingness to remain in isolation/separation may be facilitated by keeping them occupied through various activities such as the provision of television, books/magazines, games, crafts and addressing the problem of lost income.

9.1.4 Shortening length of stay in facility

Another administrative issue is the length of time patients spend in the health care institution being another major risk factor for nosocomial transmission. In many resource-limited countries, patients are traditionally treated for prolonged periods in the hospital, particularly when they come from great distances. However, this practice involves an increased risk. The risk of transmission to patients and health-care workers decreases when community-based ambulatory treatment is established and hospital stays are reduced.

With the management of M(X)DR-TB one has to weigh-up the benefits of in-patient care due to complex regimens with many side-effects and daily injections to the increased risk in terms of nosocomial transmission especially where isolation rooms can not be ensured. The recommendation is that in early phases of the program (up to a year of a specific institution) in-patient treatment should be until smear conversion and after that treatment wherever possible should be decentralized (to lower level health facilities, e.g., Health Centers).

Ambulatory patients should be advised to avoid close contact with the general public and with particularly susceptible people, such as young children or individuals with HIV infection and to practice good personal respiratory protection methods (see Section C. below).

9.1.5 Prioritizing, fast-tracking and separation in out-patient setting

It is also essential that this prioritising and separation of patients is not applied to inpatients only but care should be taken to develop suitable patient flow-patterns for out-patient departments and during cross-departmental referrals. Well designed waiting areas can reduce the risk especially when well ventilated and when patients spend less time there and crowding is avoided. A few administrative measures can be applied to reduce this risk significantly.

Try to avoid to place potential TB patients in waiting areas with other patients without TB, especially those who are immuno-compromised like people with HIV and children. All ‘coughers’ should quickly be triaged in waiting areas, prioritised and seen first by doctor, X-rayed first, their lab specimens are processed first, etc to reduce transmission to others. When additional medication from pharmacy is required a healthy family member or health assistant should queue for the medication while the ‘cougher’ can wait outside.
A separate consultation area should be available for confirmed M(X)DR-TB patients with open-air waiting area.

9.1.6 Education of all staff on infection control plans and procedures

To ensure efficient implementation of infection control practices all staff should understand the importance of infection control and their role in implementing them. Each staff member should receive basic training but where applicable job-category-specific instructions and orientation need to be provided (e.g. triage nurse to prioritize ‘coughers’, laboratory staff to follow SOPs.) Training and orientation should be given when employed and then updated regularly.

Basic training and orientation for all health workers should prioritise non-medical staff like cleaners and maintenance staff as they often spend more time in the wards than for instance doctors placing them at higher risk. Training should include:

- Basic concept of TB transmission and pathogenesis
- Risk of TB transmission to staff
- Symptoms and signs of TB
- Basic concept of M(X)DR-TB
- Impact of HIV infection on increasing risk of TB
- Preventive measures available for staff with HIV
- Specific infection control measures and practices that reduce TB transmission
- Importance of the infection control plan and the responsibility of each staff
- Measures staff can take to protect themselves from TB and M(X)DR-TB and their rights

9.1.7 Protection of staff

All health staff are not at equal risk of acquiring infection, and for many cadres of Health staff the risk is almost equal to that of the general community. Those at high risk are staff in prolonged close contact with infectious (smear-positive) M(X)DR tuberculosis cases, eg. nursing staff and other staff in M(X)DR tuberculosis wards/centres; staff involved in aerosol-producing procedures, eg. pulmonary physicians, respiratory technicians and other medical staff performing bronchoscopy, sputum induction, tracheal intubation, aerosolised pentamidine therapy and autopsy procedures. Staff who are HIV-positive should not be involved in regular M(X)DR tuberculosis patient management. Health staff in primary health care centres involved in sputum collection from TB suspects and those in prolonged close contact with retreatment tuberculosis patients are also considered at risk.

The importance of a continuous awareness of risk situations and their avoidance should be stressed. Staff should refrain from unnecessarily entering the high-risk areas. Health staff should be informed about the increased risk of acquiring tuberculosis (and M(X)DR disease) should they become HIV positive.

A baseline assessment of staff which includes standardised questionnaire on past TB disease, BCG status, underlying medical conditions and past contact with TB cases, as well as a baseline chest x-ray should be performed. A baseline blood serum sample could also be collected for HIV testing, after proper confidential counselling. Every six months, health staff should be screened for signs and symptoms of TB (using the standardized questionnaire) and
of HIV. Annually, the health staff should be offered a chest x-ray examination for evidence of recent TB disease.

9.2 Environmental Controls

Environmental (or engineering) controls assume that unsuspected, untreated TB patients will enter hospitals despite all efforts to identify them. In addition, there are certain high-risk settings, such as laboratory, sputum induction rooms, and rooms for the evaluation of newly admitted patients who may have untreated TB or M(X)DR-TB, where engineering interventions are necessary to reduce risk. Engineering controls attempt to reduce the concentration of infectious droplet nuclei in the air. They include:

- natural and/or mechanical ventilation,
- ultraviolet germicidal irradiation (UVGI),
- high efficiency particulate air filtration (Hepa-filtration).

N.B Environmental methods should never replace administrative controls; in fact, they should work together.

9.2.1 Natural Ventilation

Ventilation is used to dilute the infectious aerosolised *M. tuberculosis* particles out of the air thereby reducing the chance for nosocomial transmission. Ventilation should be taken into account in the risk evaluation.

In warm climates like Ethiopia, infection control often depends on natural ventilation. The efficacy of natural ventilation has been demonstrated in Peru, but it might depend on climatic conditions. In warm climates, patients spend much of their time out of doors where transmission is highly unlikely. However, at night, for security and warmth, patients stay indoors with doors and windows usually closed tightly. Thus, patients in sub-Saharan Africa (warm climate) and in Siberia (cold climate) may endure similar high-risk conditions.

Wherever possible we must try to ensure that fresh air is moving from risk areas to the outdoors. Air from high-risk areas should not be allowed to move into lower risk areas of the facility. The use of natural ventilation is the simplest measure to employ in a resource limited setting. It should be noted that only opening a window would not be enough. The aim is to create a directional airflow. The best way to do this is to open windows on opposite sides of a room or to have air entering from under a door and exhausting out a window. When a corridor is present, ventilation must always be implemented with the doors closed to orient airflow towards the outside and not towards the corridors.

In many instances the safest place to carry out certain procedures will be outdoors. These include: waiting areas, visitation areas, sputum collection areas and sometimes even history taking and examination areas.

9.2.2 Mechanical ventilation

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The use of extraction fans to improve ventilation in closed rooms through wall vents can be extremely useful. Mechanical ventilation systems and especially filtration systems require too much maintenance and are generally too expensive. Whirly Bird is an effective method that can be used for this purpose.

An alternative could be the employment of window fans. The principle would be the same as the case with natural ventilation; a directional airflow should be created. This must exhaust the potentially infectious air out of the building and bring in fresh air from another location. The points of in-flow and exhaust should not be too near one another. This will avoid short-circuiting of the airflow and avoid the possibility for exhausted air to re-enter the facility.

A more ambitious method is exhaust ventilation systems that provide at least six air changes per hour and prevent contaminated air from escaping into ‘clean’ parts of the facility. The most common way in which such ventilation can be established is through the use of negative pressure ventilation, in which a room is kept at negative pressure relative to the surrounding area and air is drawn into the room from the corridor and exhausted directly outside.

In all cases, if natural or mechanical ventilation is used, ventilation should be periodically monitored and evaluated. Incense sticks can be used to check the ventilation in cases where natural exhaust vents exist.

However, a little ventilation is better than none, and in facilities with mechanical ventilation systems efforts should be made to ensure that they function correctly. Data from Peru, an Escombe study, which compared natural ventilation and mechanical ventilation on the Air changes per hour (ACH) and calculated TB risk clearly indicate that TB risk is lowered much better through natural ventilation.

9.2.3 Ultra-violet Germicidal Irradiation

Ventilation can be supplemented with Ultra-violet Germicidal Irradiation (UVGI) especially where sunlight is scarce. The most common form used is upper-room UVGI as it is most cost-effective and practical to implement. This has long been known to be extremely effective in inactivating infectious particles in the air above people’s heads, while not exposing them to skin or eye irritation, which is the only practical safety concern. Normal convection currents or low velocity ceiling fans usually ensure good room air mixing, thereby decontaminating air in the breathing zone. Upper-room UVGI can safely be used while rooms are occupied, and not just to sterilize empty rooms as is commonly done in some parts of the world. It is much more important to decontaminate air while the infectious source and other occupants are present, and upper-room UVGI is designed to do so without significant radiation risks.

A growing number of manufacturers of fixtures designed for upper-room use are established in low-income countries and can provide products at relatively low cost. However, there are currently no standards for these products; the buyer should obtain advice from an engineer knowledgeable in the field as a certain contact time is needed before UV light will kill infected airborne nuclei. If the air exchange is too high the lamps will not be effective and if it is too low the infected nuclei will not be transported to an area where the lamps can destroy the nuclei.

In addition to UVGI designed for upper-room use, germicidal UV is sometimes used in ventilation ducts or in fan-driven air sterilizing devices mounted on ceilings or walls, or
portable units that can be moved from room to room. However, the efficacy of these systems is limited by the number of air turnovers they can produce, especially in large spaces. By irradiating large volumes of upper-room air at one time, upper-room systems have a quantitative advantage, especially when combined with low-velocity ceiling fans to ensure room air mixing.

Laboratories that process specimens that may be M(X)DR-TB require particularly strict environmental controls.

9.3 Personal Respiratory Protection

Because administrative and engineering controls cannot provide complete protection, the third line of defence against nosocomial TB transmission is personal respiratory protection, it includes: patient education, the use of surgical masks, and respirators.

9.3.1 Patient education

Apart from achieving better adherence to M(X)DR-TB treatment regimens patient education can also help trace possible contacts and help prevent further spread of M(X)DR-TB. Education should be done on individual basis but should also include group discussions possible during in-patient period. Often already experienced patients can help provide information in an accessible format to newly diagnosed patients as experienced with expert patients in HIV setting.

Education should include the following topics:

- What is TB and M(X)DR-TB?
- What kind of symptoms do you think people with TB have?
- How do you think TB spreads?
- Have you ever known someone with M(X)DR-TB? What happened to that person?
- Do you know that M(X)DR-TB can be completely cured?
- What is the importance of regular and appropriate intake of medication?
- How can someone with TB and M(X)DR-TB avoid spreading it?
- Why should one cover mouth when coughing?
- What is the purpose of wearing a mask if already sick?
- Why and when should patient’s family wear a respirator?
- Is TB a problem for people living with HIV? Are family members tested for TB and HIV?

The education process should be an exchanging of ideas, information or messages. It should enable the patient and her/his family and friends understand the issue and take informed decisions. For this, it should be a two-way process with service user (patient) and service provider (doctor, nurse, and pharmacist) on equal footing so that it can truly lead to decision making.

9.3.2 Surgical masks

There are important differences between a face mask and a respirator. Face masks, such as surgical masks (cloth or paper):

- Are meant to prevent the spread of micro organisms from the wearer (e.g. surgeon, M(X)DR-TB patient, etc.) to others by capturing the large wet particles near the mouth
• Do not provide adequate protection to the wearer (e.g. HCW, patient, family member) from inhaling infectious droplet nuclei in the air. Masks usually have limited filtration capacity and are loosely fitted over the mouth and nose, allowing free entrance of aerosolised *M. tuberculosis*.

Although not the highest priority intervention, disposable/cloth masks can be used to reduce aerosols generated from potentially infectious M(X)DR-TB patients. Disposable or surgical masks should therefore be considered for suspect and known infectious M(X)DR-TB patients leaving the ward for medically essential procedures or other reasons.

Immediately after use these masks should be disposed of in small plastic or paper refuse bags which should be regularly changed and discarded into larger refuse bags for incineration. Surgical masks will be disinfected and sterilized according to standard procedures for later use.

9.3.3 Respirators

Respirators are a type of mask that covers the mouth and nose. Unlike surgical masks, they contain special filter material and are designed to fit tightly to the face to prevent leakage between the face and the edge of the mask. “Particulate respirators” or simply “respirators” are designed to filter very small particles and protect the wearer from tiny (1–5 µm) airborne infectious droplets including airborne *M. tuberculosis*. Disposable particulate respirators that filter more than 95% of particles is recommended, e.g. N95 respirators, are the simplest and recommended devices to be used.

For a respirator to be effective there must be a tight seal between the mask and the wearer’s face. If the respirator does not fit correctly, infectious particles will likely follow the path of least resistance, i.e. through gaps between the respirator and the wearer’s face rather than through the filter material. Any leak between the face and the mask is a potential entry point for infectious droplet nuclei. Ideally, respirators should be “fit tested” to individual wearers. In addition to choosing the proper model for each worker, this process serves to educate workers on how to properly put on their respirator to minimize face-seal leakage.

Disposable respirators are relatively costly, but may be reused if maintained properly. They should be discarded when they become soiled, wet, or appear to lose their structural integrity, such that a tight seal can no longer be maintained between the edge of the mask and the wearer’s face. The main factors responsible for their deterioration are humidity, dirt, and crushing. The durability of these devices varies among designs and products, and the extent of use. There is often a trade-off between durability and cost. If respirators are to be re-used, they should be stored in a clean, dry location. Plastic bags should never be used since they retain humidity. Some authorities suggest respirators should be discarded after having been used for eight hours.

Because they are visible and relatively expensive, it is sometimes assumed that personal respirators alone will prevent TB transmission. However, they cannot be worn continuously and are likely not to be in use when unsuspected TB cases, or unsuspected M(X)DR-TB, are encountered. For these reasons, administrative controls that aim to detect and separate cases, and engineering controls that can reduce the risk even for unsuspected cases, are more important.
CHAPTER TEN: HUMAN RESOURCES: STAFFING AND ROLES

The development of human resources for DR-TB control programmes requires specific planning within the national TB control plan. A programme that correctly implements and manages MDR-TB cannot simply be added to the responsibilities of staff currently implementing the DOTS strategy. As well as the organization of special training courses, the availability of sufficient staff in all categories of personnel involved in the programme at all levels (clinical, laboratory, pharmaceutical and managerial) must be ensured to reach a specific long-term goal for professional competence in programme implementation.

Ensuring competent and sufficient human resources for the implementation of a DR-TB control programme of high quality requires ongoing management. As programme implementation expands, the management of human resources will become more complex because of the continued and diversified demands on staff at all levels.

10.1 Human Resources Development Plan for DR-TB Control Programmes

There are numerous constraints to the effective performance of the health workforce. In many instances, additional staff with appropriate expertise has to be recruited to manage the activities of the programme at the central and other levels. Central management should estimate staff requirements for the implementation of all aspects of the programme. 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 programme. Issues to be addressed include the level of effort and support systems (e.g. transportation) required for prolonged DOT, for health-care worker visits, for social support and for clinical and laboratory personnel. The HRD plan for the DR-TB control programme will be part of the national HRD plan which in turn is part of national strategic plan for TB/HIV 2007-2011.

10.2 Responsibilities at Various Level of Health System

The MDR-TB program requires special support arrangement and the roles and responsibilities at each level should be clearly defined. The job description for the human resource at central as well as lower management and treatment site level should include the following tasks;

10.2.1 Central level (FMOH)

**Staffing:**

The central level of MDR-TB program at federal ministry of health should be staffed with qualified professionals who are capable enough the lead and coordinate the role of partners. Medical doctor with additional training in public health is most appropriate qualification for this position.

**Roles and responsibilities:**

- Coordinate the implementation of MDR-TB program by the National TB program and all partners, by providing guidance, joint planning, coordinating logistic and resource mobilization and management
• Lead development and updating of policy directions and visions through designing and regular updating of guidelines
• Conduct supportive supervision and mentorship at regional and site level implementation of MDR-TB program to ensure the implementation meets expected standards of quality
• Plan and conduct capacity building activities for program management and clinical staff at central, regional and site level. This involves developing of training materials, conduct training need assessment and conduct the training.
• Conduct monitoring and evaluation of the MDR-TB program through standardized recording and reporting system: developing database, distribution of the formats and communication of results
• Lead the national MDR-TB scale up plan in consultation with regional health bureaus and relevant stakeholders
• Advocate for feasible staff retention mechanism which could include; compensation, insurance, practically applicable incentive options with the aim of insuring staff motivation, recognition of good performance, priority to access MDR-TB treatment when needed, etc.
• Assess the supply requirement, quantification, procurement and distribution of the MDR-TB program including drugs, reagents, laboratory equipments as well as infection control items.
• Coordinate improving working atmosphere at MDR-TB sites including
  o adjusting human resource number and capacity to match workload,
  o supporting renovation of infrastructure in line with infection control principles
  o supporting application of TB infection control measures by facilitating the availability of required supplies and consumables
• Identify logistic needs of the MDR-TB program at the various level and act for fulfilling the requirement, according to availability of resources.

10.2.2 Regional Health Bureau

Regional health bureaux take charge of leading and coordinating the implementation of MDR-TB program in the respective regions under guidance and collaboration with federal ministry of health. The recommended qualification for MDR-TB staff at regional level is medical doctor or degree in health related fields such as health officer or nursing. The health bureaus are responsible for the following tasks:
• Assign a focal person who is responsible for leading MDR-TB program, and serve as contact person in the region
• Coordinate with NTP in selecting hospitals to establish MDR-TB treatment sites in the region
• Lead the selection of health centers for the follow up of MDR-TB patients after they complete their in-patient phase of treatment.
• Support the capacity building of selected health facilities for MDR-TB program, in terms of infrastructure improvement and human resource
• Coordinate the training of staff on MDR-TB training
• Support the logistic need of the MDR program in transportation, provision of supplies, drugs and other necessary inputs.
• Conduct monitoring and evaluation of the MDR-TB program through regular supportive supervision, timely collection and analysis of report and review meetings
10.2.3 MDR-TB treatment hospital

The MDR-TB program at treatment hospital level will be lead by a team of health care providers (See chapter Two). The job description at hospital level MDR-TB program should include the following;

- Lead the clinical management of MDR-TB cases
  - Identification of suspects
  - Confirm diagnosis through clinical assessment and laboratory investigation
  - Decide on starting confirmed cases on treatment including choice of regimen
  - Conduct follow-up treatment during the in-patient phase
  - Conduct monthly check up of MDR-TB patients on follow-up at health center following discharge
- Coordinate the supply management for MDR-TB
  - Quantify drug and related supplies requirement and submit request to NTP on regular basis
  - Distribute drug to treatment health centers based on the number of discharged patients and their dosage
  - Quantify laboratory and infection control supplies requirement and submit request to NTP on regular basis
- Organize case discussion to strengthen experience sharing among practitioners
- Coordinate the recording and reporting of patients information through maintaining adequate amount of formats and registers, and submit reports to NTP regularly
- Support the application of infection control procedures including administrative, environment and personal protection measures
- Conduct health education on MDR-TB in health facility
- Supportive supervisory visit to treatment centers to ensure quality of care given to MDR-TB patients during their follow-up period
- Training of health workers at selected treatment center on patient specific information for proving outpatient MDR-TB treatment

10.2.4 Treatment follow up centre

After patients are discharged from hospital, they receive their treatment at a health center selected based on the agreed criteria. The job descriptions at such treatment centers should include;

- Identification of suspects and refer them to the MDR-TB hospital for investigation and start of treatment
- Provide treatment during the daily injection phase for patients that completed in-patient phase at the MDR-TB hospital
- Refer MDR-TB patients for monthly check up at MDR-TB hospital
- Quantify drug and related supplies requirement and submit request to NTP on regular basis
- Support the application of infection control procedures in health center as well as household level
- Conduct health education on MDR-TB in health facility
- Recording of patient information and submit report to MDR-TB hospital regularly
- Training of family or community MDR-TB DOT provider for daily supervision of treatment at household level
- Refill of drug to family DOT provider on monthly basis
• Supportive visit to patient’s home during the home based phase of treatment follow up
• Conduct contact tracing
• Conduct retrieval of absentees

10.3 Training

All health care workers involved in diagnosis and treatment of MDR-TB patients should be given training on MDR-TB management. As the county doesn’t have standardized training curriculum for MDR at the moment, during the beginning phase of the program two basic approached will be applied. The first step is to arrange an overseas training to countries with proven good record of MDR-TB program and that are known to conduct international level training. This arrangement will give chance for core MDR-TB team to achieve good level of knowledge and skill that enable establish strong MDR-TB program in Ethiopia. National TB program has secured adequate funding from partners to cover the cost of overseas training required during the starting phase of the program.

Second approach will be to organize in country training program. This is will be facilitated by the team who attended the overseas training with technical assistance by international MDR-TB experts. It is planned that this approach will enable to train adequate number of health workers to establish the required qualified pool of staff. Such training can be organized serially to meet the demand of the growing MDR-TB program. In order to ensure sustainability of good quality standardized training program, a training module on MDR-TB will be developed by NTP together with partners.

10.4 Staff Retention Mechanisms

A difficult challenge to the introduction of MDR-TB treatment within the existing DOTS program is the issue of retaining the human resource. Given the limited opportunity of training health workers in MDR-TB management and its related cost as well as the fact that it is just new program to the country, it is not realistic to expect adequate number of qualified MDR experts. Therefore, MDR-TB program has the lowest degree of tolerance to staff turn over as it is nearly impossible to look for replacement.

MDR-TB doesn’t pose extra risk of TB transmission, other than the usual risk in non-MDR forms of TB, however, staff involved in MDR-TB treatment usually fear risk of acquiring the infection and they request for some sort of compensation to protect their health. While improving the awareness of health workers on infection prevention measures to minimize risk of MDR-TB, remains the principal modality of increasing staff confidence, it is also advisable to implement some alternative mechanisms that help retaining the experienced work force. Based on the reality at implementation level various staff retention mechanism can be applied and generally the following option could be considered.

• Health insurance
  o Health care providers, who develop MDR-TB because of their exposure to the disease in their work place, should be entitled for priority for free treatment of MDR-TB including all required concomitant medication.

• Compensation
  o Health workers, who develop MDR-TB because of their exposure to the disease in their work place, should be entitled for:
- Full payment of salary even if duties have to be interrupted for some time (at least while staff remains sputum smear positive, or while too sick to work).
- Reasonable placement to other area of work as appropriate with full payment if complication remains.
- Assisted access to free M(X)DR-TB treatment including all concomitant medication required.

- Incentive
  - Resource permitting, health care providers working in MDR-TB treatment should be given some sort of incentive to encourage their performance. This can range from the easiest incentive such as ‘recognizing good performance in form of certificate’ to monetary form which should be consistent with the national human resources management policies.
  - Health workers in MDR-TB treatment sites should be used as trainers, depending on their capacity, while conducting local training. This fosters their professional development and enhances social responsibility and is opportunity for associated financial benefits.

- Staff placement
  - Health care workers who are known to have HIV infection should be entitled for reasonable placement to other area of work that help to minimize their risk of acquiring MDR-TB
CHAPTER ELEVEN: MANAGEMENT OF SECOND-LINE ANTI-TB DRUGS

One of the crucial issues to consider in designing and implementing an effective MDR-TB treatment program is the sustainable availability of quality assured second-line drugs. Especially, considering the individual level and public health consequences of treatment interruption, the need for effective supply of these drugs becomes imperative. The purpose of this chapter is, therefore, to provide information and guide on the critical issues of second-line anti-TB drugs management in Ethiopia.

In general, the management of the second-line drugs will be governed by the national public sector pharmaceutical logistics system principles that are in effect for all pharmaceutical products. Moreover, in line with the direction of the Federal government, the logistics management of these crucial drugs will be integrated with that of the first-line anti-TB drugs and, when feasible, with the management of products of other programs as well. However, some aspects of managing the second-line drugs might require special considerations as outlined in this chapter.

In the future, with in the framework of the national pharmaceutical logistics system, a comprehensive standard operating procedure (SOP) shall be developed for first line and second line anti-TB drugs management.

11.1 Selection and Quantification of Second-Line Drugs

11.1.1 Selection of second-line drugs:

The selection process for second-line medicines differs considerably from selection of first-line treatment because:

- Only a limited supply of second-line treatments is available.
- More medicines are needed for longer periods of time (from 18 up to 24 months) than with first-line treatment.
- Second-line medicines are much more expensive (up to 100 times more) than first line.
- Second-line medicines are more toxic than first line.
- Second line-medicines are not as effective as first line.
- Second line drugs have short shelf life compared to first line drugs

The Criteria for selection of second line drugs, is based on the recommendations of WHO. Therefore, the national TB and Leprosy Control Team (TLCT) of the Federal Ministry of Health (FMOH) selected the list of second-line medicines for Ethiopia by using such criteria. These drugs are listed in Chapter four of this guideline. Therefore, selection of drugs for procurement purposes should be based on and limited to the list incorporated in this guideline.

A crucial point to note is that every regimen shall have at least four proven effective drugs and must be designed in such a way that it contains proper combination of medicines among the different groups.

For the initial phase of the MDR-TB treatment, the drugs will be selected for both the standardized and individualized regimens. For subsequent procurements, selection will be based on the rate of service expansion, lessons learnt from treated individuals and consumption pattern.
11.1.2 Quantification:

Quantification of second-line drugs is important to prepare and justify the budget for a MDR-TB treatment and resupply the program with subsequent orders. However, quantification of these drugs differs from that of first-line drugs for the following reasons:

- Their shelf life is usually short: 24–36 months for most medicines.
- Treatment duration may even exceed shelf life.
- The lead time may be longer because no local manufacturers are located in the country.
- Ancillary medicines and supplies for managing adverse effects should be considered simultaneously.
- MDR-TB treatment project is new to the country, unlike first-line TB treatment, where there are trained personnel with many years of experience estimating drug requirements.
- Reliable epidemiological data for MDR-TB are not as readily available as for first-line treatment.
- For individualized regimens, the data requirements needed for quantification are more difficult to collect, aggregate, and use for estimating medicines requirements.

In general, quantification of second-line drugs will be conducted annually with flexibility for revision before placing an order for procurement. The following factors should be considered during the quantification and revision processes.

- Epidemiology of Drug resistance TB in Ethiopia (Morbidity reports and surveys)
- DST confirmed profile of previous cohorts (the resistance pattern and serotype)
- Determined cohort number and cohort size
- Duration of treatment for both intensive and continues phase
- The standardized and individualized protocols based on the national MDR-TB guideline
- Consumption report and experience of previous cohorts
- Maximum shelf life of Drugs and lead time for delivery and utilization of drugs.
- Availability of fund for all determined amount of drugs including freight, quality checking, port clearance and inland transport and insurance cost.

Based on the experience from the initial cohort, subsequent orders shall be quantified based on morbidity method (number of cases × the standardized regimen). The subsequent orders should also be adjusted by observed consumption. However, for the individualized treatments, a reasonable stock will be made available for six months as the requirements are difficult to predict.

11.2 Procurement

Like all other drugs, the guiding principles of anti-TB drugs procurement are to procure the most effective medicines in the right quantities, to select reliable suppliers of high-quality products, to ensure timely delivery, and to achieve the lowest possible cost for all products. However, there are major challenges with regards to second-line TB medicines procurement as they are expensive and often not immediately available, even in international markets.
To coordinate all second line anti-TB drugs provision and to exploit bulk procurement advantages, second-line drugs procurement shall be managed centrally by FMoH for the national program. The procurement shall be based on the national need forecasted by FMoH and the best modality of procurement, which helps to ensure sustainable availability of quality drugs, shall be adopted among the available alternatives.

The two practical options available for second-line anti-TB drugs procurement are: a competitive tender in international markets using standard procedures; and direct procurement using the Green Light Committee mechanism.

At this particular time, the quotable price advantage of competitive bidding that is expected to arise from high competition of suppliers does not seem to apply for second-line anti-TB drugs. This is explained by the fact that the demand for these drugs is very low, which means few suppliers are interested in meeting the low demand; as a result, little competition exists, which, in turn, implies higher prices. On the other hand, pooled procurement by an organization that procures on behalf of several countries, thus increasing the number of patients who require second-line medicines, remains a practical strategy to bring down the price.

Accordingly, for the first phase, the procurement of second-line anti-TB drugs for Ethiopia shall be managed by the procurement agent of GLC/GDF, which is currently IDA.

11.2.1 Drug registration and importation

To import a drug product into the country, the following requirements should be fulfilled among others:

- the drug has to be included in the ‘List of Drugs for Ethiopia’ (LIDE)
- the drug product (be it generic or brand) has to be registered by the Drug Administration and Control Authority of Ethiopia (DACA)
- the manufacturer has to have a good manufacturing practice (GMP) certificate from WHO and it must be approved by DACA (sometimes after physical GMP inspection by DACA experts)

Drug Administration and Control Authority (DACA) is in charge of updating the essential list of drugs for Ethiopia (LIDE) and maintaining registration of pharmaceutical products. For registration of drug products, the supplier must file an application to DACA and has to provide relevant documents as per the guideline of ‘Registration for Human Drugs’.

Currently, some of the second-line drugs are not included in the LIDE and most of them are not registered in the country; TLCT/FMOH shall work in close collaboration with suppliers and DACA to facilitate registration of these important drugs.

11.2.2 Quality Assurance and Quality Control

Second line anti-TB drugs will be procured from WHO prequalified companies through the GLC approval by current GLC/GDF procuring agent. In-country quality control activities are the responsibilities of DACA; onsite physical inspection before port clearance and sampled laboratory analysis shall be conducted according to the rules and regulations of DACA.

11.2.3 Shelf life
On arrival in country, all second-line anti-TB drugs procured by the public health system must have the minimum shelf life set by the standard. This is especially very important for second-line drugs as their shelf lives are very short.

### 11.3 Storage and Distribution

#### 11.3.1 Storage

The storage of second-line anti-TB drugs at all levels in the supply chain shall be as per the appropriate recommendation indicated for each item by the manufacturer. At all levels, the drug products shall be physically inspected during each transaction and problems shall be documented, if any. The PFSA, at national level, and selected MDR TB management centers are responsible for the proper storage, inventory, and monitoring of second-line anti-TB drugs. TLCT/FMOH, Regional Health Bureaus, DACA, and partner shall conduct supportive supervision and provide technical support to ensure proper storage practices in MDR management centers and satellite treatment sites. The FMOH shall be responsible to set the standard for pharmaceutical storages and shall work with relevant internal and external stakeholders to build health facilities storage capacity.

#### 11.3.2 Distribution

Up on arrival at port, PFSA shall be responsible for clearance and in-country distribution of the drugs as per the national system. Centrally, second-line anti-TB drugs shall be stored at PFSA warehouse and shall be distributed to selected treatment centers as per the distribution plan prepared and endorsed by TLCT/FMOH. Distribution of these drugs shall be integrated with that of the first-line anti-TB drugs to maximize efficiency of the management. Special fast track distribution mechanism can be arranged with in this framework if the need arises.

For the first phase of MDR-TB treatment, second-line drugs shall be distributed to St. Peters’ Hospital, which will be the first site to initiate the service. As the service expands to other Hospitals and regions, treatment sites shall receive their drugs from PFSA as per the national public sector pharmaceutical system.

### 11.4 Inventory Control

Second-line anti-TB medicines require a strong inventory management as compared to the general pharmaceuticals. This special consideration arises from the serious health consequences of running out of stock and the huge resource implications of wastage due to expiry. Therefore, all staff working at the different levels of the supply chain should be aware of the need for strong inventory management and act accordingly.

Distribution of second-line anti-TB drugs shall be every three months; and it will be based on logistics reports from the treatment sites. At all levels, first-expiry first-out (FEFO) procedure shall be followed irrespective of the chronological order of receipt of drugs.

### 11.5 Logistics Management Information System (LMIS)

Currently, there is a national plan to develop an integrated LMIS for all pharmaceuticals, which will ultimately be applied for second-line anti-TB drugs as well. But, in the interim relevant logistics data shall be collected from all levels using the previously designed tools.
including the government vouchers. To ensure proper stock management of these drugs, TLCT/FMOH in collaboration with PFSA might develop an operational LMIS system, if found important.

11.6 Roles and Responsibilities

11.6.1 The Federal Ministry of Health (FMOH)

The FMOH will have the following roles and responsibilities through TB and Leprosy Control Team (TLCT):
- Develop/revise the national MDR TB clinical treatment guideline;
- Ensures timely inclusion of second-line anti-TB drugs in the LIDE;
- Facilitate registration of second-line drugs;
- Develop/revise and introduce a national standard operating procedures for the management of second-line drugs;
- Solicit fund for procurement of drugs for MDR/XDR TB;
- Works in close collaboration with PFSA and partners with regards to second-line drugs supply and management activities at national level;
- Lead the national quantification and revision of second-line drugs;
- Ensure availability of adequate buffer stock of second-line drugs at central PFSA warehouse;
- Coordinate distribution of second-line drugs with first line anti-TB drugs and other health products, as appropriate;
- Prepare and endorse distribution plan for second-line drugs;
- Ensure rational use of the second line drugs.

11.6.2 Pharmaceuticals Fund and Supply Agency (PFSA)

- Integrate the supply management of second-line anti-TB drugs with first line drugs and other health products;
- Lead the procurement activities of second-line drugs;
- Clear, store and distribute the drugs to its regional branches and/or health facilities as per the distribution plan prepared/endorsed by TLCT/FMOH;
- Prepares and submits distribution and stock on hand report to TLCT/FMOH on monthly basis;
- Respond to emergency requests in consultation with TLCT/FMOH;
- Work with partners responsible for drugs supply management

11.6.3 Drug Administration and Control Authority (DACA)

- Is responsible for all quality assurance and quality control activities;
- Participates in the preparation/revision of national MDR/XDR drugs supply, management and use policies and guidelines;
- Facilitates inclusion of second-line drugs in the LIDE and the registration of the drug products;
- Revise and update pre-qualified manufacturers and suppliers list and make them available;
- Inspect quality of drugs imported into the country on an on going basis;
- Receive and assess second-line anti-TB drugs quality related problems from stakeholders and give appropriate feedback on time;
- Provide all reporting formats for adverse drug reactions (ADR), side effects (SE) and quality issues;

11.6.4 MDR-TB Treatment Service Providing Health Facilities

- Ensure proper prescription and dispensing of second-line drugs;
- Ensure availability of sufficient second-line drugs in the facility;
- Receive, store and dispense second-line drugs appropriately;
- Distribute the monthly drug requirement for treatment centers for transferred out patients and conduct regular monitoring of proper utilization.
- Ensure proper inventory management of second-line drugs, prepare logistics reports and submit on regular basis;
- Communicate TLCT/PFSA for emergency orders;
- Report adverse drug reactions associated with these drugs timely to DACA/TLCT;

11.6.5 Partners and Donors

- Participate in the revision of national MDR/XDR drugs supply, management and use policies and guidelines;
- Allocate fund for procurement of these drugs;
- Provide technical support to TLCT/FMOH, PFSA and treatment centers on second-line drugs supply and management;
- Support TLCT/FMOH in printing and distributing the different tools, SOPs and guidelines;
- Provide technical and financial support to FMOH on quantification and distribution of OI drugs;
CHAPTER TWELVE: RECORDING AND REPORTING FORMATS

This chapter describes the management information system for Category IV 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 IV treatment. Tools are also introduced to track screening and enrolment efforts. Lastly, the chapter presents additional optional components that programs should use when it is feasible and relevant.

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

- A standardized method of recording and reporting should be implemented in DR-TB programs.
- DR-TB treatment cards should have an expanded section for information on patients with HIV.*
- International Health Regulations should be followed.*

12.1 Aims of the Information System and Performance Indicators

The aims of the information system are twofold:

a) To allow managers of national TB control programmes at different levels to monitor overall programme performance (such as 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;

b) 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).

12.2 Scope of the Information System

The information system for treatment of DR-TB is based upon, and is an extension of, the basic DOTS information system (1–5). The forms have therefore been designed to be as similar as possible to the standard forms used in DOTS programmes.

The core information system should be consistent across settings to permit comparison. The forms may be modified as necessary to suit the local context. For instance, additional variables that are considered valuable in specific situations can be included.

The core system does not include all of the detailed information that treatment units may need to manage individual patients; that information should be contained in clinical records and other special forms used in the wards or clinics, and depends on local requirements and practices.

12.4 Main Forms and Registers and Flow of Information
The forms and registers include the following:
- Category IV Treatment Card (Form 01);
- Category IV Register (Form 02);
- Request for sputum examination (Form 03);
- Laboratory Register for culture and DST (Form 04).

Reports include:
- Quarterly report on MDR-TB detection and Category IV 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 IV treatment (Form 07).

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

12.4.1 Category IV Treatment Card (Form 01)

When the relevant health authority (such as a review panel) decides that a patient should start Category IV treatment, the health staff in the treatment unit should enter the patient in the Category IV Register (Section 18.4.2). The staff should complete the Category IV 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 ticking off the supervised administration of drugs. The card represents the primary source of information to complete and periodically update the Category IV Register. The card, or a copy of the card, must always follow the patient (e.g., from a specialized hospital to an ambulatory facility). A copy of the card may be used as a notification form and later also to report the final outcome of treatment.

The Category IV Treatment Card contains the following sections:

- **Basic demographic and clinical information.** Name, address, sex, age, weight, site of disease.
- **Category IV registration number.** This is a new unique identification number assigned when the patient is entered in the Category IV register.
- **Date of Category IV registration.** The registration date in the Category IV register.
- **Previous district TB registration number and date of registration.**
- **Registration group according to result of previous antituberculosis treatment.** See Chapter 4, Section 4.5 for definitions.
- **Previous TB treatment episodes:** Lists and describes any previous antituberculosis 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 review panel (medical commission, selection committee, concilium).** These guidelines promote periodic meetings with the group of caregivers involved with
Category IV patients. This section provides a space to record major decisions by the panel.

**Page 2**
- **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 ART and/or CPT.
- **HIV flow sheet.** This section is only filled in for HIV-infected patients.
- **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.

**Page 3**
- **Medical diagnoses other than TB.** Record all other important medical diagnoses here including diabetes, hypertension, cardiomyopathy, HIV, opportunistic infections, etc.
- **Monitoring and recording side effects.** Record date, adverse effects, and suspected drug.

**Page 4**
- **DST results.** Record the date of sputum collection and results of all DST performed.
- **Monitoring of chest X-ray.**
- **Monitoring of smear and culture.** Date of sputum collection, sample number in the laboratory register and result of smear and culture should all be recorded. “Prior” refers to the sample used to indicate Category IV registration; include the date and result of that sample. Month “0” is the time of specimen collection at the start of the Category IV regimen. Requirements for monitoring of smear and culture are described in Chapter Five.

**Pages 5 and 6**
- **Regimen.** The initial Category IV 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.
- **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”. An alternative is a more detailed system containing one box for each drug prescribed daily, since there may be some inconsistency in administration among drugs.
- **Outcome of treatment.** The outcome should be recorded when the final bacteriology results become available.

12.4.2 Category IV Register (Form 02)

The national TB control programme should have two TB registers: a District Tuberculosis Register and a Category IV Register. The Category IV Register is the record of all patients who start Category IV treatment (see Chapter Five, for a general definition of Category IV patients). This register allows quick assessment of the implementation of Category IV, facilitating quarterly reporting and analysis of treatment start and outcomes.
The District Tuberculosis Register is the traditional register used by DOTS programmes in which all TB patients are first registered. In order to integrate the treatment of Categories I, II, III and IV, this register should be modified in three ways:

1. If culture is being done in addition to smear examination in a substantial number of cases, dates of collection and results should be added to both the initial testing and the follow-up areas.

2. Capability to record DST should be added, including the date of collection of the sample and the drugs that are being tested.

3. Any patient who is switched to a Category IV regimen because of resistance (without meeting the formal criteria of failure) should have the outcome category “Change to Category IV” entered in the Unit Tuberculosis Register.

When a patient is starting Category IV treatment, the health staff in the treatment unit should enter the patient in the Category IV register and indicate in the district register that the patient has entered Category IV. The date of registration should be the day when the health staff enters the patient in the Category IV Register. In some countries it may be the date of the review panel meeting. The Category IV Register should be updated regularly from the Category IV 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.

These guidelines recommend that patients infected with strains with relatively simple resistance patterns (H, HS, HE, and HZ) stay in the Unit Tuberculosis Register, where adjustment of their regimen should be recorded, including any second-line agents used. Patients infected with more complicated mono- and poly-resistance strains (involving rifampicin or HEZ resistance) or any mono- and poly-resistant strains that may have developed into MDR-TB should be entered into the Category IV Register.

Some patients started on Category IV regimens may be found to have drug-susceptible disease. Patient in this situation can be removed from Category IV treatment and placed on appropriate first-line therapy. The patient should be crossed out of the Category IV register (but the name still 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 who it has been determined should stay in the DR-TB programme should not be crossed out in the Category IV Register. Whether the patient continues on the same Category IV regimen (often done in programs using standardized regimens) or gets an individualized regimen based on DST can be documented on the treatment card and the final outcome reported in the Category IV Register. 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.

The following information is recorded in the Category IV Register:

- Category IV registration number.
- Date of Category IV 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 IV Register.

• **Site of disease (from treatment card, p. 1).** Pulmonary, extrapulmonary or both. Patients with both pulmonary and extrapulmonary TB should be classified as a case of pulmonary TB.

• **Registration group (from treatment card, p. 1).** Described in Chapter Five.

• **Second-line drugs received for more than one month prior to registration (from treatment card, p. 1).**

• **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 IV 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 IV regimen (from treatment card, p. 5).** Record the initial Category IV regimen using the drug abbreviations. Include milligram doses and number of tablets.

• **Date of start of Category IV 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 Five, for definitions.

• **HIV status (from treatment card, p.2)** Testing results, CPT and ART treatment information.

• **Comments.**

12.4.3 Request for sputum examination (Form 03)

Form 03 is the same as that recommended for DOTS programmes in the *Revised TB Recording and Reporting Forms and Registers – version 2006* (5); the upper portion is for requesting smear microscopy, the middle portion for culture and the lower for DST; the last section is used for reporting the results. When DST is requested, the registration group should be added. Results should be sent stepwise as they become available.

12.4.4 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 Laboratory Register should be compared regularly with the Category IV Register to ensure that all confirmed MDR-TB cases are entered in the Category IV Register.

12.4.5 Quarterly report on MDR-TB detection and Category IV 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 should be made quarterly in
line with the routines of the NTP. The report should be made by the unit managing MDR-TB. 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). Optionally, the patients could be split by registration group.
- The number of MDR-TB patients started on Category IV treatment during the quarter, taken from the Category IV Register (Form 02).

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

Since there may be a considerable delay between Category IV registration and the start of Category IV treatment, the patients who start treatment during the quarter may not be the same as the ones detected with DR-TB. The information gives however an approximate indication of treatment coverage. These guidelines encourage programs to calculate the average delay between detection of DR-TB and treatment start.

12.4.6 Six-month interim outcome assessment of confirmed MDR-TB case (Form 06)

Since treatment takes on average two years before final results are known, the TB programme needs more updated information on treatment outcome. Form 06 can be 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, transferred out patients are all recorded. Bacteriological results are based on the smear and culture data during months 5 and 6 of treatment. Consider the 6-month outcome assessment unknown for a particular patient if a culture or smear results is unknown for either month 5 or 6.

All cases from the Category IV Register should be included in this report.

The form should be 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. For instance, TB patients who started treatment during the first quarter of a year (1 January to 31 March), should have the form filled in 1 January of the following year.

12.4.7 Annual report of treatment result of confirmed MDR-TB patients starting Category IV 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 IV 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.
12.5 Addressing the Backlog of Patients in Whom Category IV Treatment Failed in the Past

When Category IV treatment is being introduced, there may be a large group of patients who are still sputum smear-positive after supervised Category II treatment from previous years. There may also be patients 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. While preparing for Category IV treatment, TB programmes should keep a list of these patients. When Category IV treatment becomes available, such cases with evidence of active disease should follow the national protocol for Category IV treatment start, ideally having a DST done at the start to confirm MDR-TB.

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

12.6 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. The staff require basic knowledge of the DOTS information system, with additional training on the specifics of the Category IV forms.

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 Category IV management should regularly (at least weekly) compare the Category IV Register with the DST register in all the laboratories performing DST to ensure that all patients diagnosed with MDR-TB are started on Category IV treatment. The inclusion of MDR-TB patients from the Laboratory Register should take into consideration the quality of the DST performed in the laboratory. Patients diagnosed with MDR-TB in laboratories without proper quality assurance (i.e. in many private laboratories the quality of DST is completely unknown) should not be included in the Laboratory Register for Culture and DST (Form 04) until their DST has been confirmed in a qualified laboratory.

12.7 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 IV Treatment Card, and lists similar to the Category IV Register can then be generated. Print-outs of the list may be compared with the handwritten Category IV 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 IV Register should be kept, since otherwise corrections can not be seen.
## ANNEX I. WEIGHT-BASED DOSING OF DRUGS FOR TREATMENT OF DR-TB

Weight-based dosing of antituberculosis drugs in the treatment of drug-resistant TB

<table>
<thead>
<tr>
<th>Medication (Drug Abbreviation), (Common Presentation)</th>
<th>Weight Class</th>
<th>&lt;33 KG</th>
<th>33–50 KG 51–70 KG</th>
<th>&gt;70 KG (Also Maximum Dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GROUP 1: FIRST-LINE ORAL ANTITUBERCULOSIS DRUGS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid (H) (100, 300 mg)</td>
<td>4–6 mg/kg daily or 8–12 mg 3 x wk</td>
<td>200–300 mg daily or 450–600 mg 3 x wk</td>
<td>300 mg daily 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>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>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>30–40 mg/kg daily</td>
<td>1000–1750 mg</td>
<td>1750–2000 mg</td>
<td>2000–2500 mg</td>
</tr>
<tr>
<td><strong>GROUP 2: INJECTABLE ANTITUBERCULOSIS DRUGS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptomycin (S) (1 g vial)</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>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>15–20 mg/kg daily</td>
<td>500–750 mg</td>
<td>1000 mg</td>
<td>1000 mg</td>
</tr>
<tr>
<td>Capreomycin (Cm) (1 g vial)</td>
<td>15–20 mg/kg daily</td>
<td>500–750 mg</td>
<td>1000 mg</td>
<td>1000 mg</td>
</tr>
</tbody>
</table>
### GROUP 3: FLUOROQUINOLONES

<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>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) (250, 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>Moxifloxacin (Mfx) (400 mg)</td>
<td></td>
<td>7.5–10 mg/kg daily</td>
<td>400 mg</td>
<td>400 mg</td>
<td>400 mg</td>
</tr>
</tbody>
</table>

### GROUP 4: ORAL BACTEROSTATIC SECOND-LINE ANTITUBERCULOSIS 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>Ethionamide (Eto) (250 mg)</td>
<td></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) (250 mg)</td>
<td></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) (250 mg)</td>
<td></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) (300 mg)</td>
<td></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 (PAS) (4 g sachets)</td>
<td></td>
<td>150 mg/kg daily</td>
<td>8 g</td>
<td>8 g</td>
<td>8-12 g</td>
</tr>
<tr>
<td>Sodium PAS</td>
<td></td>
<td>Dosing can vary with manufacture and preparation: check dose recommended by the manufacturer.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thioacetazone (Th)</td>
<td></td>
<td>Usual dose is 150 mg for adults</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 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-ARE NOT ESTABLISHED

<table>
<thead>
<tr>
<th>MEDICATION (DRUG ABBREVIATION), (COMMON PRESENTATION)</th>
<th>OPTIMAL DOSES FOR DR-</th>
<th>Dose</th>
<th>Dose</th>
<th>Dose</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clofazimine (Cfz)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usual adult dose is 100 mg to 300 mg daily. Some clinicians begin at 300 mg daily and decrease to 100 mg after 4 to 6 weeks.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linezolid (Lzd)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usual adult dose is 600 mg twice daily. Most reduce the dose to 600 mg once a day after 4 to 6 weeks to decrease side effects.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin/Clavulanate (Amx/CIV)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dosages for DR-TB not well defined. Normal adult dose 875/125 mg twice a day or 500/125 mg three times a day. Dosages of 1000/250 have been used but adverse side-effects may limit this dosing.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thioacetazone (Thz)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usual adult dose is 150 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imipenem/cilastatin (Ipm/Cln)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usual adult dose is 500-1000 mg IV every 6 hours.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarithromycin (Cln)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usual adult dose is 500 mg twice daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-dose isoniazid (High-dose H)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-20 mg/kg daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## ANNEX II. SUMMARY OF THE GENERAL PRINCIPLES FOR DESIGNING TREATMENT REGIMENS

<table>
<thead>
<tr>
<th>Basic Summary Principles</th>
<th>Comments</th>
</tr>
</thead>
</table>
| 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. | Effectiveness is supported by a number of factors (the more 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 resistance to the drug.  
- Drug resistance survey documents resistance is rare in similar patients.  
- The drug is not commonly used in the area. |
| 2. Do not use drugs for which there is the possibility of cross-resistance | Many antituberculosis agents 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). |
| 3. Eliminate drugs that are not safe in the patient | 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. |
| 4. Include drugs from Groups 1 to 5 in a hierarchal order based on potency | Use any of the first-line oral agents (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. |
## ANNEX III. SIDE EFFECT AND ITS MANAGEMENT STRATEGIES

<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>Gastritis</td>
<td>PAS, Eto/Pto</td>
<td>1. H2-blockers, proton-pump inhibitors, or antacids.</td>
<td>1. Severe gastritis, as manifested by haematemesis, melaena or haematechezia, is rare.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Stop suspected agent(s) for short periods of time (e.g., one to seven days).</td>
<td>2. Dosing of antacids should be carefully timed so as to not interfere with the absorption of antituberculosis drugs (take 2 hours before or 3 hours after antituberculosis medications).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Lower dose of suspected agent, if this can be done without compromising regimen.</td>
<td>3. Reversible upon discontinuation of suspected agent(s).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Discontinue suspected agent if this can be done without compromising regimen.</td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td>Cs, H, fluoroquinolones</td>
<td>1. Suspend suspected agent pending resolution of seizures.</td>
<td>1. Anticonvulsant is generally continued until MDR-TB treatment is completed or suspected agent discontinued.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Initiate anticonvulsant therapy (e.g. phenytoin, valproic acid).</td>
<td>2. History of previous seizure disorder is not a contraindication to the use of agents listed here if a patient’s seizures are well controlled and/or the patient is receiving anticonvulsant therapy.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Increase pyridoxine to maximum daily dose (200 mg per day).</td>
<td>3. Patients with history of previous seizures may be at increased risk for development of seizures during MDR-TB therapy.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Restart suspected agent or reinitiate suspected agent at lower dose, if essential to the regimen.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Discontinue suspected agent if this can be done without compromising regimen.</td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Cs, H, S, Km, Am, Cm, Vi, Eto/Pto, fluoroquinolones</td>
<td>1. Increase pyridoxine to maximum daily dose (200 mg per day).</td>
<td>1. Patients with co-morbid disease (e.g. diabetes, HIV, alcohol dependence) may be more likely to develop peripheral neuropathy, but these conditions are not contraindications to the use of the agents listed here.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Change injectable to capreomycin if patient has documented susceptibility to capreomycin.</td>
<td>2. Neuropathy may be irreversible; however, some patients may experience improvement when offending agents are suspended.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Initiate therapy with tricyclic antidepressants such as amitriptyline. Non-steroidal anti-inflammatory drugs or acetaminophen may help alleviate symptoms.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Lower dose of suspected agent, if this can be done without compromising regimen.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Discontinue suspected agent if this can be done without compromising regimen.</td>
<td></td>
</tr>
<tr>
<td>Hearing loss.</td>
<td>S, Km, Am, Cm, Clr</td>
<td>1. Document hearing loss and compare with baseline; audiometry if available</td>
<td>1. Patients with previous exposure to aminoglycosides may have baseline hearing loss. In such patients, audiometry may be helpful at the start of MDR-TB therapy.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Change parenteral treatment to capreomycin if patient has documented susceptibility to capreomycin.</td>
<td>2. Hearing loss is generally not reversible.</td>
</tr>
<tr>
<td>Condition</td>
<td>Drugs</td>
<td>Actions</td>
<td></td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>----------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Psychotic symptoms</td>
<td>Cs, H, fluoroquinolones, Eto/Pto</td>
<td>1. Stop suspected agent for a short period of time (1-4 weeks) while psychotic symptoms are brought under control.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Initiate antipsychotic therapy.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Lower dose of suspected agent if this can be done without compromising regimen.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Discontinue suspected agent if this can be done without compromising the regimen.</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>Socio-economic circumstances, chronic disease, Cs, fluoroquinolones H, Eto/Pto.</td>
<td>1. Improve socioeconomic conditions.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Group or individual counseling.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Initiate antidepressant therapy.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Lower dose of suspected agent if this can be done without compromising regimen.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Discontinue suspected agent if this can be done without compromising regimen.</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>PAS, Eto/Pto</td>
<td>1. Initiate thyroxine therapy.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. The combination of ethionamide/protonamide with PAS is more frequently associated with hypothyroidism than the individual use of each drug.</td>
<td></td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>Eto/Pto, PAS, H, E, Z</td>
<td>1. Assess for dehydration; initiate dehydration if indicated.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Initiate antiemetic therapy.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Lower dose of suspected agent, if this can be done without compromising regimen.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Discontinue suspected agent if this can be done without compromising regimen – rarely necessary.</td>
<td></td>
</tr>
<tr>
<td>Hepatitis</td>
<td>Z, H, R, Eto/Pto, PAS, E, fluoroquinolones.</td>
<td>1. Stop all therapy pending resolution of hepatitis.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Eliminate other potential causes of hepatitis.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Consider suspending most likely agent permanently. Reintroduce remaining drugs, one at a time with the most hepatotoxic agents first, while monitoring liver function</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>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.</td>
<td></td>
</tr>
</tbody>
</table>

3. Increase frequency and/or lower dose of suspected agent if this can be done without compromising the regimen (consider administration three times per week).

4. Discontinue suspected agent if this can be done without compromising the regimen.

3. The risk of further hearing loss must be weighed against the risks of stopping the injectable in the treatment regimen.

3. The risk of further hearing loss must be weighed against the risks of stopping the injectable in the treatment regimen.

1. Some patients will need to continue antipsychotic treatment throughout MDR-TB therapy.

2. Previous history of psychiatric disease is not a contraindication to the use of agents listed here but may increase the likelihood of psychotic symptoms developing during treatment.

3. Psychotic symptoms are generally reversible upon completion of MDR-TB treatment or cessation of the offending agent.

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.

1. Completely reversible upon discontinuation of PAS or ethionamide /protonamide.

2. Generally reversible upon discontinuation of suspected agent.
<table>
<thead>
<tr>
<th>Renal toxicity</th>
<th>S, Km, Am Cm, Vi</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Discontinue suspected agent.</td>
<td>1. History of diabetes or renal disease is not a contraindication to the use of the agents listed here, although patients with these comorbidities may be at increased risk for developing renal failure.</td>
</tr>
<tr>
<td>2. Consider using capreomycin if an aminoglycoside had been the prior injectable in regimen</td>
<td>2. Renal impairment may be permanent.</td>
</tr>
<tr>
<td>3. Consider dosing 2 to 3 times a week if drug is essential to the regimen and patient can tolerate (close monitoring of creatinine).</td>
<td></td>
</tr>
<tr>
<td>4 Adjust all TB medications according to the creatinine clearance.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Electrolyte disturbances (hypokalaemia and hypomagnesaemia)</th>
<th>Cm, Km, Am, S</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Check potassium</td>
<td>1. If severe hypokalaemia is present, consider hospitalization.</td>
</tr>
<tr>
<td>2. If potassium is low also check magnesium (and calcium if hypocalcaemia is suspected).</td>
<td>2. Amiloride 5–10 mg QD or spironolactone 25 mg QD may decrease potassium and magnesium wasting and is useful in refractory cases.</td>
</tr>
<tr>
<td>3. Replace electrolytes as needed.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Optic neuritis</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Stop E.</td>
<td>1. Usually reverses with cessation of E.</td>
</tr>
<tr>
<td>2. Refer patient to an ophthalmologist.</td>
<td>2. Rare case reports of optic neuritis have been attributed to streptomycin.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arthralgias</th>
<th>Z, fluoroquinolones</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Initiate therapy with non-steroidal anti-inflammatory drugs.</td>
<td>1. Symptoms of arthralgia generally diminish over time, even without intervention.</td>
</tr>
<tr>
<td>2. Lower dose of suspected agent, if this can be done without compromising regimen.</td>
<td>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>
<tr>
<td>3. Discontinue suspected agent if this can be done without compromising regimen.</td>
<td></td>
</tr>
</tbody>
</table>
## ANNEX IV  POTENTIAL OVERLAPPING AND ADDITIVE TOXICITIES OF ART AND ANTI-TBC THERAPY

(Developed in close collaboration with the Antiretroviral Therapy Department (Missouri Department of Health) and with the appropriate authority.

[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>
</table>
| Peripheral neuropathy             | D4T, ddI, ddC        | Lzd, Cs, H, Aminoglycosides, Eto/Pto, E | Avoid use of D4T, ddI and ddC in combination with Cs of 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 Chapter 11. |
| Central nervous system (CNS) toxicity | EFV                  | Cs, H, Eto/Pto, Fluoroquinolones | 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 EFV alone. |
| Depression                        | EFV                  | Cs, H, Eto/Pto, Fluoroquinolones, H, Eto/Pto | 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. |
| Headache                          | AZT, EFV             | Cs                     | 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. |
| Nausea and vomiting               | RTV, D4T, NVP, and most others | Eto/Pto, PAS, H, E, Z and others | Nausea and vomiting are common adverse effects and can be managed with modalities described in Chapter 11. Persistent vomiting and abdominal pain may be a result of developing lactic acidosis. |

---

7 (Bristol-Myers Squibb, letter to providers, March 2005)
<table>
<thead>
<tr>
<th>Condition</th>
<th>Associated Medications</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>All ART treatment has been associated with abdominal pain</td>
<td>Abdominal pain is a common adverse effect and often benign; however, abdominal pain may be an early symptom of severe adverse effects such as pancreatitis, hepatitis, or lactic acidosis.</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>D4T, ddl, ddC</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, ddl, or ddC) in the future. Also consider gallstones or alcohol as a potential cause of pancreatitis.</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>All protease inhibitors, ddl (buffered formula)</td>
<td>Diarrhea is a common adverse effect. Also consider opportunistic infections as a cause of diarrhea, or clostridium difficile (a cause of pseudomembranous colitis).</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>NVP, EFV, all protease inhibitors (RTV &gt; other protease inhibitors), all NRTIs</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>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, ddl, AZT, 3TC</td>
<td>If an agent causes lactic acidosis replace it with an agent less likely to cause lactic acidosis.</td>
</tr>
<tr>
<td>Renal toxicity</td>
<td>TDF (rare)</td>
<td>TDF may cause renal injury with the characteristic features of Fanconi syndrome, hypophosphatemia,</td>
</tr>
</tbody>
</table>
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 antituberculosis medications need to be dose adjusted for renal insufficiency.

<table>
<thead>
<tr>
<th>Nephrolithiasis</th>
<th>IDV</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrolyte disturbances</td>
<td>TDF (rare)</td>
<td>Cm, Aminoglycosides</td>
</tr>
<tr>
<td>Bone marrow suppression</td>
<td>AZT</td>
<td>Lzd, R, Rfb, H</td>
</tr>
<tr>
<td>Optic neuritis</td>
<td>ddl</td>
<td>E, Eto/Pto (rare)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Protease inhibitors, EFV</td>
<td>None</td>
</tr>
</tbody>
</table>

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.

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.

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.

Suspend agent responsible for optic neuritis permanently and replace with an agent that does not cause optic neuritis.

No overlapping toxicities regarding hyperlipidemia have been documented between ART and antituberculosis medications. Follow WHO ART.
<table>
<thead>
<tr>
<th>Condition</th>
<th>Medication</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipodystrophy</td>
<td>NRTIs (especially D4T and ddI)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></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>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>D4T</td>
<td>Eto/Pto, PAS</td>
</tr>
<tr>
<td></td>
<td></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>
## ANNEX V. COMMONLY USED ANCILLARY MEDICATIONS

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>DRUG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea, vomiting, upset stomach</td>
<td>Metoclopramide, dimenhydrinate, promethazine, bismuth subsalicylate</td>
</tr>
<tr>
<td>Heartburn, acid indigestion, sour stomach, ulcer</td>
<td>H2-blockers (ranitidine, cimetidine, etc.), proton pump inhibitors (omeprazole, 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>fluoxetine, 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 benzotropine 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>dimenhydrinate, 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 lotions</td>
</tr>
<tr>
<td>Systemic hypersensitivity reactions</td>
<td>diphenhydramine, chlorpheniramine, dimenhydrinate, prednisolone, dexamethasone</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>Salbutamol, inhaled corticosteroids beclomethasone, oral prednisolone; injectable steroids eg. Hydrocortisone, dexamethasone,</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Levothyroxine</td>
</tr>
<tr>
<td>Electrolyte wasting</td>
<td>Potassium (KCl) and magnesium replacement</td>
</tr>
</tbody>
</table>
## ANNEX VI. TEMPLATE FOR STAFF HEALTH CHECK

### Baseline Screening
- Previous BCG vaccination: [ ] No [ ] Yes
- Previous tuberculosis treatment: [ ] No [ ] Yes

### Baseline Screening
- If yes, year:
- Outcome: [ ] Cured
- [ ] Treatment completed
- [ ] Treatment interrupted
- [ ] Treatment failed

### Signs and Symptoms of Tuberculosis
- Cough > 3 weeks: [ ] No [ ] Yes
- Chest pain: [ ] No [ ] Yes
- Weight loss: [ ] No [ ] Yes
- Anorexia: [ ] No [ ] Yes
- Lethargy: [ ] No [ ] Yes
- Night sweats: [ ] No [ ] Yes

### Signs and Symptoms of Tuberculosis
- Other Illnesses:

### Chest X-Ray
<table>
<thead>
<tr>
<th>Date</th>
<th>TU</th>
<th>Date</th>
<th>Result</th>
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</table>

### Sputum Investigation
<table>
<thead>
<tr>
<th>Date</th>
<th>Microscopy Result</th>
<th>Culture Result</th>
<th>Drug Susceptibility Result</th>
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### Weight (kg)
<table>
<thead>
<tr>
<th>Date</th>
<th>Microscopy Result</th>
<th>Culture Result</th>
<th>Drug Susceptibility Result</th>
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</table>

### HIV Test Offered
- [ ] No [ ] Yes
- Accepted: [ ] No [ ] Yes
## ANNEX VII. CONTACT TRACING FORM

<table>
<thead>
<tr>
<th>List all house hold members</th>
<th>Age</th>
<th>Symptoms</th>
<th>HIV status</th>
<th>Examination</th>
<th>AFB</th>
<th>CXR</th>
<th>Action</th>
<th>Comments</th>
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**List all hospital contacts**

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**List all close work contacts**

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</table>
ANNEX VIII: CATEGORY IV TREATMENT CARD (FORM 01)

Name: ______________________________________

Category IV registration number: _______________________

Date of Category IV registration: __/__/____

District TB registration number: ________________________

Date of district TB registration: __/__/____

Address: _________________________________________

Region/District: sub city ____________________________

Treatment center: _________________________________

Sex: □ M □ F

Age: ________ Date of birth __/__/____

Initial weight (kg): _______ Height (Cm): _______

Site: □ Pulmonary □ Extrapulmonary □ Both

If extra pulmonary, specific site: _______________________

Review panel meetings: dates and decisions

<table>
<thead>
<tr>
<th>Date</th>
<th>Decision</th>
<th>Next date</th>
</tr>
</thead>
<tbody>
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</tbody>
</table>

Previously tuberculosis treatment episodes

<table>
<thead>
<tr>
<th>Registration group</th>
<th>Select one only</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 New</td>
<td></td>
</tr>
<tr>
<td>2 Relapse</td>
<td></td>
</tr>
<tr>
<td>3 After default</td>
<td></td>
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<tr>
<td>4 After failure of first treatment</td>
<td></td>
</tr>
<tr>
<td>5 After failure of retreatment</td>
<td></td>
</tr>
<tr>
<td>6 Transfer in (from another category IV treatment site)</td>
<td></td>
</tr>
<tr>
<td>7 Other (previously treated without known outcome status)</td>
<td></td>
</tr>
</tbody>
</table>

Classification of previous drug use:

Used second-line drugs previously? □ Yes □ No

If yes, specify ____________________________

Drug abbreviations

First line drugs
H= Isoniazid
R=Rifampicin
e=Ethambutol
Z= Pyrazinamide
S-Streptomycin
(Th= Thiocacetazone)

Second-line drugs
Am= Amikacin
Km=kanamycin
Cm=Capreomycin
Ctx=ciprofloxacin
Ofl=Ofloxacin
Lfx=Levofloxacin
Mtx=Moxifloxacin
Gtx=Gatifloxacin
Pto=prothionamide
Eto=Ethicnamide
Cs=Cycloserine
**Patient Name_______________________**

**HIV Information (Fill for all patients)**

- **HIV testing done:**
  - Y
  - N
  - Unknown

- **Date of test:** ___/___/___
- **Results:**

- **Started on ART:**
  - Y
  - N
  - Date: ___/___/___

- **Started on CPT:**
  - Y
  - N
  - Date: ___/___/___

**ART = antiretroviral therapy;**

**CPT = co-trimoxazole preventive therapy**

---

**Antiretroviral Flow Sheet**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Start date</th>
<th>Stop date</th>
<th>Reason for stop/change</th>
</tr>
</thead>
<tbody>
<tr>
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</table>

**Reasons for interruption of medications:**

1 = Failure  
2 = Tuberculosis/Interaction  
3 = Adverse effects  
4 = Pregnancy  
5 = Stock out  
6 = Dose change  
7 = Patient refusal  
8 = PMTCT ended  
9 = Other (specify)

**Abbreviations:**

- NRT  
- 3TC = Lamivudine  
- D4T = Stavudine  
- INRT  
- ABC = Abacavir  
- DDI = Didanosine  
- TDF = Tenofovir  
- ININRT  
- NVP = Nevirapine  
- EFV = Efavirenz  
- IP  
- LDP/R = Lopinavir/ritonavir  
- NFV = Nelfinavir  
- R = Ritonavir

---

**Weight monitoring**

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

---

**Laboratory monitoring**

- **Date**
- **ALT/SGPT**
- **AST/SGOT**
- **Creatinine**
- **K**
- **TSH**
- **Hemoglobin**
- **WB count**
- **CD4**
- **Lipase**
- **HIV test**
- **Pregnancy test**
<table>
<thead>
<tr>
<th>Medical Diagnosis other than tuberculosis</th>
<th>Date</th>
<th>Type (i.e. diabetes, hypertension, cardiomyopathy, HIV, opportunistic infections)</th>
</tr>
</thead>
<tbody>
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<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Date</th>
<th>Type (i.e. neuropathy, hepatitis, rash, etc.)</th>
<th>Suspected drug</th>
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</thead>
<tbody>
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</table>

Patient Name________________________
Drug-susceptibility testing (DST) results (notation method for DST: r = resistant, s = susceptible, c = contaminated)

<table>
<thead>
<tr>
<th>Date*</th>
<th>S</th>
<th>H</th>
<th>R</th>
<th>E</th>
<th>Z</th>
<th>Km</th>
<th>Am</th>
<th>Cm</th>
<th>Fq</th>
<th>Pto/Eto</th>
<th>PAS</th>
<th>Cs</th>
<th>Other</th>
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Chest x-ray

Date | Result
-----|--------
     |        
     |        
     |        

Notes:
* All dates in the tables that report smears, culture and DST are dates the specimen was collected from the patient.
** The date the sputum was collected that led to the patient being registered with MDR-TB (if performed).

Notation method for recording smears (for non-centrifuged specimens)

<table>
<thead>
<tr>
<th>No. AFB</th>
<th>1-9 AFB per 100 HPF</th>
<th>Scanty (and report number of AFB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-99 AFB per 100 HPF</td>
<td>+</td>
<td></td>
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<tr>
<td>1-10 AFB per HPF</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>&gt;10 AFB per HPF</td>
<td>+++</td>
<td></td>
</tr>
</tbody>
</table>

Notation method for recording cultures

<table>
<thead>
<tr>
<th>No growth reported</th>
<th>0</th>
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</thead>
<tbody>
<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>
Patient Name_________________________________

Category IV Regimen (date treatment started and dosage (mg), change of dosage, and cessation of drugs)

<table>
<thead>
<tr>
<th>Date</th>
<th>H</th>
<th>R</th>
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<th>Cm</th>
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Administration of Drugs (one line per month):

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|-------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
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Make in the boxes:

O=directly observed
N=not supervised
T=drugs not taken
### Administration of Drugs (continued):

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**Make in the boxes:**

- O = directly observed
- N = not supervised
- T = drugs not taken

### Comments

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<tr>
<th>Outcome</th>
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Comments

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**ANNEX IX: CATEGORY IV REGISTER (FORM 02)**

<table>
<thead>
<tr>
<th>Unique Cat. IV Register No</th>
<th>Date entered in Cat. IV Register</th>
<th>Name (in full)</th>
<th>Sex M/F</th>
<th>Age Date of birth d/m/y</th>
<th>Address</th>
<th>District TB Register number</th>
<th>Date of registration</th>
<th>Site of Disease (P/EP)</th>
<th>Registrat ion group*</th>
<th>Result of drug susceptibility testing (DST)</th>
<th>Date sample taken for DST</th>
<th>Second line drugs already received</th>
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<td>(enter the DST that resulted in the patient being registred as a Cat IV patient. If the DST is pending it should be filed in which the results are known. See treatment card for full history of DST data)</td>
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<td>R=resistant S=susceptible C=Contaminated</td>
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*1. New  
2. Relapse  
3. After default  
4. After failure of first treatment  
5. After failure of retreatment  
6. Transfer in (from another category IV treatment site)  
7. Other
### Category IV Register

Smear (S) and Culture (C) results during treatment  
(If more than one smear or culture done in a month, enter the most recent positive result)

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<th>Category IV treatment</th>
<th>Start of treatment</th>
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<td>Transferred out</td>
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<table>
<thead>
<tr>
<th>Date of outcome given</th>
<th>HIV testing</th>
<th>ART/Y/N</th>
<th>CPT Y/N</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Date of test</td>
<td>Result</td>
<td>Start date</td>
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</tbody>
</table>

**National method for recording smears**
(for non-centrifuged specimens)

<table>
<thead>
<tr>
<th>No. AFG</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1-9 AFB per 100 HPF</td>
</tr>
<tr>
<td></td>
<td>Scanty (and report number of AFB)</td>
</tr>
<tr>
<td>1</td>
<td>10-99 AFB per 100 HPF</td>
</tr>
<tr>
<td>2</td>
<td>1-10 AFB per HPF</td>
</tr>
<tr>
<td>3</td>
<td>&gt;10 AFB per HPF</td>
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<td>4</td>
<td>+</td>
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<td>5</td>
<td>++</td>
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<tr>
<td>6</td>
<td>+++</td>
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</tbody>
</table>

**National method for recording cultures**

<table>
<thead>
<tr>
<th>Result</th>
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<tbody>
<tr>
<td>0</td>
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<tr>
<td>Fewer than 10 colonies</td>
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<tr>
<td>Report number of colonies</td>
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<tr>
<td>10-100 colonies</td>
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<tr>
<td>+</td>
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<tr>
<td>More than 100 colonies</td>
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<tr>
<td>++</td>
</tr>
<tr>
<td>Innumerable or confluent growth</td>
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<td>+++</td>
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<tr>
<td>HPF= high-power field</td>
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</table>

**Drug abbreviations**

**First line drugs**
- H= Isoniazid
- R= Rifampicin
- E= Ethambutol
- Z= Pyrazinamide
- S= Streptomycin
- (Th= Thiocetazone)

**Second-line drugs**
- Am= Amikacin
- Km= Kanamycin
- Cm= Capreomycin
- Ct= Ciprofloxacin
- Of= Ofloxacin
- Lf= Levofloxacin
- Mx= Moxifloxacin
- Gt= Gatifloxacin
- Pto= Protonamide
- Eto= Ethionamide
- Cs= Cycloserine
PAS=Paminosalicylic acid
ANNEX X: REQUEST FOR SPUTUM EXAMINATION FOR MDR-TB PROGRAM
(to be completed by treatment center)

Name of Treatment Unit/Hospital __________________________

Patient name ___________________ Age ____________ Sex (mark one) □ M  □ F

Address (in full) ________________________________________________________________

Specimen: □ Sputum  □ Pus  □ Stool  □ Other __________________________________________

Reason for examination (mark one): □ Diagnosis  □ Follow-up examination (M= _______)

Test request (mark any that are needed): □ Smear  □ Culture  □ 1st line DST  □ 2nd line DST

Date: ________________________________

Requested by: __________________________

Signature: _____________________________
ANNEX XI: LABORATORY REGISTER FOR CULTURE AND DST (FORM 04)

<table>
<thead>
<tr>
<th>Date specimen received</th>
<th>Laboratory serial number</th>
<th>Type of specimen received</th>
<th>Referring health facility</th>
<th>Patient name</th>
<th>Patient address if new</th>
<th>Sex M/F</th>
<th>Date of birth</th>
<th>Date specimen collected</th>
<th>Date specimen inoculated</th>
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</tbody>
</table>
## Laboratory Register for Culture and DST

<table>
<thead>
<tr>
<th>Reason for examination</th>
<th>Result of culture**</th>
<th>Result of confirmatory test for M. tuberculosis (positive or negative)</th>
<th>Culture sent to DST (Yes or No)</th>
<th>Name of person reporting DST results</th>
<th>Signature</th>
<th>Date results reported</th>
<th>Comments</th>
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</tbody>
</table>

**New patients or patients starting a re-treatment 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>No growth reported</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fewer than 10 colonies</td>
<td>Report number of colonies</td>
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<tr>
<td>10-100 colonies</td>
<td>*</td>
</tr>
<tr>
<td>More than 100 colonies</td>
<td>**</td>
</tr>
<tr>
<td>Innumerable of confluent growth</td>
<td>***</td>
</tr>
</tbody>
</table>
# Laboratory Register for culture and DST

<table>
<thead>
<tr>
<th>R</th>
<th>H</th>
<th>E</th>
<th>S</th>
<th>Km</th>
<th>Cm</th>
<th>Fq</th>
<th>Other</th>
<th>Other</th>
<th>Other</th>
<th>DST Results</th>
<th>Name of person reporting DST results</th>
<th>Signature</th>
<th>Comments</th>
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Report DST results as s = susceptible, r = resistant, c = contaminated
ANNEX XII: 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:

<table>
<thead>
<tr>
<th>MDR-TB</th>
<th>XDR-TB</th>
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<tbody>
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</table>

2 - Number of MDR-TB patients who started Category IV treatment during the quarter

<table>
<thead>
<tr>
<th></th>
<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>Confirmed cases</td>
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<tr>
<td>Suspected cases</td>
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1st quarter: July - September
2nd quarter: October - December
3rd quarter: January - March
4th quarter: April - June

Signature ________________________________
ANNEX XIII: 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 5 and 6 months of treatment</th>
<th>No longer on treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative (all smears and cultures negative during month 5 and 6, and at least a smear and culture done each month)</td>
<td>Died</td>
</tr>
<tr>
<td></td>
<td>Positive (any smear or culture is positive during month 5 and 6)</td>
<td>Defaulted</td>
</tr>
<tr>
<td></td>
<td>Culture and smear unknown (Consider unknown if a culture or smear results is not done for either month 5 or 6)</td>
<td>Transferred Out</td>
</tr>
</tbody>
</table>
ANNEX XIV: ANNUAL REPORT OF TREATMENT RESULT OF CONFIRMED MDR-TB PATIENTS STARTING CATEGORY IV TREATMENT (FORM 07)
(to be filled in 24 and 36 months past the closing date of year of treatment)

Year of treatment start: ________

<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>
</tr>
</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 both first- and second-line drugs</td>
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