GUIDELINES FOR THE MANAGEMENT OF DRUG RESISTANT TUBERCULOSIS (DR-TB) IN MYANMAR

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The core team revising the academic portion of the guidelines includes, Professor Tin Maung Cho, Professor Win Naing, Professor Yadanar Kyaw and Professor Ye Htun. The team members, who revised the portion of program management, includes Dr Thandar Lwin, Dr Win Maung, Dr Myo Zaw, Dr Tin Mi Mi Khaing, Dr Saw Thein, Dr Si Thu Aung, Dr Thandar Hmun, Dr Tin Tin Mar, Dr Wint Wint Nyunt, Dr Khin Zaw Latt, Dr Thynn Lei Swe, Dr Htet Myet Win Maung, Dr Aung Thu and Dr Aye Thida.

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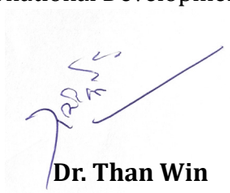

Dr. Than Win
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LIST OF ABBREVIATIONS

aDSM	Active TB drug-safety Monitoring and Management
AFB	Acid-fast bacilli
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
BHS	Basic Health Staff
CPB	Cetylpyridinium bromide
CPC	Cetylpyridinium chloride
CPT	Cotrimoxazole preventive therapy
CXR	Chest X-ray
DOH	Department of Health
DOT	Directly Observed Treatment
DOTS	the basic package that underpins the Stop TB Strategy (Directly Observed Treatment Short-Course Strategy)
DR-TB	Drug-resistant tuberculosis
DRS	Drug resistance survey
DST	Drug susceptibility testing
FLD	First-line drugs
FQ	Fluoroquinolone
GDF	Global Drug Facility
HA	Health assistant
HC	Health centre
HCW	Health-care worker
HIV	Human immunodeficiency virus
IC	Infection control
INGO	International nongovernmental organization
IR	Initial Regimen
IV	Intravenous
LHV	Lady Health Visitor
LJ	Lowenstein-Jensen
LPA	Line probe assay
MDR-TB	Multidrug-resistant tuberculosis
MMA	Myanmar Medical Association
MO	Medical Officer

MS	Medical Superintendent
MSF	Médecins Sans Frontières
NGO	Nongovernmental organization
NHL	National Health Laboratory
NSAID	Non-steroidal anti-inflamatory drug
NTP	National Tuberculosis Programme
NTRL	National TB Reference Laboratory
OPD	Out-patient department
PCR	Polymerase chain reaction
PHS	Public Health Supervisor
PICT	Provider-initiated HIV counselling and testing
PSI	Population Services International
PTB	Pulmonary tuberculosis
QA	Quality assurance
QD	Once a day (quaque die)
RR	Retreatment Regimen
RR-TB	Rifampicin-resistant TB
R/S	Regional/State
R/S TBC	Regional/State Tuberculosis Centre
R/S TBO	Regional/State TB Officer
SCC	Short Course Chemotherapy
SNRL	Supranational Reference Laboratory
TAD	Treatment after default
TAF	Treatment after failure
THNO	Township Health Nurse Officer
TB	Tuberculosis
TBC	TB Center
TMO	Township Medical Officer
TPHO	Township Public Health Officer
TSH	Thyroid-stimulating hormone
UMTBL	Upper Myanmar TB Laboratory
UV	Ultraviolet
WHO	World Health Organization
XDR-TB	Extensively drug-resistant tuberculosis

ANTI-TUBERCULOSIS DRUG ABBREVIATIONS

Amikacin	Amk
Amoxicillin/clavulanate	Amx/Clv
Bedaquiline	Bdq
Capreomycin	Cm
Clarithromycin	Clr
Clofazimine	Cfz
Cycloserine	Cs
Delamanid	Dlm
Ethambutol	E
Ethionamide	Eto
Imipenem/Cilastatin	Ipm
Isoniazid	H
Kanamycin	Km
Levofloxacin	Lfx
Linezolid	Lzd
Moxifloxacin	Mfx
Ofloxacin	Ofx
p-aminosalicylic acid	PAS
protionamide	Pto
Pyrazinamide	Z
Rifabutin	Rfb
Rifampicin	R
Streptomycin	S
Thioacetazone	Thz

INTRODUCTION

The World Health Organization (WHO) estimated that the incidence of MDR/RR-TB in Myanmar was 14 (8.9-18) thousands in 2015. Extensively drug-resistant TB (XDR-TB) has been reported since 2007 and National TB Reference Laboratory diagnosed 12 Pre XDR-TB and 14 XDR-TB patients by Second Line Solid DST in 2015. The third nationwide drug resistance survey (2012 – 2013) showed an MDR-TB rate of 5% among new cases and 27.1% among previously treated cases.

Myanmar's Ministry of Health established a National Drug-Resistant TB Committee and National Expert DR-TB Committee in September 2006, and by the end of 2007 the Green Light Committee approved an MDR-TB pilot project. The DOTS-Plus Pilot Sites were established in Yangon and Mandalay Regions and recruitment of patients was carried out in 10 townships of Yangon and Mandalay Regions, in close collaboration with WHO and Médecins Sans Frontières (MSF-Holland).

Following the encouraging initial results of the pilot project, an expansion plan for the programmatic management of drug-resistant TB (PMDT) has been developed and formed part of the Five Year National Strategic Plan for TB Control (2011-2015). With the help of Professor Michael Rich first version of the National Guideline for the management of Multi-drug Resistant Tuberculosis in Myanmar was published in May, 2013. At the end of 2015, a total of 108 townships are designated for PMDT. The cumulative number of treated patients reached 5,212 at the end of 2015. While more patients have been put on treatment, the treatment success rate has been sustained; 83% for 2013 cohort-667 patients.

WHO has also developed guidelines for the management of drug resistant TB since 2006 and made successive updates in accordance with new developments, accumulating data and evidences. The last update was released in May, 2016. A "Companion handbook", originally developed by PIH and partners (November, 2014), to the WHO guidelines for the programmatic

management of drug-resistant tuberculosis was also approved as part of WHO guidelines.

In order to improve management of DR-TB and expand nation-wide PMDT in commensurate with new developments, the National Expert DR-TB committee organized meetings in 2016 to update the existing national guideline.

This updated guideline has been prepared principally for use by NTP managers and staff, as well as partner organizations and all professionals, involved in delivering DR-TB care and implementing DR-TB control activities in Myanmar.

The following major updates are incorporated into this version:

- Xpert MTB/RIF testing algorithm
- Patient education and counseling
- Infection Control
- Medicines recommended for the treatment of rifampicin-resistant and multidrug-resistant TB
- Monitoring of patient including follow up cultures
- National aDSM
- Mono-resistant TB and Poly-resistant TB other than MDR-TB
- Pre XDR-TB and XDR-TB

The recommendations contained in these guidelines will provide necessary technical support to all the medical personnel, at different levels, taking care of patients with drug-resistant TB.

The process in preparation of the revised and extended guidelines.

The first guideline, published in May 2013, was largely developed by Professor Michel Rich after consultation with the responsible persons from National TB Program and the National Expert DR-TB committee. As new evidences emerged in both diagnosis and treatment of MDR-TB the need for updating the guidelines become obvious.

The revision of the guideline was initiated in October 2015 by the National Expert DR TB committee with assigning of various chapters to personnel involved in practical implementation of the activities mentioned in the chapters. (See table.)

	Chapters	**Assigned Persons**
Clinical Management Chapters	5, 8, 9, 10,13, 14 and 15	Prof. Tin Maung Cho, Prof. Win Naing, Prof. Yadanar Kyaw, Prof. Ye Tun
Program Management Chapters	1,20	Dr. Thandar Lwin, Dr. Si Thu Aung
	2,7	Dr. Saw Thein
	3	Dr. Tin Tin Mar, Dr. Wint Wint Nyunt, Dr. Khin Zaw Latt, Dr. Thynn Lei Swe
	4	Dr. Myo Zaw, Dr Aung Thu
	6	Dr. Tin Mi Mi Khaing
	11	Dr. Thardar Hmun
	12	Dr. Aye Thida
	16	Dr. Htet Myet Win Maung
	17	Dr. Win Maung
	18	Dr. Myo Zaw
	19	Dr. Tin Mi Mi Khaing, Dr. Aye Thida

The revised facts and procedures were discussed in details in the second Expert DR TB committee meeting held on 30th October 2016. Some changes were made in accordance with the inputs provided in the Expert DR TB committee meeting.

Final collection, compilation, edition and proof were done in December, 2016.

MOHS approved after some corrections and additions guided by MOHS in January 2017.

Chapter

1

DR-TB COMMITTEES

The National TB Programme has established a number of committees to plan, implement and monitor the DR-TB Management. The Regional/State Committees for DR-TB Management oversee direct enrolment and care of DR-TB patients.

1.1 National Committee for DR-TB Management

A National Committee for DR-TB Management was established in 2006 by the Ministry of Health to oversee the response to the DR-TB situation in the country.

Terms of reference:

1. To prepare and plan for the management of DR-TB in Myanmar
2. To provide draft recommendations on the national policy framework for management of DR-TB
3. To develop DR-TB management guidelines

Frequency of meeting: biannual

Members:

1. Deputy Director General (Disease Control), DOPH (Chairperson)
2. Deputy Director General, National Health Laboratory, Department of Medial Services
3. Professor/Head, Department of Medicine , University of Medicine (1), Yangon
4. Professor/Head, Department of Child Health, University of Medicine (1), Yangon
5. Professor/Head, Department of Respiratory Medicine, 500 Bedded Yangon Specialist Hospital, University of Medicine (1)
6. Professor/Head, Department of Respiratory Medicine, Thingungyun San Pya General Hospital, University of Medicine (2)
7. Professor/Head, Department of Respiratory Medicine, Mandalay General Hospital, University of Medicine, Mandalay
8. Professor, Special Infectious Disease Hospital, Waibargi

9. Director (Disease Control), DOPH
10. Director (Drug), Department of Food & Drug Administration
11. Medical Superintendent (MS), Aung San TB Hospital
12. Medical Superintendent (MS), Patheingyi TB Hospital
13. Regional TB Officer, Yangon Region & Lower Myanmar TB Office
14. Regional TB Officer, Mandalay Region & Upper Myanmar TB Office
15. Senior Consultant Microbiologist, National TB Reference Laboratory
16. Assistant Director, NTP, DOPH
17. Medical Officer – TB, WHO
18. Representative from MSF-Holland
19. Representative from Population Services International
20. Representative from Myanmar Medical Association
21. Programme Manager, NTP (Secretary)
22. Senior Consultant Physician, Aung San TB Hospital (1st Joint Secretary)
23. Technical Officer – TB, WHO (2nd Joint Secretary)

1.2 National Expert DR-TB Committee

The National Expert DR-TB Committee was established in 2006.

Terms of reference:

1. To advise the National Committee for DR-TB Management on technical policies
2. To oversee Regional/State Committees for DR-TB Management on all aspects of programmatic management of DR-TB including clinical management
3. To advise the Regional/State Committees for DR-TB Management on infection control
4. To involve in GLC Mission for technical aspects

Frequency of meeting: biannual and ad hoc (if necessary)

Members:

1. Professor/Head, Department of Medicine, University of Medicine (1), Yangon
2. Professor/Head, Department of Child Health, University of Medicine (1), Yangon
3. Professor/Head, Department of Respiratory Medicine, 500 Bedded Yangon Specialist Hospital, University of Medicine (1)
4. Professor/Head, Department of Respiratory Medicine, Mandalay General Hospital, University of Medicine, Mandalay
5. Professor/Head, Department of Respiratory Medicine, Thingungyun San Pya General Hospital, University of Medicine (2)
6. Commandant, Medical Research Center, Directorate of Medical Services, Ministry of Defense
7. Professor, Special Infectious Disease Hospital, Waibargi
8. Director (Disease Control), DOPH
9. Director, National Health Laboratory, DOMS

10. Medical Superintendent, Aung San TB Hospital
11. Medical Superintendent, Patheingyi TB Hospital
12. Chief Medical Officer, Prison Department, Ministry of Home Affairs
13. Senior Consultant Physician, Aung San TB Hospital
14. Regional TB Officer, Yangon Region & Lower Myanmar
15. Regional TB Officer, Mandalay Region & Upper Myanmar
16. Senior Consultant Microbiologist/Consultant Microbiologist, NTRL
17. Assistant Director, NTP, DOPH
18. Medical Officer – TB, WHO
19. Dr. Win Maung, Director (DC) Retired
20. Programme Manager, NTP (Secretary)
21. Technical Officer – TB, WHO (1st Joint Secretary)

1.3 Regional/State Committee for DR-TB Management

The Regional/State Committee for DR-TB Management meets on a quarterly basis to monitor and address programmatic issues related to the implementation of DR-TB diagnosis, treatment and care. The Regional/State Committee for DR-TB Management will perform, monitor and supervise the duties of the District/Township DR-TB Committee until decentralization has taken place.

Terms of Reference:

1. Plan and oversee operational steps in implementing, monitoring, and evaluating DR-TB management at Regional/State level
2. Supervise all aspects of programmatic management of DR-TB (including drug and supply management chain related to DR-TB) at district/township levels
3. Oversee inter-ministerial and inter-departmental coordination and collaboration on DR-TB, including transfer to other Regions/States (TB hospitals, Regional/State Tuberculosis Centre (R/S TBC), township hospitals, health facilities, communities, prisons, psychiatric hospitals, general hospitals)
4. Identify organizational bottlenecks, formulate and follow up action steps to address these bottlenecks
5. Give feedback to the National Expert DR-TB Committee on the progress of DR-TB management
6. Oversee the notified, enrolment and treatment initiation of DR-TB patients
7. Support medical management of complicated cases, including patients with concomitant diseases (e.g. HIV/AIDS, diabetes) and patients suffering from severe adverse events
8. To consult with National Expert DR-TB Committee for technical issue whenever necessary

Frequency of meeting: quarterly

Members:

1. Regional/State Public Health Director (Chairperson)
2. Medical Superintendent of Regional/State hospitals
3. Senior Consultant Physician, Hospitals
4. Senior Consultant Paediatricians
5. Senior Consultant Psychiatrists
6. Regional/State HIV/AIDS Officer
8. Microbiologist/Pathologist
9. Medico-social workers
10. District Public Health Officer
11. District (TB and Leprosy) Team Leader/MO
12. Township Public Health Officers (TPHOs)
13. Nongovernmental organizations (NGOs) involved in DR-TB management
14. Regional/State TB Officer or Regional/State AD for TB and Leprosy (Secretary)

The Secretary will present on the implementation status and challenges and give feedback on the District/Township DR-TB Committee meetings.

1.4 District/Township DR-TB Committee

The District/Township DR-TB Committee (formally known as the Hospital DR-TB Committee) meets on a monthly basis, and ad hoc as required to consult on individual patients. The committee provides an opportunity for physicians to get the highest possible consultations regarding complicated cases and to share the responsibility when making decisions in unclear situations.

Terms of Reference:

1. To notify, refer and initiate MDR-TB treatment
2. To support medical management of patients
3. To link with community DOT
4. To monitor and supervise the continuous drug and supply management chain
5. To endorse and oversee the implementation of DOT action plan
6. To periodically supervise all aspects of programmatic management of DR-TB at Township Health Centres

Frequency of committee meeting: monthly and ad hoc (if necessary)

Members:

1. District Public Health Officer/Township Public Health Officer (Chairperson)
2. MS of District/Township
3. NGOs involved in MDR-TB management at district/township level
4. Physicians
5. Paediatricians
6. Counsellors

7. Laboratory Technician
8. Pharmacist/Compounder
9. District/Township MO related to TB (Secretary)

The information that will be presented at the Regional/State Committee for DR-TB Management and/or the District/Township DR-TB Committee meetings includes:

1. Enrolment of DR-TB patients at District/Township
2. Patient progress: Medical management, logistics/drugs to be presented by District/Township Disease Control Team Leader
3. Community programme progress to be presented by TPHO
4. Programme progress to be presented by TPHO
5. Linkage between community DOT action plan to be presented by concern trained NGOs/INGOs
6. To consult with Region/State DR-TB Committee for technical issue whenever necessary

Six main areas should be discussed:

I. Situation of notified Rifampicin Resistant TB cases and enrolled MDR-TB patients

a. Patient's identity
b. Social status
c. Medical information (laboratory investigation results within 2 weeks)
d. Past anti-TB drug history
e. Pre-treatment counselling and informed consent
f. DOT action plan

Attach the laboratory investigation results, DST results and chest X-ray (CXR). Laboratory investigations (baseline) are done within 2 weeks at the National Health Laboratory (NHL) in Yangon; General Hospital Laboratory in Mandalay and other Regional/State laboratories are acceptable. If private laboratories are used, they must adhere to NTP quality standards.

II. Resolution of the DR-TB treatment by the Team

- Agree to initiate the treatment.
- Signed by at least three team members (Chair, Physician, District/Township TB Team Leader or relevant Township Public Health Officer).

III. Monitoring of patients' progress

- All patients on DR-TB treatment, summarize according to smear status, culture status, DST status, X-ray finding, weight and general condition.
- DR-TB treatment duration, dosage and side-effect are to be presented by consultant physician.
- Current drug stock balance and expiry date are to be presented by R/S TB Officer

or relevant Township Public Health Officer (current NTP report on logistic/drug stocks will be used).

IV. Community programme progress

- Township Public Health Officer and concerned Organization NGOs should present the number of patients on DR-TB drugs, any side-effects, any missed doses, drug stocks, number of supervisory visits by DOT Supervisors and any problems.

V. Programme progress

- Patients' progress
- Programme performance details such as: DOT Provider training, number of supervisory visits, number of meetings conducted and waiting list, drug balance in stock, turnaround time at laboratory to get the results, any problems to be presented by District/Township TB Team Leader.

VI. Linkage between communities DOT

- To be presented by Township Public Health Officer, NGO and medico-social workers on DOT action plan for each patient: home visits, counselling before and after discharge from hospital, plan for defaulter tracing, incentive/enabler for patients, DOT Provider and DOT Supervisor.

NOTE [Distict / Township DR-TB committe needs to consult with Region / State DR-TB committee whenever necessary]

Figure 1.1 Hierarchies of DR-TB Committees

Chapter
2

CASE-FINDING STRATEGIES FOR MDR-TB

2.1 Definitions of drug resistance

Drug-resistant tuberculosis (DR-TB) is a type of TB that has developed a genetic mutation(s) such that certain drug (or drugs) is (are) no longer effective against the bacteria. DR-TB is confirmed through laboratory tests (see Chapter 3) that demonstrate in-vitro growth of infecting isolates of Mycobacterium tuberculosis in the presence of one or more anti-TB drugs. By definition, there are five different categories of drug resistance, namely:

- **Mono-resistance:** Resistance to one anti-TB drug.
- **Poly-resistance:** Resistance to more than one anti-TB drug, other than isoniazid plus rifampicin.
- **Multidrug-resistant TB (MDR-TB):** Resistance to at least isoniazid plus rifampicin, the two most potent anti-TB agents.
- **Rifampicin-resistant TB (RR-TB):** Resistance to rifampicin detected using pheno-typic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, including mono-resistance, multi-drug resist- ance , poly-resistance (other than MDR-TB) and XDR-TB.
- **Extensively drug-resistant TB (XDR-TB):** MDR-TB, plus resistance to at least one of the fluoroquinolones, ***and*** at least one of three injectable second-line drugs (capreomycin, kanamycin and amikacin).

DR-TB patients. Any patient who falls into one of these categories of drug resistance is considered a DR-TB patient.

2.2 Patient categories to be tested for MDR-TB

Whenever possible, screening for MDR-TB should be done with molecular rapid testing, preferably with Xpert MTB/RIF (see Chapter 3 for more details). The Regional/State office is responsible for overseeing that patients in the following categories have a specimen sent for Gene Xpert at the start of TB treatment:

1. Retreatment TB cases including Retreatment regimen failure, Initial regimen failure, relapse and return after loss to follow up and others
2. Close contacts of MDR-TB patients who develop active TB
3. All TB patients and presumptive TB cases living with HIV/AIDS
4. Sputum smear positive at the end of intensive phase (non-converter and positive converter)
5. TB patients residing in area with high MDR TB Prevalence (MDRTB among new TB patients is >10%).
6. TB patients with diabetes mellitus*
7. All smear Positive new TB cases
8. Other cases to be considered individually by MDR-TB committee

All presumptive** MDR-TB cases need to undergo DST and all diagnosed RR-TB cases should be recorded in Township Notification Register for RR-TB/DR-TB (MDR-TB Form 06: Notified DR-TB Register) patients in each township. Monthly and quarterly township report should be sent to Region/State and Central levels.

** These categories have been started in mid-2016 in the townships with Xpert machine.*
*** The term, "presumptive MDR-TB cases", may have to be reviewed when Xpert MTB/RIF is more extensively used for case finding of TB in general.*

2.3 Patient categories to be enrolled in the MDR-TB Programme

Any patient found to have resistance to isoniazid and rifampicin (or rifampicin alone) should be enrolled in the MDR-TB programme for an MDR-TB regimen (see Chapter 5 for the standardized MDR-TB regimens to be used). Figure 2.1 to 2.4 illustrate the diagnostic algorithms for the detection of RR/MDR-TB.

There are 7 registration categories for MDR-TB:

1. New
2. Non-converter ☐ IR ☐ RR
3. Treatment after loss to follow up ☐ IR ☐ RR
4. Treatment after failure of treatment ☐ IR ☐ RR
5. Relapse ☐ IR ☐ RR
6. Treatment after MDR-TB treatment

6.1 Standard Regimen

6.2 Other Regimen
(☐ LFU, ☐ Failure, ☐ Relapse)

7. Others (a. Unknown regimen/outcome of previously treated TB
b. patient who does not fit in registration group 1-6)

Special considerations for MDR-TB programme enrolment. While not common, there can be some conditions which may not be suitable or practical for use of MDR-TB regimens. The R/S/D TBO is responsible for identifying any such situation of MDR-TB patients and reporting them to the R/S/D MDR-TB Committee. Any decision to defer a patient from treatment should be done by the R/S/D MDR-TB Committee.

Table 2.1 Special considerations for MDR-TB treatment enrolment

Criteria	Reason for special consideration on MDR-TB enrolment
Willingness to consent to treatment	Any patient refusing treatment including the refusal of DOT, after repeated counseling and persuasion will not be included in the programme. They can be enrolled when they give consent anytime later.
Residency	Township Public Health Department is responsible for approval of patient's residency. Continuously migrating persons should not be enrolled unless uninterrupted treatment could be arranged through coordination of regions he moved in.
Alcohol	When alcohol use is too heavy to get in the way of safe treatment the patient may not be enrolled in the MDR-TB programme. While alcohol use is strongly discouraged, patients who have alcoholism should not be uniformly excluded from the programme even if they have relapses into alcohol use, as long as they can continue to take the medicines regularly.
Drug abuse	Active illicit drug use may be against safe and effective regular MDR-TB treatment. Efforts to help the patient with their drug addiction should be made. A history of illicit drug use, per se, is not an exclusion criterion.
Severe co-morbidities (liver, renal, epilepsy, major psychiatric disorders, etc.)	In most cases, patients with co-morbidities can still receive an MDR-TB regimen. Exclusion should be done on a case-by-case basis. End-stage organ disease, where the patient is not expected to tolerate or survive long enough for MDR-TB treatment, e.g malignancy, liver or kidney disease is considered a criterion for non-enrollment.

History of second-line anti-TB drug use	A history of second-line anti-TB drug use is NOT a reason for exclusion. However, the patient may need a special regimen or even a regimen for the treatment of XDR-TB. When the resistance pattern or evidence suggest that no regimen with second-line anti-TB drugs is possible, palliative care can be considered.

2.4 Case-finding of MDR-TB in children

The important criteria to suspect MDR-TB in children are as below[1]:

- Close contact with a person with known MDR TB
- Close contact with a person that has died or has failed TB treatment or is non-adherent to TB treatment
- The child has had previous treatment for TB within the past 12 months
- The child has been taking first-line treatment but has failed to improve clinically by 2 months (completion of intensive phase), i.e. persistence of symptoms, failure to gain weight, or persistence of positive smear

MDR-TB in children can be harder to diagnose because bacterial load is usually lower and getting a specimen for DST is difficult. The sputum specimens from children including induced sputum and Gastric lavage or aspirate can be used for Xpert testing. CSF and lymph nodes aspirate can be used to diagnosis of Extra-pulmonary MDR-TB in children. Studies on sensitivity and specificity of using Xpert MTB/RIF on non-sputum specimens in children (as well as in adults) are lower than sputum specimen. Children will be selected for enrolment for MDR-TB by pediatricians well versed with MDR-TB and according to the national guidelines on childhood TB management, if they meet any of the following criteria:

1. DST-proven MDR-TB (or rifampicin resistance);
2. Clinically unresponsive to first-line TB treatment (radiologically active and progressive TB disease while on first-line TB treatment) and other non-TB causes of disease progression have been ruled out;
3. Close contact with known MDR-TB case.

2.5 Case-finding of MDR-TB in HIV-positive patients

It is important to diagnose MDR-TB in HIV-positive patients, because untreated MDR-TB in an HIV-infected patient carries a high mortality and they can be sources of spread in the community. Per WHO recommendation HIV-infected patients with TB will have a rapid DST (with Xpert MTB/RIF) at the start of TB treatment as case finding for MDR-TB. Moreover PLHIV with presumptive TB symptoms will be tested with Xpert MTB/RIF for the diagnosis of TB/MDR-TB. (Figure 2.2)

1 *Revised National Guideline for Management of Tuberculosis in Children by National Tuberculosis Program and Senior Pediatricians in Myanmar, 2016.*

2.6 Case-finding of XDR-TB

Any patient who falls into one of the following categories will be targeted for DST* to second-line drugs to determine if the patient has XDR-TB or additional resistance upon MDR-TB:

1. Any patient who has had a past history of a previous second-line anti-TB drug;
2. Any patient who remains culture-positive in or after Month 4 of the Standard MDR-TB regimen or who reconverts to a positive culture after culture conversion;
3. Contacts with an individual with documented XDR-TB.

* Use of LPA to exclude resistance to injectables/ fluoroquinolones for shorter MDR-TB regimen, is not considered as an activity for case-finding of XDR-TB although it may identify some of them during the examination.

2.7 Summary of MDR-TB case-finding

The introduction of Xpert MTB/RIF can improve both MDR-TB and drug-sensitive TB case detection. This section summarizes the case-finding strategies for both categories, when a facility has access to Xpert MTB/RIF. Diagnostic algorithms include:

1. Figure 2.1 Diagnosis of MDR-TB in patients with risk factor for resistance
2. Figure 2.2 Diagnosis of TB/MDR-TB in HIV-positive patients
3. Figure 2.3 Diagnosis of TB in HIV-negative patients with no significant risk for MDR-TB
4. Figure 2.4 Diagnosis of TB/MDR-TB from EP specimen in patients with risk factor for TB

Figure 2.1 Diagnosis of MDR-TB in patients with risk factor for resistance

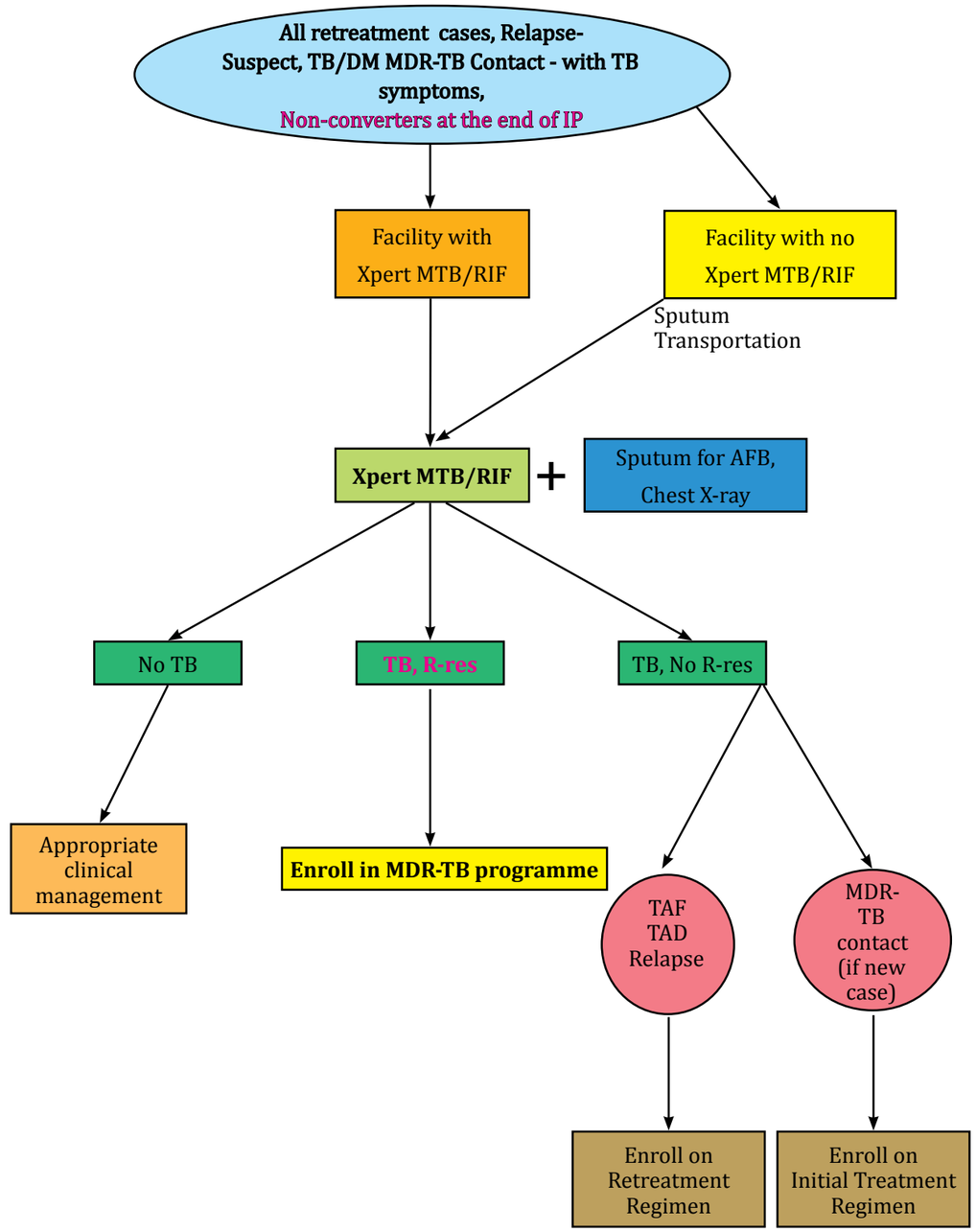


Figure 2.2 Diagnosis of TB/MDR-TB in HIV-positive patients

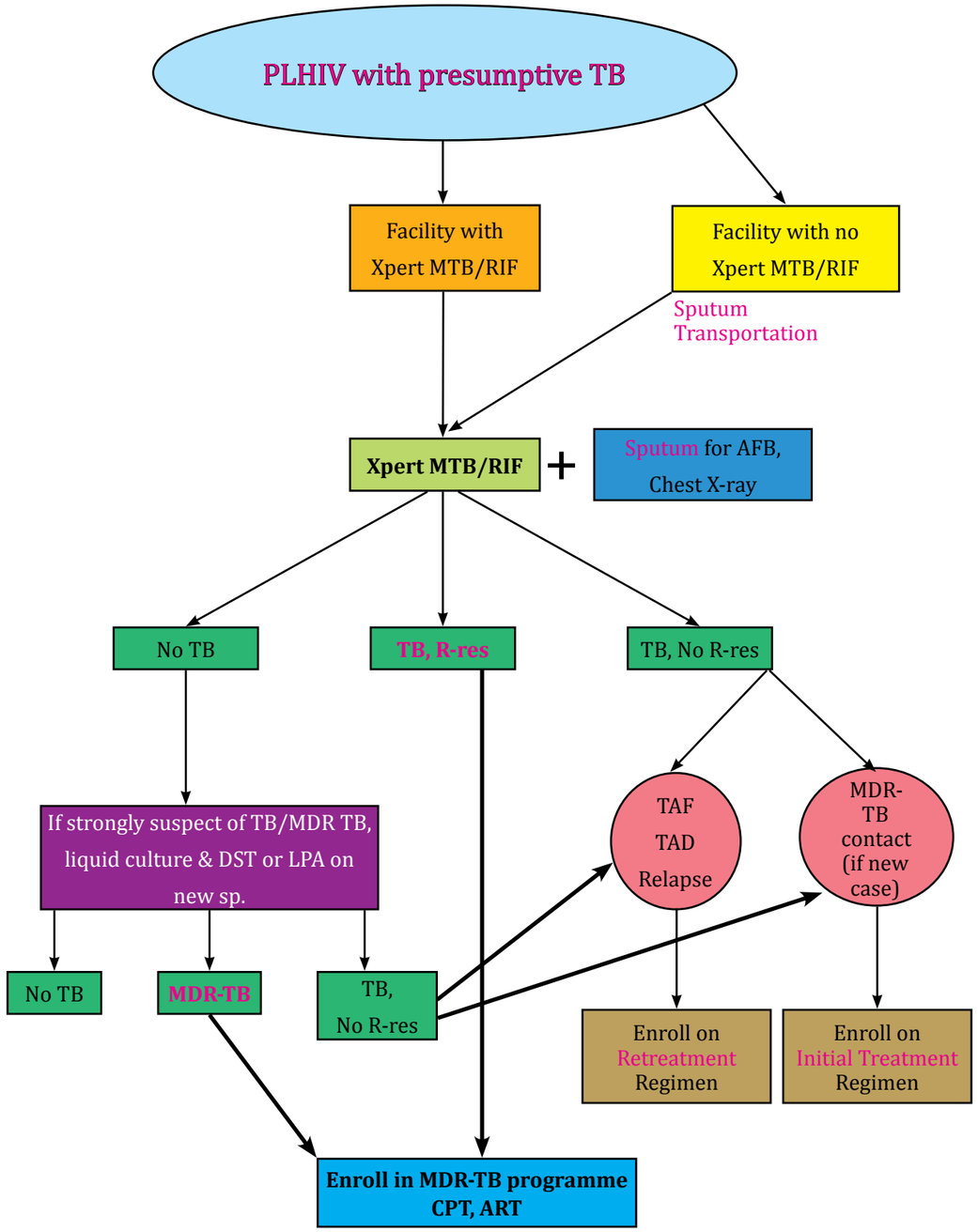
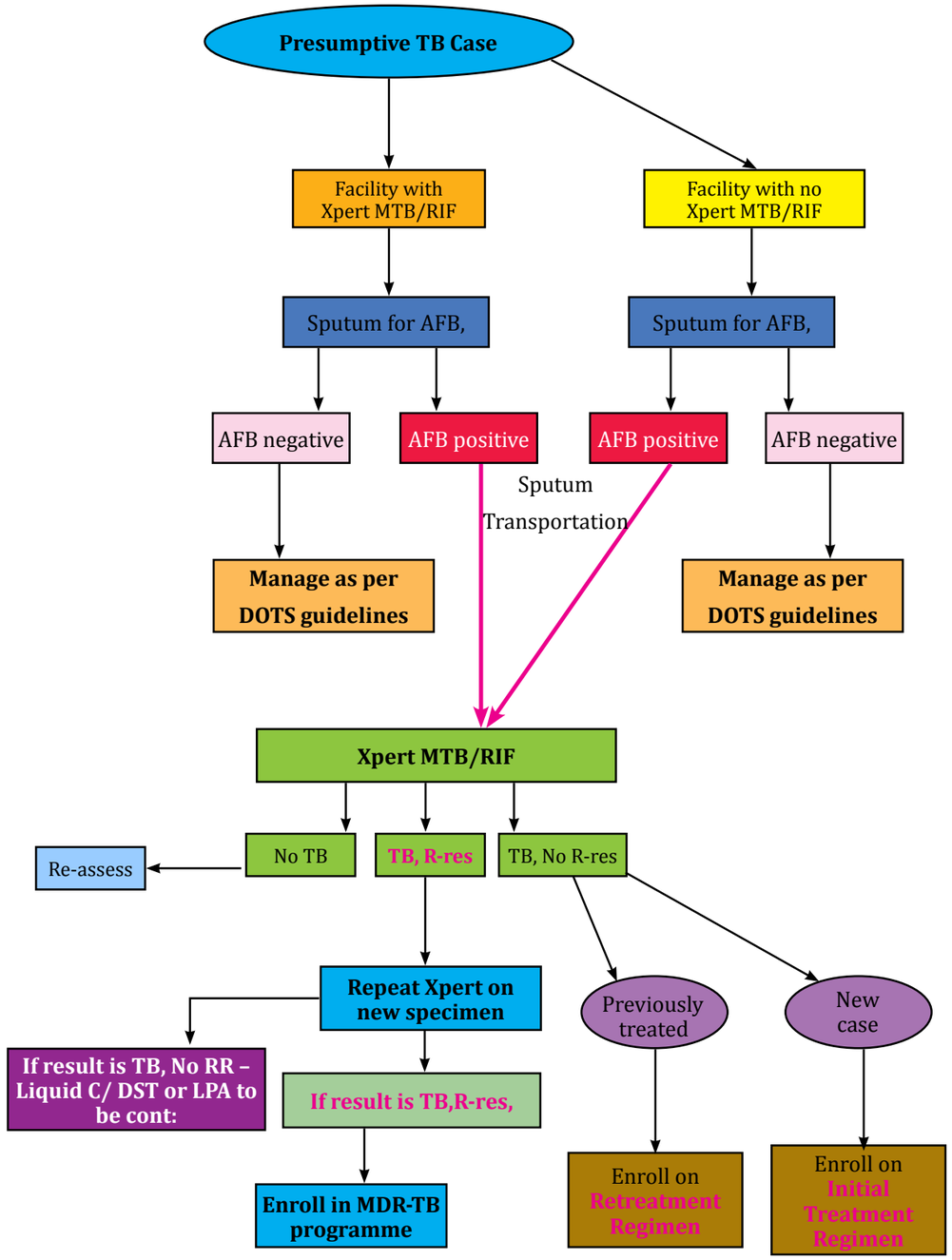


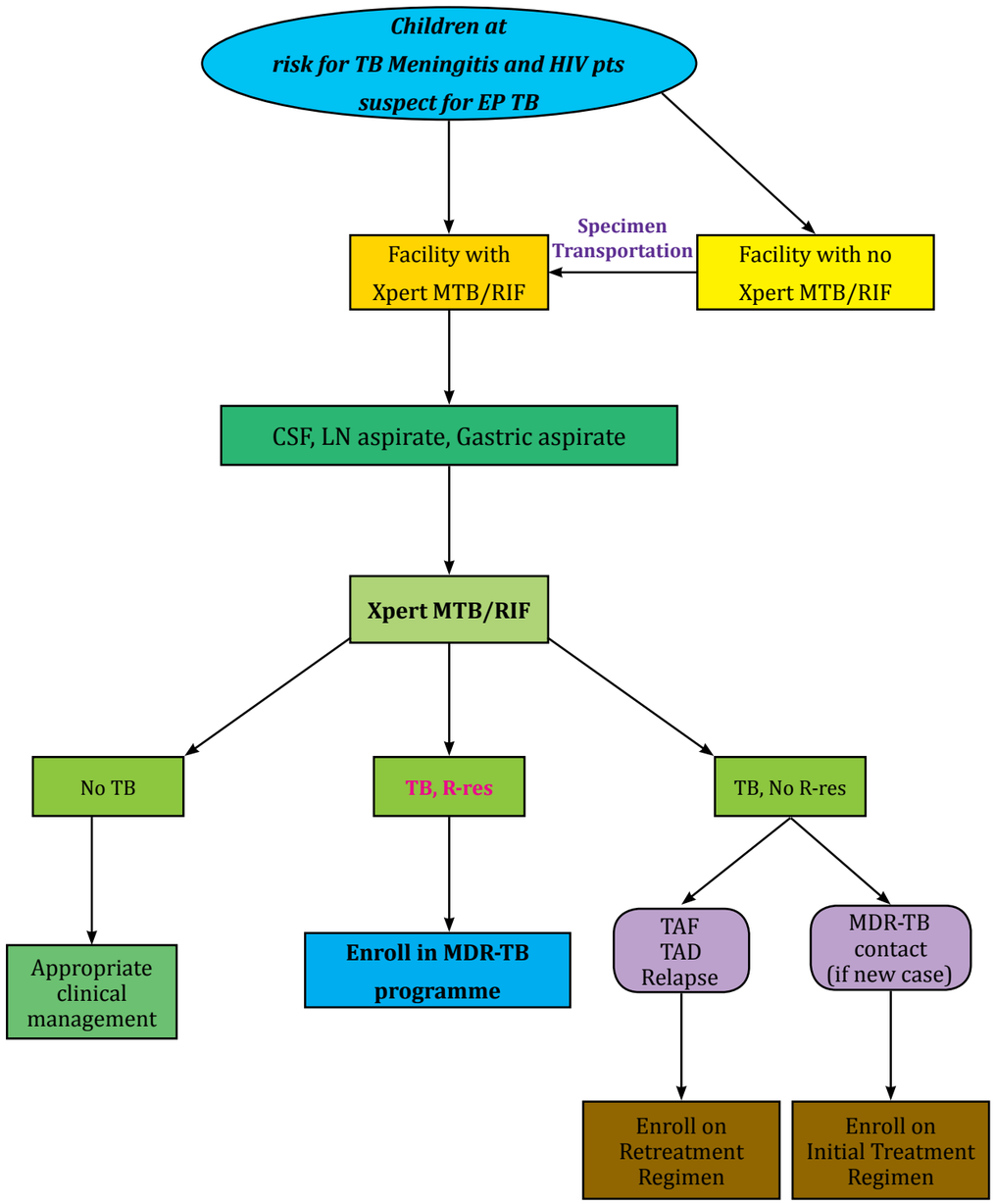
Figure 2.3* Diagnosis of TB in HIV-negative patients with no significant risk for MDR-TB



****In Yangon Region Xpert MTB/RIF is done in all registered TB cases.***

* This algorithm will need to be reviewed when the use of Xpert MTB/RIF becomes more liberal in the case finding of TB in general.

Figure 2.4 Diagnosis of TB/MDR-TB from EP spec. in patients with risk factor for TB



Chapter
3

LABORATORY ASPECTS OF MDR-TB

Since MDR-TB is based on microbiological (phenotypic and molecular) diagnosis, the quality-assured laboratory results play an essential role in the management of MDR-TB patients. MDR-TB diagnosis can be done by isolating the bacteria by culture, identifying it as belonging to the M. tuberculosis complex (MTBC), and conducting drug susceptibility testing (DST) using solid or liquid media or by performing molecular tests to detect TB DNA and mutations associated with resistance.

Early detection of drug resistance allows the use of appropriate treatment regimens for patients, which has an important impact on improved TB control. Spread of drug-resistant TB strains and the management of patients diagnosed with DR-TB are among the most challenging tasks faced by national TB control programme.

In addition to MOHS contribution substantial laboratory support came from international initiative with Expand TB Project which is a collaborative effort between UNITAID, Global Laboratory Initiative, Global Drug Facility (GDF) and Foundation for Innovative New Diagnostics. Biosafety level-3 (BSL-3) laboratories have been established in Yangon and Mandalay since 2010. The expansion of plan for BSL-3 in Taunggyi and in Mawlamyaing has started which will be followed by the setting up of Regional TB Reference Laboratories in the future.

The full monitoring requirements of patients clinically, bacteriologically, and for adverse effects are described in Chapter 10 and 11. This chapter addresses only laboratory aspects of diagnosis of MDR-TB, monitoring MDR-TB management, and laboratory monitoring for adverse effects.

3.1 General definitions for the laboratory and drug susceptibility testing (DST)

The following are definitions of the laboratory aspects in relation to DST discussed in this chapter:

- **Phenotypic DST (conventional DST)**: Phenotypic testing determines if an isolate is resistant to an anti-TB drug by evaluating the growth (or metabolic activity) in the presence of the drug.
- **Genotypic DST (molecular DST)**: Genotypic testing detects the genetic mutation in M.TB bacterium/ genome responsible for or associated with the resistance. (Note: genotypic testing is also used to detect the presence of the TB bacterium itself).
- **Cross-resistance**: Mutations that confer resistance to one anti-TB drug may also confer resistance to some or all of the members of the drug family and, less commonly, to members of different drug families.
- **Direct testing**: Direct testing refers to testing directly from a clinical sample (most commonly a sputum specimen). In direct DST the clinical sample (after processing) is used directly to inoculate the media or as the clinical sample in a molecular test.

Indirect testing: Indirect testing refers to testing performed on a culture isolates of M. tuberculosis that has been grown from a clinical sample.

3.2 Sputum collection and transport system

Good quality specimens are essential for proper laboratory diagnosis of TB and drug-resistant TB. However, collecting sputum, the most frequent specimen for Pulmonary TB testing, represents a significant hazard as coughing produces potentially infectious aerosols. Therefore, specific measures must be taken to minimize exposure. Wherever possible, sputum specimens should be collected in open air where infectious droplets are rapidly diluted and UV rays can rapidly inactivate TB bacilli. Sputum specimens should not be collected in laboratories, toilets, waiting rooms, reception rooms, or any other enclosed space. Collecting a good specimen in a safe manner also requires staff trained to provide the patient with effective instructions as well as with adequate material and procedures, using wide-mouthed containers that are clear and leak-proof (with screw caps).

Each MDR-TB suspect should have two specimens collected: one spot and one early morning home sputum sample. The sputum collection must be done in accordance with the national guidelines (Annex 1). There are two options for screening specimens:

1. **Screened for MDR-TB with an Xpert MTB/RIF test** (this is the test of choice as it is simple, rapid, and is specific for ruling out rifampicin resistance). Xpert MTB/RIF is done on only one sample: choose the specimen that has the most phlegm or is smear-positive on microscopy. If both specimens are the same appearance, use the early morning specimen.

(Note: a RIF-positive specimen is supposed to be a surrogate marker for MDR-TB (This supposition can change with increased use of Xpert MTB/RIF in patients with no known risk for MDR-TB); Mean time the following algorithm is used in the management. If the patient is from high risk of MDR-TB group, he can be started on an MDR-TB regimen without continuing confirmation DST and If the patient is from low risk of MDR-TB group and if the Xpert MTB/RIF result is positive, repeat the test with new specimen. If the second result is negative/ discordant only 2nd result must be taken as a final result. But if Physician still suspects of MDR TB the new specimen should be sent for confirmation DST (by either phenotypic or genotypic DST).

2. **Tested with direct microscopy, culture and DST (solid and liquid), and/or LPA** at the NTRLs in Yangon and Mandalay or other Regional/State laboratories.

The quality of sputum is also important to get the quality assured laboratory results.

Specimens should be collected in wide-mouthed containers that are clear, and leak-proof. Specimens should be promptly transported to the laboratory in leak-proof containers surrounded by absorbent material in a shock-resistant outer package. Patient information should be written on the container (not on the lid).

Prior to transport, specimens should be kept in a cool place, preferably in a refrigerator at +4°C. If travelling time is long, cold boxes should be used during the transportation. If it is likely that storage and transit time will total more than 3 days, or if the specimen is likely to be exposed to room temperatures for extended periods of time, a transport medium can be used. Cetylpyridinium chloride (CPC)[1] 1%, or cetylpyridinium bromide (CPB) 1%, are two common transport media. Note that CPC and CPB are strictly not permitted for liquid media. CPC and CPB can crystallize at low temperatures (they should not be refrigerated or frozen). CPC and CPB specimens can be used with Xpert MTB/RIF.

It is preferable to transport specimens rather than have the patient travel long distances to provide a specimen. The logistics of the transport system are described in Annex 1. If the patient lives close to the MDR-TB diagnostic centre, he or she can present themselves for sputum collection at the place of DST. Annex 1 summarizes sputum collection procedures.
(Note: New method such as Gene Omni will be piloted.)

3.3 Procedures for smear, culture, and DST

All procedures of culture and DST for presumptive TB or DR-TB samples must be handled in a Class II biological safety cabinet in bio-safety level 3 laboratories.

[1] CPC is not used in current situations and instead cold chain is used for specimen transportation.

Smear microscopy

Smear microscopy is a low-cost and essential frontline tool for diagnosis of TB (but not drug-resistant TB).The sputum smears are stained using the Ziehl-Neelsen staining method and examined with a bright field binocular microscope and graded according to WHO grading for AFB microscopy. Auramine staining with a fluorescence microscopy is also used instead of bright field microscopy especially in high microscopy workload centers and can increase sensitivity by more than 10%. Microscopy for AFB cannot distinguish viable from non-viable organisms nor differentiate between drug-susceptible and drug-resistant M. tuberculosis. Thus its usefulness in drug-resistant TB treatment monitoring is limited. The main purposes of microscopy for drug-resistant TB are to assess initial bacterial load and to confirm the presence of AFB rather than contaminants in the culture media before proceeding to drug susceptibility testing.

Culture

Both solid and liquid cultures were used for MDR-TB treatment diagnosis and monitor. But after introducing (and expansion of) Xpert MTB/RIF machines in NTP culture is usually used to monitor the patient's response to treatment.

For culture, pretreatment decontaminating procedure of sputum was done and inoculate on Lowenstein-Jensen (LJ) media or Middlebrook 7H9 broth bottles according to standard operating procedures. In solid culture, the culture bottles must be incubated at 37 °C and read weekly until colonies are observed. If there is no growth by six to eight weeks, the result will be given as "culture-negative". In liquid culture the culture bottles are incubated in Mycobacterium Growth Indicator Tube system (MGIT-960®) and the machine automatically read the culture bottles every 60 minutes. Positive growth can be detected within a week and if there is no growth after 42 days, culture negative result will come out from the machine.

Identification of M. tuberculosis

Isolated strains of mycobacterium is not always M.tuberculosis and as virulence and drug susceptibility pattern varies according to the species of mycobacterium all positive mycobacterium cultures must be tested to confirm M. tuberculosis complex (MTBC). The growth from any positive culture either from solid or liquid is identified by growth rate, colonial morphology, smear microscopy from positive growth and rapid immunochromatographic assay from culture isolates to ratify MTBC. This assay is based on the detection of a specific protein, MPT64, which secreted specifically by members of MTBC. The results are available within 15 minutes.

Drug Susceptibility Testing (DST) on solid culture

DST for both first and second line anti- TB drugs on solid media (LJ media) can be performed in Yangon and Mandalay BSL-3 laboratories. DST on solid culture media is performed at baseline only for diagnosis of MDR-TB or for confirmation of an Xpert MTB/RIF tests during the

DOTS Plus pilot project period and early PMDT period. But now no further routine confirmation of solid DST is needed whenever rifampicin resistant is shown by Xpert MTB/RIF test for individual case management. DST result will be obtained in two and a half to three months after the original collection of the sputum as culture is grown first and then DST is performed.

For first-line anti-TB drugs, resistance to isoniazid, rifampicin, streptomycin and ethambutol are tested. The second-line DST is performed whenever the culture result yields positive at 3rd month of DR- TB treatment monitoring and tested for amikacin, capreomycin, levofloxacin, cycloserine and ethionamide resistance. For each strain, the number of organisms resistant to each drug concentration must be expressed as a percentage of the number of organisms growing on the drug-free tubes. Resistance is defined when 1% or more growth occurs in drug-containing tubes compared to the drug-free tubes.

Liquid culture and liquid DST

Liquid culture and DST is done through the Mycobacterium Growth Indicator Tube system (MGIT-960®). This system uses a liquid medium, Middlebrook 7H9 broth, which has better recovery and faster growth of mycobacteria. The growth supplement and a combination of antimicrobial agents (PANTA) are added to suppress the growth of contaminants. The inoculated tubes are put in MGIT machine which can hold 960 tubes at one time and incubated at 37 °C. The calibrated tubes in the machine evaluated the inoculated tubes for growth detection in every 60 minutes. The positive tubes are shown by a flashing red indicator lamp on the screen of the machine drawer. Tubes flagged positive are removed after 24 hours and further tested for confirmation of M. tuberculosis. (The tubes can also be visualized manually under ultraviolet light or can be read with the MGIT Tube Reader.) Growth can be detected as early as 4 to 12 days. Negative tubes are shown by a flashing green indicator lamp on the screen of the machine drawer 42 days after inoculation of the tubes. The DST is performed in the same MGIT machine from inoculated liquid culture positive tubes into the drug containing tubes.

The drugs tested for first-line anti-TB drugs by liquid media are isoniazid, rifampicn, streptomycin and ethambutol. With the collaboration of DMR PZA susceptibility testing using liquid media will be started in 2017. The drugs tested for second-line anti-TB drugs by liquid media are amikacin, capreomycin, and levofloxacin. Results are mostly available within 3 weeks from the inoculation of M.tuberculosis isolates into drug containing MGIT tubes.

Genotypic testing (molecular tests)

Genotypic methods have considerable advantages when PMDT is being scaled up, in particular with regard to their speed, the standardization of testing, their potential high throughput and reduced requirements for biosafety. Nucleic acid amplification technologies, which can amplify either DNA or RNA, use polymerase chain reaction (PCR) and this genotypic DST hold promises for significant gains in speed and performance for DST. Three types of genotypic test-

ing are used in NTP: Genotype MTBDR plus Test, Xpert® MTB/RIF assay and Genotype MTBDR sl Test.

In 2008, WHO endorsed the use of line probe assay (LPA) to detect MTBC and mutations that indicate resistance of isoniazid and rifampicin. The Genotype MTBDR plus Test (Hain Life Science) is used at both BSL-3 laboratories to detect mutations that cause rifampicin resistance (rpoB gene) and isoniazid resistance (katG and inhA genes). The limitation of the test is that it can perform only on, either a high smear positive sputum specimen or isolate of solid or liquid culture growth, although results are available within 3 days. Negative and low positive specimens must first be grown in culture and then tested, but this adds a number of weeks to the turnaround time for results.

In 2010, WHO endorsed the Xpert® MTB/RIF assay which is an automated cartridge-based nucleic acid amplification test for simultaneous detection of TB and rifampicin resistance. Xpert MTB/RIF is a fully automated molecular diagnostic test that can detect DNA of MTBC and common mutations associated with rifampicin resistance (rpoB gene mutation) directly from sputum specimens within two hours. This test now plays as an initial priority rapid test for diagnosis of MDR-TB. The assay has similar sensitivity, specificity and accuracy as culture on solid media and can be used from both smear positive and negative specimens. In most settings, particularly where fixed dose combination first line anti-TB drugs are used, resistance to rifampicin is highly associated with resistance to isoniazid. Detection of rifampicin resistance therefore serves as a reliable (although not complete) proxy for MDR-TB in many settings leading to development of MDR-TB. Another significant advantage of using Xpert MTB/RIF is that it can be done in a simple laboratory setting and does not require highly skilled technicians if proper training has been provided.

The detection of gene mutations to second-line anti-TB drugs (Genotype MTBDR sl Test) is recommended by WHO in May 2016 as a reliable test to rule out resistance to second- line anti-TB drugs. This novel diagnostic test is a DNA-based test that identifies MTBC and its resistance to fluoroquinolones, aminoglycosides/cyclic peptides and ethambutol. The results are available within 3 days as in Genotype MTBDR plus Test. This test indicates the resistance of fluoroquinolones by detecting gyrA gene mutation, resistance of aminoglycoside (Kanamycin or Amikacin) and cyclic peptides (Capreomycin or Viomycin) by detecting rrs gene mutation and resistance of ethambutol by detecting embB gene mutation.

The confirmatory test of choice for molecular testing is liquid culture and liquid DST as it is relatively quick and has high sensitivity and specificity. Genotype MTBDR plus test can also be used for confirmation of rifampicin resistance with Xpert MTB/RIF but requires a positive smear from sputum, or from culture positive isolates. A summary of culture and DST methods is provided in Table 3.1

Table 3.1 Summary of culture and DST methods

Diagnostic Platform	Test Name	Turnaround Time	Description and comments
Solid Culture and DST	Lowenstein-Jensen	8-10 weeks 8 weeks smear negative	Egg-based medium, inexpensive. First- and second-line DST can be done.
Liquid culture and DST	MGIT®	21 days smear positive 42 days smear negative	Present recommeded standard for TB culture and test of choice for DST confirmation. Fully automated system exists with MGIT 960. First- and second-line DST can be done.
Molecular Testing	Line Probe Assay (LPA)	3 days direct 21 days indirect	DNA targets are amplified by PCR and hybridized to immobilize oligonucleotide targets. Genotype MTB DRplus test identifies MTBC, isoniazid resistance by detecting KatG and inhA gene mutations and rifampicin resistance by rpoB gene mutation. Genotype MTB DRsl test identifies MTBC, fluoroquinolones resistance by detecting gyrA gene mutation, aminoglycosides and cyclic peptides resistance by rrs gene mutation and ethambutol resistance by embB gene mutation. Can only be done directly from smear positive or from liquid or solid culture positive colonies.
	X pert® MTB/RIF	2 hours	The test that uses nested real-time PCR to identify MTBC and rifampicin resistance by detecting rpoB gene mutation. Can be done directly from smear-positive or smear-negative specimens.

3.4 Laboratory monitoring of response to therapy with sputum microscopy and culture (follow-up smears and cultures)

Response to therapy is monitored through smears and cultures. A combination of solid and liquid cultures is used. Smear examination is done monthly during the whole treatment and culture is done on the same specimen for the months that culture is indicated. Monitoring is not done with molecular tests as they will pick up dead bacilli, which can be seen in patients with culture conversion and even in patients who are cured.

Table 3.2 provides the schedule for smears and cultures. In general, no laboratory monitoring will be continued after the treatment is declared as failure. In most cases, it is highly likely that treatment failure has already been declared if culture conversion has not been achieved after 8 months of treatment (culture report of which is due at the beginning of 10th month). In many cases, patients will have been switched to an XDR-TB treatment as new treatment before reaching Month 12. It is indicated to repeat first-line DST and to do second-line drugs DST including Amk, Cm, and Lfx if the patient remains culture positive at or after the third month of treatment.

Table 3.2 Sputum and culture testing schedule for follow-up

Tests	**Timeframe (months)**																							
	Intensive Phase (IP)								**Continuation Phase (CP)**															
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Smear	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√				
Culture * (Bac: conversion at end IP)				S	S	L	L	L	L				S		S		L		S		L				
Culture ** (Late Convertor)				S	S	L	L	L	L	L	L		S		S		L		S		L				

Note:

Follow-up smear examinations are done monthly throughout the course of treatment.
S=Solid Culture and L=Liquid Culture must be done as mentioned in the table 3.2.

* Bacteriological conversion/ Conversion (to negative): Culture is considered to have converted to negative when two consecutive cultures, taken at least 30 days apart, are found to be negative. In such a case, the specimen collection date of the first negative Culture is used as the date of conversion.

**Later convertor: A patient whose culture conversion is achieved only in last 1-2 months of 8-month intensive phase. These potential late-convertors need to be instructed to submit specimens to do liquid cultures in month 9 (±10).

3.5 Laboratory monitoring for adverse effects

Laboratory monitoring is required for patients receiving a regimen with second-line anti-TB drugs. Adverse effects can be occult (not obviously noted by taking the history of the patient or by physical examination). Note the following important aspects of laboratory monitoring for adverse effects:

• **Renal toxicity monitoring**. Nephrotoxicity is a known complication of the injectable drugs, both of the aminoglycosides (kanamycin and amikacin) and of capreomycin. This adverse effect is occult in onset but can be fatal. These guidelines advise checking serum creatinine monthly while on the injectable agent. In addition, patients with a history of renal disease (including co-morbidities such as HIV and diabetes), advanced age or any renal symptoms should be monitored more closely, particularly at the start of treatment with creatinine every two weeks.

• **Electrolyte monitoring**. Electrolyte wasting is a known complication of the anti-TB injectable drugs, especially capreomycin. It can be fatal if the potassium or other electrolytes get too low. Since electrolyte wasting is often occult in the early stages and can be easily managed with electrolyte replacement, serum potassium should be checked monthly while on the injectable agent. It is especially important to check regularly in high-risk patients (HIV patients), and in all patients taking capreomycin.

• **Monitoring for hypothyroidism**. Hypothyroidism is a late effect provoked by *p*-aminosalicylic acid (PAS) and/or ethionamide/prothionamide. The use of these agents, PAS plus ethionamide or prothionamide together can produce hypothyroidism in up to 30% of patients. Since the symptoms can be subtle, it is recommended that patients who are taking either PAS and ethionamide/prothionamide be screened for hypothyroidism with a serum thyroid-stimulating hormone (TSH) at baseline, three months, and then tested again every six months or sooner if symptoms arise.

• **Monitoring liver toxicity**. Drug-induced hepatitis can be resulted from pyrazinamide, PAS and less commonly with the other second-line anti-TB drugs. Liver enzymes are checked for all patients who exhibit signs of hepatotoxicity.

• **Pregnancy testing**. A pregnancy test should be done at baseline and repeated whenever indicated.

• **Audiometry**. Hearing loss is associated with the injectable agents and can be permanent. Evaluating hearing monthly is strongly advised while on the injectable agents. Table 3.3 shows normal values for laboratory monitoring. Blood laboratory tests are either done at the R/S TB Centers or Hospitals or at the NHL/MGH.

3.6 Infection control and bio-safety in the laboratory

Laboratory biosafety is the process of applying a combination of administrative controls, containment principles, safety equipment, good laboratory practices, standard operating procedures, emergency preparedness and facilities to enable laboratory staff to work safely with potentially infectious microorganisms.

Transmission of TB/DR-TB is a recognized risk for laboratory workers. Specimens should be handled in Class 2 Biological Safety Cabinets for all procedures of culture and DST. (Smear and Xpert MTB/RIF specimens can be with the same conditions as smear microscopy alone and do not require special safety cabinets, although if available they can be used.) When handling potential MDR-TB specimens (including for smear or Xpert MTB/RIF processing), laboratory technicians should use an N-95 respirator and be in a well-ventilated area, with an exhaust fan if adequate window and natural ventilation is not available). For liquid culture and LPA, Biosafety level 3 laboratories are needed. Instructions on safe handling of specimens must be strictly followed. The health status of laboratory workers must be monitored by annual CXR. Laboratory workers who report signs and symptoms suggestive of TB at any time should undergo a sputum examination and CXR and to undergo Xpert testing if s/he has TB.

3.7 Quality assurance

To ensure that results of DST are reliable and comparable between different country areas, a system of TB quality assurance (QA) has been developed. As a part of internal quality control, the quality of the staining solution and the media prepared will be controlled for each batch. For QA, susceptibility testing must be performed on the standard H37Rv strain when each new batch of LJ media and drug containing LJ media is prepared for DST. The Supranational Reference Laboratory (SNRL) in Bangkok, Thailand assesses proficiency of Culture & DST (both solid & liquid) and LPA annually with specific QA protocols. Quality assurance of the blood laboratory tests for monitoring adverse effects is also done regularly as per the standards of the specific instrument measuring blood chemistries.

3.8 Surveillance using DST

Drug resistance surveys (DRS) should be done every five years and the strategies of case detection and treatment adjusted according to these results. In addition, ongoing surveillance can be done for the different groups such as failures of initial regimen and retreatment regimen, close contacts, relapse, return after default. The fourth DRS will be conducted in 2018.

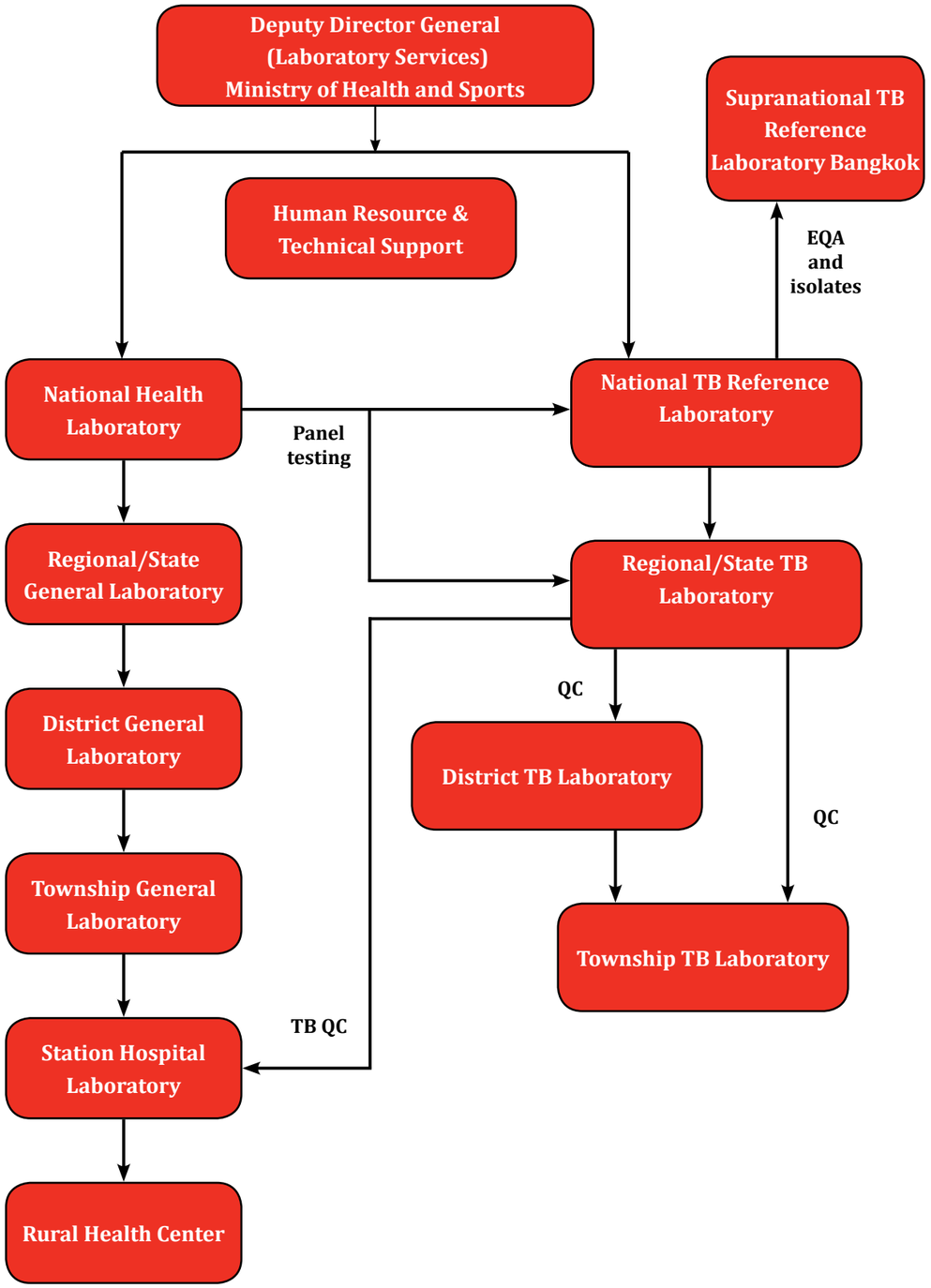
3.9 Organizational structure of laboratories in TB control

Figure 3.1 provides the organizational structure and the relationship between the National Health Laboratory, the NTRL and all TB support laboratories down to the township level.

Table 3.3 Normal ranges for blood monitoring tests (note that values can vary by method and instrument)

Sr. No.		Reference range		Reference range (international units)	
1	Serum Creatinine	0.6–1.6	mg%	M 60–106	mmol/L
		0.4- 1.6	mg%	F 40–106	mmol/L
2	Serum Potassium			3.6–5.1	mmol/L
3	Serum Uric Acid	3.5 - 7	mg%	M 240–530	umol/l
				F 150–450	umol/l
4	Blood sugar				
	Radom blood sugar	80 - 180	mg%	60 - 140	mg/dl
	Fasting blood sugar	70 - 110	mg%	70 - 110	mg/dl
5	Liver function test				
6	Total Bilirubin	up to 1.0	mg%	<17	umol/l
	Direct Bilirubin			0-3	umol/l
	Indirect Bilirubin			3.0-14	umol/l
7	Alk. Phosphatase	40-190	IU/L		
				M 40–129	U/L
				F 35–104	U/L
8	ASAT/SGOT	9.0-35	IU/L	M ≤ 40	U/L
				F ≤ 32	U/L
9	ALAT/SGPT	9.0-43	IU/L		
				M ≤ 41	U/L
				F ≤ 33	U/L
10	Thyroid Hormone				
	T3			0.69–2.02	ng/ml
	T4			M 4.4–10.8	ug/dl
				F 4.8–11.6	ug/dl
	TSH			0.3–6.2	ml u/l

Figure 3.1 functional relationships of laboratories in TB control



Chapter

4

MDR-TB PATIENTS EDUCATION AND COUNSELLING

All patients and their families must receive education and counseling about MDR-TB, giving information about benifits of regular treatment and good outcomes, consequences of no (or) irregular treatment and bad outcomes, its treatment duration, possible adverse drug effects which are largely manageable and the importance of adherence to therapy. Education and counselling should commence at occasion on pre-test for MDR-TB, the beginning of therapy and continue throughout the course of treatment. General atmosphere of all stages of counseling should be encouragement rather than discouragement to start and go on with treatment.

Patient education & counseling is an essential component of any MDR-TB control programme and is based upon trusting interpersonal communication between patients and medical personnel. It influences treatment adherence and, as a result, successful treatment outcomes. It is also important to recognize that education and counseling reduces the spread of the disease among contacts and the public. The more patients are aware about the disease, the more actively they will adhere to MDR-TB regimens and take responsibility for their health and the environment. Moreover, the voluntary health workers, well-informed and cured patients can also assist medical personnel in delivering information to the community by sharing knowledge about TB and the availability of a cure.

Education can be provided by Medical Officers (MOs), medico-social workers, nurses, voluntary health workers, DOT providers and NGO members. Counseling should be given by health workers specifically trained in MDR-TB counselling.

4.1 Social, emotional, and economic support

Because of the nature of MDR-TB, some patients may become unemployed or homeless or may face internal family problems. Such socioeconomic problems can make patients non-adherent to treatment. The long duration of treatment, combined with severe side-effects of the drugs, may contribute to depression, anxiety and further difficulty with treatment adherence. Provision of emotional support to MDR-TB patients may increase the likelihood of adherence.

It is the goal of the National MDR-TB Programme for patients on treatment to receive monthly financial support. With the guiding of NTP, many INGOs and NGOs supply financial & nutritional support to all MDR-TB patients monthly up to completion of the treatment.

4.2 Maintaining confidentiality

The MDR-TB health team should explore the need of the patient to maintain strict confidentiality regarding their disease. In some cases, this may entail working out a system where the patient can receive medication without the knowledge of others. Therefore the role of DOT provider is important in dealing with the MDR-TB patients in community for the long treatment duration.

4.3 MDR-TB patient's Health Education

Informing and educating patients and their families about drug-resistant tuberculosis (DR-TB) is an essential part of treatment. Because of the complexity of the diagnostic and treatment process, it is important that health workers take sufficient time to provide adequate information and answer questions in a clear and **supportive manner** to facilitate education. It is also essential to identify and address the key concerns and priorities for the patient at every stage of their diagnosis and treatment, and check whether they have understood thoroughly the information given to them or not. Before giving information, it is necessary to assess level of awareness of DR-TB in order to provide appropriate information, to give information at an appropriate level, and to correct any misconceptions.

When a patient is presumed to have DR-TB, it is necessary during the initial meeting to discuss the process of diagnosis and treatment. Information on how TB and DR-TB are spread should be provided so that patients can take precautions to avoid transmitting the disease to others. Measures to prevent or mitigate stigma and discrimination should be addressed, preferably together with the patient's family. The patient should also be asked whether anyone they know has similar symptoms, is receiving or has ever received treatment for TB.

At the time of diagnosis or before starting MDR-TB treatment of the second-line TB regimen, patients need basic information about the disease, the process of being enrolled for treatment, and their rights and responsibilities. They may have questions about how they have become infected, the difference between TB and DR-TB, the implications of a diagnosis of TB on

the quality of life and the options to reduce its impact. Patients most likely will be anxious, and need reassurance that the disease can be cured in most instances with correct, uninterrupted treatment. Though the patient and the family need to understand that DR-TB is not always possible to cure and treatment options may become limited, it is important not to give information in discouraging tones.

Before starting treatment, the patient needs to understand the nature of medicines to be taken, the treatment process and the necessity of directly observed treatment (DOT) to monitor the treatment and offer regular support. It is crucial to obtain the agreement of the patient to undertake DR-TB treatment and to make clear that the patient will require DOT (7) days per week for at least 20 months. Any potential difficulty the patient foresees in their ability to attend for DOT should be assessed and arrangements agreed upon before beginning treatment.

Daily visits for DOT offer many opportunities to provide information, support, and answer the questions the patient might have about prevention, diagnosis and treatment. At some visits, health worker may want to explain the need and schedule for follow-up sputum examinations. At all visits, health staff need to check for new factors affecting the quality of life of the patient and anything which might make it difficult for the patient to attend for their treatment. At every visit, welcoming and supportive attitude should be shown so that patients will be willing to return for their next treatment. If the patient has side-effects or questions or concerns, it is imperative that health worker takes the time to discuss the problem and offer appropriate care, provide additional information and encouragement.

Busy health-care workers may feel unable to provide the supportive, friendly attitude needed; however, under no circumstance should the patient be treated with a hostile, humiliating or judgmental attitude or language. Encourage regular attendance by making DOT as quick and easy for the patient as possible: try to avoid making a patient with DR-TB in queue and, when that is unavoidable, try to ensure that some entertainment or education material is available for the waiting patients. The health worker may need to give repeated encouragement to patients who feel that daily treatment is too time-consuming and inconvenient. Whenever possible, liaise with properly trained community-based health-care workers to provide additional support, especially if you do not have the time or resources needed.

The physician at the DR-TB management centre will also provide information and motivation to the patient during monthly monitoring visits. Remember that providing verbal motivation without listening to and enabling the patient to solve the major barriers they may be facing, such as problems with work, breakdown of relationships, addiction or other health problem may be useless.

Good communication is needed not only to inform patients of important messages about DR-TB and its treatment but it is also critical to encouraging patients to return for the next treatment visit, day after day and month after month. One of the reasons that patients are lost to fol-

low up is the attitude of the health worker. Patients who are lost to follow up often report that the health worker was insensitive, impatient or seemed too busy to pay attention. For patients with DR-TB, the relationship with their health worker will last 20 months or more. It is vital to the success of treatment to maintain a harmonious relationship. Every patient deserves to be treated with respect.

Steps of communication skills are:-

- Ask relevant questions and active listening.
- Demonstrate a caring, respectful and friendly attitude
- Praise and encourage the patient
- Speak clearly and simply.
- Encourage the patient to ask questions
- Ask checking questions (that is, use open-ended questions to check understanding).

4.4 Topics to be included in education sessions

Each MDR-TB patient should receive the following information during the education sessions:

- What is TB and MDR-TB?
- TB transmission and ways of preventions
- What resistance is and how it develops
- The main symptoms of TB & MDR-TB
- Reasons for performing a sputum examination for microscopy, Xpert MTB/RIF test and culture& DST
- What adequate TB and MDR-TB treatment is
- Why DOT is important. Possible side-effects of treatment with second-line drugs and their effective management.
- Why it is important to complete treatment
- Consequences of defaulting
- How MDR treatment is organized: time, place and frequency of TB drugs intake
- How the treatment plan is designed
- How to live with MDR-TB

4.5 Organizational principles of patient education

The organization of patient education should be considered equally with the other components of the MDR-TB programme (such as detection, diagnostics, and drug supply, etc.)(See Diagram 4.1) Most importantly, it is necessary to provide the majority of education before the patient begins MDR-TB treatment. The patient's knowledge and understanding of his/her role in achieving a successful treatment outcome is an essential component for treatment. Signing the Patient Informed Consent Form should not be considered simply a bureaucratic pre-condition to

treatment. It should demonstrate that the patient **knows** and **comprehends** the complexity of MDR-TB treatment and has the **confidence** to complete a complex treatment regimen. A copy of the informed consent form is in Annex 3.14, DR-TB Form 14.

The health educator should use standardized information, education and communication materials developed by NTP, and it can be conducted on an individual basis or as group education. Information should be provided in an understandable manner. As a result of any education session, MDR-TB patients should know, comprehend and perform all necessary aspects of TB treatment and prevention.

NTP Pamphlet for MDR-TB Patients

4.6 Monitoring the effectiveness of patient education activities

Evaluation of the effectiveness of patient education will be based on results from questionnaires distributed to the MDR-TB patients at the end of each education session (see Table 4.1 & 4.2 for an example of the questionnaire). The questionnaire will be translated into the local language and administered by the health worker. The following indicators will be analyzed:

- Patient's knowledge and understanding of the disease
- Patient's role in the treatment

Additionally, patient practices will be evaluated by the treatment default rate versus cure rate. The following questionnaire will be administered to MDR-TB patients and close family members caring for the patient.

Table 4.1 Questionnaire on MDR-TB knowledge and attitudes

Correct answers are in red font. For all questions, there may be more than one correct answer.

(1) Which of these statements about TB are correct?

- It is caused by a bacterium (a type of germ) called Mycobacterium tuberculosis
- It is a contagious disease
- It mostly occurs in the lung
- It can be cured
- It is a non-contagious disease

(2) What are the main symptoms of TB?

- Cough
- Expectoration (coughing up phlegm)
- Haemoptysis (coughing up blood)
- Weight loss
- Black colour of urine

(3) How is TB transmitted?

- By air (by coughing, sneezing, laughing and talking)
- By eating contaminated food
- By drinking contaminated water
- By skin contact
- Unknown

(4) What is MDR-TB?

- Tuberculosis disease caused by a strain of TB that is resistant to at least Isoniazid and Rifampicin
- Tuberculosis disease that is resistant to one anti-TB drug
- A form of TB that requires treatment with expensive drugs
- A form of TB that requires treatment which gives more side-effects

(5) How can TB transmission be prevented?

- Treat all TB cases (especially infectious cases)
- Cover mouth and nose when cough, sneezing, laughing and talking
- Keep the windows and doors of the house closed
- Good lighting
- Use a special expensive soap on clothes
- Dispose of patient's waste products safely

(6) Why is it important to complete treatment?

- To be cured
- If the treatment is not completed, the TB has a high chance of coming back
- Repeated interruption of treatment leads to more drug resistance and possible treatment failure
- Untreated TB can result in death

(7) What are the possible consequences of defaulting on TB treatment?

- The TB is not cured and it will come back again
- Patient may die
- Patient may develop extensively drug-resistant TB (XDR-TB)
- Nothing bad will happen
- Longer duration of absence from patient's job (source of income)

(8) Is it important to inform family members?

- Yes, they can help the patient to complete treatment
- Yes, they can protect themselves from TB infection
- Yes, they can help identify TB cases among their family members
- Yes, they can be screened to detect TB easily and early
- Yes, they can send the patient to another house

Table 4.2 Questionnaire on MDR-TB knowledge and attitudes

အဖြေမှန်များကို အနီရောင်ဖြင့် ဖော်ပြထားသည်။ မေးခွန်းတိုင်းအတွက် အဖြေမှန်သည် တစ်ခုမက ဖြစ်နိုင်သည်။

(၁) တီဘီရောဂါနှင့်ပတ်သက်၍ မည်သည့်အကြောင်းအရာများသည် မှန်ကန်ပါသနည်း။

- တီဘီရောဂါသည် *Mycobacterium tuberculosis* ခေါ်သော တီဘီရောဂါပိုးကြောင့်ဖြစ်သည်။
- လူတစ်ဦးမှတစ်ဦးသို့ကူးစက်တတ်သောရောဂါဖြစ်သည်။
- အဆုတ်တွင်အများဆုံးဖြစ်ပွားသည်။
- သေသေချာချာကုလျှင် ရောဂါပျောက်ကင်းနိုင်သည်။
- လူတစ်ဦးမှ တစ်ဦးသို့ မကူးစက်နိုင်ပါ။

(၂) တီဘီရောဂါ၏ အဓိကလက္ခဏာများမှာ

- ချောင်းဆိုခြင်း။
- ချောင်းဆိုး၍ သလိပ်၊ သလိပ်ခဲများထွက်ခြင်း။
- ချောင်းဆိုးသွေးပါခြင်း။
- ကိုယ်အလေးချိန်လျော့ကျခြင်း။
- ဆီးအမည်းရောင်သွားခြင်း။

(၃) တီဘီရောဂါမည်သို့ ကူးစက်နိုင်သနည်း။

- လေမှ တဆင့်(ချောင်ဆိုးခြင်း၊ နှာချေခြင်း၊ ရယ်မောခြင်းနှင့် စကားပြောခြင်း) ကူးစက်နိုင်သည်။
- မသန့်ရှင်းသော အစားအစာကို စားသုံးမိသောကြောင့်ကူးစက်နိုင်သည်။
- မသန့်ရှင်းသောရေကို သောက်သုံးမိသောကြောင့် ကူးစက်နိုင်သည်။
- လူတို့၏အာ ရေပြားအချင်းချင်း ထိမိခြင်းကြောင့် လည်းကူးစက်နိုင်သည်။
- သိပ်ပံနည်းကျ မဖေါ်ထုတ်နိုင်သေးပါ။

(၄) ဆေးယဉ်ပါးတီဘီရောဂါဆိုသည်မှာ အဘယ်နည်း။

- အနည်းဆုံး Isoniazid နှင့် Rifampicin တီဘီဆေးနှစ်မျိုး သို့မဟုတ် ၎င်းထက်ပိုများသော ဆေးများကို ယဉ်ပါးနေသော တီဘီရောဂါ ပိုးကြောင့်ဖြစ်သော တီဘီရောဂါ တစ်မျိုးဖြစ်သည်။
- တီဘီဆေးတစ်မျိုးတည်းကိုသာ ယဉ်ပါးနေသော တီဘီရောဂါ တစ်မျိုးဖြစ်သည်။
- ဈေးနှုန်း ကြီးမြင့်သော တီဘီဆေးများဖြင့် ကုသရန် လိုအပ်သော တီဘီရောဂါ တစ်မျိုး ဖြစ်သည်။
- ဘေးထွက်ဆိုးကျိုးပိုမိုများပြားသော တီဘီဆေးများဖြင့် ကုသရန်လိုအပ်သော တီဘီရောဂါ တစ်မျိုးဖြစ်သည်။

(၅) တီဘီရောဂါမကူးစက်အောင် မည်သို့ကာကွယ်နိုင်သနည်း

- တီဘီလူနာများအားလုံးကို ဆေးကုသပေးခြင်း။ (အထူးသဖြင့် သလိပ်ပိုးတွေ့လူနာများ)
- ချောင်ဆိုးခြင်း၊ နှာချေခြင်း၊ ရယ်မောခြင်းနှင့် စကားပြောခြင်း တို့တွင် ပါးစပ်နှင့်
- နှာခေါင်းတို့ကိုလုံအောင်ပိတ်ခြင်း။
- အိမ်ရှိတံခါးနှင့် ပြတင်းပေါက်များကို ပိတ်ထားခြင်း။
- သဘာဝအလင်းရောင် ကောင်းစွာရရှိခြင်း။
- အထူးစျေးကြီးသော ဆပ်ပြာများဖြင့် အဝတ်များလျော်ခြင်း။
- လူနာ၏ စွန့်ပစ်ပစ္စည်းများကို လုံခြုံစွာစွန့်ပစ်ခြင်း။

(၆) ပြီးဆုံးသည်အထိ ဆေးကုသရန် အဘယ်ကြောင့်အရေးကြီးသနည်း။

- ရောဂါပျောက်ကင်းရန်။
- အကယ်၍ ပြီးဆုံးသည်အထိ ဆေးမကုသပါက ရောဂါပြန်ဖြစ်နိုင်ခြင်း။
- ခဏခဏ ဆေးသောက်မှုပျက်ကွက်ပါက ဆေးယဉ်ပါးမှုပိုမိုဖြစ်နိုင်ပြီး ဆေးကုသမှု မအောင်မြင်နိုင်ခြင်း။
- ဆေးမကုသပါက အသက်သေဆုံးနိုင်ခြင်း။

(၇) ဆေးကုသမှု ပျက်ကွက်ခြင်းကြောင့် ဖြစ်စေနိုင်သော နောက်ဆက်တွဲဆိုးကျိုးများမှာ

- ကုသ၍ မပျောက်ကင်းနိုင်ဘဲ ရောဂါပြန်လည်ဖြစ်ပွားခြင်း။
- သေဆုံးခြင်း။
- ပိုမိုဆိုးဝါးသော (XDR-TB) ဆေးယဉ်ပါးတီဘီရောဂါဖြစ်ပွားခြင်း။
- မည်သည့်ဆိုးကျိုးမှ မဖြစ်ပွားနိုင်ပါ။
- အလုပ်အကိုင် ကြာမြင့်စွာ မလုပ်နိုင်ခြင်း။

(၈) မိသားစုဝင်များကို ရောဂါအကြောင်း အသိပေးရန် အရေးကြီးပါသလား။

- မိသားစုဝင်များသည် ဆေးကုသမှု ပြီးဆုံးအောင် ကူညီနိုင်သောကြောင့် အရေးကြီးပါသည်။
- မိသားစုဝင်များသည် မိမိကိုယ် မိမိ တီဘီရောဂါ ကူးစက်ခြင်းမှ ကာကွယ်နိုင်သောကြောင့်
- အရေးကြီးပါသည်။
- မိသားစုဝင်များအတွင်းမှ တီဘီရောဂါရှိသူများအား ရှာဖွေဖော်ထုတ်နိုင်သောကြောင့်
- အရေးကြီးပါသည်။
- မိသားစုဝင်များကို တီဘီရောဂါရှိ/မရှိ စောစီးလွယ်ကူစွာ ရှာဖွေနိုင်ခြင်းကြောင့် အရေးကြီးပါ သည်။
- မိသားစုဝင်များမှ တီဘီလူနာကို အခြားနေအိမ်သို့ရွှေ့ပြောင်းပေးနိုင်ခြင်းကြောင့်
- အရေးကြီးပါသည်။

4.7 MDR-TB patient's Counseling

Confidential dialogue between a medical provider and a client (MDR-TB patient) helps a client to define his/her feelings, cope with stress, and make informed decisions regarding treatment.

Characteristics of Effective Counseling:

There are 4 Characteristics: - (1) Client-centred (MDR-TB patient) (2) Interactive (3) Private and confidential and (4) Individualized

Tools for Effective Counseling:-

There are 3 tools:- 1) Communication skills 2) Technical information 3) Understanding the stages of the counseling process

Objectives of TB counseling

1. Prevention of TB transmission.
2. Provision of emotional support to TB clients (MDR-TB patient),
3. Motivating TB clients (MDR-TB patient) to complete treatment.
4. Helping clients (MDR-TB patient) make their own informed decisions about their behavior and supporting them in carrying out their decisions.

Counseling Steps:-

1. Creating a pleasant and comfortable atmosphere for the client.
2. Collecting information.
3. Listening actively.
4. Providing information.
5. Using printed materials.
6. Getting feedback.
7. Helping clients make decisions.
8. Making "contracts" with clients.
9. Providing information about the next visit or referring to specialized care.

Specific DR-TB counselling aims to encourage optimal adherence to the difficult treatment regimen and to increase the likelihood of a successful outcome for individual patients. It further stipulates that relevant information and educational materials, which are culturally sensitive and appropriate to the literacy levels of the population, should be made available for patients diagnosed with any form of DR-TB. The DR-TB patient's journey is complicated by a number of obstacles including side effects of drugs, high number of pills to swallow, the necessity to attend clinic daily for DOT (Directly Observed Therapy), and a long duration of treatment which impacts their ability to maintain their usual daily activities (work, school, caring for family, among others).

A diagnosis of DR-TB can be emotionally traumatic to the patients. Intolerance to or omission of specific drugs may result in suboptimal treatment regimens which could lead to the development of further drug resistance and subsequent treatment failure due to potentially suboptimal treatment regimens. There is a clear need for comprehensive counseling and support in order to ensure that patients adhere to the full treatment regimen. DR-TB is an infectious airborne disease; it affects not only the patient's well-being, but also that of their families, close contacts and local communities in which they live. Thus provision of information and education for the patient and their family should be comprehensive, culturally appropriate, and easy to understand.

There should be a structured, standardized, patient-centered counselling approach which may be used by lay counsellors (the volunteers) and healthcare workers to support DR-TB patients. It includes the sessions that provide necessary information, deal with a variety of adherence issues, and address other potential challenges that patients may face during their treatment period.

4.7.A Steps in MDR-TB counseling

1. Pre-Test Counseling for presumptive MDR-TB patient
2. Pre-Treatment Counseling for MDR-TB patient
3. Treatment Adherence counseling
   (a) Motivational interviewing counseling
   (b) Treatment Adherence counseling
4. Ambulatory Treatment Adherence counseling

1. Pre-Test Counseling for MDR-TB (presumptive MDR-TB patient)

The following points should be informed and well understood by the patients

(a) Explanation about Xpert MTB/RIF test; why & where to do the test, quality & minimal amount of the sputum required, when the result will be received, information revealed by the test and subsequent likely actions to be taken.

(b) Early treatment initiation is prevention of spread of tuberculosis to family members & close friends and relatives.

2. Pre-Treatment Counseling for MDR-TB patient

Counselors from Region and State's TB Center, District/Township TB Center, and TB Hospitals have to do Pre-Treatment Counseling for MDR-TB patient. The following facts should be informed and well accepted by the patients

(a) Remind the relevant facts which was informed in Pre-Test Counseling section

(b) Explain the needs of the investigations including blood test and psychological test before SLD treatment.

(c) It is a costly treatment and all expenses will be borne by NTP.

(d) Plan of treatment, drugs to be used and likely course in an understandable language.

(e) Social & some financial support will be available during treatment.

(f) Confirmation of residency and explanation of treatment plan according to their residency status.

(g) Information on how to live in home & workplace, minimizing chance of spread to close family members and friends (TB-IC methods).

Table 4.3 Summary of Psycho-Social Assessment for MDR-TB Patient

1st session - - /- /20 - (R/S/D TBC, TMO station, TBH, INGO Clinic Visit)

2nd session - - / - /20 - (Home Visit)

1	Name		
2	Age/Date of Birth		
3	Gender M/F		
4	Psychological	Mental illness - history	
		Depression or anxiety	
		Suicidal ideation or attempts	
		Current sleeping/eating problems	
		Current mood	
5	Substance Use	Alcohol-History of use/abuse - Current use - Any treatment	
		Illicit Drugs – History of use - Current use - Any treatment	
		Smoking – History of use - Current use - Any treatment	
6	Employment/Income		
7	Continuously migrant/ People from border area		
8	TB & MDR-TB Knowledge		
9	Support	Family members	
		Friends	
10	Main motivation factors to treatment		
11	Patient motivation level to treatment (Low, Ambivalent, High)		
12	Main issue/Likely to be de-motivation Factor to Adherence		
13	Decision for enrolment to MDR-TB programme		
14	Need next counseling session		

3. Treatment Adherence counseling

Method of motivational-interviewing is used for adherence counselling. Essential ingredients of this strategy of counselling include:

1) Building engagement (Alliance of Work)
2) Identify the problem/difficulty
3) Clarify to get better understanding
4) Action to solve problem/difficulty

Adherence means following the treatment with own autonomy. Adherence is based on an agreement between the patient and the health care team, and the patient's own agreement to play an active role in his/her health care. It is an interactive process, based on the client's understanding of treatment, commitment to treatment, and relationships with health care staff. Adherence Counselling consists of enhancing motivation to adhere and reducing barriers to adherence. These two are closely related and one affects the other. The objectives: are

I. Identify and prioritize motivators and barriers.
II. Establish the level of motivation

Assessing Motivators and Barriers to Adherence:- they are (a) Medical Factors – understanding & experience of illness and treatment, health problems, side effects, relationship with health provider. (b) Social/Family Factors – Level of relationships, caregivers/ dependants, living situation. (c) Economic Factors – income, work, housing. (d) Psychological Factors – Attitude toward illness/life. (e) Mental Health – depression, anxiety, intellectual capacity. (f) Alcohol/Drug Use – past/present, frequency, amount, type. (g) Discrimination – stigmatization, disclosure

Assessing the Level of Motivation to Adherence:- Three levels are recognized.

- High Motivation
- Ambivalent/Unsure
- Low motivation

Motivation can be high, low or varying degrees of ambivalence. Motivation can change dramatically, day to day. High and Low motivation is easy to spot but ambivalence is harder to understand.

Counsellor should constantly be assessing changes in motivation from one assessing to the next. Treatment Adherence counseling should be practiced in R/S/D TBC / TMO station or TB Hospital at least 3 times before & during initial SLD treatment. It should be done one week apart in a month.

(a) <u>First time counseling (initial session)</u>. This can be done in or equivalent to pre-treatment counseling. Counselor has to discuss on

1. Patient's general health, history of smoking, drug abuse, alcoholic, HIV disease, pregnant or not

2. Important of regularity of drug taking and unfavourable outcome of irregularity of drug taking
3. Number of drugs to be taken, doses, frequency, length of the treatment. To consult to physician if the patient suffers any S/E
4. To make sure the date for 2nd counseling section

(b) Second time counseling (preparation to start treatment), counselor has to discuss on

1. Remind the facts discussed in previous 1st time counseling session
2. Give new information on the investigation & treatment
3. Discussion on the problems the patient asks and find the possible solution

(c) Third time counseling (confirm readiness), counselor has to discuss on

1. Remind the facts discussed in previous 2 times counseling sessions
2. Discussion on the problems the patient asks and finds the possible solution

4. Ambulatory Treatment Adherence counseling: -

There are 3 types of counseling

(a) Counseling in 1st week of SLD treatment in community

(b) Monthly counseling in community

(c) Counseling in community after discharge from TB hospital (if patient was hospitalized.)

These counseling are usually done at patient's home or township TB clinic.

(a) Counseling in 1st week of SLD treatment in community

The counselors (usually BHS) have to counsel the patient how they will meet for DOT including injection, explain SLD S/E (may be repetition for the patient, but it remind previous counseling facts) and also discuss on any problem that the patient might encounter.

(b) Monthly counseling in community

Usually DOT provider (BHS or volunteers) have to counsel on 1) important of regularity of treatment 2) TB-IC such as wearing surgical mask till sputum culture is negative, to sleep separately, adequate lighting and ventilation in patient's room, good sputum disposable in patient's home 3) Provision of psychological support and the social support (the monthly nutritional and financial support). 4) the importance of follow up sputum smear/culture examination. 5) HE to the family members and conduct contact tracing usually at the start of treatment and at 6th month of treatment.

(c) Counseling in community after discharge from TB hospital

Most of the information are same as mention above, but DOT provider has to negotiate with the patient how DOT will be implemented (at home or in Clinic)

4.7.B Treatment Interruption counselling session and follow-up support

Cent percent adherence to any treatment is desirable but not easily achievable, thus occasional treatment interruption will be part of any patient's treatment journey. Treatment interruption may lead to eventual loss from treatment if new or existing challenges are not identified and addressed. In the 'treatment interruption' counselling session, the counsellor (health worker) discusses potential reasons for treatment interruption, specific to the individual and they work together on a condensed version of the adherence plan. The counsellor (health worker) helps patients to set themselves personal short term goals which are easily achievable. Follow up sessions are carried out by the MO or nursing staff in the clinic to ensure these goals are met. The aim of involving MO or nursing staff is also to strengthen the health worker-patient relationship. Clinic staff members are encouraged to observe the dialect or body language used to address the patient's challenges in order to be more supportive and motivating.

4.7.C XDR – TB Counselling session

A potential and undesired complication that patients face is the risk of developing more extensive drug resistance (pre- XDR and XDR) which is usually only detected 4-6 months after the start of MDR treatment. This requires additional counselling to inform patients of the change of their diagnosis (which can be confusing) and the need to modify their treatment. In addition, diagnosis of additional drug resistance can be devastating news, since there is a lower chance of cure with the current treatment available for extensively drug resistant TB. Nevertheless the counseling for this complication should be in supportive rather than discouraging tone. This session includes a clinical component that briefly explains the various treatment options available to them at this stage (to be expanded upon by the clinician).

4.7.D Palliative Care Counselling session

Not all patients who start DR-TB treatment win the battle against DR-TB: treatment may fail in some patients despite optimal adherence to treatment. The current treatment outcomes for XDR-TB in Myanmar are not clear yet. There is a lot of uncertainty regarding the optimal management of these patients and their families, given the infectious nature of the disease. The palliative care counselling session aims to gently inform patients and their families about their condition and their prognosis. This session provides practical information on the clinical management of the patient (whether or not treatment has been withdrawn) and guidance on how to access palliative support services.

Conclusion The standardized patient support model provides appropriate counselling support for patients across the entire spectrum of their treatment journey: treatment initiation, transition from intensive phase to continuation phase, treatment interruption, extensive drug resistance diagnosis and DR-TB treatment failure.

The patient centered approach offers individual support for patients to identify strategies to overcome their own barriers to adherence. Clinicians gain confidence in the patient support component of DR-TB treatment through standardized counseling messages and appropriate counselling supervision.

Counsellors undergo professional development through training on the counselling model. Supportive supervision of counsellors as they implement the counselling support package promotes quality assurance and counsellor confidence.

It is essential that all clinicians, nurses and counsellors DR-TB work together to ensure productive and successful support for patients with drug resistant tuberculosis; this support is as essential as the pills they take every day, and must continue throughout the long treatment journey.

Figure 4.1 Settings in MDR-TB management where health education & counseling is possible.

Psycho-social assessment	R/S/D TBC, TMO station, TBH, INGO clinic & Patient's home (Pretreatment counseling)
Prompt referal of RR-TB patient to MDR-TB initiating center	TMO station, INGO clinic
Discussion on actual MDR-TB enrolment from townships	R/S/D TBC (MDR-TB Centers)
R/S or District DR-TB committee meeting	R/S or District DR-TB committee including Members from Townships INGO
Arrange for further Inv: and	R/S or District DR-TB committee including Members from Townships INGO
INGO patients send for Inv; & treatment	R/S or District DR-TB Center
Adherence Counseling for MDR-TB patients	R/S TBC or District TBC, TB Hospital
Send to TMO station	TMO station, INGO clinic & patient's home
Adherence counseling continue	TMO station, INGO clinic & patient's home

Chapter 5

TREATMENT STRATEGIES FOR MDR-TB

5.1 Background on the design of the treatment strategy

The design of the treatment strategy used in Myanmar is based on DRS data, the history and the resources and capacity to implement a MDR-TB programme. The strategy also takes into account the prevalence of drug resistance in new patients as well as in different groups of re-treatment cases (failure, relapse, return after loss to follow up and other cases). As DST for first and second line anti-TB drugs are being developed to be available on a wider scale it is likely that modifications of standardized regimen started on an individual patient will become more common in near future.

5.2 Groups of anti-TB drugs

The groups of anti-TB drugs have traditionally been divided into first- and second-line drugs, with isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin being the primary first-line drugs. (Table 5.1) An alternative grouping consisting of 5 groups was recommended by WHO for treatment of MDR-TB and it is the basis for formulating the standardized regimens in PMDT Myanmar. However recently released WHO Guidelines for DRTB has introduced a new system of grouping aimed for treatment of DRTB. (Table 5.2)

Table 5.1 First-line Anti-TB drugs

	Drug	Symbol
Injectable	Streptomycin	S
Oral drugs	Isoniazid Rifampicin Ethambutol Pyrazinamide	H R E Z

First-line agents. The most potent and best tolerated anti-TB agents. They are used in drug-susceptible and some mono- and poly-resistant TB other than MDR-TB. (e.g. Classical "initial & retreatment regimens")

Table 5.2 Medicines recommended for the treatment of rifampicin-resistant and multi-drug-resistant TB[1]

A. Fluoroquinolones[2]	Levofloxacin Moxifloxacin Gatifloxacin		Lfx Mfx Gfx
B. Second-line injectable agents	Amikacin Capreomycin Kanamycin (Streptomycin)[3]		Am Cm Km (S)
C. Other core second-line agents[2]	Ethionamide /Prothionamide Cycloserine / Terizidone Linezolid Clofazimine		Eto / Pto Cs / Trd Lzd Cfz
D. Add-on agents (not part of the core MDR-TB regimen)	D1	Pyrazinamide Ethambutol High-dose isoniazid	Z E H^h
	D2	Bedaquiline Delamanid	Bdq Dlm
	D3	p-aminosalicylic acid Imipenem-cilastatin[4] Meropenem[4] Amoxicillin/clavulanate[4] (Thioacetazone)[5]	PAS Ipm Mpm Amx-Clv (T)

1 WHO treatment guidelines for drug-resistant tuberculosis, 2016 update. This regrouping is intended to guide the design of conventional regimens; for shorter regimens lasting 9-12 months the composition is usually standardized.

2 Medicines in Groups A and C are shown by decreasing order of usual preference for use (subject to other considerations; see text)

3 Refer to the text for the conditions under which streptomycin may substitute other injectable agents. Resistance to streptomycin alone does not qualify for the definition of extensively drug-resistant TB (XDR-TB)[1]

4 Carbapenems and clavulanate are meant to be used together; clavulanate is only available in formulations combined with amoxicillin

5 HIV-status must be tested and confirmed to be negative before thioacetazone is started

1 Case definition for extensively drug-resistant tuberculosis. Wkly Epidemiolo Rec. 2006 Oct20;81 (42):408.

Group A – Fluoroquinolones.

FQs are often the **most effective anti-TB drugs in an MDR-TB regimen**. Currently, the most potent available FQs, in descending order based on in vitro activity and animal studies, are: moxifloxacin = gatifloxacin> levofloxacin.[1], [2] Although gatifloxacin is similar to moxifloxacin in efficacy against TB, it is associated with serious cases of hypoglycaemia, hyperglycaemia,and new-onset diabetes. For this reason gatifloxacin is not widely available. But analysis of new data (although limited) showed that serious adverse events were not very common and thus the drug can now be considered as a choice for treatment of DR-TB. Ofloxacin was phased out from the list and ciprofloxacin is never used for TB. In summary, moxifloxacin or levofloxacin are the FQs of choice.

Group B – Injectable anti-TB drugs.

A Group B injectable agent will be used in all MDR-TB regimens. These guidelines suggest the use of amikacin (or kanamycin) as the first choice of an injectable agent. Given the high rates of streptomycin resist and 100% in failure of retreatment in Myanmar and extensive use of streptomycin in programme, it not recommended even if DST shows susceptibility. Amikacin and kanamycin have a high frequency of cross-resistance between them. Amikacin has a lower minimum inhibitory concentration and may be the most efficacious of the two [3] (but clinical comparison is lacking). Capreomycin may have cross-resistance with amikacin/kanamycin if the rrs gene mutation is present, but the clinical implications of this are not well understood. Limited evidence suggests capreomycin has fewer adverse effects than the aminoglycosides. If an isolate is resistant to both streptomycin and kanamycin (or amikacin), then capreomycin is considered to be the injectable of choice.

In cases of XDR-TB where the strain is resistant to all the second-line injectable drugs (amikacin, kanamycin, and capreomycin) but susceptible to streptomycin, stretptomycin should be considered, as there is little cross-resistance between streptomycin and the other injectable agents. All of the Group 2 drugs are given intramuscularly; most commonly the drugs are injected deeply into the upper outer quadrant of the gluteal muscle. Group B drugs can also be given intravenously (IV) but must be given slowly, over 60 minutes.

1 Alvirez-Freites EJ, Carter JL, Cynamon MH. In vitro and in vivo activities of gatifloxacin against Mycobacterium tuberculosis. Antimicrob Agents Chemother 2002; 46(4): 1022-5.

2 Baohong JI, Nacer L, Maslo C, Truffot-Pernot C, Bonnafous P, Grosset JH. In Vitro and in vivo activities of moxifloxacin and clinafloxacin against Mycobacterium tuberculosis. Antimicrob Agents Chemother 1998; 42:2006-2069.

3 Dooley KE, Mitnick CD, DeGroote MA, Obuku E, Belitsky V, Hamilton CD, Makhene M, Shah S, Brust JCM, Durakovic N, Nuermberger E. Old Drugs, New Purpose: Retooling Existing Drugs for Optimized Treatment of Resistant Tuberculosis. Clinical Infectious Diseases 2012;55(4):572-81.

Group C - Other core second-line anti-TB drugs.

Both ethionamide and prothionamide are prodrugs that need activation by mycobacterial enzymes. There is no clear advantage to ethionamide compared to prothionamide; efficacy and side-effects appear similar. These guidelines recommend ethionamide, but one can substitute prothionamide if need be. Of the Group 4 drugs, ethionamide/prothionamide performed best in the WHO-sponsored meta-analysis of MDR-TB treatment.

However, it should be noted that the inhA gene mutation in the TB bacteria has been associated with cross-resistance, with low-level isoniazid resistance and high-level ethionamide resistance.[1] Some commercial LPA tests can be used to detect the inhA gene mutation (see Chapter 3). If the inhA gene mutation is present, ethionamide/prothionamide in a MDR regimen may have to be replaced as it can not be counted as a "likely effective second-line anti-TB drug". Cycloserine and/or PAS should be included in MDR regimens. Both PAS and cycloserine share no cross-resistance to other anti-TB drugs. Since the combination of ethionamide/prothionamide and PAS often causes a high incidence of gastrointestinal side-effects and hypothyroidism, these agents are usually used together only when 4 core agents are not met by usual choices. The drugs in Group C may be started at a low dose and escalated over 3 to 10 days to reduce side-effects (this is known as dose-ramping).[2]

Group D -Add-on agents

Except pyrazinamide Group D drugs are not for routine use in MDR-TB treatment because their contribution to the efficacy of MDR-TB regimens is unclear or being investigated. Although they have demonstrated some activity in vitro or in animal models there is limited evidence of their efficacy in humans for the treatment of MDR-TB. Most of these drugs are expensive and in some cases require IV administration. However, they can be used in cases of XDR-TB, where adequate regimens are impossible to design with the medicines from Groups A-C. They should be used in consultation with an expert in the treatment of MDR-TB. If a situation requires the use of Group D drugs, often experts will recommend using two to three drugs from the group, given the limited knowledge about their efficacy.

Among the group D drugs 2 new drugs, bedaquiline and delamanid, are being extensively investigated by operational research around the world due to their potential effectiveness in drug resistant tuberculosis. WHO has issued an interim policy (in 2013 and 2014)[3] on these 2 new drugs.

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[1] Banerjee A, Dubnau E, Quemard A, Balasubramanian V, Um KS, Wilson T, Col ins D, de Lisle G, Jacobs WR Jr. i gene encoding a target for isoniazid and ethionamide in Mycobacterium tuberculosis. Science 1994; 263(5144):227-30.

[2] Drug-resistant tuberculosis: a survival guide for clinicians. San Francisco, Francis J. Curry National Tuberculosis Centre and California Department of Health Services, 2004.

[3] The use of bedaquiline in the treatment of multidrug-resistant thberculosis.(WHO/HTM/TB/2013.6) The use of delamanid in the treatment of multidrug-resistant tuberculosis.(WHO/HTM/TB/2014.23)

Bedaquilie is a diarylquinoline compound which inhibit mycobacterial adenosine triphosphate synthase. It has a long half-life of 5.5 month. Delamanid is a dihydronitroimidazole (nitromidoxazole) compound. It inhibits synthesis of methoxy-mycolic and keto-mycolic acids which are essential components of mycobacterial cell wall. It is a pro-drug requiring metabolic activation before it exerts pharmacologic action on its target. It has a much shorter half-life of a few days only. Full range of side effects of these 2 drugs is not yet known. But adverse effects of particular importance are drug-drug interactions (e.g with ARVs) and their tendency to cause QT prolongation predisposing to cardiac arrhythmias. Potential synergistic effect when used together with moxifloxacin and clofazimine is of particular concern. Their use in patients younger than 18 years is not yet approved and effect on pregnancy is unknown. Concurrent use of these two drugs is not advisable.

Linezolid is used for other bacterial infections also. Chemically it is an oxazolidinones. It is bactericidal and act by inhibition of protein synthesis. It's major adverse effects include anaemia, thrombocytopaenia (myelosuppression), lactic acidosis, peripheral neuropathy and optic neuropathy.

Clofazimine is an iminophenazine. It was once extensively used for leprosy before rifampicin was introduced. It's in vitro activity against M.tuberculosis has been known although there is little data for in vivo effectiveness. Discoloration of skin is a notorious side effect which many patients dislike.

5.3 Standardization of MDR-TB treatment regimens

The NTP uses standardized regimens for the treatment of MDR-TB. A standard MDR-TB regimen may have some variation depending on the patient's situations (see Sections 5.4 and 5.5). Most importantly, any patient who enters the Myanmar National MDR-TB Programme is fully monitored and supported for the full course of their treatment. The Standard MDR-TB Regimen is based on DST patterns of different groups. Standardized MDR-TB regimens have a number of advantages over individualized MDR-TB regimens, which include

- Simpler operational aspects of implementation
- Easier for scale-up and improved access
- Simpler drug ordering
- Easier in training
- Less likelihood of mismanagement
- Less dependence on highly technical laboratories

5.4 MDR-TB regimen and delivery of treatment

The following basic principles are involved in the MDR-TB regimen design:

- The choice of the regimen is based on treatment history and the category the patient belongs to (i.e. failures of Category II, new patient diagnosed with MDR-TB, etc.).
- Early MDR-TB detection, before there is extensive lung damage, and prompt initiation of an effective treatment are important factors in obtaining successful outcomes.
- MDR-TB regimens should include a least four core second-line drugs (from Group A, B, C) considered "likely to be effective" plus pyrazinamide.
- An anti-TB drug is considered "likely to be effective" when:
    1. The drug has not been used in a regimen that failed to cure the individual patient;
    2. DST performed on the patient's strain indicates susceptibility (DST for H, R, Groups A and B drugs is considered reliable; DST for all other drugs is considered insufficiently reliable for individual patient management);
    3. There is no known resistance to drugs with high cross-resistance;
    4. There are no known close contacts with resistance to the drug;
    5. Drug resistance surveys demonstrate resistance is rare to the drug in patients with similar TB history. (This last point is relevant in the absence of DST or for drugs in which individual DST is not reliable).
- There are conditions where drugs may be added to the standard MDR-TB regimen or where drug substitutions have to be made (i.e. when a patient has a severe allergy to one drug in the standard MDR-TB regimen, a different drug must be substituted).
- Do not use drugs for which the patient is known to have a strong contraindication of usage (i.e. known drug-drug interactions, overlying toxicities, history of severe allergy, pregnancy).
- The later-generation FQ (levofloxacin) will be used in the regimen. (Note: in the case of XDR-TB the later-generation FQ of moxifloxacin will be used).
- The length of the intensive phase (period when a Group B injectable agent is used) and the total treatment length are discussed below.
- Each dose is given under DOT throughout the treatment. A treatment card is marked for each observed dose. DOT can be performed either facility-based or home-based (often referred to as community-based). Adherence and social support are important components of treatment delivery.
- Treatment of adverse effects of drugs should be immediate and adequate to minimize the risk of treatment interruptions and prevent increased morbidity and mortality due to serious adverse effects.
- Antiretroviral therapy (ART) is strongly recommended for all patients with HIV and

MDR-TB requiring second-line anti-TB drugs, irrespective of CD4 cell-count, as early as possible (within the first 8 weeks) following initiation of the anti-TB treatment.

- The drug dosage should be determined by weight. A suggested weight-based dosing scheme is shown in Table 5.3. Paediatric dosing is described in Table 8.1.
- The oral drugs should be given 7 days a week. The injectable drugs can be given 6 or 7 days a week depending on the availability of a skilled medical person to give the injection.
- Pyrazinamide, ethambutol, and FQs should be given once a day, as the high peaks attained in once-a-day dosing may be more efficacious. Once-a-day dosing is permitted for the oral second-line anti-TB drugs from Group C depending on patient tolerance; however, ethionamide/prothionamide, cycloserine and PAS have traditionally been given in split doses during the day to reduce adverse effects. Pyrazinamide is used for the entire treatment. In patients doing well, pyrazinamide can be stopped with the injectable phase if the patient can continue with at least three certain, or almost certain, effective drugs.
- **Patients with MDR-TB should be treated using mainly ambulatory care methods and long hospitalizations should be avoided.**

5.5 Standardized MDR-TB regimens used in Myanmar

Based on the above principles for designing MDR-TB regimens and based on the results of the MDR-TB Pilot Project, the standard MDR-TB treatment regimen to be used in Myanmar is:

Standard MDR-TB Regimen: 6-8(Amk Z Lfx Eto Cs)/12-14 (Lfx Eto Cs Z)

The Standard MDR-TB Regimen will be used for all patients with whom the TB treatment history, contact information, and DST results (if available) suggest that all the second-line anti-TB drugs in the regimen are "likely to be effective" (see Section 5.4 for criteria of a "likely effective drug"). With future additional data on first- and second-line drug resistance patterns among different patient categories, the standardized MDR-TB regimen will be reviewed.

PAS/Clofazimine will be added to the Standard MDR-TB Regimen for patients with the following conditions:

1. Failures of Category II; (retreatment regimen)
2. The patient's strain tests resistant to ofloxacin (i.e. determined in a survey for DST to second-line anti-TB drugs or because of an indication for second-line DST);
3. The presence of the inhA gene on LPA (because ethionamide may not be effective):
4. The patient has a history of second-line drug use;
5. The patient is a contact of a patient who died on second-line drug regimen or a contact of a patient with a known history of resistance to second-line drugs.

PAS/Clofazimine can also be used in the following situations:

- If the patient cannot tolerate cycloserine in Standard MDR-TB Regimen, then PAS/ Clofazimine can be substituted for cycloserine;
- If the patient cannot tolerate ethionamide in Standard MDR-TB Regimen, then PAS/Clofazimine can be substituted for ethionamide;
- If the patient is pregnant, after consultation with the MDR-TB Committee a special regimen is designed to include PAS.

Capreomycin will be used in the following situations:

- If the patient cannot tolerate amikacin (or kanamycin) in Standard MDR-TB Regimen, then capreomycin can be substituted for amikacin (or kanamycin);
- If the patient's strain tests resistant to amikacin or kanamycin (i.e. determined in a survey for DST to second-line drugs or because of an indication for second-line DST) then capreomycin should be used.

Kanamycin can be used as a substitute for amikacin if needed.

5.6 Duration of intensive phase and treatment

Both the duration of the intensive phase and the total duration of treatment are guided by culture.

Intensive phase.

General rule for the period during which injectable agents are used is 8 months. But in whom culture conversion is achieved at the end of 7th month injectable may have to be extended for 1 month. Like-wise for those whose cultures start to convert at the end of 8th month injectables may have to be extended for 2 months. This is due to turn-around time needed for culture reports. It may be stopped earlier, but not less than 6 months, at 4 months after achieving culture conversion*. Thus duration of intensive phase is defined as 6 - 8(9,10) months.

* See criteria for culture conversion in treatment outcomes.

Note:

- It is recommended to review cultures, smears, X-rays and the patient's clinical status aids when deciding whether or not to continue an injectable agent longer than the above recommendation.
- A change to intermittent therapy with the injectable agent (3 times weekly) is done when signs of toxicity are noticed.
- Early suspension of the injectable agent should be considered when toxicity becomes very severe, e.g. renal, auditory (hearing loss or ringing in the ears) or vestibular (severe dizziness).

Total length of treatment. The duration of the treatment is guided by culture. It is recommended to continue therapy for 20 months. Absence of culture reversion should be shown at the last month of treatment. (i.e by culture at the end of 20 month.) Continuation of treatment beyond this duration should be rarely necessary and may be considered individually in some patients.

5.7 Shorter-course MDR-TB regimen

A shorter-course regimen, such as one introduced as Bangladesh regimen, is not yet applied in Myanmar NTP. The regimen is a standardized regimen rationale of which is unclear. The following is the regimen.

4-6 Km Gfx/Mfx Pto Cfz Hh E Z / 5 Gfx/Mfx Cfz E Z

WHO set 2 main preconditions before using this regimen.

a) Those who have not been previously treated with second-line drugs

b) Resistance to fluoroquinolones and second-line injectable agents is excluded or considered as highly unlikely.

It seems that combination of a later-generation quinolone and clofazimine with ethambutol and pyraqinamide enabled the regimen to be shortened significanty. Thus it would sound logical to ascertain that the bacillus is susceptible to ethambutol and pyrazinamide before starting this shorter- course regimen. Although current DST technology is stated as not 100% reproducible results by a quality-controlled laboratory service should be taken as guidance for applicability of this standardized regimen on each patient.

5.8 Treatment of extra-pulmonary MDR-TB

The treatment strategy is the same for patients with pulmonary and extra-pulmonary MDR-TB. If the patient has symptoms suggestive of central nervous system involvement and is infected with MDR-TB, the regimen should use drugs that have adequate penetration of the central nervous system. Rifampicin, isoniazid, pyrazinamide, flouroquinolones, protionamide/ ethionamide, linezolid and cycloserine have good penetration; kanamycin, amikacin and streptomycin penetrate effectively only in the presence of meningeal inflammation; PAS and ethambutol have poor or no penetration. There is little data for capreomycin, clofazimine, bedaquiline and delaminid.

5.9 Surgery in MDR-TB treatment

Surgical treatment of TB was common before the advent in the 1950s of highly effective anti-tuberculosis drug combinations. When rifampicin and pyrazinamide were combined with isoniazid in the 1960s and 1970s, short-course chemotherapy became so effective that nearly all patients could be cured without surgery, and the indications for surgical intervention, especially

in pulmonary TB (PTB), declined. Without safe, highly effective short-course chemotherapy, surgical intervention for specific indications may once again be necessary in selected cases of MDR-TB regimen to maximize the likelihood of cure. Surgery for TB requires highly experienced surgeons as well as careful patient selection, appropriate pre- and post-operative care, trained support personnel and specialized facilities with availability of safe blood transfusion services.

Specialized facilities should also include stringent infection control measures, since infectious substances can be aerosolized in large quantities during surgery, mechanical ventilation and postoperative pulmonary hygiene manipulations. The most common operative procedure in patients with pulmonary MDR-TB is surgical resection (lobectomy or wedge resection). It is considered to be an adjunct to chemotherapy. It is to be offered alongside the recommended MDR-TB regimen. Surgery is not indicated in patients with extensive bilateral disease.

The timing of surgery is important. It is recommended earlier in the course of the disease, when the patient's risk of morbidity and mortality is lower and when the disease is still localized to one lung or one lobe of lung. Generally, at least two months of therapy should be given or culture conversion obtained before surgical resection to decrease the bacterial infection in the surrounding lung tissue. The MDR-TB regimen should continue without interruption except for the immediate one or two days during the postoperative period. Doctors and nurses of the surgical departments must be familiar with the drugs used in the MDR-TB regimens. Even with successful resection, a full course of MDR-TB treatment should be continued.

General indications for surgical resection include patients who remain sputum positive (smear and/or culture), with resistance to a large number of drugs, and have localized pulmonary disease.

Surgical resection is not currently part of Myanmar's National MDR-TB Programme.

5.10 Adjunctive therapies in MDR-TB treatment

In addition to surgery (discussed above), a number of other measures can be used to lessen adverse effects and morbidity as well as improve MDR-TB treatment outcomes.

Nutritional support. In addition to causing malnutrition, MDR-TB can be exacerbated by poor nutritional status, low body mass index and severe anaemia. Without nutritional support, patients can become enmeshed in a vicious cycle of malnutrition and disease, especially those already suffering from baseline hunger. Second-line drugs may also further decrease the appetite, making adequate nutrition a greater challenge. Nutritional support can take the form of providing free staple foods, and whenever possible these should include a source of protein. Vitamin B6 (pyridoxine) should also be given to all patients receiving cycloserine to prevent adverse neurological effects. If multivitamins or minerals (zinc, iron, calcium, etc.) are given, they should be administered at a different time from the FQs, as they can interfere with the absorption of these drugs.

Table 5.3 Weight-based dosing of anti-TB drugs for adults

Drugs	Daily dose	30-35Kg	36-45Kg	46-55Kg	56-70Kg	>70 Kg
Isoniazid	4-6 mg/kg once daily	150mg	200mg	300mg	300Mg	300mg
High-dose Isoniazid	15-20mg/kg once daily	600-1000mg	1000-1500mg	1500mg	1500mg	1500mg
Rifampicin	8-12 mg/kg once daily	300mg	450mg	450mg	600mg	600mg
Rifabutin	5-10 mg/kg once daily	300mg	300mg	300mg	300mg	300mg
Pyrazinamide	20-30 mg/kg once daily	800mg	1000mg	1200mg	1600mg	2000mg
Ethambutol	15-25 mg/kg once daily	600mg	800mg	1000mg	1200mg	1200mg
Levofloxacin	750-1000mg once daily	750mg	750mg	1000mg	1000mg	1000mg
Moxifloxacin	400mg once daily	400mg	400mg	400mg	400mg	400mg
Gatifloxacin	400mg once daily	400mg	400mg	400mg	400mg	400mg
Ethionamide/ Prothionamide	500-750mg/day in 2 divided doses	500mg	500mg	750mg	750mg	1000mg
Cycloserine	500-750mg/day in 2 divided doses	500mg	500mg	500mg	750mg	750mg
para-aminosalicylic acid[1]	8 g/day in 2 divided doses	8g	8g	8g	8g	8-12g
Bedaquiline	400mg once daily for 2 weeks, then 200mg 3 times per week for 22 weeks					
Delamanid	100mg twice daily (total daily dose = 200mg) for 6 months					
Clofazimine	200-300mg daily (2 first months) then reduce to 100mg daily. (alternate dosing 100mg daily)					
Linezolid	600mg once daily	600mg	600mg	600mg	600mg	600mg
Clavulanic acid (available only in combination with amoxicillin. (Amx-Clv)[2]	125mg orally or 200mg I/V 30 minute before cabapenems	125mg orally/ 200mg IV	125mg orally/ 200mg IV	125mg orally/ 200mg IV	125mg orally/ 200mg IV	125mg orally/ 200mg IV
Amoxicillin/ Clavulanic acid (Amx-Clv)	(As an add- on drug per se) 80 mg/kg/day (based on amoxicillin component) in 2 divided doses. Maximum dose: 4000 mg amoxicillin and 500 mg clavulanic acid.					
Imipenem/ cilastatin	1000mg imipenem/ 1000mg cilastatin twice daily					
Meropenem	1000mg three times daily (alternate dosing is 2000mg twice daily)					

1. Dosing with sodium salt of PAS can vary with manufacturer. *See table 8.1for paediatric dosing.
2. WHO recommends to use clavulanic acid only with cabapenems.

Source: Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis

Corticosteroids. The use of corticosteroids in MDR-TB patients can be beneficial in cases of severe respiratory insufficiency and central nervous system involvement. Prednisolone (or prednisone) is commonly used, starting the dose at approximately 1 mg/kg, with gradual decrease in the daily dose by 10 mg per week when a longer course is indicated. Corticosteroids may also alleviate symptoms in patients with an exacerbation of obstructive pulmonary disease. In these cases, prednisolone (or prednisone) may be given in a short tapering course over 1–2 weeks, starting at approximately 1 mg/kg and decreasing the dose by 5–10 mg per day. Injectable corticosteroids are often used initially when a more immediate response is needed.

Table 5.4 Weight-based dosing for injectable anti-TB drugs in adults ≥30 kg.

Drugs	Daily Dose	30-33 kg	34-40 kg	41-45 kg	46-50 kg	51-70 kg	>70 kg
Streptomycin	12- 18 mg/kg once daily	500mg	600mg	700mg	800mg	900mg	1000gm
Kanamycin	15-20mg/kg once daily	500mg	625mg	750mg	875mg	1000mg	1000mg
Amikacin	15-20mg/kg once daily	500mg	625mg	750mg	875mg	1000mg	1000mg
Capreomycin	15-20mg/kg once daily	500mbg	600mg	750mg	800mg	1000mg	1000mg

Chapter 6

DOT PROVISION AND CASE-HOLDING FOR MDR-TB

This chapter describes all the aspects of treatment delivery to help the patient to complete the full course of the treatment. The chapter addresses counseling and education of the patient, treatment delivery settings, the provision of DOT and techniques to prevent default.

6.1 Counseling and health education

The patient must receive three adherence counseling sessions before treatment. Each counseling session is noted in the counseling register.

The adherence counseling sessions have three steps (see details in Chapter 4 on MDR-TB patient education):

1. Initial session
2 Preparation to start treatment
3. Confirm readiness

Contents of counseling must cover

(a) Nature of disease & infectiousness

(b) Baseline and monthly laboratory investigations must be required

(c) The treatment requires full DOT and adherence (DOT provider will observe all doses

(d) The patient may require hospital admission

(e) Early and effective management of drug side effects

(f) Drug collection system

(g) Follow up examinations

During counseling sessions, particular attention must be given to:

- Previously defaulted patients
- Prisoners
- Patients without family support
- Patients with past history of taking second line anti-TB drugs
- Patients with history of adverse drug reactions
- Patients with co-morbidities
- Patients with addictions to alcohol or other drugs

When the three counseling sessions are successfully completed, the patient must sign the **Patient's Informed Consent Form** (Annex 3, Form 14).

Counseling and Heath education

Counseling and Health education can be provided by a trained person such as Medical Officer, nurse, Social worker, BHS or ORW.

Health Education can be delivered individually or in a group must be done at patient's home, in a clinic room of hospital, Regional/State TB center and township level at patient's arrival, monthly and on special occasions using multimedia approach, including Television, pamphlets, poster and video shows where available.

In addition, health education must be done by DOT provider as well as by DOT Supervisor during follow-up visit. NGOs supporting community based MDR-TB patient care have a vital role in health education as well as in counseling.

Ongoing counseling and health education

A continuum of counseling throughout the course of the treatment must be provided by the DOT provider and the DOT supervisor. Missed-dose patients and defaulter patients must attend a counseling session once traced.

6.2 Treatment delivery setting

The Myanmar MDR-TB Program principally uses three models of Treatment delivery.

1. Ambulatory treatment delivery with home based DOT: DOT provider going to the patient's home each day
2. Clinic / Health center based treatment delivery
3. Hospital based

(1) Ambulatory treatment delivery

The following requirements must be met for those patients who are starting treatment in community or are transferred from hospital.

(1) Patient's household is ready to receive the patient

(2) A DOT provider is identified

(3) The place of follow-up care

(4) Transportation for monthly follow-up care

(5) A link between township health center and Regional/State/Decentralized MDR-TB center

(6) Socioeconomic support for the patient

(2) Clinic / Health center based treatment delivery

The criteria for Clinic / Health center based treatment delivery are as follows:

1. Township having a heavy load of MDR-TB patients
2. Township having very few basic health staff
3. Patient who is not willing for home based treatment delivery
4. Patient who lives very close to clinic/health center
5. Patient who needs to be monitored very closely

(3) Hospital based treatment delivery

The criteria for admission to the hospital are as follows:

- Patient is clinically and physically unfit to receive care at home or on an ambulatory basis
- Severe side-effects
- Adherence problems
- Immobility
- Severe co-morbidities (diabetes mellitus, HIV, renal failure, hepatitis, severe anaemia, etc.)
- Patient is failing MDR-TB treatment regimens
- Vulnerability e.g. disadvantaged orphan, mentally, socially or physically handicapped

Pregnant women and children do not need to be hospitalized if clinically stable.

All TB patients hospitalized in TB Hospitals or at Special Infectious Disease Hospitals should have an Xpert MTB/RIF test. If the test shows rifampicin resistance, the patient should be separated from other patients. HIV-positive MDR-TB patients must be directly referred to TB Hospitals or put on early initiation of MDR-TB treatment. All confirmed DR-TB cases should be isolated or treated in single occupancy rooms. If rooms are available, presumptive DR-TB patients should be isolated. Hospitals should have good infection control and allow for family socializa-

tion without risk of infecting family members. Adequate nutrition and social stimulation should be provided. Access to television and other things to prevent boredom is encouraged. DOT is also done in the hospital with every dose fully observed (medicines should not be left by the bedside for the patient to take on their own).

When transitioning from the hospital to ambulatory care, (at discharge), the patient must be provided with sufficient amount of drugs to cover the travelling period, as well as a copy of the Treatment Card and the MDR-TB Referral Form. The supply of medicines will be ensured to all patients free of charge, to be taken with DOT support. The patient must be referred to the R/S TBC accompanied by the corresponding DOT Provider, and report to the R/S TBO who must be directly informed by phone by the Medical Superintendent /Medical Officer (MO) in-charge about the discharge. Arrangements for discharge from the hospital to ambulatory care setting should be made as soon as possible. Upon discharge, a transfer note should be written to the TMO and TB Coordinator.

Whether the patient starts treatment in the hospital or in an ambulatory setting, he/she is supported by a team of people. If the patient is hospitalized, he/she is to be supported, managed and supervised by a team that includes a physician, nurses and social workers.

Flow of MDR-TB patients into treatment process

- Once a patient comes to Xpert MTB/RIF center for diagnosis, he or she must summit sputum specimen.
- If he or she cannot come to Xpert MTB/RIF center, their sputum specimens could be transported by assigned township staff to this Xpert center.
- If confirmed MDR-TB patients are detected at Xpert MTB/RIF center, assigned data assistant at this center should record those confirmed MDR-TB patients in DR-TB Notification Register.
- Treatment Initiation can be started at MDR-TB Center/ District TB Center. Either the patients must contact the TMO/TB coordinator or TMO/TB coordinator must contact the MDR-TB patients through BHS.
- Initial home visits to MDR-TB patients and necessary counseling sessions will be provided by BHS and TMO.
- After assessing the clinical, psychological and motivational level of patients on treatment, TMO/TB coordinator should refer the MDR-TB patient to MDR-TB center to start MDR-TB treatment. MDR-TB patients must be recorded in the township MDR-TB register.

- If notified confirmed MDR-TB patient is still missing (eg.travel/move to other township, not meet with respective BHS and etc:), Township staff should visit patient's house repeatedly and counsel to patients and his or her family members.
- If patient has a discordant result (two Xpert test results are different), TMO/TB coordinator will inform to Regional/State TB officer and refer him or her for further diagnosis of DR-TB.

General supervision and management of any complication/problem, beyond the capacity of township personnel, is the responsibility of R/S TBO.

If the patient is ill, he or she should be referred to the hospital to start MDR-TB treatment.

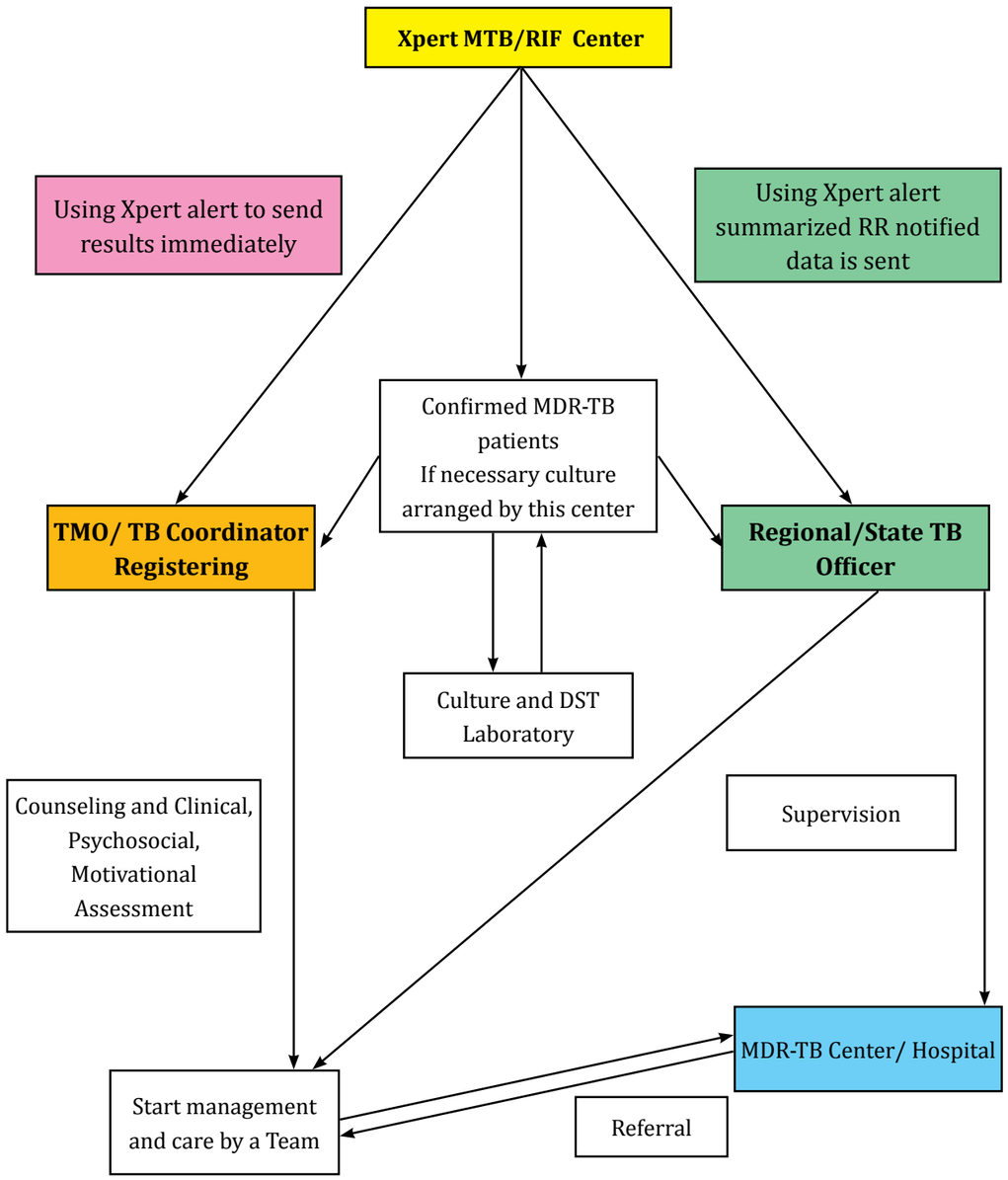
At any level of referral, the MDR-TB referral forms will be used (Annex 3, Form 15).

Reporting of RR positive results to R/S TB center and Township by using X pert Alert

If MTB RR positive results are coming out from Xpert MTB/RIF center, by using the X pert Alert system, R/S TB Officer can know these RR positive patients in details which are already described in the requisition form (name of patient, age, gender, residence township, HIV status, previous TB status, microscope result, tested date with serial number, name of X pert center which performed).

When decentralization of PMDT is started, the expansion of Xpert Alert system to decentralized sites and townships will be done to know the patients with RR positive results immediately.

Figure 6.1 Flow of MDR-TB patients into treatment process



Initial baseline investigations and follow-up

Ambulatory or hospitalized treatment will be decided by Township Medical Centre. Those requiring hospitalization will be sent to the hospital with MDR-TB inpatient facilities. For ambulatory treatment, baseline investigations will be done at the R/S TBC and decentralized MDR-TB center. At any level, the **MDR-TB referral form** must be used (Annex 3, Form 15).Consistent monthly clinical and laboratory follow-up is also free of charge and is described in Chapter 10.

6.3 Directly observed therapy (DOT)

Complete agreement on the organization of DOT is documented by the **Patient's Informed Consent Form** (Annex 3, Form 14), signed by the patient, the R/S MS or District Medical Officer (TB and Leprosy), TMO, the DOT Provider, and NGO staff if relevant. It is the responsibility of the clinical staff to supervise the fulfillment of this agreement.

DOT is one of the key components of MDR-TB management and its full implementation will help prevent the development of further resistance and XDR-TB. Each and every dose must be strictly observed regardless of the treatment delivery setting (in-patient or out-patient). DOT should not place a burden on patients and their families; therefore DOT must be conducted in the place where it is most convenient for the patient.

The DOT Provider can be a nurse, BHS, or NGO staff member trained in DOT and MDR-TB care and treatment. At the start of treatment, the DOT Provider for the outpatient phase must be identified by the TMO and counselor in agreement with the patient. Most often, the DOT Provider will be a BHS trained in MDR-TB care and management. The DOT Provider is responsible for supervising the oral intake at home or at any place appropriate for the patient. The DOT Provider should not be a family member as family relationships are often unfavorable for the MDR-TB management; a family member could be subject to subtle manipulation by the patient, relatives, employer, etc (however, a family member may be a DOT provider as a last resort if no other person can be identified).

All patients should have a secondary DOT Provider, who in some circumstances could be a family member, but it is still preferable to have a non-family member. This is for DOT delivery when the primary DOT provider is not available. The secondary DOT Provider can also be used to observe an afternoon dose if the daily-dosing is split up to lessen side-effects, allowing the primary DOT Provider to go to the patient's house only once per day.

General Principle for provision of DOT

At the clinic/health center/ hospital/ patient's home, the following procedures should be followed by the health care worker (DOT provider):

- Time of DOT for every patient (hospital ward/community level) should be permanent, determined in advance, and must be noted on the patient's MDR-TB Treatment Card.

- The patient should keep the appointed time for taking drugs with the DOT provider.
- The prescribed medications are taken under direct observation and the whole daily dose is taken in one sitting, unless the physician indicates that medicine can be split up to lessen side-effects. (Pyrazinamide, injectable agents and FQ are always given in a single dose. Ethionamide, cycloserine, and PAS are normally given twice a day to reduce side-effects.)
- Treatment is administered in the same designated place, according to the schedule, keeping the same sequence.
- The DOT Provider should lay out the pills and check the dosage.
- Before handing over the medicines, the DOT Provider should ask the name of the patient, check the note on the vial or the plastic bag containing the patient's pills. The injection should be given at the same time as oral drugs.
- The injection is to be given by either a BHS or GP. A test dose, at the start of treatment, is required for injection and should be given at a TB centre or hospital. The injection must be followed by oral intake of SLDs.
- The patient, standing or sitting in front of the responsible person, should swallow the drugs immediately.
- After swallowing the tablets, the patient drinks some water. The patient should show their mouth, palms and cup to the DOT Provider. If the patient does not do this, the DOT Provider should ask the patient to do so.
- The next patient can be served only once the Provider is sure that the previous one has taken all their medicines.
- If the patient is absent and/or does not take the drugs, the DOT Provider should inform the DOT Supervisor by the end of the working day; the DOT Supervisor reports all missed doses to the TMO/Township TB Coordinator within one working day.
- If side-effects occur, the DOT Provider should inform the DOT Supervisor immediately. DOT Supervisors are responsible for managing minor side-effects and referring to the TMO/Township TB Coordinator if major side-effects occur.
- After making sure that patient has taken all medication, the DOT Provider should make in the **List of Directly Observed Treatment** (Annex 3.13, DR-TB Form 13).
- In the Government sector, the TMO must assign a DOT Supervisor for supervision of DOT Provider activities. DOT Supervisors will be LHV, HA, PHS 1, THNO and HA 1. For NGOs and INGOs the responsible person will assign DOT supervisors according to their organization plans.

Ambulatory treatment

As mentioned above, ambulatory care patients are to be supported and managed at the township level by the TMO, TB Coordinator and DOT Provider. **DOT must be daily** regard-less of treatment delivery setting. The R/S TBO, TB Specialists, and TB focal persons at the R/S TBC must remain involved with and aware of all MDR-TB patients regardless of whether they initiated treatment in the hospital or ambulatory setting.

The MO in-charge assesses the patient's condition, reviews the MDR-TB Treatment Card and registers the patient in the township MDR-TB Register.

Treatment for patients who do not require hospitalization will be started in the ambulatory setting. The TMO or Township TB Coordinator must deliver health education/counseling to the patient and family member and confirm again and contact an appropriate and trained DOT Provider and DOT Supervisor. The DOT Supervisor must supervise the DOT Provider on a monthly basis, reporting to the TMO or Township TB Coordinator about the progress of the patient's condition and any problems encountered. An agreement must be reached by the TMO or Township TB Coordinator, the patient, and the DOT Provider on the choice of ambulatory treatment delivery (place and time of day for DOT, which is most commonly the home but can be the place of work or the clinic if it is more convenient). Pre-treatment investigations and assessment will be done at township level.

The TMO or Township TB Coordinator must refer the MDR-TB patient to the Regional/ State or township TB laboratory for follow-up sputum collection and for follow-up clinical examination. The patient must be referred to the hospital or R/S TBC:

- If any severe/ significant drug side-effects occur
- If any change in treatment is required
- At the end of the treatment

The DOT Provider must be instructed to refer the patient to the township health center if any of the above situations occur.

The DOT Provider must mark in the **List of Directly Observed Treatment** (Annex 3, Form 13) after observing the drugs intake by the patient. He/she should provide psychological support to the patient, encouraging the patient to complete the full course of treatment and give additional health education/counseling to the patient and family members on a monthly basis.

The DOT Supervisor makes an initial home visit to confirm the patient's address, to deliver health education to the patient and family members and to conduct contact investigation. The DOT Supervisor also manages all the DOT Providers and makes periodic visits with the DOT Provider to patients' homes to make sure all is functioning well.

Adherence to treatment

Adequate supportive measures must be provided to prevent non-adherence. The following measures include enablers and incentives to ensure adherence to treatment:

- Travel allowance for MDR-TB patients and DOT Providers
- Nutritional support for MDR-TB patients (this can be given in the form of food packages or monthly monetary payment).

Similar adherence approaches are used during inpatient and ambulatory phases of treatment. The following measures must be implemented to prevent non-adherence through a patient-centered approach:

Table 6.1 Adherence approaches

Action	Responsible
Education, psychological preparation and regular support, counseling	MO/nurse/social worker/BHS/DOT Provider and Supervisor/TMO/INGO (ideally the educator/counselor should remain the same over the treatment period)
Socio-economic provisions	MS/Regional/State TB Officer/TMO/INGO
Advance planning for transferring within MDR-TB designated sites	MS/Regional/State TB Officer coordinates the transfer (patient signs commitment form to remain in the area during the treatment.)
Creating DOT conditions convenient to the patient	DOT Provider flexible to supervise drug intake according to patient convenience; even injections can be given in the home or an agreed-upon convenient place by the DOT Provider and patient.
Patients from townships/ decentralized centers.	Initiation of treatment will be placed at MDR-TB treatment center. After TMO's approval, respective BHS should be trained and DOT provision should be at patient's home.

Follow-up of non-adherent or absconded patients

Any absconded/missed-dose patient must be traced immediately; the tracing mechanism must be initiated within 24 hours. If a hospitalized patient leaves the hospital during an admission period, the Medical Superintendent, R/S TBO, TMO and the Medical Officer in-charge are responsible for initiating the mechanism to trace the patient. The tracing mechanism can be conducted by the social worker of the hospital. MS, R/S TBO or MO in-charge can contact the TMO/ Township TB Coordinator for support. If the patient receives treatment from an INGO clinic, the MS/MO in-charge can directly contact the INGO staff. In any case, the Regional/State TB Officer must be informed about defaulting patients.

Once referred to township for ambulatory care, or if starting care in the ambulatory setting, the DOT Provider will report all missed doses to the TMO/Township TB Coordinator, or if the patient is not able to report at the prescribed date for treatment or follow-up examination. The TMO is responsible for tracing the patient through BHS or NGO staff for missed clinic appointments. The tracing mechanism for an absconded patient is described in Figure 6.2.

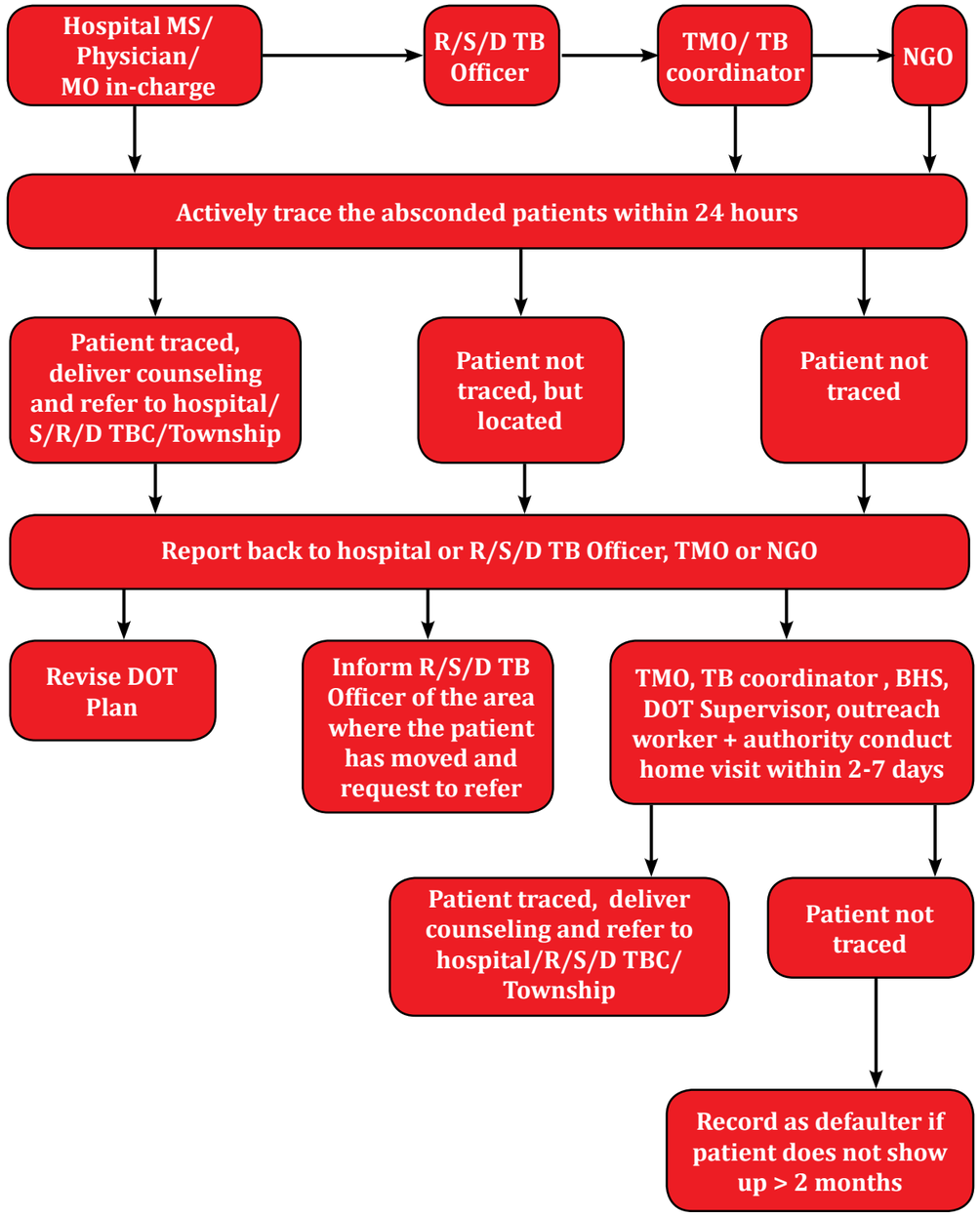


Figure 6.2 Tracing mechanism for non-adherent or absconded patients

Once a patient has been traced, the situation should be addressed in a sympathetic, friendly and non-judgemental manner. Listen to the patient's reason for missing a dose(s) or defaulting, and work with the patient and family to ensure continuation of treatment, while encouraging the patient not to default again. Depending upon whether the patient was hospitalized or already discharged, the **Register for Missed Dose Tracing** (Annex 3, Form 12) must be filled in respectively by the R/S TBO, the MS/MO in-charge at the hospital or the TMO/ Township TB Coordinator.

Measures preventing default. There are a number of strategies that can be applied to prevent patients from defaulting from treatment.

- The provision of early and complete patient education informing about illness and patient's role in treatment success (see Chapter 4).
- Training and psychological preparation of the patient for treatment and possible manageable side-effects and ways of managing them.
- Creating convenient and acceptable DOT conditions for the patient.
- Provision of social and economic support: counselling and travel allowance/ nutritional support.
- Advanced planning for transferring patient from one hospital to another or from the hospital to home-based treatment. The patient should leave the hospital only when information about the readiness of the corresponding township to continue the treatment is received by the MS or R/S TBO in-charge.
- Counselling session administered before discharge.
- MS/MO informs R/S TBO about the discharge and R/S TBO meets the patient before he/she is sent to the residing township.
- Patient supplied with drugs through DOT Provider, treatment card, referral form, travel allowance and nutritional support and referred to R/S TBO.
- R/S TBO contacts TMO to make an appointment for the patient.
- TMO contacts in advance a possible DOT Provider, if not already identified during the treatment in R/S TBC or hospitalization.

If an MDR-TB patient is admitted to prison during the TB treatment, the R/S MDR-TB Committee is responsible for ensuring the correct continuation and completion of the treatment and proper follow-up.

Patient centered community based TB Care

Community supporters or volunteers can provide comprehensive package of DOT and monitoring drug adverse side effects; patient support including nutritional and social support; health education on infection control measures; and awareness program.

Involvement of the community could be vital to maintain the quality of care in situations where work load of basic health staffs in managing MDR-TB becomes overstretched due to an increase in number of patients.

Community volunteers are recruited through the partners (MMA, MHAA and Pyigyikhin, The Union, Burnet Institute and PSI Myanmar). Before recruitment process, area mapping exercise is done to prevent the overlap and misunderstanding between partners.

The standardized training package in Myanmar language is also developed based on the pilot CAP-TB project implemented by MMA with the support of USAID and FHI 360. The trainers or facilitators are recruited from Regional Health Department, National TB Program, partners and FHI 360.Duration of the training is 2 days.

The selection criteria for community volunteers are used according to NTP guideline of community based TB Care. The volunteers are selected by a team composed of township medical officer and officer from partner organization and NTP Officer. Among them, one community volunteer will be assigned as team leader (especially for monitoring and evaluation) for summarization of monthly report. Before provision of evening DOT, chest X ray screening is done for the volunteer. The evening DOT is provided by trained community volunteer. Drugs are delivered to community volunteer once a week. Volunteer incentive is determined and provided. Maximum of 3 patients are allowed to be taken care by one volunteer. If the clustering of treating MDR-TB patients is occurred within the proximity or at one house, one community volunteer can provide evening DOT to all patients.

The comprehensive standardized package of activities of community volunteers involved in Patient centered community based MDR-TB Care is as follows:

- ✓ Evening DOT provision for MDR-TB patients
- ✓ Help in delivering of patient support package through cash giving or ATM card and help nutritional support
- ✓ Home based Care Activities including asking and checking the patient about treatment adherence, regular follow up to MDR-TB treatment center, follow-up smear and culture examination, side effects, infection control measures of patient's home,
- ✓ Contact Tracing and referral of family contact if they become symptomatic
- ✓ Health talk to patient and family members on TB, MDR-TB and Infection Control measures

- ✓ Transportation of sputum specimens and blood specimens to MDR-TB treatment center if necessary
- ✓ Record on the list of DOT
- ✓ Provide patient support through cash for pre-enrolled confirmed MDR-TB patients

Recognition of their activities should be expressed in the township review meetings between township, district TB partners and volunteers on a quarterly basis. At the meeting, the following points must be discussed.

- Training and activities of volunteers, drop-out of community volunteers and ways to further recruitment of volunteers
- Number of MDR-TB patients provided by volunteer
- Availability of cash and nutritional support
- Number of family contacts referred by volunteer
- Relationship between basic health staff and volunteer
- Problems associated with treatment adherence, side effects, accessibility

Supervision and Monitoring

Supervision and monitoring must be done using the checklist by both public sector as well as community partner. It is important to assess whether the program is functioning in the right track. The plan for joint supervision plan will be prepared and monthly, quarterly and yearly supervision will be done by township, regional/state level and central level respectively.

Chapter 7

ROLE OF OTHER PROVIDERS IN DR-TB MANAGEMENT

Private providers, engaged in TB control on a nationwide scale through a successful partnership, are the Myanmar Medical Association (MMA) and Population Services International (PSI). In 2015, 2.4% and 12.7% of TB case-finding was accounted for by MMA- and PSI-affiliated private practitioners respectively. There are three schemes available for engagement of private providers in TB control: 1) referral of presumptive TB cases, 2) referral and treatment provision[1] and 3) referral, diagnosis, treatment provision and reporting for outcomes. In 2015, MMA & PSI advocated and trained some private practitioners regarding MDR-TB case finding and management. In 2016, Xpert MTB/RIF advocacy meetings organized in Yangon Region included some private practitioners and focal persons from public hospitals so as to engage them in the DR-TB case finding activities.

By 2016, there were 25 public general hospitals involved in TB control. The NTP has plans to further expand collaboration and implementation of DOTS to additional general hospitals, and also to specialist and private hospitals.

Several other NGOs also support basic TB control in Myanmar, including referral, diagnosis, treatment and care. Some of them (Burnet Institute, MMA, MHAA, Pyi Gyi Khin, PSI, The Union,) are involved in Community based DR-TB Care and contact tracing activities of PMDT and infection control at patient's home. At present, only MSF (H) is involved in MDR-TB case management. MSF takes care of MDR-TB patients from their HIV cohort with second line drug supplied by NTP. MSF also supports for second line DST to be done at the Supranational Laboratory in Antwerp for some selected cases. Apart from those few cases, the diagnosis and laboratory monitoring of treatment progress of all enrolled cases are carried out at the NTRL, Upper Myanmar Reference Laboratory, Taunggyi Laboratory (Mawlamyaing Laboratory infrastructure has finished and solid culture lab will be installed in 2017; and Regional/State TB laboratories in near future) with liquid & conventional culture and DST facilities.

The possible role of private providers, hospitals, NGOs, community health workers and volunteers in MDR-TB management is described in Table 7.1.

[1] There is no more practice of Scheme II PPM in current situation.

Table 7.1 MDR-TB management tasks (Clinical and Public Health) for different provider categories

	Tasks	NTP	NGO	Community health-care workers and volunteers	General Practitioners affiliated with PSI and MMA	Hospitals	Private labs affiliated with PSI and MMA under NTP quality control
Clinical tasks	Identify presumptive MDR-TB cases	+	+	+	+	+	
	Collect sputum samples	+	+	+	+	+	
	Refer presumptive MDR-TB cases	+	+		+	+	
	Screened by Xpert MTB/RIF	+	+			+	+
	Diagnose MDR-TB	+					
	Notify/record MDR-TB cases*	+	+				
	Initiate MDR-TB treatment	+					
	Provide DOT during initial phase (injectable secondline agent) and identify side-effects	+	+		Only on exceptional basis if more convenient to the MDR-TB patient.	+	
	Provide DOT during continuation phase and identify side-effects	+	+	+	+		
Public health tasks	Educate patients, families and communities about MDR-TB.	+	+	+	+	+	
	Promote and implement infection control measures in health-care facilities	+	+	+	+	+	+
	Assess and improve TB infection control in the home of MDR-TB patients	+	+	+	+		
	Advocate at all levels for prevention and control of MDR-TB	+	+	+	+	+	
	Supervise and coordinate MDR-TB DOT Providers	+	+				
	Trace non-adherent or absconded patients	+	+	+			
	Trace contacts and referral for diagnosis	+	+	+			
	Identify and address socioeconomic problems	+	+	+			
	Train health-care providers	+					
	Supervision	+	+				
	Assure quality of laboratories	DR-T					
	Monitoring and evaluation	+	+				
	Manage second-line drugs and supplies	+					
	Provide stewardship and regulation	+					

* The NTP must strengthen the notification and recording and reporting of MDR-TB patients cared for by Public/Private Hospitals or private general practitioners not affiliated with PSI and MMA.

Guidelines for the Manangement of DR-TB in Myanmar

Chapter

8

MDR-TB TREATMENT IN SPECIAL SITUATIONS

Some special situations can make the treatment of MDR-TB more complex, but it can nonthe-less be successful. The following are the common special situations to be considered during the treatment of MDR-TB patients:

- Pregnancy
- Breastfeeding
- Contraception
- Children and adolescents
- Diabetes mellitus
- Renal insufficiency
- Liver disorders
- Seizure disorders
- Psychiatric illnesses
- Substance abuse

The special situation of HIV and MDR-TB is addressed in Chapter 9. MDR-TB patients with severe concomitant diseases may meet the “exclusion criteria” for enrolment as described in Chapter 2.

8.1 Pregnancy

Pregnancy is not a contraindication for treatment of active MDR-TB, given the greater risks posed by the disease to the lives of both mother and foetus. A pregnancy test should be performed on all female patients of child-bearing age as part of the initial assessment before starting second-line treatment, and women who are not pregnant should be offered advice on contraception (see Section 8.3 below).

Pregnant patients should be carefully evaluated, taking into consideration gestational age and severity of the MDR-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. For a decision regarding starting a pregnant female on treatment, the following guidelines are recommended:

- **If the condition of the patient is mild or moderate, start MDR-TB treatment in the second trimester if possible**. This is to avoid the teratogenic effects, which are more likely to occur in the first trimester. The decision to postpone the start of treatment should be agreed on by both patient and doctor after analysis of the risks and benefits.
- **If the condition of the patient is severe, start MDR-TB treatment at once**. The decision to start during the first trimester should be based on 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 infection).

When therapy is started during pregnancy, 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 due to the risk of toxicity to the developing foetal ear. Capreomycin may also carry a 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 the possibility of teratogenic effects. If possible, ethionamide should be avoided in pregnant patients. PAS could be used in pregnancy when there is no other choice.

8.2 Breastfeeding

A breastfeeding mother with active MDR-TB should receive a full course of anti-TB treatment, as timely and effective treatment is the best way to prevent transmission of tubercle bacilli to her baby. The mother and her baby should not be completely separated. However, if the mother is sputum smear-positive, the cooperation of a family member should be sought to primarily care for the infant until the mother becomes sputum smear-negative. In cases where the mother is on effective treatment, the mother and infant may spend time together, in a well-ventilated area or outdoors. The mother should wear a surgical cloth mask or an N-95 respirator during breastfeeding.

Despite the unknown risks of TB drugs in breastmilk, infant formula should only be considered when resources and training are available. When infant formula is chosen as an option

it should be ensured that fuel for boiling water and the necessary apparatus (stove, heating pans and bottles) are in place and will be available for the duration of infant formula feeding, and that the mother (or caregiver) knows how to prepare sterile infant formula.

8.3 Contraception

Women who are on treatment for MDR-TB with second-line drugs can take oral contraceptive pills, if the regimens do not contain rifampicin. For patients not using any contraceptives, contraceptive methods should be offered.

8.4 Children

Children and adolescents with MDR-TB have generally been infected through contact with adults with MDR-TB, and the majority of children infected would have primary resistance to TB. It is difficult to perform DST in younger children because of their pauci-bacillary nature and their inability to produce the sputum. In culture-negative children who have clinical evidence of active TB and close contact with MDR-TB patients, the line of treatment should be guided by DST result of the source case and the source case's history of TB drugs exposure. Second-line anti-TB drugs are not contraindicated in children, and generally they can tolerate the drugs better than adults. However there is now some evidence that outcome of children with less severe forms of MDR-TB treated with or without injectable agents does not differ. Given the facts that injections for children are unpleasant and difficult at times, and higher incidence of auditory impairment in them WHO now recommends that injectables may be excluded in this group of patients.

Quinolones have an effect on cartilage in experiments in animals but do not appear to result in the same growth retardation problems in children. It is now considered that the benefit of quinolones in treating MDR-TB in children outweighs their risk. Other drugs like PAS, cycloserine and ethionamide, which have been used effectively in children, are well tolerated. Dose must be given according to body weight and must be adjusted on a monthly basis according to body weight variations.

Up to now there is little data for use of Bedaquiline and Delamanid in children.

Table 8.1 provides the dosing for all anti-TB drugs for children, including the first-line agents (for completeness). The dosing should be applied in children that weigh less than 30 kg; for children greater than 30 kg the adult dosing table (Table 5.3 & 5.4) can be used.

Children with MDR-TB will be managed by designated paediatricians with expertise in the field of MDR-TB in accordance with the National Guidelines on Childhood TB Management – NTP/WHO 2016.

Treatment failure should be suspected in children if any of the following are present:

- Weight loss
- Failure to gain weight (failure to thrive)
- Deteriorating clinical condition or new signs and symptoms.

Table 8.1 Paediatric dosing of anti-tuberculosis medications*

Drug	Daily Dose	Maximum daily dose
isoniazid (H) (not Hh)[1]	7-15 mg/kg once daily	300 mg
rifampicin (R)	10-20 mg/kg once daily	600 mg
ethambutol (E)	15-25 mg/kg once daily	1200 mg
pyrazinamide (Z)	30-40 mg/kg once daily	2000 mg
streptomycin	20-40 mg/kg once daily	1000 mg
amikacin (Am)	15-22.5 mg/kg once daily	1000 mg
kanamycin (Km)	15-30 mg/kg once daily	1000 mg
capreomycin (Cm)	15-30 mg/kg once daily	1000 mg
levofloxacin (Lfx)	≤ 5 years 15-20 mg/kg split into 2 doses > 5 years 10-15 mg/kg once daily	1000 mg
moxifloxacin (Mfx)	7.5-10 mg/kg once daily	400 mg
ethionamide (Eto)	15-20 mg/kg once daily	1000 mg
protionamide (Pto)	15-20 mg/kg once daily	1000 mg
cycloserine (Cs)	10-20 mg/kg once daily	1000 mg
PAS (4 g sachet)[2]	200-300 mg/kg daily in divided doses	12 g
clofazimine (Cfz)	1 mg/kg once daily	200 mg
co-amoxiclav (Amx/Clv)	Amx 80 mg/kg in 2 divided doses	4000 mg of Amx and 500 mg Clv
linezolid	10 mg/kg given 3 times daily (pyridoxine should also be given)	600 mg
Meropenem[3]	20-40 mg/kg IV every eight hours	6000 mg

*Source. Companion Handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis.

1. For high-dose isoniazid (Hh) refer to adult doses Table.
2. Detail measures may differ with preparations. Please check in the manufacturer's guide
3. Meropenem is preferred to imipenem/cilastatin in children.

Doses for gatifloxacin, bedaquiline, delaminid are not yet determined.

8.5 Diabetes mellitus

Diabetic patients with MDR-TB are at risk for poor outcomes. In addition, the presence of diabetes mellitus may potentiate the side-effects of anti-TB drugs, especially renal dysfunction and peripheral neuropathy. Diabetes must be managed closely throughout the treatment of MDR-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 MDR-TB but may require the patient to increase the dosage. Use of ethionamide or protionamide 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.

8.6 Renal insufficiency

Renal insufficiency caused by longstanding TB infection itself or other concomitant renal diseases 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 8.2. If aminoglycosides have to be suspended before three months of treatment due to renal insufficiency, add PAS to the treatment regimen. Box 8.1 provides an example of calculating and adjusting the creatinine clearance.

Table 8.2 Adjustment of anti-tuberculosis medication in renal insufficiency [a]

Drug	Change in frequency?	Recommended dose[b] and frequency for patients with creatinine clearance <30 ml/min or for patients receiving haemodialysis
isoniazid	No change	300 mg once daily, or 900 mg three times per week
rifampicin	No change	600 mg once daily, or 600 mg three times per week
pyrazinamide	Yes	25–35 mg/kg per dose three times per week (not daily)
ethambutol	Yes	15–25 mg/kg per dose three times per week (not daily)
ofloxacin	Yes	600–800 mg per dose three times per week (not daily)
levofloxacin	Yes	750–1000 mg per dose three times per week (not daily)
moxifloxacin	No change	400 mg once daily
cycloserine	Yes	250 mg once daily, or 500 mg/dose three times per week[c]
prothionamide	No change	250–500 mg per dose daily
ethionamide	No change	250–500 mg per dose daily
p-aminosalicylic acid[d]	No change	4 g/dose, twice daily
streptomycin	Yes	12-15 mg/kg per dose two or three times per week (not daily)[e]
capreomycin	Yes	12–15 mg/kg per dose two or three times per week (not daily) [e]
kanamycin	Yes	12–15 mg/kg per dose two or three times per week (not daily) [e]

amikacin	Yes	12–15 mg/kg per dose two or three times per week (not daily) [e]
Linezolid	No	600 mg once daily
Clofazimine	No	200-300 mg daily in first 2 months followed by 100 mg daily
Gatifloxacin	Yes	400 mg three times a week
Bedaquiline	No	400 mg once daily for 2 weeks, then 200 mg three times per week
Delamanid	No	100 mg twice daily
Imipenem/cilastatin	Yes	For creatinine clearance 20-40 ml/min -500 mg every 8 hours For creatinine clearance <20 ml/min - 500 mg every 12 hours.
Meropenem	Yes	For creatinine clearance 20-40 ml/min - 750 mg every 12 hours. For creatinine clearance of <20/min - 500 mg every 12 hours

a Source: Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis.

b To take advantage of the concentration-dependent bactericidal effect of many anti-tuberculosis 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 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.

Box 8.1 Example of calculating creatinine clearance

$$\text{v Estimated GFR (Creatinine Clearance)} = \frac{\text{Weight (kg) x (140 – age) x (constant)}}{\text{Serum creatinine (µmol/L)}}$$

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

The creatinine is measured in the serum of the blood.

Normal values for creatinine are:

For women: 45-90 µmol/L (about 0.5 to 1.0 mg/dl)

For men: 60-110 µmol/L (about 0.7 to 1.2 mg/dl)

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

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

Weight should be entered in the formula as the ideal body weight and is calculated with the following formula:

Ideal body weight (men) = 50 kg + 1 kg/cm height over 150 cm.

Ideal body weight (women) = 45 kg + 1 kg/cm height over 150 cm.

Normal values for the creatinine clearance are:

Women: 88 to 128 ml/min

Men: 97 to 137 ml/min

Example: A female patient has a serum creatinine = 212 µmol/L, age = 46, ideal body weight = 50 kg. What is the creatinine clearance?

Calculate the creatinine clearance:

Weight (kg) x (140 – age) x (constant) / Serum Creatinine =

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

23.0 ml/min

The creatinine clearance is below 30, refer to Table 8.2 and every drug in the regimen should be examined and adjusted if necessary according to Table 8.2.

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

8.7 Liver disorders

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

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

8.8 Seizure disorders

Some patients requiring treatment for MDR-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 is required before the start of MDR-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 anti-seizure 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. Also note that isoniazid and rifampicin may interfere with many anti-seizure medications, and drug interactions should therefore be checked before their use.

8.9 Psychiatric disorders

It is advisable for psychiatric patients to be evaluated by a health-care worker with psychiatric training before the start of treatment for MDR-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.

The use of cycloserine is not absolutely contraindicated for the psychiatric patient. Side-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 side-effects. Close monitoring is recommended if cycloserine is used in patients with psychiatric disorders.

8.10 Substance dependence

Patients with substance dependence disorders should be offered treatment for their addiction. Complete abstinence from alcohol or other substances should be strongly encouraged, although active consumption is not a contraindication for anti-TB treatment. If the treatment is repeatedly interrupted because of the patient's dependence, therapy should be suspended until successful treatment of their addiction or until 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 side-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 side-effects, which are then adequately treated.

Chapter
9

MDR-TB AND HIV CO-INFECTION

HIV co-infection is a significant challenge for the prevention, diagnosis and treatment of MDR-TB. The local epidemiological prevalence of HIV, MDR-TB and HIV-associated MDR-TB is important in guiding strategies for treatment of HIV and drug-resistant TB.

9.1 Collaborative activities for TB–HIV control

Certain collaborative activities are needed to decrease the joint burden of TB and HIV. These TB-HIV collaborative activities will be established in all areas that have MDR-TB treatment.

A. Establishment of the mechanisms for collaboration

- Set up a coordinating body for TB-HIV activities effective at all levels – National, State and Region, District and Township level with an HIV expert on National as well as State and Regional TB Committees
- Conduct HIV sero-surveillance among TB patients
- Carry out joint TB–HIV planning
- Conduct monitoring and evaluation

B. Decrease the burden of TB in people living with HIV/AIDS ("Three I's")

- Intensification of TB case-finding
- Isoniazid preventive therapy
- Infection control in health-care and congregate settings

C. Decrease the burden of HIV in TB patients

- Provider-initiated HIV counselling and testing (PICT)
- Introduce HIV prevention methods
- Introduce cotrimoxazole preventive therapy (CPT) in HIV-infected patients

- Ensure HIV/AIDS care and support
- Introduce ART

The following MDR-TB/HIV activities will be followed:

- **Determine the prevalence of TB drug resistance in patients with HIV**. Data from TB DRS can be linked with HIV testing of those TB patients included in TB DRS; and/or when HIV surveillance among TB patients is implemented, DST can be included for an unbiased subset to determine resistance rates of TB in the HIV-infected.
- **Perform routine HIV testing in all MDR TB patients**. PICT will be offered to all MDR-TB patients at clinics to be able to identify early cases of co-infected patients.
- **Use Xpert MTB/RIF for co-infected patients.** This recommendation is designed both to help diagnose smear-negative patients and to screen for MDR-TB.
- **Use mycobacterial culture of sputum and other fluids and tissues**. This is helpful in the diagnosis of sputum-negative TB in HIV-infected patients.
- **Use DST at the start of TB therapy**. Unrecognized MDR-TB in an HIV patient carries a high risk of mortality. Therefore all co-infected patients should have a DST: it is recommended that this be done with Xpert MTB/RIF.
- **Introduce ART promptly in MDR-TB/HIV patients**. ART should be initiated in all MDR-TB/HIV patients as soon as MDR-TB treatment is tolerated (usually within two months), regardless of CD4 count.
- **Arrange close treatment follow-up by a specialized team** with close monitoring for treatment side-effects, clinical management and prophylaxis of opportunistic infections and nutritional support.
- **Provide additional socioeconomic support**, since MDR-TB/HIV patients are often at high risk for non-adherence to treatment.
- **Ensure strict infection control**. TB infection control should be ensured in health-care and congregate settings. Measures include early diagnosis and treatment of TB and MDR-TB patients, especially PTB and MDR-TB cases, and separation from others, especially HIV patients. Environmental and personal protection should also be considered.
- **Involve the TB-HIV coordinating committee** to ensure collaboration between different partners.

9.2 Clinical features and diagnosis of MDR-TB in HIV infected patients

The presentation of MDR-TB in the HIV-infected patient does not differ from that of drug-susceptible TB. The diagnosis of TB in the HIV-positive patient is more difficult and may be confused with other pulmonary or systemic infections. The presentation is more likely to be extra-pulmonary or sputum smear-negative than in HIV-uninfected patients. This can result in misdiagnosis or delays in diagnosis and, in turn, higher mortality and morbidity. The use of X-ray, Xpert MTB/RIF, molecular diagnostic tools and culture improves the ability to diagnose TB in HIV-infected patients.

Table 9.1 How pulmonary TB differs in early and late HIV infection

Features of PTB	Stage of HIV infection	
	Early	Late
Clinical picture	Often resembles post-primary PTB	Often resembles primary PTB
Sputum smear result	Often positive	Often negative
CXR appearance	Often cavities	Often infiltrates with no cavities

9.3 Concomitant treatment of drug-resistant TB and HIV

ART in HIV/TB co-infected patients improves survival and slows progression to AIDS. As mentioned above, ART should be initiated in all MDR-TB/HIV patients as soon as MDR-TB treatment is tolerated. This is usually within the first two months of treatment.

If the patient is already on ART and diagnosed with MDR-TB, investigation to see if the patient may be failing ART should be done. This includes clinical evaluation, CD4 count evaluation and, whenever possible, viral load testing. If there is evidence of ART failure, a new ART regimen should be initiated.

Initiation of ART in TB–HIV patients is often associated with adverse events that may be lead to interruption of both TB and HIV treatment. Therefore, the following issues need to be considered (Table 9.2).

Table 9.2 Special issues regarding the treatment of MDR-TB/HIV co-infection

Issue	Comment
Potential drug interactions in the treatment of drug-resistant TB and HIV	• Rifampicins lower the levels of protease inhibitors and non-nucleoside reverse transcriptase inhibitors, especially nevirapine, contributing to the development of resistance to these drugs. • ARVs increase the level of rifampicin and the risk of toxicity. • Non-enteric coated didanosine contains an aluminium/magnesium-based acid that if given together with FQs may result in decreased FQ absorption. It should be given six hours before or two hours after FQs.
Potential drug toxicity in the treatment of drug-resistant TB and HIV	• Peripheral neuropathy may be caused by stavudine, aminoglycoside, cycloserine, pyrazinamide. • Cutaneous reactions by nevirapine and cotrimoxazole are more common. • Gastrointestinal effects are more common with the higher pill burden. • Renal toxicity can be increased by the use of the injectables and tenofovir. Avoid the use of tenofovir with the injectable agent (only if AZT resistance is present should tenofovir be used, and with very close monitoring of the renal function – every 1 to 2 weeks). • Neuropsychiatric effects can be increased with cycloserine and efavirenz, but these drugs can be used together.
Immune reconstitution Inflammatory syndrome (IRIS)	• This syndrome can present as a paradoxical worsening of the patient's clinical status. • It generally presents within three months of the initiation of ART and more common with a low CD4 cell count (<50 cells/mm3). • 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 nonsteroidal anti-inflammatory drugs (NSAIDs) in mild disease and corticosteroids in moderate to severe disease. • Most patients can be treated without interruption of ART.
Monitoring of drug-resistant TB and HIV in co-infected patients	• When treatment for MDR-TB is administered, DOT of ART should be included. • Monitoring of CXR, smears and cultures is the same as for HIV-negative patients. Monitoring of creatinine and potassium should be increased to every two weeks while on the injectable agent. • For MDR-TB patients, in the case of treatment failure both TB treatment and ART regimen should be re-evaluated.
Implications of HIV for MDR-TB infection control	• MDR-TB outbreaks have overwhelmingly involved HIV-positive populations, commonly nosocomial transmissions. Delay in recognition of MDR-TB, prolonged periods of infectiousness, crowded wards, and mixing of TB and HIV patients all contribute to MDR-TB outbreaks that affect both HIV-positive and HIV-negative patients. Hospitals must implement adequate infection control precautions significantly to reduce nosocomial transmission.

Physicians from special infectious disease hospitals and Region/State General Hosptials managing HIV/AIDS must be members of the R/S MDR-TB Committee to provide guidance on TB–HIV co-management.

Chapter 10

MANAGEMENT OF SIDE-EFFECTS IN MDR-TB PATIENSTS

This chapter provides information on the identification and management of adverse effects caused by second-line anti-TB drugs.

10.1 Pre-treatment screening and evaluation

The required initial pretreatment clinical investigation includes a thorough medical history and physical examination. The recommended initial clinical assessment and laboratory evaluations are described in Chapter 11, Monitoring of MDR-TB Patients.

The initial evaluation serves to establish a baseline and may identify patients who are at increased risk for adverse effects. The monitoring of treatment and the management of adverse effects must be more intensive in patients with pre-existing conditions or conditions identified at the initial evaluation (diabetes mellitus, renal insufficiency, acute or chronic liver disease, thyroid disease, mental illness, drug or alcohol dependence, HIV infection, pregnancy, lactation and others).

The management of MDR-TB when these conditions exist is described in Chapter 8, MDR-TB Treatment in Special Situations.

10.2 Monitoring for adverse effects during treatment

Close monitoring of patients is necessary to ensure that the adverse effects of second-line anti-TB drugs are recognized quickly by health-care personnel. The ability to monitor patients daily for adverse effects is one of the major advantages of DOT over self-administration of MDR-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 interviewing patients since some may be reticent 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 Providers must 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
- Symptoms of electrolyte wasting (muscle cramping, palpitations)

Laboratory screening should be performed if signs and symptoms occur and as described in Chapter 11.

10.3 National aDSM

Active TB drug-safety monitoring and management (aDSM) is the active and systematic clinical and laboratory assessment of patients on treatment with new anti-TB drugs, novel MDR-TB regimens, or XDR-TB regimens to detect, manage and report suspected or confirmed drug toxicities. While all detected AEs need to be managed, the core package of aDSM requires the reporting of serious AEs (SAEs) only. M/XDR-TB treatment sites with additional resources may also monitor other AEs that are of clinical significance or of special interest to the programme, as part of comprehensive aDSM.

The overall objectives of aDSM are to reduce risks from drug-related harms in patients on second-line treatment for drug-resistant TB and to generate standardized aDSM data to inform future policy updates on the use of such medicines. aDSM includes three essential activities to achieve these objectives:

1. Patients targeted for aDSM should undergo active and systematic clinical and laboratory assessment during treatment to detect drug toxicity and AEs. Proposed schedules have been developed for use in patients on new medications or on shorter MDR-TB regimens.
2. All AEs detected should be managed in a timely manner in order to deliver the best possible patient care.
3. Standardized data should be systematically collected and reported for any detected SAE. These will eventually be used to characterize the types of SAEs, assess the safety of the treatment, and inform future policy on the use of these medicines.

The National TB Program (NTP) in Myanmar started introducing new TB drugs, bedaquiline (Bdq) and delamanid (Dlm), and repurposed drugs: linezolid (Lzd) and clofazimine (Cfz), for the treatment of MDR-TB(& XDR-TB) in May 2016. With the increased need for treatment of MDR- and XDR-TB patients who have limited treatment options with the use of the new drugs and new regimens, the establishment and implementation of a national system on active TB drug monitoring and management (aDSM) are necessary when the safety profiles of TB drugs and regimens are unknown. The national aDSM system is important to ensure patient safety and contribute to the policy development for the new TB drugs and regimens.

National coordinating committee (involving NTP, FDA, Clinical experts, Hospital administrators, MSF and WHO) has been established for this specific purpose. Health care personnel involved in the use of these drugs are now required to report SAEs related their use. The reporting form for aDSM has been developed and is shown in Annex 6.

10.4 Management of adverse effects

If the adverse effect is mild and not dangerous, continuing the treatment regimen, with the help of ancillary drugs if needed, is often the best option. In patients with highly resistant TB, a satisfactory replacement drug may not be available, so that suspending a drug will make the treatment regimen less potent.

Some adverse effects may disappear or diminish with time, and patients may be able to continue receiving the drug if sufficiently motivated. The adverse effects of a number of second-line drugs are highly dose-dependent.

Reducing the dosage of the offending drug is another method of managing adverse effects, but only in cases where the reduced dose is still expected to produce adequate serum levels and not compromise the regimen. But lowering the dose by more than one weight class should be avoided (see Table 5.2 in Chapter 5 for weight-based dosing).

Pyridoxine (vitamin B6) should be given to all patients receiving cycloserine or terizidone to help prevent neurological adverse effects. The recommended dose is 50 mg for every 250 mg of cycloserine prescribed. Oral magnesium (not magnesium oxide) at 1000-1200 mg should be given twice a day to patients with hypokalaemia.

It is extremely important that patients understand that a MDR regimen may be their last opportunity for cure. If the MDR regimen is not taken in full the strain may develop resistance to some of the drugs in the regimen, forcing any future regimen to rely on less effective and more toxic drugs.

A number of toxicities can be complicated to monitor, life-threatening or very disabling to the patient and are relatively common; they necessitate extra attention in monitoring and include:

- **Nephrotoxicity (damage to the kidneys).** Nephrotoxicity is a known complication of the injectable drugs, both the aminoglycosides and capreomycin. This adverse effect is occult in onset (not obviously noted by taking the history of the patient or by physical examination) and can be fatal. Therefore creatinine is monitored monthly while the patient is on the injectable agent.
- **Electrolyte wasting**. Electrolyte loss through the kidneys is a known complication of the anti-TB injectable drugs, most frequently with capreomycin. It is generally a late effect occurring after months of treatment, and is reversible once the injectable drug is suspended. Since electrolyte imbalance is often occult in the early stages and can be easily managed with electrolyte replacement, serum potassium should be checked at least monthly in all patients while they receive an injectable agent.
- **Hypothyroidism**. Hypothyroidism is an effect provoked by PAS and/or ethionamide /prothionamide. It is suspected by clinical assessment and confirmed by testing the serum level of TSH. Since the symptoms can be subtle, it is recommended that patients be screened for hypothyroidism with a serum TSH every 3 months for the first 6 months, and then every 6 months thereafter. Screening with TSH should occur sooner if symptoms of hypothyroidism arise. The dosing of thyroid replacement therapy should be guided using serum levels of TSH every month until a stable dose of thyroid replacement hormone is reached (also see Table 10.1). Goiters can develop due to the toxic effects of PAS, ethionamide and/or prothionamide. In areas where iodine deficiency goiters are endemic, treatment with iodine is indicated, in addition to assessment and treatment for hypothyroidism.
- **Liver toxicity**. A chemical hepatitis can result from pyrazinamide, PAS and, less commonly, with the other second-line anti-TB drugs. Liver enzymes should be checked for all patients who exhibit signs of hepatotoxicity. It is recommended that HIV-positive patients on pyrazinamide check serum liver enzymes monthly.
- **Ototoxicity**. Ototoxicity refers to damage to cranial nerve VIII, usually manifested by hearing loss, tinnitus (ringing in the ear), and/or other vestibular symptoms, such as nystagmus, ataxia, and disequilibrium. Presentation is most commonly observed in patients receiving large cumulative doses of aminoglycosides and/or capreomycin. Concomitant use of furosemide, particularly in the setting of renal insufficiency, may exacerbate ototoxic effects of these medications. Patients starting therapy with hearing loss at baseline from prior aminoglycoside use are at the highest risk. Hearing loss is generally not reversible upon discontinuation of therapy. Audiometry for baseline and/or follow-up testing is required to pick up early hearing loss. It is recommended to do audiometry monthly while on the injectable agent. If hearing loss is detected, stopping the injectable agent is usually required, although close monitoring (weekly audiometry) and decreasing the

frequency of the injectable agent to three times weekly is preferred in some cases where the injectable agent is thought critical to cure.

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

Table 10.1 summarizes the common adverse effects, the likely responsible agents and the suggested management strategies. Management often requires the use of ancillary medications to eliminate or lessen the adverse effects. Table 10.2 is a list of commonly used medications for the management of adverse reactions and their indications.

Table 10.1 Common adverse effects, suspected agent(s) and management strategies*

Adverse effect	Suspected agent(s)**	Suggested management strategies	Comments
Rash, allergic reaction and anaphylaxis	**Any drug**	1. For serious allergic reactions, stop all therapy pending resolution of reaction. In the case of anaphylaxis manage with standard emergency protocols. 2. Eliminate other potential causes of allergic skin reaction (like scabies or other environmental agents). 3. For minor dermatologic reactions, various agents may be helpful and allow continuation of the medication. They include: • Antihistamines • Hydrocortisone cream for localized rash • Prednisone in a low dose of 10 to 20 mg per day for several weeks can be tried if other measures are not helpful. • Phototoxicity may respond to sunscreens, but these can also cause rash • Dry skin may cause itching (especially in diabetics); liberal use of moisturizing lotion is recommended. Dry skin is a common and significant problem with clofazimine. 4. Once rash resolves, reintroduce remaining drugs one at a time, with the most likely culprit last. Consider not re-introducing in the challenge any drug that is highly likely to be the culprit. 5. Suspend permanently any drug identified to be the cause of a serious reaction.	1. History of previous drug allergies should be carefully reviewed. Any known drug allergies should be noted on the treatment card. 2. Flushing reaction to rifampicin or pyrazinamide is usually mild and resolves with time. Antihistamines can be used. Hot flashes, itching, palpitations can be caused with isoniazid and tyramine-containing foods (cheese, red wine). If this occurs advise patients to avoid foods that precipitate the reaction. 3. Hives (urticaria) can be caused by any drug. To identify the drug, introduce the drugs one at a time. In the case of hives a desensitization attempt can be made; methods are described elsewhere. 4. Any drug that resulted in anaphylaxis or Steven-Johnson syndrome should never be re-introduced to the patient, not even as a challenge.

* Adapted from PIH Guide to the Medical Management of Multidrug-Resistant Tuberculosis (2003) and the Francis J
Curry 2nd edition of Drug Resistant Tuberculosis: A Clinician's Survival Guide (2008)
** Bolded agents are more likely to cause the indicated adverse effect

Adverse effect	Suspected agent(s)**	Suggested management strategies	Comments
Nausea and vomiting	**Eto, Pto, PAS,** H, E, Z, Amx/ Clv, Cfz	1. Assess for danger signs including dehydration, electrolyte disturbances and hepatitis; initiate rehydration therapy if indicated and correct any electrolyte disturbances. If blood in the vomit, check haemoglobin and treat possible bleeding ulcers. 2. Initiate stepwise approach to nausea and vomiting. • **Phase 1: Adjust medications and conditions without lowering overall dose:** • Give the Eto/Pto at night • Give Eto or PAS twice or thrice daily. • Give a light snack (biscuits, bread, rice, tea) before the medications. • Give PAS 2 hours after other anti-TB drugs • **Phase 2: Start antiemetic(s):** • Metoclopramide 10 mg 30 minutes before anti-TB medications. • Ondansetron 8 mg 30 minutes before the anti-TB drugs and again 8 hours after. Ondansetron can either be used on its own or with metoclopramide. (If ondansetron is not available, promethazine can be used) For refractory nausea 24 mg 30 minutes before the dose can be tried. • **Phase 3: Decrease dose of the suspected drug** by one weight class if this can be done without compromising regimen. Rarely is it necessary to suspend the drug completely.	1. Nausea and vomiting universal in early weeks of therapy and usually abate with time on treatment and adjunctive therapy. Some nausea and even vomiting may need to be tolerated at least in the initial period. 2. Creatinine and electrolytes should be checked if vomiting is severe. Give IV fluids and replace electrolytes as needed. 3. Another strategy is to stop a responsible medicine for two or three days and then add it back, gradually increasing the dose (advice the patient the medicine will be increased back to a therapeutic dose in a manner that will be better tolerated). 4. Odansetron is serotonin 5-HT3 receptor antagonist and considered to have strong anti-emetic properties. It is on the WHO essential drug list. A number of other anti-emetics from this class of serotonin 5-HT3 receptor antagonists exist. Trying different anti-emetics, even if from the same class, may be helpful for some patients. 5. For patients particularly anxious about the nausea (and who have "anticipatory nausea and vomiting"), a small dose of an anti-anxiety medicine (5 mg of diazepam) 30 minutes prior to the anti-TB drugs can help.

** Bolded agents are more likely to cause the indicated adverse effect

Guidelines for the Manangement of DR-TB in Myanmar

Adverse effect	Suspected agent(s)**	Suggested management strategies	Comments
Gastritis and abdominal pain	**PAS, Eto, Pto, Cfz,** FQs, H, E, and Z	1. Abdominal pain can also be associated with serious adverse effects such as pancreatitis, lactic acidosis, and hepatitis. If any of these are suspected, obtain appropriate laboratory tests to confirm and suspend suspected agent. 2. If symptoms are consistent with gastritis (epigastric burning or discomfort, a sour taste in mouth associated with reflux), initiate medical therapy with the use of H2-blockers (ranitidine 150 mg twice daily or 300 mg once daily) or proton-pump inhibitors (omeprazole 20 mg once daily). Avoid the use of antacids as they decrease absorption of FQs. 3. For severe abdominal pain, stop suspected agent(s) for short periods of time (one to seven days). 4. Lower dose of suspected agent, if this can be done without compromising regimen. 5. Discontinue suspected agent if this can be done without compromising regimen.	1. Severe gastritis, as manifested by blood in the vomit or stool, is relatively rare. 2. If antacids must be used, they should be carefully timed so as to not interfere with the absorption of the FQs (take 2 hours before or 3 hours after anti-TB drugs). 3. Stop any nonsteroidial anti-inflamatory drugs (NSAIDs) the patient may be taking. 4. Diagnose and treat Helicobacter pylori infections. 5. Severe abdominal distress and surgical abdomen have been reported with the use of clofazimine. Although these reports are rare, if this effect occurs, clofazimine should be suspended.
Diarrhoea and/or flatu-lence	**PAS,** Eto/ Pto	1. Encourage patients to tolerate some degree of loose stools and flatulence. 2. Encourage fluid intake. 3. Treat uncomplicated diarrhoea (no blood in stool and no fever) with loperamide 4 mg by mouth initially followed by 2 mg after each loose stool to a maximum of 10 mg per 24 hours. 4. Check serum electrolytes (especially potassium) and dehydration status if diarrhoea is severe. 5. Fever and diarrhoea and/or blood in the stools indicate the diarrhoea may be secondary to something other than a simple adverse effect of the anti-TB drugs	1. Consider other causes of diarrhoea: • Pseudo-membranous colitis related to broad-spectrum antibiotics such as the FQs is a serious and even life-threatening condition. Fever, bloody diarrhoea, intense abdominal pain and increased white blood cells are danger signs of possible pseudomembranous colitis. • Parasites and common water-borne pathogens in the area should be looked for in the patient and treated if present. • Lactose intolerance, espe-cially if patient has been exposed to new foods in a hospital not normally part of their diet. 2. Loperamide can be used in children over 2 years old.

** Bolded agents are more likely to cause the indicated adverse effect

Adverse effect	Suspected agent(s)**	Suggested management strategies	Comments
Hepatitis	**Z, H, R, Pto/Eto,** and PAS	1. If enzymes are more than three times the upper limit of normal, stop all hepatotoxic drugs and continue with at least three non-hepatotoxic medications (an example of three non-hepatotoxic drugs are the injectable agent, fluoroquinolone and cycloserine). If hepatitis worsens or does not resolve with the three-drug regimen, stop all drugs. 2. Eliminate other potential causes of hepatitis (viral hepatitis and alcohol-induced hepatitis being the two most common causes) and treat any identified. 3. Consider suspending most likely agent permanently. Reintroduce remaining drugs one at a time, with the least hepatotoxic agents first, while monitoring liver function by testing the enzymes every three days, and if the most likely culprit is not essential, consider not re-introducing it.	1. History of previous drug hepatitis should be carefully analyzed to determine most likely causative agent(s); these drugs should be avoided in future regimens. 2. Viral serology should be done to rule out other etiologies of the hepatitis if available, especially to A, B, and C. 3. Alcohol use should be investigated and alcoholism addressed if found. 4. Generally, hepatitis due to medications resolves upon discontinuation of suspected drug.
Hypothyroidism	**Eto/Pto, PAS**	1. Most adults will require 100 to 150 mcg of levothyroxine daily. Start levothyroxine in the following manner: • Young healthy adults can be started on 75 to 100 mcg daily • Older patients should begin treatment with 50 mcg daily • Patients with significant cardiovascular disease should start at 25 mcg daily. 2. Monitor TSH every 1 to 2 months and increase dose by 12.5–25 mcg until TSH normalizes. Adjust dose more slowly in the elderly and patients with cardiac conditions.	1. Symptoms of hypothyroidism include fatigue, somnolence, cold intolerance, dry skin, coarse hair, and constipation, as well as occasional depression and inability to concentrate. 2. Do not start treatment unless TSH is above 1.5 to 2.0 times upper normal limit. 3. Completely reversible upon discontinuation of PAS and/or ethionamide/protionamide. 4. The combination of ethionamide / protionamide with PAS is more frequently associated with hypothyroidism than is the individual use of each drug.

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Adverse effect	Suspected agent(s)**	Suggested management strategies	Comments
Arthralgias	**Z,** Fluoroquinolones	1. Initiate therapy with non-steroidal anti-inflammatory drugs (indomethacin 50 mg twice daily or ibuprofen 400–800 mg three times a day). 2. Lower dose of suspected agent (most commonly pyrazinamide), if this can be done without compromising regimen. 3. Discontinue suspected agent, if this can be done without compromising regimen.	1. Symptoms of arthralgia generally diminish over time, even without intervention. 2. Uric acid levels may be elevated in patients on pyrazinamide. There is little evidence to support the addition of allopurinol for arthralgias, although if gout is present it should be used. 3. If acute swelling, redness, and warmth are present in a joint, consider aspiration for diagnosis (gout, infection, autoimmune disease, etc).
Tendonitis and tendon rupture		1. If significant inflammation of tendons or tendon sheaths occurs: • Consider stopping FQs • Give an NSAID (ibuprofen 400 mg four times daily) • Rest the joint 2. If treatment failure is likely without the fluoroquinolone •Reduce dose if possible •Strict resting of the joint •Inform patient of the possible risk of tendon rupture and discuss the risks and benefits of ongoing use of the FQ.	1. Tendon rupture with FQ use is more likely in patients doing new physical activities and more common in older patients and diabetics. 2. Tendon rupture is relatively rare.
Electrolyte disturbances (hypokalaemia and hypomagnesaemia)	**Cm, Km, Am, S**	1. Check potassium. 2. If potassium is low, also check magnesium and calcium (if unable to check for magnesium, consider empiric treatment with magnesium in all cases of hypokalemia). 3. Replace electrolytes as needed. Dose oral electrolytes apart from FQ as they can interfere with FQ absorption. ALSO SEE ANNEX 4 - MANAGEMENT OF ELECTROLYTE DISTURBANCES	1. If severe hypokalaemia is present, consider hospitalization. 2. Amiloride 5–10 mg per day or spironolactone 25 mg per day may decrease potassium and magnesium wasting and is useful in refractory cases. 3. Oral potassium replacements can cause significant nausea and vomiting. Oral magnesium may cause diarrhoea.

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Adverse effect	Suspected agent(s)**	Suggested management strategies	Comments
Nephrotoxicity (Renal toxicity)	**S, Km, Am, Cm**	1. Discontinue suspected agent. 2. Consider using capreomycin if an aminoglycoside had been the prior injectable in regimen. 3. Consider other contributing etiologies (NSAIDs, diabetes, other medications, dehydration, congestive heart failure, urinary obstruction, etc.) and address as indicated. 4. Follow creatinine (and electrolytes) closely, every 1 to 2 weeks. 5. Consider dosing the injectable agent at 2-3 times a week if the drug is essential to the regimen and patient can tolerate (close monitoring of creatinine). If the creatinine continues to rise despite 2-3 times a week dosing, suspend the injectable agent. 6. Adjust all TB medications according to the creatinine clearance (Table 8.2).	1. History of diabetes or renal disease is not a contraindication to the use of the agents listed here, although patients with these co-morbidities may be at increased risk for developing renal failure. 2. An example of how to calculate a creatine clearance based on the serum creatinine is provided in box 8.1. 3. Renal impairment may be permanent.
Vestibular Toxicity (tinnitus and dizziness)	**S, Km, Am, Cm,** Cs, FQs, H Eto, Lzd	1. If early symptoms of vestibular toxicity appear, change the dosing of the injectable agent to 2 or 3 times a week. Also, consider using capreomycin if an aminoglycoside had been the prior injectable in regimen. 2. If tinnitus and unsteadiness worsen with the above adjustment, stop the injectable agent. **This is one of the few adverse reactions that cause permanent intolerable toxicity and necessitate discontinuation of a class of agents.**	1. Ask the patient monthly about tinnitus and unsteadiness. 2. Fullness in the ears and intermittent ringing are early symptoms of vestibular toxicity. 3. A degree of disequilibrium can be caused by Cs, FQs, Eto/Pto, INH or Linezolid. Some clinicians will stop all drugs for several days to see if symptoms are attributed to these drugs. Symptoms of vestibular toxicity generally do not improve with withholding medications.

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Adverse effect	Suspected agent(s)**	Suggested management strategies	Comments
Hearing loss (also see vestibular toxicity above)	**S, Km, Am, Cm,** Clr	1. Document hearing loss and compare with baseline audiometry if available. (Some degree of hearing loss occurs with most patients, starting with high-frequency loss). 2. If early symptoms of hearing loss are documented, change the dosing of the injectable agent to 2 or 3 times a week. Also, consider using capreomycin if an aminoglycoside had been the prior injectable in regimen. 3. Discontinue the injectable agent if this can be done without compromising the regimen.	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. 2. Hearing loss may be reversible or permanent (often permanent). 3. Some patients may choose to tolerate significant hearing loss to achieve a higher chance of cure. This should be discussed between a physician trained in MDR-TB and the patient. **Continuing the injectable agent despite hearing loss almost always results in deafness.** 4. While the benefit of hearing aids is minimal to moderate in auditory toxicity, consider a trial use to determine if a patient with hearing loss can benefit from their use.

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Adverse effect	Suspected agent(s)**	Suggested management strategies	Comments
Peripheral neuropathy	**Cs, Lzd, H, S, Km, Cm, H,** Fluoro-quinolones, rarely Pto/ Eto, E	1. Correct any vitamin or nutritional deficiencies. Increase pyridoxine to maximum daily dose (200 mg per day). 2. Consider whether the dose of cycloserine can be reduced without compromising the regimen. (Lowering the dose of likely culprits can also be done – linezolid, isoniazid, ethionamide). If possible, switching the aminoglycoside to capreomycin may also be helpful. 3. Initiate medical therapy: • NSAIDs or acetaminophen may help alleviate symptoms. • Therapy with tricyclic antidepressants such as amitriptyline (start with 25 mg at bedtime; the dose may be increased to a maximum of 150 mg). Do not use tricyclic antidepressants with selective serotonin reuptake inhibitors (SSRIs) anti-depressant drugs. • Carbamazepine, an anticonvulsant, at 100–400 mg twice daily can be tried. 4. Rarely, medication may be discontinued, but only if an alternative drug is available and the regimen is not compromised.	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. 2. Neuropathy may be irreversible but many patients experience improvement when offending agents are suspended. However, the neuropathy associated with linezolid is common after prolonged use and often permanent (for this reason suspension of this agent should be considered when neuropathy develops).
Depression	**Socioeconomic circumstances, chronic disease, Cs,** fluoro-quinolones, H, Eto/Pto	1. Assess and address underlying socioeconomic issues. 2. Assess patients for co-existing substance abuse and refer to treatment if appropriate. 3. Initiate individual counselling (or group counselling if the patient is smear- and culture-negative). 3. When depression is more significant, initiate antidepressant therapy (amitryptiline, fluoxetine or similar). Tricyclic antidepressants and SSRIs should be given together and should not be given to patients on linezolid. 4. Lower dose of suspected agent if this can be done without compromising the regimen. (Reducing the dose of cycloserine and ethionamide to 500 mg daily to see if the depression is lessened is a common strategy). 5. Discontinue suspected agent if this can be done without compromising regimen.	1. Socioeconomic conditions and chronic illness should not be underestimated as contributing factors to depression. 2. Depressive symptoms may fluctuate during therapy and may improve as illness is successfully treated. 3. History of previous depression is not a contraindication to the use of the agents listed but may increase the likelihood of depression developing during treatment. If significant depression is present at the start of treatment, avoid a regimen with cycloserine if possible. 4. Question the patient regarding suicidal ideation any time the depression is judged to be more than mild.

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Adverse effect	Suspected agent(s)**	Suggested management strategies	Comments
Suicidal ideation	**Cs,** H, Eto/ Pto	1. Hospitalize the patient and put under 24-hour surveillance. 2. Discontinue cycloserine. 3. Request psychiatric consultation. 4. Initiate antidepressant therapy. 5. Lower the dose of Eto/Pto to 500 mg daily until the patient is stable.	1. Keep the patient in the hospital until risk of suicide has passed. 2. If no improvement occurs after holding cycloserine, hold H and/ or Eto/Pto.
Psychotic symptoms	**Cs, H,** FQs	1. Stop suspected agent for a short period of time (1–4 weeks) while psychotic symptoms are brought under control. The most likely drug is cycloserine followed by high-dose isoniazid. 2. If moderate to severe, initiate antipsychotic therapy (haloperidol). 3. Hospitalize in a ward with psychiatric expertise if patient is at risk to himself/ herself or others. 4. Increase pyridoxine to maximum daily dose (200 mg per day). 5. Lower dose of suspected agent (most commonly cycloserine to 500 mg a day) if this can be done without compromising regimen. 6. Discontinue suspected agent if this can be done without compromising regimen. 7. Once all symptoms resolve and patient is off cycloserine, anti-psychotic therapy can be tapered. If cycloserine is continued at a lower dose, anti-psychotic therapy may need to be continued and any attempts at tapering should be done with a psychiatrist trained in the adverse effects of second-line anti-TB drugs.	1. Some patients will need to continue antipsychotic treatment throughout MDR-TB therapy (and discontinue upon completion of MDR-TB therapy). 2. Previous history of psychiatric disease is not a contraindication to the use of cycloserine, but its use may increase the likelihood of psychotic symptoms developing during treatment. 3. Some patients will tolerate cycloserine with an antipsychotic drug, but this should be done in consultation with a psychiatrist as these patients will need special observation and this should only be done when there is no other alternative. 4. Psychotic symptoms are generally reversible upon completion of MDR-TB treatment or cessation of the offending agent. 5. Always check creatinine in patients with new-onset psychosis. A decrease in renal function can result in high blood levels of cycloserine, which can cause psychosis.

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Adverse effect	Suspected agent(s)**	Suggested management strategies	Comments
Seizures	**Cs, H, fluoro-quinolones**	1. Hold cycloserine, FQs and isoniazid pending resolution of seizures. 2. Initiate anticonvulsant therapy (carbamazepine, phenytoin, or valproic acid are most commonly used). 3. Increase pyridoxine to maximum daily dose (200 mg per day). 4. Check serum electrolytes including potassium (K+), sodium (Na+), bicarbonate (HCO3−), calcium (Ca2+), magnesium (Mg2+), chloride (Cl−). 5. When seizures have resolved, restart medications one at a time. Cycloserine should not be restarted unless it is absolutely essential to the regimen. If cycloserine is reinitiated, start a dose one weight band lower.	1. Anticonvulsant is generally continued until MDR-TB treatment is completed or suspected agent discontinued. 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. (Do not include cycloserine if an alternative drug is available). 3. Patients with history of previous seizures may be at increased risk for development of seizures during MDR-TB therapy. 5. Always check creatinine in patients with new-onset seizures. A decrease in renal function can result in high blood levels of cycloserine, which can cause seizures. Adjusting the dose of cycloserine in the presence of low creatinine may be all that is needed to control the seizures.
Optic neuritis	**E,** Eto/Pto, Lzd, Cfz, rifabutin, H, S	1. Stop ethambutol. Do not restart. 2. Refer patient to an ophthalmologist.	1. The most common drug responsible is ethambutol. 2. Usually reverses with cessation of ethambutol. 3. Improve diabetic control in diabetic patients.
Metallic Taste	**Eto/Pto,** Clr, FQs	1. Encourage the patient to tolerate this side-effect. 2. Sucking hard candy or chewing gum can be helpful.	1. Normal taste returns when treatment is stopped.
Gyneco-mastia	**Eto/Pto**	1. Breast enlargement can be a troublesome side-effect of Eto/Pto therapy, especially for male patients. Galactorrhoea has also been reported. 2. Encourage patients to tolerate this side-effect.	1. Resolution occurs after treatment is stopped.

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Adverse effect	Suspected agent(s)**	Suggested management strategies	Comments
Alopecia	**H, Eto/Pto**	1. Hair loss can occur or there can be significant thinning of the hair, but this is temporary and not progressive during treatment. 2. Encourage patients to tolerate this side-effect.	1. Significant cosmetic change has not been reported.
Superficial fungal infection and thrush	**FQs** and other antibiotics	1. Topical antifungal agents or short-course oral antifungal drugs are helpful. 2. Exclude other diseases if response to treatment is not prompt (such as HIV).	1. Vaginal or penile candidiasis, oral thrush or cutaneous candidiasis in skin folds may occur with antibiotic treatment.
Lactic Acidosis		1. Stop linezolid if lactic acidosis occurs.	1. Lactic acidosis can be monitored with a blood test to measure lactic acid.
Dysglycaemia and Hyperglycaemia	**Gfx,** Eto/Pto	1. Stop gatefloxacin and replace with different later-generation FQ like moxifloxacin. 2. Treat diabetes as needed. Good glucose control is important during treatment.	1. These guidelines do not recommend the routine use of gatifloxacin in MDR-TB treatment.
QT prolongation	FQs, Bdq, Dlm	1. Values of QT greater than 500 ms should cause concern. For any patient found to have a value greater than 500 ms: • Strictly keep electrolytes within normal range, monitoring every two weeks. (It is suggested to maintain potassium levels of more than 4 mEq/L and magnesium levels of more than 1.8 mg/dL) • Avoid other drugs that increase the QT intervals. • Monitor the patient's renal and hepatic and adjust dose of fluorquinolones if impairment is present. 2. Consider suspension of the FQ if risk of torsades de pointes outweighs the benefits of the drug.	1. QT prolongation is characteristic of the entire FQ class. Of the currently available agents, moxifloxacin causes the greatest QT prolongation and levofloxacin and ofloxacin have a low risk of QT prolongation. 2. Patients who experience a prolonged QTc interval are at risk for developing torsade de pointes (torsades). Torsades is a life-threatening arrhythmia, but not every patient who has a prolonged QTc develops torsades. 3. Currently, electrocardiogram monitoring prior to the initiation and during MDR-TB therapy is not required as the therapeutic benefit of FQs is considered to outweigh the risks associated with QT prolongation.

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Adverse effect	Suspected agent(s)**	Suggested management strategies	Comments
Haema-tological abnormali-ties	**linezolid**	1. Stop linezolid if myelosuppresson (suppression of white blood cells, red blood cells or platelets) occurs. 2. Consider blood transfusion for severe anaemia.	1. Haematological abnormalities (leukopaenia, thrombocytopenia, anemia, red cell aplasia, coagulation abnormalities, and eosinophilia) can rarely occur with a number of other anti-TB drugs. See individual drug sheets. 2. There is little experience with prolonged use of liniezolid.

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Table 10.2 Commonly used ancillary medications

Indication	Drug
Nausea, vomiting, upset stomach	Metoclopramide, dimenhydrinate, prochlorperazine, promethazine, bismuth subsalicylate
Heartburn, acid indigestion, sour stomach, ulcer	H2-blockers (ranitidine, cimetidine, famotidine, etc.), proton pump inhibitors (omeprazole, lansoprazole, etc.) Avoid antacids because they can decrease absorption of FQ
Oral candidiasis (non-AIDS patient)	Fluconazole, clotrimazole lozenges, nystatin suspension
Diarrhoea	Loperamide
Depression	Selective serotonin reuptake inhibitors (fluoxetine, sertraline), tricyclic antidepressants (amitriptyline)
Severe anxiety	Lorazepam, diazepam
Insomnia	Dimenhydrinate
Psychosis	Haloperidol, thorazine, risperidone (consider benzotropine or biperiden to prevent extrapyramidal effects)
Seizures	Phenytoin, carbamazepine, valproic acid, phenobarbital
Prophylaxis of neurological complications of cycloserine	Pyridoxine (vitamin B6)
Peripheral neuropathy	Amitriptyline
Vestibular symptoms	Meclizine, dimenhydrinate, prochlorperazine, promethazine
Musculoskeletal pain, arthralgia, headaches	Ibuprofen, paracetamol, codeine
Cutaneous reactions, itching	Hydrocortisone cream, calamine, caladryl lotions
Systemic hypersensitivity reactions	Antihistamines (diphenhydramine, chlorpheniramine, dimenhydrinate), corticosteroids (prednisone, dexamethasone)
Bronchospasm	Inhaled beta-agonists (albuterol, etc.), inhaled corticosteroids (beclomethasone, etc.), oral steroids (prednisone), injectable steroids (dexamethasone, methylprednisolone)
Hypothyroidism	Levothyroxine
Electrolyte wasting	Potassium and magnesium replacement

All the drugs listed in Table 10.2 are available in Myanmar and are on the WHO essential drug list. Loperamide has no Drug Administrative Committee registration.

Table 10.3 describes the situations where a patient with side-effects must be referred to a specialist. However, the MDR-TB treating physician should be aware that many specialists are not familiar with the adverse effects of second-line anti-TB drugs. Therefore, excellent communication between the MDR-TB treating physician and specialists is needed, and the MDR-TB physician should stay informed and approve any therapy changes or treatment prescribed by a specialist.

Table 10.3 Role of specialists in management of side-effects and/or any other complications

Side-effect	Referral to specialist
• Difficult to control with Oral Hypoglycaemic Agent • Brittle diabetes • Problems of hypo-/hyperglycaemia • Thyroid problems	Endocrinologist
• Treatment complications with underlying liver disease like Hepatitis B/C infection • Cirrhosis of liver	Hepatologist
• Complication of haematemesis and melaena	Gastroenterologist
• Severe psychiatric problems, e.g. severe depression, anxiety or neurosis • Major psychiatric disorders, e.g. schizophrenia or new-onset psychosis	Psychiatrist
• Progressive renal impairment • Severe enough for renal replacement therapy	Nephrologist
• Unexpected complications, e.g. severe dermatitis not relieved from withdrawal of likely causal drugs and not responding to routine anti-allergic agents and treatment	Dermatologist

Chapter 11

MONITORING OF MDR-TB PATIENTS

11.1 Monitoring schedule during treatment

Each MDR-TB patient should be monitored closely for signs of both treatment efficacy and adverse effects of the medications. The success of the programmatic treatment depends on the intensity and quality of monitoring and supervision activities. A key component of monitoring the progress of treatment is patient-centred directly observed therapy (DOT). Table 11.1 presents the combined monitoring schedule for response to treatment and for adverse effects.

Table 11.1 Monitoring schedule during MDR-TB treatment

Monitoring	Recommended Frequency
Clinical evaluation by physician	• At baseline • On monthly basis until smear conversion • Then every 2–3 months ***In particular, clinical monitoring for hypothyroidism if receiving ethionamide/protionamide and/or PAS; for hepatitis if receiving pyrazinamide and closely for signs of treatment failure.***
Weight assessment by physician or nurse	• At baseline • Then monthly until treatment completion
Height	• At baseline (To assess BMI throughout treatment) • Monthly for children (To assess growth)
Monitoring of side-effects by DOT Provider	• Daily at every DOT encountered by the DOT provider

Monitoring	Recommended Frequency
Sputum smear and cultures (see Chapter 3)	• Smears on monthly basis. Cultures at the month of 3,4,5,6,7,8 / 12,14,16,18,20. (9,10 for late converter)
Drug susceptibility testing (DST)	• At baseline for diagnosis of RR/MDR-TB • Second line DST should be done if the culture of patient remains positive at Month 3 of treatment
Chest radiograph	• At baseline, and then every six months
Visual assessment by physician	• On monthly basis if receiving ethambutol
Psychological assessment by psychiatrist	• At baseline • Repeat if indicated
Serum creatinine	• At baseline (patients with baseline renal insufficiency, diabetes or HIV should be monitored frequently) • Then monthly (while receiving an injectable drug)
Serum potassium	• At baseline (patients with baseline renal insufficiency, diabetes or HIV should be monitored frequently) • Then monthly (while receiving an injectable drug)
CP and serum uric acid	• At baseline • Repeat if indicated
Thyroid stimulating hormone (TSH)	• At 3rd month, 6th month and repeat if indicated. TSH is sufficient for screening for hypothyroidism. It is not necessary to measure thyroid hormone level.
Liver serum enzymes	• At baseline • Monthly in patients at risk for or with symptoms of hepatitis • Monthly in patients who are HIV infected
HIV test, HBs antigen and HVC antibody	• At baseline •-Repeat if clinically indicated
Pregnancy tests	• At baseline for women of childbearing age (all women of child-bearing age should be provided with family planning counselling.)
Assessment by physician with expertise in HIV/AIDS for MDR-TB HIV co-infected patient	• At baseline • Repeated if indicated
Audiometry	• At baseline and monthly while on the injectable agent.

Specialist consultations will be available also from specialists (endocrinologist, neurologist, dermatologist, nephrologist, psychiatrist etc.) if recommended by physician in charge of the MDR-TB patient (also see Table 10.3).

11.2. Assessment of patients when treatment failure is suspected

Any patient not showing any sign of response to therapy after several weeks should be considered at risk for failure. The following steps are recommended in such a situation.

The treatment card and DOT card should be reviewed to confirm that the patients fully adhered to treatment.

The supervisor of the DOT provider should confirm that the patient has taken all the prescribed medicines correctly. A **non-confrontational interview** with the patient should be undertaken with or without the DOT provider being present. Questions should be asked to rule out the possible manipulation by the DOT provider. If manipulation is suspected, the DOT provider should be changed. He/she should receive additional training and be closely supervised by his/her supervisor whenever he/she is assigned as another DOT provider's role again. If the DOT provider fails to fulfill his/her duties for second time, she/he may be removed from the task.

Review the case management

- ✓ Appropriateness of dose of medication for existing body weight.
- ✓ History of glycaemic control and effectiveness of DM management for MDRTBDM cases.
- ✓ Timely initiation of ART, drug-drug interaction between anti-TB drugs and ART.
- ✓ Look for undetected co morbidities
- ✓ These co morbidities, such as NTMs, fungal infections, lung infections, or a pulmonary malignancy, illnesses that may decrease the absorption of medicines (eg, chronic diarrhoea), immune suppression (eg. HIV infection) should be excluded.
- ✓ The bacteriological data should be reviewed.
- ✓ Review the DST.
- ✓ Review treatment regimen.

11.3 Post-treatment monitoring

Once the patient has completed the course of treatment, the assessment must be performed every six months during the following two years. The assessment should include the following examination:

1. Sputum smear examination and culture (if sputum is available)
2. Body weight
3. Chest X-ray
4. DST (if culture result is positive)

Relapse of TB is a known risk for cured patients. It is pertinent to instruct the patient to return to the clinic if there is cough of more than two weeks, or persistent fever and weight loss for any medical concerns.

If during any post-treatment examination the patient shows evidence of active TB, second line DST must be done; consultation with DRTB committee for probable XDRTB treatment is required.

If the patient has stopped treatment before completing the recommended full treatment, the patient should be traced and assessed every 6 months for at least 2years to detect signs and symptoms of TB, to do investigations and re-treatment if indicated.

Chapter 12

TREATMENT OUTCOMES OF MDR-TB PATIENTS

12.1 Treatment outcomes

The treatment outcome definitions for MDR-TB patients are based on the use of laboratory smear and mycobacterial culture as monitoring tools. There are seven mutually exclusive MDR-TB outcomes corresponding to the outcome categories for drug-susceptible TB. All patients should be assigned the **first** outcome they experience for the treatment being evaluated **for recording and reporting purposes**. The outcome definitions are as described in Table 12.1.

Table 12.1 Definitions of MDR-TB treatment outcomes

TREATMENT OUTCOME DEFINITION	
Cured	Treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.*(a)*
Treatment completed	Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase. *(a)*
Treatment succeeded[1]	A patient who either was cured or completed treatment

[1] Total number of patients who succeeded treatment (total cured patients+ total treatment completed patients) will be used as numerator to calculate Treatment Success Rate (TSR) of Programmatic Management of Drug Resistant TB (PMDT).

TREATMENT OUTCOME DEFINITION	
Treatment failed	Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of: • Lack of conversion *(b)* by the end of the intensive phase *(a);* or • Bacteriological reversion *(b)* in the continuation phase after Conversion *(b)* to negative; or • Evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs; or • Adverse drug reactions.
Died	A patient who dies for any reason during the course of treatment.
Lost to follow-up	A patient whose treatment was interrupted for two consecutive months or more.
Not evaluated [2]	Patient for whom no treatment outcome is assigned. (This includes "transferred out" to another treatment unit and whose treatment outcome is unknown).
Moved to XDR TB [3]	Patient who is diagnosed as XDRTB during MDRTB treatment and move to XDRTB treatment

(a) For Treatment failed, lack of conversion by the end of the intensive phase implies that the patient does not convert within the maximum duration of the intensive phase applied by the programme. If no maximum duration is defined, an 8-month cut-off is proposed. For regimens without a clear distinction between intensive and continuation phases, a cut-off eight months after the start of treatment is suggested to determine when the criteria for Cured, Treatment completed and Treatment failed start to apply.

(b) The terms 'conversion' and 'reversion' of culture as used here are defined as follows:

Conversion (to negative): Culture is considered to have converted to negative when two consecutive cultures, taken at least 30 days apart, are found to be negative. In such a case, the specimen collection date of the first negative Culture is used as the date of conversion.

Reversion (to positive): Culture is considered to have reverted to positive when, after an initial conversion, two consecutive cultures, taken at least 30 days apart, is found to be positive. For the purpose of defining Treatment failure, reversion is considered only when it occurs in the continuation phase.

[2]&[3] Patients under this category will be deducted from both denominator and numerator for the cohort analysis.

Patients who have transferred in should have their outcome reported back to the treatment center at which they were originally registered. The responsibility for reporting their final outcomes rests with the original treatment center. Note that the category "Transferred out" (referring to a patient who moved to another treatment center but whose definitive outcome at the end of treatment was not established) may inform the programmer manager about patient mobility, but is not an outcome of treatment.

12.2 Cohort analysis

An MDR-TB patient cohort is defined as a group of patients diagnosed with MDR-TB and registered in the MDR-TB registration during a specified quarter. The recommended time frame for Standard Regimen cohort analysis reflects the long duration of MDR-TB regimens. Cohort analyses should be carried out at 24 months and repeated at 36 months after the last patient starts treatment.

In order to perform adequate analysis on all patients that meet the criteria of MDR-TB, four dates should be recorded:

1. Date of initial registration as a TB case (if applicable). (DOT enrolment date in TB Register)
2. Date of specimen collection for DST
3. Date of registration in MDR-TB Register (or date of results of DST)
4. Date of starting MDR-TB Regimen

Example:

Cohort of patients enrolled in the third quarter of July 1, 2015–Sept 31, 2015 will have cohort analyses on:

- Oct 1, 2017 for the 24th month analysis (preliminary analysis)
- Oct 1, 2018 for the 36th month analysis (final cohort analysis)

Some patients will be registered as starting on the Standard MDR-TB Regimen but later will be found to have drug-susceptible or mono- or poly-drug resistance. These patients will stay in the register but will not receive a final outcome for MDR-TB treatment. For these patients, a notation "transferred back to IR/RR" or "regimen modified for mono- or poly-drug resistance" should be incorporated into the comment section of the register. Patients will not be analyzed in the cohort of MDR-TB patients if they are proven by DST not to have MDR-TB.

The analysis is conducted at 24th month because most patients will have finished treatment, therefore allowing for the preliminary assessment of cure rates. Since a few patients may require longer than 24 months for treatment, the cohort analysis is repeated at 36 months after the

last patient started treatment. The 36-month evaluation is considered the final treatment cohort analysis result. Patients who remain on treatment at the end of a designated cohort treatment period must be identified as “still on treatment”.

Note the following:

- Any case of XDR-TB also gets put into the MDR-TB Register. The results of the DST should indicate that they are resistant to Amikacin, kanamycin or capreomycin and a Fluoroquinolone.
- The XDR-TB cases will be deducted from both numerator and denominator and analyzed separately as an XDR-TB cohort.

Chapter
13

MANAGEMENT OF MDR-TB TREATMENT FAILURE

The decision to stop MDR-TB treatment because of failure requires analysis of several factors before finally deciding that treatment should be withdrawn. The definition of treatment failure in programmatic management is described in Chapter 12, Treatment Outcomes of MDR-TB Patients.

13.1 When to suspect treatment failure

The following points are general guidelines for beginning a process leading to withdrawal of treatment from a patient:

- Clinical, radiological and bacteriological evidence of progressive disease after 8 months of treatment:
- Persistent positive smear/culture in the intensive phase 8 months. (fail to achieve culture conversion in intensive phase)
- After culture conversion, two consecutive positive cultures at least 1 month apart (reversion) in continuation phase; (for definitions of culture conversion and reversion see in Chapter 12)
- Extensive and progressive lung disease excluding option of surgical treatment.
- Reappearance (resurgence) of disease after 8 months of treatment:
- Clinical deterioration (e.g. respiratory insufficiency; intolerable side-effects,
- Resistance to second-line drugs leaving no option for a regimen with effective drugs.

Bacteriological data are the strongest evidence of failure and culture is more useful than smear in this matter.

Cautions:

- A single positive culture in the presence of good clinical response could be due to laboratory error. A subsequent negative culture or decreasing colony counts will indicate a good response to present treatment.
- Positive smear with negative culture may be due to dead bacilli (reliable culture facilities).
- Repeated smear- and culture-negative results in a patient with deteriorating clinical and radiological states may indicate a disease/course other than MDR-TB.

Other conditions to terminate the treatment are not considered failures but are classified as lost to follow up:

- A patient whose MDR-TB treatment was interrupted for two or more consecutive months.
- Patients who persistently interrupted (≥3 times) the treatment within two months may have their treatment terminated after discussion within the R/S MDR-TB Committee. But means and ways to resume effective treatment should be explored exhaustively before taking this option.

13.2 Assessment of the patient failing MDR-TB treatment

A number of checks are to be done before choosing an action for a patient with apparent MDR-TB treatment failure:

1. Confirmation of adherence to treatment. One way of doing this is checking the Treatment Card and discussing with the patient and the DOT Provider.
   a. Assess socioeconomic status of the patient that might interfere with adherence to the treatment.
   b. Assess if side-effects occur during treatment, preventing the patient from properly continuing with the drug intake.
   c. Confirm that DOT was actually practised. Otherwise the question of whether the patient had actually taken all prescribed medicine will arise.
2. Exclusion of co-morbid conditions that will affect drug administration or immunological competency (e.g. chronic diarrhoea, uncontrolled diabetes mellitus, HIV co-infection).
3. Review of present treatment regimen in relation to medical history, DST reports and particulars of contacts.

When treatment is interrupted to manage side-effects the treatment is declared a failure:

1. If patient has life threatening side-effects requiring removing two or more drugs.
2. If control of side-effect is not possible and treatment regimen not appropriate after removal of causal agents.
3. If a clinical decision has been made to terminate or change treatment (addition of two classes of anti-TB drugs).

13.3 Change of regimen

If the current regimen seems to be inadequate, a new regimen containing at least four effective drugs should be designed. The current treatment should be declared as a treatment failure and the patient should be re-registered. Adding one or two drugs to a failing regimen should be avoided.

13.4 Indications to terminate treatment

There is no single indicator to determine treatment failure. It takes at least 3-4 months to evaluate effectiveness of a changed regimen. Continuation of ineffective therapy would lead to undue cost, unnecessary morbidity from side-effects of drugs and amplification of drug resistance (against second-line drugs). The MO and counsellor should have a sympathetic discussion with the patient. For treatment suspension it is necessary to make him/her understand and accept the withdrawal of treatment.

The final decision to terminate the treatment must be taken by the R/S MDR-TB committee.

13.5 Options after termination of MDR-TB treatment

- Supportive care is the only option left after suspension of treatment.
- Ensure clinical and bacteriological follow-up of the patient every 3 months.
- Adequate nursing care and symptomatic relief if patient is severely ill (e.g. in certain circumstances hospice care and nursing home care may be seriously considered).
- Nutritional support (if budget available) or linking the patient to NGO support.
- Psychosocial support and continuing health education (by government counseling staff or by NGO peer educators/counsellors).
- **MDR-TB treatment termination is not abandonment of the patient.**

Strict infection control measures must be appropriately applied to prevent spread of disease to contacts including health-care workers (see Chapter 16,***Infection control of MDR-TB***). Township Health Centres should have infection control measures in Township TB Clinic.

Chapter
14

MANAGEMENT OF XDR-TB

Emergence of further resistacet beyond MDR-TB was reported as early as 2006. A terminology of extensively drug-resistant tuberculosis (XDR-TB) was introduced and defined as MDR-TB plus

MDR-TB = resistant to isoniazid and rifampicin.

XDR-TB = resistant to isoniazid + rifampicin+ second-line injectables+ fluoroquinolones.

Lately a state of resistance which falls slightly short of XDR-TB (MDR-TB + resistance to fluoroquinolones/ second-line injectables) was recognized and many view it as a pro-state for MDR-TB. Thus it was frequently referred to as pre-XDR-TB. Myanmar now also shares these burdens which can become a significant problem for NTP. Likelihood of cure is lower with the currently available anti-TB drugs. The development of new anti-TB drugs provides some hopes for successful management of this category. Many operational researches are underway using newly developed or repurposed drugs. The results would be available in the next few years and it is expected to help improve outcomes in this relatively new category.

14. 1. Principles of drug-treatment of XDR-TB*

There is as yet no consensus upon strategy to apply in management of XDR-TB. However limited data suggested that treatment success was higher if at least **six** drugs were used in the intensive phase and **four** in the continuation phase. It also suggested that a later-generation fluoroquinolone might be useful even though DST showed resistance to a representative fluoroquinolone. The followings are some logical principles for drug treatment of XDR-TB.*

1. Pyrazinamide should be used at least in the intensive phase, and probably for the whole course.
2. Group A. Use a higher-generation fluoroquinolone such as moxifloxacin or gatifloxcin.

3. Group B. An injectable agent to which the strain is susceptible (if any) should be used. An extended duration (12 months or more) should be considered. (Normally 8 months) If the bacillus is resistant to all second-line injectables a regimen without an injectable is considered. Alternatively an injectable which was never used before may be utilized. In this respect even streptomycin can be considered if this drug had not been used before and reliable DST shows its effectiveness. (If an injectable agent is considered as essential and its use is limited by toxicity, inhaled therapy via a nebulizer may be considered even though there is no data of efficacy for this mode of drug-delivery in TB.)
4. Use Group C drugs which had not been used or are likely to be effective.
5. Use drugs from Group D2 and D3. Use of new drugs, bedaquiline and delamanid, should be in accordance with WHO guidelines. Particular attentions should be given to drug-drug interactions and active pharmacovigilance. (Refer to WHO guidelines on bedaquiline & delamanid.)
6. High-dose isoniazid may be considered if low-level resistance or absence of katG gene is proved.
7. Ethambutol may also be considered as an add-on agent if it was not used before and DST shows susceptibility. e.g MDR-TB in a patient never treated before for tuberculosis.
8. Use of a new investigational drug may be considered if policy of WHO endorses its use under the compassionate use scheme.
9. Adjuvant surgery should be considered if the disease is localized.
10. Strict respiratory infection control measures must be applied at the site of treatment.

* Adapted from Companion handbook to the WHO guidelines for the programmatic management of drug-resistant TB.

14. 2 Regimens for XDR-TB

The most appropriate regimen for these patients would be the individualized ones bases upon DST on SLDs (and FLDs as well). Falling short of that Myanmar NTP will use the following standardized regimen to treat XDR-TB.

6 Z Cm Lzd Cfz Bdq(Dlm)* PAS / 2-6 Z Cm Lzd Cfz PAS / 12 Z Lzd Cfz PAS.

* Delamanid may be considered in place of bedaquiline in certain conditions. E.g concomitant use of drugs, such as ARVs. But substituition of bedaquiline with delamanid after a certain time of therapy is not advisable due to long half-life of bedaquiline. (6-month wash-out time is

required.) Use of both drugs in patients under 18 years of age is not yet approved.

Under certain circumstances (e.g all aminoglysides and polypettyides are not effective) the following regimens may also be considered.

1. 8-12 Z Cm Mfx Lzd Cfz PAS Amx-Clv / 12 Z Mfx Lzd Cfz PAS Amx-Clv .
2. 6 Z Mpm#(+Clv) Lzd Cfz Bdq(Dlm)* PAS / 14 Z Lzd Cfz PAS.
3. 6-8 Z Mpm#(+Clv) Mfx Lzd Cfz PAS / 12-14 Z Mfx Lzd Cfz PAS.
 # Imipenem-cilastatin may be used.

14. 3 Regimens for pre-XDR-TB.

Following regimens are suggested for pre-XDR-TB.

1. Resistance to injectables.

6 (Cm) Lfx Eto Cs PAS Bdq(Dlm) Z / 2 (Cm) Lfx Eto Cs PAS Z / 12 Lfx Eto Cs PAS Z.

2. Resistance to fluoroquinolones.

6 Am Eto Cs PAS Bdq(Dlm) Lzd Z / 2 Am Eto Cs PAS Lzd Z / 12 Eto Cs PAS Lzd Z.

These suggested regimens may have to be modified once the availability of DST to SLDs is improved.

Chapter 15

TREATMENT OF MONO AND POLYRESISTANT (OTHER THAN MDR AND XDR) TUBERCULOSIS

There is scant data dealing with various types of mono and polyresistant TB. WHO could not produce evidence-based recommendations for these forms of DRTB. However it is logical to suggest that most types of mono-resistant TB would be effectively treated with current re-treatment regimen. The exception is rifampicin-resistant TB detected by Xpert MTB/RIF, which is currently recommended to be treated with MDRTB regimens assuming that rifampicin-resistance is a surrogate marker for INH-resistance too. This might not be true in all cases and thus in the following suggestions a regimen (other than MDRTB regimen) is mentioned for pure mono-rifampicin resistant TB. The regimens suggested are based upon general principles of therapeutic, extrapolations from some observational studies and expert opinions.

15. 1 Base-line requirements

There are some important considerations before choosing a regimen. Firstly, DST results may not accurately reflect the bacterial population at the time of report if there is significantly long turn-around time (usually taken as one month or more) for the results. Possibility of functional mono-therapy during that time should always be considered. (e.g treating with rifampicin and isoniazid when the patient is turned out to have INH-resistant bacilli in DST, which effectively means rifimpacin monotherapy leading to probable rifampicin resistance too.)

Secondly, it is assumed that pyrazinamide susceptibility is also tested. If DST for pyrazinamide is not carried out it may not be depended upon as an effective drug. In those circumstances regimens intended for pyrazinamide resistance are to be considered. Some physicians add pyrazinamide to those regimens in the hope that some patients might have benefit if their strains happen to be susceptible to pyrazinamide.

Thirdly, it is assumed that there is a quality-controlled laboratory service and DST results from the laboratory are reliable.

Lastly, it is important that when a regimen is modified/changed from the standard SCC regimen, one which is likely to be most effective should be chosen. Effective drugs should not be withheld for later use.

15. 2 Regimens

Table 15.1 Suggested regimens for mono- and poly-drug resistant TB (other than MDRTB and XDRTB)*

PATTERN OF DRUG RESISTANCE	SUGGESTED REGIMEN	MINIMUM DURATION OF TREATMENT (MONTHS)	REMARKS
H (± S)	R, Z, E (±fluoroquinolone)	6 - 9	A fluoroquinolone may strengthen the regimen for patients with extensive disease.
H and Z	R, E, fluoroquinolone	9 - 12	A longer duration of treatment should be used for patients with extensive disease.
H and E (±S)	R, Z, fluoroquinolone	9 - 12	A longer duration of treatment should be used for patients with extensive disease.
R#	H, E, fluoroquinolone, plus at least 2 months of Z **(or)** ***Full MDR-TB regimen (±H)****	12 - 18	An injectable agent may strengthen the regimen for patients with extensive disease.
R and E (± S)#	H, Z, fluoroquinolone, plus a second line injectable agent for at least the first 2-3 months. **(or)** ***Full MDR-TB regimen (±H)****	18	A longer course (6 months) of the injectable agent may strengthen the regimen for patients with extensive disease.
R and Z (±S)#	H, E, fluoroquinolone, plus a second line injectable agent for at least the first 2-3 months. (or) ***Full MDR-TB regimen (±H)****	18	A longer course (6 months) of the injectable agent may strengthen the regimen for patients with extensive disease.
H, E, Z (± S)	R, fluoroquinolone, plus ethionamide, plus a second line injectable agent for the first 2-3 months. (±Z)	18	A longer course (6 months) of the injectable agent may strengthen the regimen for patients with extensive disease.

*Adapted from (1) Guidelines for the programmatic management of drug- resistant tuberculosis. Emergency Update 2008 (2) Companion handbook to the WHO Guidelines for the programmatic management of drug-resistant tuberculosis.

These suggested regimens assume that reliable DST for all the FLDs are available and used before these regimens are started. Without this service they should be treated as having MDR-TB.

** Lately WHO recommends to use full MDR-TB regimen (±H) to all patients showing either rifampicin mono- or poly-resistance. (WHO treatment guidelines for drug-resistant tuberculosis. 2016 update)

Guidelines for the Manangement of DR-TB in Myanmar

Chapter 16

LOGISTICS MANAGEMENT OF SECOND-LINE ANTI-TB DRUGS

16.1 Objectives of the Chapter

This chapter provides information on the current procedures and practices of Logistics management of the second-line drugs used in the treatment of drug-resistant TB in Myanmar.

16.2 Drug management cycle of second-line anti-TB drugs

Proper management of second-line anti-TB drugs is critical to the success of the MDR-TB programme. The management cycle of second-line anti-TB drugs comprises the following elements:

1. Drug selection;
2. Quantitative assessment of drug requirements (Quantification; Forecasting);
3. Ordering and arrival of second-line drugs
4. Management of storage and distribution;
5. Monitoring and supervision
6. Reporting
7. Accountability

The management is overseen by NTP, but health-care staffs and non-health-care staffs at all levels are participating in the management of these drugs in order to assist the MDR-TB Program.

16.3 Drug Selection and Quantitative assessment of Drugs requirement

A number of factors must be considered when selecting second-line anti-TB drugs, including the efficacy of the drugs, success of the treatment regimen, adherence, the treatment strategy, possible side effects, and the cost of the treatment.

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

• Consumption-based approach

Usually, the most precise method for demand forecasting and projection of future needs is based on records of past consumption of individual drugs. In this method, it is assumed that the data are complete, accurate, and properly adjusted for stock-outs and anticipated changes in demand and use.

• Morbidity-based approach

This method is usually used for the initial phase of activities and in this method, the standardized treatment regimen and the number of patients to be treated are taken into account. Moreover, other key factors are also considered such as the existing stock (current stock), lead time of procurement and delivery, safety stock (buffer) needed and the shelf lives of the drugs.

Currently, NTP is using one of the advance electronic quantification tools, Quan TB, which is based on both consumption and morbidity approaches for quantitative assessment of future drug requirements for National Tuberculosis Programme.

16.4 Ordering and arrival of second-line drugs

Second line Anti-TB drugs ordering is based upon the quantities resulted from National TB Program annual forecasting. The ordered quantities could be adjusted in exceptional conditions. Importation and other procedures such as registration (for the drugs which were not registered in Myanmar) and customs clearances were under domains of MOHS (Ministry of Health and Sports) and will be performed by relevant authorities. A joint annual order of second-line anti-TB drugs including shipment plans and importation is made to GDF (Global Drug Facilities) for both NTP itself and NGOs. NTP will receive all drugs and place in the Central TB Medical Store, after which the drugs stock for NGOs will be dispatched to their respective drug Stores.

16.5 Management of storage and distribution

In Myanmar National Tuberculosis Program, anti-TB drugs storage and distribution channel is streamlined into Central TB store, Upper and Lower Myanmar TB store, Region/ State TB store, District TB store and Township TB store. Electronic inventory management tool,

mSupply, is currently used in TB store for the purposes of effective and efficient inventory control except District and township level TB store. It is planned to use mSupply in all TB stores soon.

At the central level

When ordered drugs are received at NTP central TB store, they are checked by responsible staffs. If any possible damage is detected, prompt checking procedures are performed in the presence of NTP Medical Officer (PSM in-charge) of the Central TB store, one staff member who involved in the drug management and the person who delivered the drugs. If there is any discrepancy or damage seen, the Medical Officer (PSM in-charge) must report to NTP Programme Manager (NTP Headquarter), funding agencies and responsible agents (Forwarder/Supporters), GDF, CMSD, WHO and other relevant partners by means of written documents. Further actions are decided by NTP Programme Manager.

If goods are correct and acceptable, the drugs cartons are placed and store at Central TB Medical Store following WHO drugs storage guidelines and practices. Good acceptance Note or Report must be sent within one week of receiving goods. There are two types of goods acceptance note or report, 1. Unpacking and Checking Form (Annex 2, Form 01) and 2. Goods Receiving Report (GRR)(Annex 2, Form 02). The use of forms depends upon the requirements of funding agencies/partners and organizations. In any report format, findings must be completely noted and reported. The responsible person from Central TB Medical Store will distribute SLD to Lower and Upper Myanmar TB stores based on the number of MDR-TB cases to be enrolled by quarterly basic. Lower and Upper Myanmar TB stores are responsible to distribute SLD to the respective State and Regional level stores by quarterly basis. The Regional and States TB stores will also distribute SLD to District and Township Health TB centers based on the number of MDR-TB cases to be enrolled by quarterly basis. The Township Medical Officer (TMO) will issue the drugs to the DOT Provider monthly or weekly. The DOT Provider must provide the drugs to the patient daily or as necessary according to the treatment regimen under the supervision of the BHS or TMO.

TB Hospitals (In-Patient)

Second-line drugs are requested by TB hospitals from the Regional TB Store of Yangon and Mandalay Regions using the drug Indent/requisition form (Annex 2, Form 03) quarterly. Second-line drugs will be issued using the Issue Voucher form (Annex 2, Form 04) to the TB hospitals.

Second-line drugs may be requested by the MDR-TB wards for admitted patients from the respective Hospital Main Drug Stores using the Second-Line Drug Requisition Form (Annex 2, Form 05) monthly. After getting the authorization of release of the second-line drugs for the listed patients from the R/S MDR-TB Committee, Hospital Main Drug Store can issue the drugs to

the wards by using the Second-Line Drug Issue Voucher (Annex 2, Form 06) quarterly.

In the MDR-TB ward, the second-line drugs are registered in a separate Sub-stock book. Drugs are issued to the DOT Provider and from the DOT Provider to the patients daily under the supervision of ward in-charge physician and the MO.

Surplus or leftover drugs

All drugs that are surplus or leftover, for whatever reason, must be returned to the R/S TBC or Township TBC.

16.6 Monitoring and supervision

Monitoring of the drug management must be done throughout the project by respective personnel; the Physician in the Hospital wards, MS in the TB Hospitals, R/S TB specialist in TB OPDs, TMO in the Townships and R/S Health Director and R/S TB Officer in the Region/ State implementing Hospitals, TB OPDs and Townships TB centers. The Medical Officer (PSM in-charge) monitors overall drug-stock condition and any feedback from the field. Supervision of proper drugs storage and rational use of drugs is also critical point of drug management and that was performed regularly by Program Manager and responsible officers.

16.7 Reporting

Implementing R/S TB Centers/Hospitals must report quarterly to central NTP, providing a copy to the respective R/S TB Officers using the Quarterly Drug Report Form(Annex 2, Form 07).

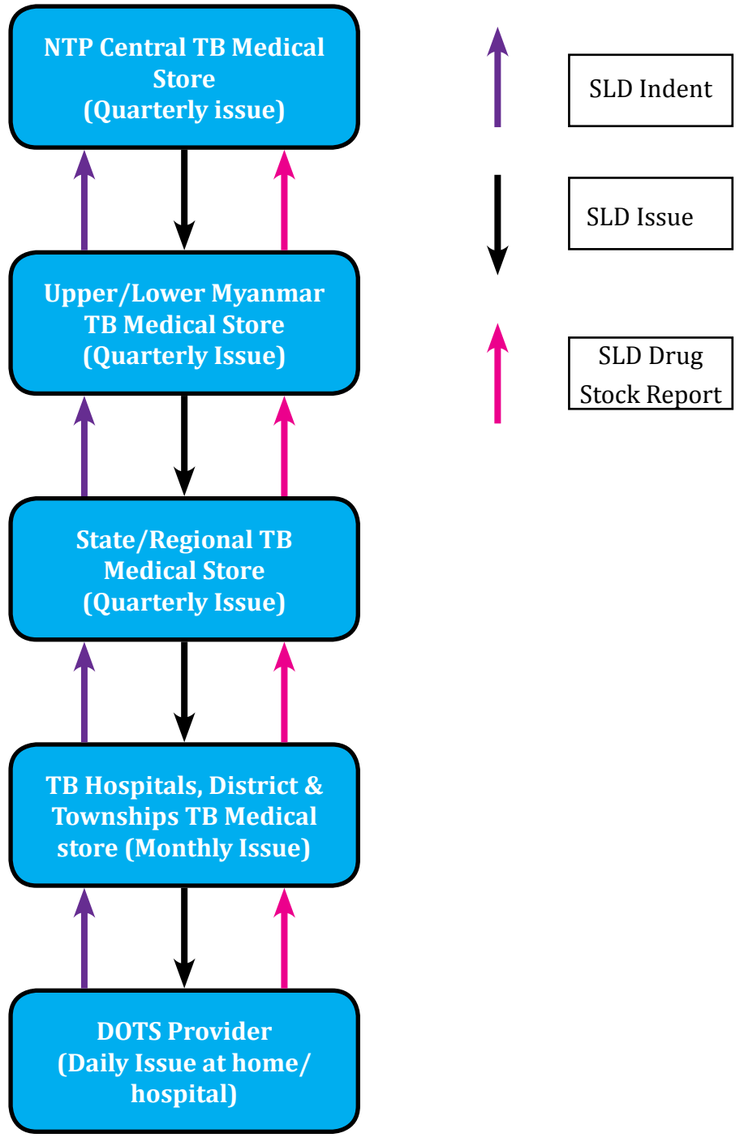
16.8 Accountability

Second-line drugs at the R/S TB Stores will be managed by the designated MO from the R/S TBCs. They will issue drugs to the TB OPDs and TB hospitals for the patients authorized by the R/S MDR-TB Committee for MDR-TB treatment. The TB OPDs and Hospital Main Drug Store will release the drugs only with the authorization of the R/S MDR-TB Committee.

Tracking of the main stock, the sub-stock and the daily stock should occur on a regular basis by responsible personnel.

Note : Ancillary drugs for management of MDR-TB drug adversed effects (A/E) are also important as SLD and management is more or less the same.

Figure 16.1 Second-line Anti-TB Drugs Management Flow



Find Annex 2 for Forms in separate sheet.

Chapter
17

INFORMATION SYSTEM AND DATA MANAGEMENT FOR DR-TB

The aim of the DR-TB information system (for diagnosis/notification, enrollment and treatment registration, recording and reporting under the DR-TB programme) is to monitor the trend of drug resistance and the overall programme performance in controlling DR-TB. Additionally, the information system helps staff in treatment units to provide adequate management of the individual patient. To this end, the NTP is responsible for supplying the following recording and reporting forms and registration within the DR-TB Programme.

Table 17.1 List of forms, registrations and reports

MDR-TB Form No.	Recording and reporting forms	Where to be kept	Responsible for filling in the form
01	MDR-TB Treatment Card	MDR-TB center	MO at MDR-TB Center
		Decentralized MDR-TB township	Team leader/TB coordinator
02	MDR-TB register	MDR-TB center	MO at MDR-TBC
		Decentralized MDR-TB township	Team leader/TB coordinator
03	MDR-TB patient›s identity booklet	Patient	MO at MDR-TB Center
TB-05	Request for examination of biological specimen for TB	All township	TB coordinator
TB-04	Lab. register for sputum microscopy and Xpert MTB/ RIF	All township	Lab Technician

MDR-TB Form No.	Recording and reporting forms	Where to be kept	Responsible for filling in the form
05	Laboratory register for MDR TB	TB Lab (Culture & DST& Township TB lab)	Microbiologist
		X pert site	Lab Technician in charge
06	Notified DR TB register	All townships	TB coordinator
07	Quarterly report on MDR-TB case registration	All townships	TB Team leader or TB coordinator
08	9-month interim progress assessment report	All townships	TB Team leader or TB coordinator
09	12-month interim progress assessment report	All townships	TB Team leader or TB coordinator
10	Annual report of MDR-TB treatment outcome	All townships	TB Team leader or TB coordinator
11	Quarterly MDR-TB laboratory report	TB Lab (Culture & DST& Township TB lab)	Microbiologist
	Monthly/Quarterly Xpert Report	Xpert site	Lab Technician in charge
12	Register for missed dose tracing	All townships	TB Team leader or TB coordinator
13	Directly observed treatment Card	All townships	DOT Provider
14	Patients' informed consent for treatment	All townships	MO or TB Team leader or TB coordinator
15	MDR-TB referral form	MDR TB center	MO or TB Team leader or TB coordinator
		Decentralized MDR TB township +INGO	INGO-Staff
16	Quarterly second line Drug Report	All townships	TB Team leader or TB coordinator

17.1 Recording and reporting system

MDR-TB Form 01: MDR-TB Treatment Card

This card is a key instrument for health staff who administers drugs to patients on a daily basis. When a patient is registered for MDR-TB treatment, an MDR-TB treatment card must be filled in by the MO in-charge at the MDR-TB Center. The card must be filled in completely since it is the primary source of information for the MDR-TB register.

The original MDR-TB treatment card must be kept at the MDR-TB Center and a duplicate must be given to the MDR-TB Decentralized Township TBC or the INGO clinic, depending on which the patient belongs to.

The MDR-TB treatment card contains the following information:

- Basic demographic information: name, age, sex, address, etc.
- Registration number: this is a new unique identification number for each patient. The NTP will use serial number for each MDR-TB Center
- Date of registration
- Patient registration group: one of seven possible groups must be assigned to each patient
- Previous anti-TB treatment episodes: record previous township TB number, the previous treatment regimen in abbreviations, and information on the history of second-line anti-TB treatment for more than one month
- HIV information: specify if HIV testing has been performed, the date of the test and whether the patient is on ART and/or CPT
- Result of X-pert and DST including SLD
- Record any remark from the DR Committee for MDR-TB Management.
- Date of smear microscopy and culture, including sample number and result of the follow-up examinations (Month "0" corresponds to the day of the specimen collection).
- Date and result of each CXR
- Treatment regimen and any change in regimen: one line is used for each date on which a drug(s) is changed.
- Administration of drugs: this is a copy of the records from the DOT Card: one line per month is used to assess adherence. One box is marked for each day the treatment is administered.
- Weight and laboratory examinations: date and results
- Treatment outcome: include the date
- Comments: information related to side-effects, non-adherence and retrieval action taken, etc. should be recorded in this section

MDR-TB Form 02: MDR-TB Register

For enrolment into the MDR-TB treatment programme, MDR-TB patient information must be recorded in the MDR-TB Register that is kept at the MDR-TB Center, TB Hospitals and Decentralized Townships.

The register is filled in based on the information entered on the patient's MDR-TB Treatment Card. Information on smear and culture results can be updated on a monthly basis during the patient's regular appointments, and for patients who have treatment outcomes confirmed, this information can be transferred to the register on a monthly basis as well.

The MDR-TB Register contains the following information:

- Serial No.
- Patient name, sex, age, date of birth, address
- Previous treatment regimen(s)
- Type of TB patient (PTB or extra-pulmonary TB; record as pulmonary if a patient has both)
- Patient registration category: refer to the numbered categories listed on the bottom of the register page
- Date of DST and results (patients may have more than one DST: enter the DST that resulted in the patient being registered as an MDR-TB patient)
- Second-line drugs already received
- MDR-TB regimen (date of treatment start and regimen used)
- Date of smear and culture examinations and results
- Treatment outcome
- HIV status, if known
- Comments: information related to side-effects, non-adherence, retrieval action taken, etc. should be recorded in this section.

If the patient is enrolled in the MDR-TB programme, it must be noted in the comments section of the MDR-TB master register.

MDR-TB Form 03: MDR-TB Patient Identity Booklet

This booklet contains all the general information related to the MDR-TB patient, such as the name and address, disease classification, patient registration category and treatment regimen. The MO in-charge marks the next appointment date on the reverse side of this card, which is kept at all times with the patient.

MDR-TB Form 05: Laboratory Register for Xpert MTB/RIF, Culture and DST

This is the standard laboratory register, to be kept at any TB laboratories where culture and/or DST are performed under the NTP network; it must be maintained by the laboratory personnel. The register records culture and DST results of any MDR-TB/MDR-TB suspect. The Culture and DST Register and Xpert result must be compared regularly with the MDR-TB Register to ensure that all MDR-TB cases eligible for treatment are properly entered in both registers and accordingly reported. Patient's registration group of any confirmed MDR-TB case must be specified in the Remarks column of the register.

MDR-TB Form 06: Notified DR-TB Register

This register is kept at the any R/S, District, Township HC and INGO clinic filled by the MO at MDR-TB Center, TMO/Township TB Coordinator and the INGO staff, respectively. All Rif-Resistant/ MDR-TB must be entered in this register and then referred to the MDR-TB Center for programme enrolment in the MDR-TB enrolled Register.

MDR-TB Form 07: Quarterly Report on MDR-TB Case Registration

(to be completed at the end of the quarter (from MDR-TB Register)

This report is completed with data from the MDR-TB Register kept at MDR-TB Center and Decentralized MDR-TB Township. This quarterly report records the number of confirmed MDR-TB cases (or confirmed RR-TB) registered in the MDR-TB programme. This report is completed quarterly for the previous quarter by the MO in-charge at MDR-TB Center and DC MDR-TB Township. The report must be submitted on a regular basis directly to the R/S TBC and R/S compiled and sent to central NTP and copied to District TBC/ MDR-TB Center.

Example: TB patients with Rif-Resistant/ DST results for MDR-TB who started treatment during the 1st quarter (01 January to 31 March) of 2012 must be reported in the first Week of the 2nd quarter of 2012.

All MDR-TB patients not enrolled in the MDR-TB programme and treated at their own cost or in a private centre must be recorded and reported to the central NTP by the R/S TBO, who will use the same recording and reporting system described above.

MDR-TB Form 08: 9 Month Interim progress assessment

(to be completed 12 months after treatment initiation)

This report evaluates the interim progress after 9 months of MDR-TB treatment, which is helpful for tracking progress since final treatment outcomes are only available two to three years after the start of treatment. The report is prepared by using data from the MDR-TB Register kept at the MDR-TB Center or Decentralized Center. Concerned MO or TB- Coordinator is responsible for the timely and regular submission of the report to the the R/S TBC and copy to District. Report were compiled at R/S level and sent to the central NTP office.

The interim results will be reported 12 months after treatment initiation, which allow for complete culture results for the intensive phase (1st 8 Months) of treatment.(e.g. cohort of 1st Quarter- 2012 is reported in 1st Week of April 2013).

Example: TB patients registered during the 1st quarter (01 January to 31 March) of year 2017 must be reported in the 9-Month Interim progress assessment Report of April 2018.

The number of patients who have negative cultures at Months 3,4, 5,6,7 (with at least two specimens collected for both smear and culture) gives an early estimate of the number of patients who are likely to be cured.

MDR-TB Form 09: MDR-TB Treatment 12-month progress Report

(to be completed 15 months after treatment initiation)

Each quarterly cohort defined by the date of MDR-TB registration should have a culture conversion and patient`s progress report submitted after 15 months of treatment initiation. This report should be completed by the concerned MO or TBC Coordinator from the MDR-TB Register.

MDR-TB Form 10: Annual Report of Treatment Outcomes of MDR-TB Cases

This report shows the final treatment outcomes for patients in the MDR-TB Programme, showing overall success of the programme over a full treatment regimen cycle. The annual report should be completed 24 and 36 months after the treatment initiation. 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 still on treatment for longer than 24 months, for those patients the form is completed again at 36 months after the starts treatment. The 36-month evaluation is considered the final “treatment cohort analysis” (see Fig 17.1). (Note: for 20 Month Treatment duration, 24 Month may be final)

The annual report is completed by using data from MDR-TB Register kept at District/MDR-TB center and township TBC. The MO in-charge at MDR-TB Center or Township TB Coordinator is responsible for the timely and regular submission of the report to the R/S TBO and copy to District TBC. R/S compiled the reports and sent to NTP Central Office.

All MDR-TB patients not enrolled in the programme must be recorded and reported to NTP central office by the R/S TBO, who will use the same recording and reporting system described above, but the results will be kept separate from those of enrolled patients.

MDR-TB Form 11: Quarterly Laboratory MDR-TB Report

This report includes the results of all the culture and DST conducted at the laboratories where these tests are available within the NTP network. The report must be prepared by the laboratory personnel in-charge and submitted on a quarterly basis to NTP.

MDR-TB Form 12: Register for Missed Dose Tracing

This register is kept at the R/S TBC, TB Hospital, District and township HC for each MDR-TB patient and it must be filled in any time a patient absconds and one or more treatment dose(s) are missed. Once the patient is traced, the MO in-charge at the MDR-TBC, hospital or the TPHO or TB Coordinator at township level must specify the number of missed dose(s), the reasons for missing treatment, decision taken and then sign the register in agreement with the patient.

MDR-TB Form 13: List of Directly Observed Treatment

This form is used to record the patient's drug intake on a daily basis, by ticking the appropriate box of month and day. This form is kept by DOT-provider/ the MDR-TB patient and filled in by the DOT Provider BHS or Volunteer. The form has then to be reviewed by the DOT Supervisor who will copy the drug intake records into the MDR-TB Treatment Card. The same form must be used during the hospitalization as well as after discharge when the DOT is administered at the township level.

MDR-TB Form 14: Patient's Informed Consent Form for MDR-TB Treatment

This form formalizes the contract between the patient and the MDR-TB Center to encourage compliance with treatment. This form must be read aloud to the patient by the counselor at the MDR-TB Center or TB Hospital after the three adherence counseling sessions have been successfully conducted. The concerned MO of the MDR-TB Center or the hospital must read and explain the content of the consent form to the patient. The form must be signed by the patient and the MO of the MDR-TB Center, as well as the patient and the DOT Provider before starting the treatment.

If the patient is discharged from the Hospital, MDR-TB Center and referred to a Decentralized MDR-TB Townships for continuation of DOT treatment. If the patient is transferred out to a different treatment centre entirely, a new Patient Consent Form must be filled out. The form must be kept at the MDR-TB Center, and upon discharge or transfer or refer, a copy must be sent with the patient to the new treatment center.

MDR-TB Form 15: MDR-TB Referral Form

This form should be used by any health-care provider who identifies an presumptive MDR-TB who needs to be assessed at the MDR-TB Center for eventual enrolment into the MDR-TB programme. This form should also be used by the MDR-TB Center, TB Hospital staff at discharge of the MDR-TB patient for referral to Decentralized MDR-TB township treatment centers. This form should also be used by the TMO at the township level any time the patient needs to report to the MDR-TBC or hospital for follow-up examinations or for any complications/side-effects that cannot be managed properly at township/district level. INGO staff should also use this form any time the presumptive MDR-TB or MDR-TB patient has to be referred to the MDR-TB center, the hospital, or the district or township treatment centre. When TMO from Decentralized MDR-TB township wants to transfer a patient to another MDR-TB township, he can use the same MDR-TB referral form.

MDR-TB Form 16: Quarterly Drug Report Form

This form is used to report the current drug stock at the Central TB Drug Store, the R/S TBC, MDR-TB Centre/Decentralized Townships, TB Hospital ward and the NGO clinic. This report should be completed on a quarterly basis and sent to the R/S TBO and NTP Central Office. More information on the use of this form can be found in Chapter 13, Management of Second-line Anti-TB Drugs.

17.2 Computerized system

At present, data entry and compilation is carried out manually at township and R/S levels. However, NTP is working on the development of an electronic recording and reporting system/ the case based system "Open MRS" for recording of MDR-TB patients' information and auto-reporting for scheduled time frame.

Figure 17.1 Reporting schedule for MDR-TB programme

Progress assessment Report																					
	Year -1					Year -2						Year -3					Year - 4				
	Q1		Q2	Q3	Q4	Q1		Q2		Q3	Q4	Q1		Q2	Q3	Q4	Q1		Q2	Q3	Q4
Qly report on Lab MDR-TB																					
Qly report on MDR-TB case Registration																					
9 Months Progress Reports																					
12 Months Progress Report																					
24 Months Annual Report																					
36 Months Annual Report																					

For example, yellow represents the cohort beginning in the first quarter of Year 1. For the "yellow" cohort, the quarterly report on MDR-TB case registration is due in April of Year 1, 9-month interim progress report (Blue) is due in 1st Week of April of Year 2, 12-month progress report (Green) is due in July of Year 2, 24-month annual report of treatment outcomes (Red) is due in April of Year 3, and 36-month annual report of treatment outcomes (Brown) is due in April of Year 4.

(Note: Townships need to report "Quarterly report on notified DR-TB")

17.3 The MDR-TB Centers and Decentralized MDR-TB Townships

At the beginning of 2016, all townships (320-330) were covered by PMDT project. Out of which 69-70 district TB centers (some district at R/S TBC), 2 TB hospitals, and INGO (AZG) will become MDR TB center. The rest (small districts and all townships) will be decentralized MDR TB townships/sites.

The responsibilities for PMDT of a service delivery point will be based on its available facilities and capacity to diagnose and initiation of MDR TB treatment.

MDR TB center: (Treatment Initiation & Side effect Management)

1. Can diagnose MDR TB (Rif resistance with Xpert MTB/RIF)
2. Can initiate MDR TB treatment
3. Can test baseline lab investigation
4. Can manage adverse effect of second line drug

Decentralized MDR TB Township (Continuation of DOT)

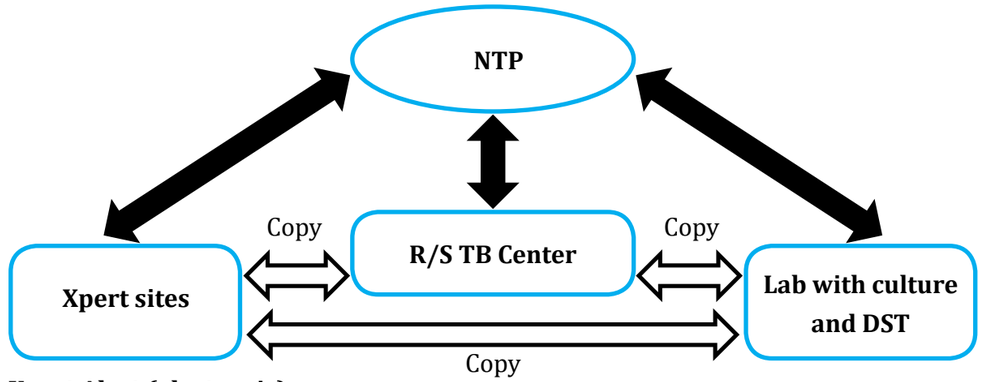
1. Identified presumptive MDR-TB cases among TB patient (Eg. Non converter group, all retreatment cases, new case with MDR-TB contact or PLHIV or Smear positive or All new case), are recorded in Xpert TB Lab register
2. Send sputum specimen to Xpert site to test X pert for Rif-Resistant TB
3. If X pert result show Rif resistance, filled in the Notified DR Register and arrange to refer the patient to MDR-TB center to get treatment after proper counseling.
4. Patients referred back from MDR-TB center with (Treatment Card, Consent form and referral form), are recorded in the township MDR-TB register book TB by Coordinator and the consent form is signed between patient and DOT provider (BHS/volunteer).
5. Continue DOT for MDR-TB treatment, ensure monthly follow up smear at township and F/U culture examination, (send sputum to the Culture Lab at 3,4,5,6,7,8,12,14,16,18,20 Month of treatment) and monitor the drug adverse effect. Treat for minor A/E and refer major A/E to MDR-TB Center.
6. M&E home visit and monthly meeting
7. Recording and reporting on quarterly basis.

Figure 17.2 Health centers and their responsibilities in MDR-TB management

Decentralized MDR TB site/township	MDR-TB Center	Lab with cultures only or with DST facility
1. To identify presumptive MDR TB among TB patients 1.1 Enter Xpert Lab register 1.2 Send sputum to X pert site (TB 05) 2 X pert result showed Rif resistant 2.1 Fill the Notified DR Reg. and send patient to MDR-TBC after counselling 2.2 Patient referred back from MDR-TBC, arrange DOT-provider to continue treatment 2.3 Signing between patients and providers in the patient informed consent form 2.4 Fill in the T/S MDR-TB register 2.5 Follow up monthly sputum examination at township and send sputum to culture lab. 2.6 Monitoring the adverse effect of SLD and manage minor side effect and refer to MDR-TBC for major side effect. 3 Report to R/S TBC and copy to district TB center. Reports are 3.1 Qly report on MDR TB case registration (07 form) 3.2 9 and 12 month interim progress assessment report (form 08, 09) 3.3 Annual report of MDR-TB treatment outcome (form 10) 3.4 Qly drug report (form 16) 4 Provider support, patient support including nutrition 5 Infection Control	1. To follow responsibilities (1-5) of decentralize MDR-TB T/s 2. Test the X pert and send back GeneX pert result to respective township. Fill in the X pert register. 3. Arrange for baseline lab investigation and counselling 4. Initiation of DR treatment 4.1Signing between patient and MO in patient informed consent 4.2 Fill in treatment card (form 01) 4.3 Enter in the MDR TB register (form 02) 5. After initiation of treatment (2-4 week), patient should be refered back to DC Township with treatment card and refer form 15 and Pt consent form 6. Manage the adverse effect of SLD patient both major and minor, If necessary change regimen 7. Discussed about all registered DR cases at DR Committee meeting 8. Give supervision to DC townships and MDR-TB centers from upper level. 9. Conduct evaluation at R/S level 10. Quarterly reports to upper level	1. To do Culture, F/U Culture and DST including second line drug 2. Send back Culture and DST result to MDR-TB center & decentralized township 3. For EQA, send specimen to supra national ref lab 4. Quarterly lab reports 5. Infection control 6. To conduct laboratory monitoring, supervision and evaluation

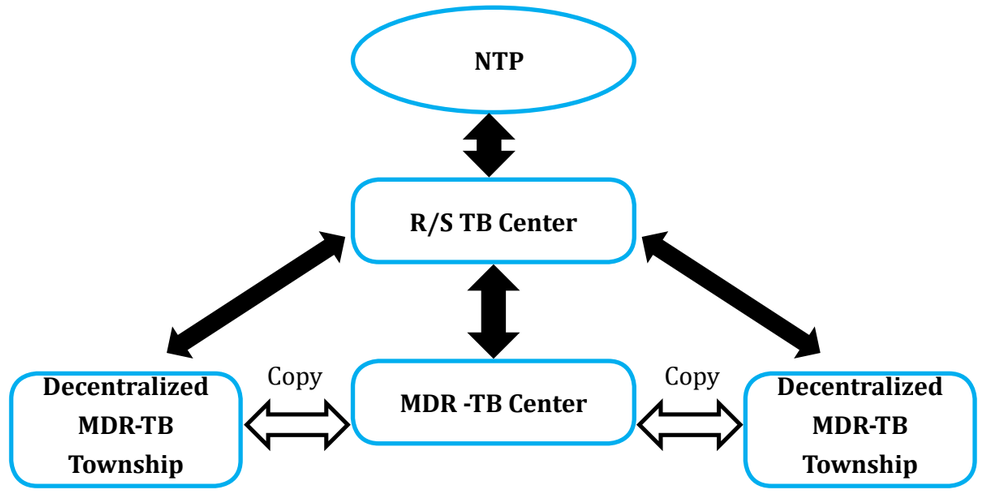
Figure 17.3 Algorithm for PMDT recording and reporting

1. MDR-TB diagnosis/ Notification report (from X pert site and Culture/DST lab)



Xpert Alert (electronic)

2. MDR-TB treatment report (from MDR-TB register)



Chapter
18

INFECTION CONTROL OF MDR-TB

18.1 Basic TB infection control

TB infection control (TB IC) is a combination of measures aimed at minimizing the risk of TB transmission within populations. The foundation of such infection control is early and rapid diagnosis, and proper management of TB patients. TB IC is an essential component in the implementation of core interventions in TB control, HIV control and strengthening of health systems.

Rationale TB infection control is growing in importance because of the association of TB with HIV and the emergence of DR-TB. The situation is worsened by the increasing number of patients without corresponding infrastructure expansion and more health care worker production, leading to overcrowding of patients and delayed diagnosis & treatment resulting in increased TB transmission.

Health care workers are at increased risk of TB infection compared to the general population. Non-medical staff in health care settings is also at risk because undiagnosed pulmonary TB patients with cough are the source of TB infection to all close contacts. Waiting rooms and corridors where patients wait to receive medical care are often areas of particular risk.

Incidence of TB among people living or working in congregate settings (e.g. correctional facilities or nursing homes) and among household contacts of TB patients also exceeds the incidence found in the general population.

18.2 Set of TB IC activities

The set of national and subnational level managerial activities is given & described in detail below. At this level, activities 1-7 are all managerial, they provide policy makers at national and subnational level with a comprehensive framework that can support and facilitate the implementation, operation and maintenance of TB infection control in health-care facilities, congregate settings and households. This managerial framework should be based within existing national and subnational infection control management structures.

Set of managerial activities for national and subnational TB infection control:

1. Identify and strengthen a coordinating body for TB infection control
2. Develop a comprehensive budgeted plan that includes human resource requirements for implementation of TB infection control at all levels.
3. Ensure that health facility design, construction, renovation and use of building are appropriate.
4. Conduct surveillance of TB disease among health workers, and conduct assessment at all levels of the health system and in congregate settings.
5. Address TB infection control advocacy, communication and social mobilization (ACSM), including engagement of civil society.
6. Monitor and evaluate the set of TB infection control measures.
7. Enable and conduct operational research.

18.3 Set of control measures for health-care facility level TB infection Control.

These various elements that can be combined to achieve TB infection control at health-care facility level. The set of TB infection control measures that apply at facility level are listed below.

1. Identify and strengthen local coordinating bodies for TB infection control as part of the facility-wide comprehensive infection prevention and control programme, and develop a facility plan (including human resources, and policies and procedures to ensure proper implementation of the controls listed below) for implementation.
2. Re-think the use of available spaces and consider renovation of existing facilities or construction of new ones to optimize implementation of controls.
3. Conduct on-site surveillance of TB disease among health workers and assess the facility.
4. Address advocacy, communication and social mobilization for health workers, patients and visitors.
5. Monitor and evaluate the set of TB infection control measures.

6. Participate in research efforts. Implementation of the national and subnational managerial activities described above facilitate the implementation of measures described in this section and should therefore be implemented as a set.

Managerial Activities:- Facility-level managerial activities constitute the framework for setting up and implementing the other controls at facility level. The managerial activities should ensure political commitment and leadership at facility level as well as at national level. Other types of control measures at this level also include administrative and environmental controls, and personal protective equipment, each of which is discussed below. These types of control should be implemented together because they are complementing one another.

Administrative controls: Administrative controls should be implemented as a first priority because they have been shown to reduce transmission of TB in health-care facilities. Such controls are a vital part of sound infection control practices which include prompt identification and separation of people with TB symptoms (triage), control of the spread of pathogens in the environment (cough etiquette and respiratory hygiene) and minimization of the time spent in health care facilities. The physical separation of TB patients or people suspected of having TB requires use of rational design in construction and renovation of buildings. Health authorities should provide a package of prevention and care interventions for health-care workers, including HIV prevention, antiretroviral therapy and isoniazid preventive therapy for HIV-positive health workers.

Environmental controls: Environmental controls include methods to reduce the concentration of infectious respiratory aerosols (i.e. droplet nuclei) in the air, and methods to control the direction of infectious air. The choice of environmental controls is intimately related to building design, construction, renovation and use of building, which in turn must be tailored to local climatic and socioeconomic conditions. Well-tailored natural ventilation system is the choice for resource-limited states. If it is not possible, mixed ventilation (natural & mechanical ventilation) may be required. Ultraviolet germicidal irradiation fixtures may have to be used when adequate ventilation cannot be achieved.

Personal protective equipment: Personal protective equipment (particulate respirators, N95) should be used together with administrative and environmental controls in situations where there is an increased risk of transmission.

18.4 Infection control for congregate settings

The recommendations for congregate settings are less specific than those for health-care facilities, because congregate settings are so diverse. They include a mix of settings that range from correctional facilities and military barracks, to homeless shelters, refugee camps, dormitories and nursing homes. Each facility differs in the type of population it contains and the

duration of stay of dwellers; in turn, this affects the dynamics of TB trans-mission. The incidence of TB infection and TB disease among individuals in congregate settings exceeds the incidence among the general population. The association of HIV and MDR-TB & XDR-TB increases the need to give urgent and appropriate attention to implementation of TB infection control in congregate settings, and to prioritize some elements.

Managerial activities: As a first step, policy makers responsible for congregate settings should be made part of the coordinating system for planning and implementing interventions to control TB infection. In particular, the medical service of the ministry of Health should be fully engaged and encouraged to implement TB infection control. In any congregate setting, overcrowding should be avoided because it can lead to non-infected individuals being exposed to TB. Congregate settings should be part of the country surveillance activities, and should be included in facility assessment for TB infection control. Such assessment will be useful in determining the level of risk of the facility or building. Any advocacy and information, education and communication material should include a specific focus on congregate settings, as should monitoring and evaluation of TB infection control measures. Facility-level managerial activities should also apply with some adaptation to congregate settings. These activities will facilitate the implementation of the different types of controls described below.

Administrative controls: To decrease TB transmission in congregate settings, cough etiquette and respiratory hygiene, and early identification followed by separation and proper treatment of infectious cases should be implemented. In particular, all inmates of long-term stay facilities and inhabitants of other congregate settings should be screened for TB before entry into the facility. All staff should be given appropriate information and encouraged to undergo TB diagnostic investigation if they have signs and symptoms suggestive of TB. People suspected of having TB should be diagnosed as quickly as possible. People suspected of having TB and infectious patients should always be separated and/or isolated in an adequately ventilated area, until sputum smear conversion. Directly observed therapy (DOT) while a patient is on treatment is also recommended. In short-term stay congregate settings, such as jails and shelters, a referral system for proper case management of cases should be established. In congregate settings, patients living with HIV and other forms of immunosuppression should be separated from those with suspected or confirmed infectious TB. All staff and persons residing in the setting should be given information and encouraged to undergo HIV testing and counselling. If diagnosed with HIV, they should be offered a package of prevention and care that includes regular screening for active TB. In congregate settings with patients having, or suspected of having, drug-resistant TB, separation of such patients from other patients (including other TB patients) should be done, and referral for proper treatment should be established.

Environmental controls: Buildings in congregate settings should comply with national norms and regulations for ventilation in public buildings and specific norms and regulations for prisons.

Personal protective equipment: When a person residing in a long-term stay congregate setting is suspected or diagnosed as having TB or MDR-TB and is physically separated, the same recommendations on infection control as for health-care facilities apply.

Personal protective equipment (particulate respirators) should always be used together with administrative and environmental controls.

18.5 Reducing transmission of TB in households

Various actions are needed to reduce transmission of TB or MDR-TB in households because household members of persons with infectious TB or MDR-TB are at high risk of becoming infected with TB or MDR-TB and consequently developing the disease. Studies show that the major risks for infection are close contact (exposure) to the infectious case before diagnosis and treatment. Whether the patient subsequently remains at home or moves to a sanatorium appears to have little impact on household transmission, provided the patient is treated effectively. Patients with MDR-TB usually achieve sputum conversion later than those with drug-susceptible TB. This is probably due to the limited efficacy of second line drugs. For this reason, patients with drug-resistant TB remain infectious for much longer, even if treatment is initiated. This may prolong the risk of transmission in the household. Early case detection remains one of the most important interventions for reducing the risk of TB transmission in the household. TB contact investigation should be undertaken. In addition, basic infection control behavior-change campaigns should be part of any community information, education and communication messages. The infection control messages need to promote the importance of early identification of cases, adherence to treatment and implementation of proper TB infection control measures in the household, before and after diagnosis of TB or MDR-TB. Behavior-change campaigns for family members of smear-positive/ culture- positive TB or MDR-TB patients should aim to minimize stigma and exposure of non-infected patients to those who are infectious.

To reduce exposure in households:

- ❖ houses should be adequately ventilated, particularly rooms where people with infectious TB or MDR-TB spend considerable time (natural ventilation may be sufficient to provide adequate ventilation)
- ❖ anyone who coughs should be educated on cough etiquette and respiratory hygiene, and should follow such practices at all times
- ❖ while smear positive, TB patients should:
  - spend as much time as possible outdoors
  - sleep alone in a separate, adequately ventilated room
  - spend as little time as possible in congregate settings and should not use public transport

Additional IC measures for confirmed MDRTB patients:

The following practices should be observed whenever a MDR-TB patient is culture positive[1]

- Cough etiquette and respiratory hygiene (including use of surgical masks) should be practiced.
- Health care providers should wear particulate N95 respirator or equivalent when attending to patients in enclosed spaces.
- Family members living with HIV or family members with a high likelihood of having HIV infection (for example, the spouse of the patient with HIV and MDR-TB), should not provide care for patients with culture positive MDR-TB. If there is no alternative, HIV positive family members should wear N95 respirator or equivalent.
- Children below five years of age should spend as little time as possible in the same living spaces as culture positive MDR-TB patients. Such children should be followed up regularly for early detection of TB disease, and if diagnosed with TB, drug susceptibility testing should be conducted to get proper treatment design.
- Culture positive extensively drug-resistant TB (XDR-TB) patients should be in respiratory isolation at all times, especially when treatment options have been exhausted, and any person in contact with such a patient should wear a N95 respirator or equivalent. If at all possible, HIV-positive family members, or family members with a strong clinical evidence of HIV infection, should not share a household with culture positive XDR-TB patients.
- If possible, potential renovation of the patient's home should be considered, to improve ventilation (e.g. building of a separate bedroom, or installation of a window or wind catcher, or both).

18.6 Impact of effective treatment on TB transmission

All the measures described above correspond to the traditional framework for TB infection control: administrative, environmental and respiratory protection. They are complex and challenging to fully implement at the institutional and household levels. The most important means of TB transmission control are active case finding, rapid diagnosis, rapid drug susceptibility testing, and prompt implementation of effective treatment.

It is important to emphasize effective treatment, because it is routine practice to register as TB in OPD or admit patients to hospital wards without initial drug susceptibility testing and to treat them for drug-susceptible TB while observing for clinical or bacteriological treatment

1 Shenoi SV, Escombe AR, Friedland G. Transmission of drug-susceptible and drug-resistant tuberculosis and the critical importance of airborne infection control in the era of HIV infection and highly active antiretroviral therapy rollouts. Clinical Infectious Diseases 2010;50 (Suppl 3):S231–S237.

failure months later. Only then does the clinician realize that the treatment was not effective and that transmission of drug-resistant TB continued. In general, active case finding through cough surveillance of all OPD attendants and admissions in medical and non-TB specialty wards will avoid days or weeks of transmission from unsuspected TB cases, as reported from active surveillance studies[1], [2]

The rapid impact of effective chemotherapy on TB transmission, including drug-resistant strains, is the other critical information needed to reprioritize TB transmission control efforts. The impact of effective treatment on TB transmission is extremely rapid and profound, including that for MDR-TB (but transmission is ongoing if an ineffective regimen is used, for example when a first-line regimen is used in a case of MDR-TB or a MDR-TB regimen is used in a case of XDR-TB).[3]

This understanding comes at a time when advances in rapid diagnostics will allow the rapid diagnosis of TB and drug resistance, potentially eliminating the admission of unsuspected TB and unsuspected drug resistance, the key sources of institutional TB transmission today. (All registered TB patients in NTP TB clinic in Yangon region have been allowed to test Xpert MTB/RIF test for Rif Resistance and there is a plan to use Xpert to all admission with presumptive TB cases in large teaching Hospitals situated in Yangon).

While a focus on rapid diagnosis and treatment has always been part of administrative controls, the rapid action of effective treatment has to be more fully appreciated, especially now that tools for rapid diagnosis and rapid molecular DST are becoming increasingly available. From an institutional TB transmission control perspective the strategic implementation of each step is critical.

Critical questions to address while linking infection control with case finding and treatment

Who will do cough surveillance?
How will sputum be obtained?
How can the laboratory turnaround be optimized?
How will effective treatment based on drug susceptibility testing be started within days of presentation?
How will these operational steps be monitored?

1 Gelmanova IY et al. Barriers to successful tuberculosis treatment in Tomsk, Russian Federation: nonadherence, default and the acquisition of multidrug resistance. Bulletin of the World Health Organization. 2007;85(9):703–11.

2 Willingham FF et al. Hospital control and multidrug-resistant pulmonary tuberculosis in female patients, Lima, Peru. Emerging infectious diseases. 2001;7(1):123–127

3 Dharmadhikari AS, Mphahlele M, Venter K, Stoltz A, Mathebula R, Masotla T, et al. Rapid impact of effective treatment on transmission of multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 18:1019-1025.

18.7 Implementing infection control measures in MDR-TB

The management or implementation of infection control in MDR-TB does not significantly alter the basic TB IC strategies. The main goals of the infection control programme are:

- To prevent others from getting TB
- To detect TB disease early (the use of Xpert MTB/RIF in all MDR-TB suspects avoids patients being erroneously placed on first-line anti-TB drugs when they have MDR-TB and decreases the spread of MDR-TB)
- To promptly admit in a separate ward and start MDR-TB treatment as early as possible. (Note: XDR-TB patients should not be mixed with MDR-TB patients).

The probability of becoming infected with MDR-TB is high among medical personnel working in direct contact with patients during their contagious period. This group includes hospital staff (including non-medical staff), laboratory staff, X-ray room staff and medical personnel working in the health centers (e.g. TB staff and BHS). Another group at risk of getting infection is people living in close contact with MDR-TB patients.

Therefore, TB IC measures must be implemented in the following areas:

- Hospitals
- Laboratories and radiological facilities
- R/S TBCs
- Township Health Centers
- The MDR-TB patient's home
- HIV clinics

The primary measures for preventing infection, when some form of contact with infectious person is unavoidable, aim to:

- Reduce concentration of or destroy Mycobacterium tuberculosis in the air;
- Reduce or avoid spending time in a shared air environment with person excreting or coughing M. Tuberculosis; (duration of exposure)
- Create mechanical barriers to prevent the spread of mycobacterium.

18.8 Infection control plan

18.8.1 Hospital ward

MDR-TB patients and suspects must be placed in a separate ward at the hospital. The ward should never be overcrowded and should always be kept clean (floors should be cleaned with a wet mop daily, although there is no evidence that sweeping floors results in transmission of TB). Bedding should be washed weekly with normal laundry detergent. Powerful bleaches and disinfectants are not needed. Upon admission, all TB patients at TB hospitals and at specialist hospitals should have an Xpert MTB/RIF test to allow for rapid separation if rifampicin resistance is detected. All hospitalized presumptive or confirmed XDR-TB patients should be isolated.

Waste Disposal. Waste disposal should be managed as follows:

- **Sputum containers.** In wards where patients are coughing regularly, sputum containers should be sealable (if possible), non-sterile containers of at least 200 ml capacity. Replace the containers daily. In Myanmar a spittoon with a cover is used (Htwe gan). A plastic bag is placed inside the spittoon. The patient must spit in the plastic bag and then tie the plastic bag and put on the cover. At the end of the day, the plastic bag must be disposed of outside. Another option is to use a metal spittoon with a cover but without a plastic bag. In the evening, water is added to the metal spittoon and boiled, and the contents are discarded in a latrine or earth pit. In the laboratory, for diagnosis, sputum containers are smaller (25-35 ml), with hermetic cap, non-sterile and for single use.
- **Disposal of sputum containers.** Used containers should be collected in a trash bag and incinerated. They must not be re-used. Do not fill the containers with chlori solution before incineration (this can produce toxic gases).
- **Sharps waste and soft waste.** Standard infectious health-care waste-treatment measures should be respected. There are no specific measures for TB services.
- **Gloves, masks and gowns.** Gloves, masks and gowns can be disposed of in the regular trash unless they have soft waste (blood, stool, sputum or other infectious material) on them, in which case they should be incinerated.

Whenever MDR-TB patients have to leave the ward for any reason, and when health personnel enter their ward, they must wear a cloth mask. In fact it would be desirable to wear the masks most of the time. Those masks must be washed with antiseptic solution on a daily basis and can be reused. Moreover, patients must be instructed to turn their heads when coughing and cover their mouth and nose with a handkerchief, or at least with sleeves of the shirt.

Nurses in-charge, under the supervision of the ward in-charge sister, are responsible for distributing cups and masks and for monitoring the correct use of these items.

N95 Respirators. N95 respirators must be used by all hospital staff in the ward and at OPD level; respirators must closely fit the face to prevent leakage around the edges. Respirators that are classified as "disposable" can be re-used.

The general rule is to use them for a maximum of one week if used frequently, and two weeks if not used daily. The main factors responsible for the deterioration of respirators are humidity, dirt, crushing and relaxing of the tie. Respirators should be labelled with the wearer's name and hang on a peg in a clean and dry location (for example in a paper bag with punched holes or in pigeon holes).

Note: M. tuberculosis is trapped in the filter of a mask, and will not be released with shaking or other physical movements of the mask. It eventually dies once outside the human body.

Respirators can be disposed of in normal garbage and do not need to be disinfected.

Prompt and adequate treatment of MDR-TB cases. Diagnosed MDR-TB patients must start the appropriate MDR-TB treatment as early as possible so as to shorten the hospital stay and prevent transmission to hospital staff and other patients.

Sputum Collection. Sputum collection at health-facility level or at the patient's home must be done outside (open environment) and away from other people, not in small rooms such as bathrooms or other enclosed areas.

Adequate natural ventilation in the hospitals. It must be ensured that the health-care setting (ward, OPD, X-ray room, laboratory) has ample natural ventilation, doors&windows are open and the fans are running. Electric fans must be positioned so as to direct the airflow from HCWs towards the patients.

Periodic follow-up for staff in contact with TB patients. The following should be done for all staff in regular contact with patients:

- A baseline clinical examination and chest X-rays should be done at start of service.
- A clinical examination should be performed once per year. Chest X-ray should only be done in staff clinically suspect for TB.
- Any person becoming pregnant or presenting with a recent risk of immuno-compromised state (HIV-positive, immunosuppressant treatment, etc.) cannot remain exposed and should be transferred to the least TB-exposed position.
- Free screening for TB and HIV is available for any staff member who develops symptoms suspect for TB or HIV.
- Fit testing for N95 respirator should be done once a year and ongoing refresher trainings conducted on infection control.

Recreation room in the hospitals. MDR-TB patients should have access to a designated recreation room, where it is mandatory for them to use masks and individual sputum containers as mentioned above. The room must be kept well ventilated and under direct sunlight.[1]

1 Implementing the WHO policy on TB infection control in health care facilities, congregate settings, and households. Tuberculosis Coalition for Technical assistance (TBCTA) (http://stoptb.org/wg/tb_hiv/assets/documents/TBICImplementationFramework1288971813.pdf)

18.8.2 Outpatient counselling rooms and X-ray room in the hospitals, R/S/D TBC, Township Health Centre

These rooms must be well lit and ventilated; the waiting rooms cannot be crowded and must be open on three sides. Patients and health-care personnel must wear cloth masks and N95 respirators, respectively. Patients should be taught to turn their heads and cover their mouth and nose with a handkerchief or piece of cloth when they are coughing. Only one patient at a time should be allowed to be in the examination room, to reduce the chance of transmitting M. tuberculosis to other patients.

18.8.3 Laboratory

Culture and DST laboratories must be well ventilated and outfitted with UV lights; laboratory technicians must wear N95 respirators, especially those performing culture and DST. The culture preparation must be done under the protective hood (Bio-safety Level 2). Access to the laboratory should be strictly limited to health-care personnel. A pass-through window should be used to deliver sputum samples, to reduce the transmission of infection.

The use of a Biological Safety Cabinet is not mandatory for laboratories performing simple smear microscopy or for Xpert MTB/RIF preparation. Preferably the specimen preparation is done outside or in a very well-ventilated workstation. The laboratory technician must wear an N95 mask during specimen manipulation and preparation.

18.8.4 HIV clinics

HIV patients should always be kept away from sputum smear-positive TB and MDR-TB patients. HIV patients with TB should also be separated from other people living with HIV. HIV clinics should be well lit and ventilated. Waiting rooms should not be over-crowded and should have open passage of air on three sides.

18.8.5 MDR-TB patient's house

Household infection control measures are as follows:

- Sputum smear-positive ambulatory patients should be advised to avoid contact with general public and with particularly susceptible people such as young children, the elderly and PLHIV. Note that smear-negative patients on effective therapy pose little or no risk to the community.
- Assess the risk of TB transmission in the household: gather information on the number of people that live in the house, number of rooms, etc.
- Screen contacts for TB.
- Patients should be instructed to turn their heads and cover their mouth and nose with a handkerchief when coughing. Educate the whole household on cough etiquette.
- The communal house rooms must be well ventilated, keeping a window open at all times if weather permits.
- Ideally, the patient should sleep in a separate room with the door closed from the rest of the house and window kept open.
- Any sputum must be properly collected and discarded
- Entry into the house by visitors should be kept to a minimum
- The patient's room should be cleaned with a wet mop and soap powder.
- Family members with HIV, or suspected of having HIV, should not provide care for infectious MDR-TB patients and if possible should not share the same household while the patient is smear- or culture positive.
- Children under age five should spend as little time as possible in the same living spaces as culture-positive MDR-TB patients (although the risk to the child is greatly reduced once a patient starts an effective regimen).
- Protect infants. When the mother and infant are together, this common time should be spent in well-ventilated areas or outdoors. The mother should use a surgical mask while tending the baby until she becomes sputum smear-negative. Until the mother is smear-negative (and ideally culture-negative also) the bulk of the infant care should be done by other family members if possible.
- Offer TB education on transmission, airborne precautions, waste management, clinical symptoms, etc.
- Personal protective measures for the household include:
    - Cloth masks or surgical facemasks should be worn by the patient at least when in contact with family members if the patient is culture-positive. In fact it would be prudent to wear the mask most of the time.
    - Any person attending to the patient in enclosed spaces should use a respirator (N-95 mask). A fit test should be performed and the person should be well educated on the proper use of masks.

Once the patient is smear-negative and doing well on therapy, household infectious control measures can be relaxed, although it is wise to continue with good ventilation.

18.8.6 Infection control in the community.

Sputum smear-positive MDR-TB patients should avoid overcrowded public places whenever possible, and should cover the nose and mouth when coughing. There are two options in TB infection control measures for MDR-TB patients who must travel. If the MDR-TB patient is still sputum smear- and culture-positive, the patient should be advised not to travel with public

transport. If the patient cannot avoid travelling, he/she should use private transport with a separate cabin for the patient and other health personnel, including driver. If the patient is sputum smear- and culture-negative, no travel restrictions are required.

18.9 Monitoring and evaluation of infection control interventions

The National Expert MDR-TB Control Committee is responsible for guiding the Regional/ State Committee for MDR-TB Management that directly monitors, evaluates and makes recommendations on the overall proper implementation of the IC plan at all levels of health-care: hospitals, regional TBCs, township HCs.

Additionally, the National Expert MDR-TB Committee and the Regional/State Committee for MDR-TB Management are responsible for conducting periodic supervision of the IC measures in place at hospitals, R/S TBCs, Township Health Centers, and MDR-TB patients 'homes. Focal points are assigned at each level to conduct supervision by using the following checklists to assess that all health-care personnel and patients are following the protocol.

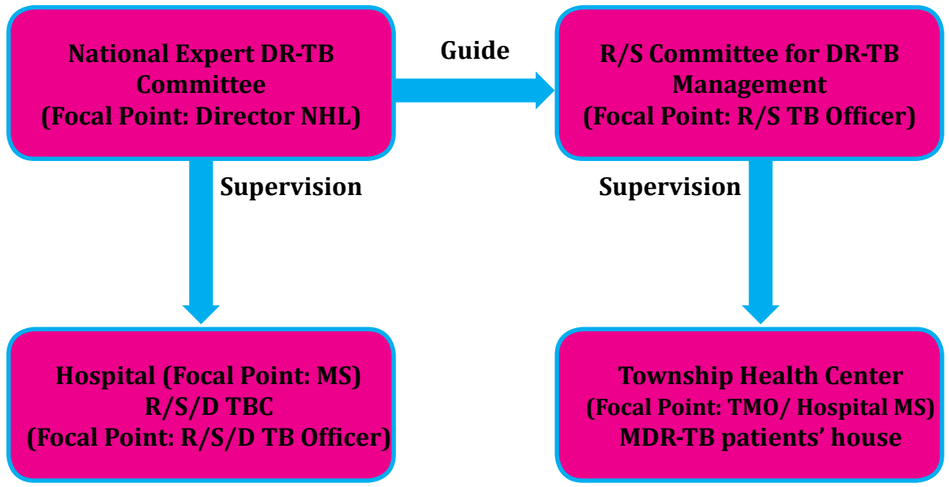


Figure 18.1 Supervision of infection control at various levels

MS: Medical Superintendent; MO: Medical Officer; TMO: Township Medical Officer; NHL: National Health Laboratory

Table 18.1 Checklist for hospital supervision

Laboratory		
Adequate specimen collection system for smears and cultures	Yes	No
Dedicated laboratory space	Yes	No
Biosafety measures in place	Yes	No
Proper waste disposal	Yes	No
Ventilated laboratory space	Yes	No
UV light in the laboratory space	Yes	No
Laboratory technicians using N95 mask	Yes	No
Ward		
Separate ward for MDR-TB patients	Yes	No
Cleaning and disinfection on daily basis	Yes	No
Patients using cloth masks during health personnel visit	Yes	No
Patients using cloth masks in the recreation room	Yes	No
Sputum containers with lids used by the patient	Yes	No
Bedding and linen washed on weekly basis	Yes	No
Health staff use N95 respirators	Yes	No
Ward well ventilated and lighted	Yes	No
Ward not overcrowded	Yes	No
Proper waste disposal	Yes	No
OPD		
Health staff use N95 respirators	Yes	No
OPD well ventilated and lighted	Yes	No
Waiting room not overcrowded	Yes	No
Patients using cloth masks	Yes	No
X-ray room		
Health staff use N95 respirators	Yes	No
X-ray room well ventilated	Yes	No
Waiting room not overcrowded	Yes	No
Patients using cloth masks	Yes	No

Table 18.2 Checklist for regional TBC supervision

R/S TBC		
Health staff use N95 respirators if MDR-TB patient is still smear-positive	Yes	No
OPD well ventilated and lighted	Yes	No
Waiting room not overcrowded	Yes	No
Patients using cloth masks	Yes	No

Table 18.3 Checklist for township HC supervision

Township		
Health staff use N95 respirators if MDR-TB patient is still smear-positive	Yes	No
OPD well ventilated and lighted	Yes	No
Waiting room not overcrowded	Yes	No
Patients using cloth masks	Yes	No

Table 18.4 Checklist for patient home supervision

Patient's house		
House well ventilated and good lighting	Yes	No
Sputum properly collected and discarded	Yes	No
Patient covers mouth and nose with handkerchief/ hands when coughing	Yes	No
Patient's room cleaned and disinfected and not overcrowded	Yes	No

Table 18.5: Infection control in health facility (In general)

S.N	Area of Service	Managerial	Administrative	Environmental	Personal Protection
1	Outpatient Area	TB IC focal person	Triage & Screening	Natural ventilation	Surgical Masks & N-95 provision to patients, attendants and Health Care Workers
		Tb Risk (re) Assessment	Fast Tracking	Mixed Mode Ventilation	
		Development of TB IC Plan	Separation Rooms		
		ACSM Plan	Minimize Time Spent	Safe Waste Disposal	
		Monitroing & Evaluation	Cough Etiquettes		
		Staff Training	Periodic TB Staff Screening	UVGI & ACH maintainace	
2	Sputum Microscopy Laboratory	Medical Technologist Responsible	Separate (open space) Sputum Collection Area	Natural Ventilation Mixed Mode Ventilation Safe Waste Disposal	PlanN-95 or FFP2 fit testing when performing DST
		Bio-Risk Assessment	Minimize Time Diagnosis		
		Bio safety paln with training	Periodic TB Staff Screening		Fit Testing Staff
		Monitoring & Evaluation			
3	Sputum Collection & Smearing Centre	TB IC Risk (re) Assessment	Well ventilated waiting area	Natural Ventilation	N-95 provision
		TB IC Plan with Training	Cough Etiquettes Face Masks		
		ACSM Plan with Training	Minimize Time Diagnosis	Safe Waste Disposal	
		Monitoring & Evaluation	Periodic TB Staff Screening		
4	Radiography	Radiographer Responsible	MDR patients priority	Natural Ventilation Mixed Mode Ventilation	Masks and N-95 provision to patients and staff
		Policies for handling suspects	Fast Tracking		
		Development of SOPs	Proper Spacing of patients		

S.N	Area of Service	Managerial	Administrative	Environmental	Personal Protection
5	MDR-TB ward	TB IC focal person	Separation and isolation rooms	Natural Ventilation	N-95 or FFP2 staff
		TB IC Risk (re) Assessment	Visitors Restriction	Mixed Mode Ventilation	
		Monitoring & Evaluation	Cough Etiquettes, Face Masks Minimize Time Spent	UVGI & ACH maintain ace	N-95 or FFP2 visitors when indoors
		TB IC Plan with Traning	Periodic TB Staff Screening	Safe Waste Disposal	Fit Testing Staff
6	XDR-TB Ward	TB IC focal person	Separation and isolation rooms	Natural Ventilation	N-95 or FFP2 staff
		TB IC Risk (re) Assessment	Visitors Restriction	Mixed Mode Ventilation	
		Monitoring & Evaluation	Cough Etiquettes, Face Masks Minimize Time Spent	UVGI & ACH maintain ace	N-95 or FFP2 visitors when indooFit Testing Staff
		TB IC Plan with Traning	Periodic TB Staff Screening	Safe Waste Disposal	
	Responsibility	Hospital/NTP Administrator	Hospital/ NTP Infection Control Team	Hospital/NTP Management	Hospital Management/ NTP for Fit testing

Chapter
19

TRAINING ON MDR-TB MANAGEMENT

One of the primary purposes of the NTP Human Resource Development is to address the management of training activities and issues related to staff motivation and staff retention. Within this framework, this chapter focuses solely on trainings for MDR-TB control.

The training courses target all related health-care staff as well as non-health staff involved in MDR-TB management from the hospitals, township and district health departments and NGO clinics, including support staff and treatment volunteers. The training programme is coordinated and delivered by staff from NTP central office, staff from Region/ State/ District TB centers in collaboration with the WHO.

The curriculum of the training courses on MDR-TB control includes the following topics:

- MDR-TB definitions: case registration, bacteriology and treatment outcomes
- Specific case-finding strategies
- Laboratory services for essential laboratory examinations and MDR-TB detection
- Treatment strategies for MDR-TB
- Counselling at various stages of management
- Treatment of MDR-TB in special conditions
- HIV infection and MDR-TB
- Monitoring of treatment
- Management of adverse effects
- DOT, treatment adherence, missed-dose and defaulter tracing
- MDR-TB patient Education and Counselling
- Management of patients after MDR-TB treatment failure
- Management of contacts of MDR-TB patients
- Recording and reporting system

- Supervision, monitoring and evaluation
- Logistic management of second-line anti-TB drugs
- Infection control of MDR-TB

However, depending on the level of health-care provider to be trained, the course was modified to include relevant information on specific responsibilities and roles of each individual in MDR-TB control. The chapters on clinical management and recording and reporting should be provided with special attention towards staff from MDR-TB centers (staff from district hospitals and district NTP team). Likewise, chapters on case holding and contact tracing for instance will be emphasized in the trainings for the staff from decentralized sites. Target audiences, topics, and course duration are outlined in Table 17.1.

MO: Medical Officer; TMO: Township Medical Officer; R/S/D TBC: Regional/State/District TB Centre; BHS: Basic Health Staff

Table 19.1 MDR-TB training courses targeted for health staff from different health facilities

Target	Topics	Course Duration
Medical Doctors from hospitals, NTP teams, I/NGOs	The full curriculum of the training following these guidelines.	3 days
Nurses, Data officers/ assistants, TB coordinators, Township Health Assistants, Township Health Nurses, laboratory technicians	The full curriculum of the training following these guidelines with BHS manual (Myanmar language)	3 days
Township Medical Officers from Decentralized Sites	The full curriculum of the training following these guidelines.	2 days
Basic Health Staff from Decentralized Sites	The modified curriculum of the training following these guidelines with BHS manual (Myanmar language)	2 days
Store officers	Store management (On the Job Training)	1 days
Office staff	R&R system and data management (On the Job Training)	1 days
Menials	Basic information on MDR-TB (On the Job Training) Infection control	1 days

NGO staff (DOT Provider)	1. MDR-TB case-finding 2. Counselling for MDR-TB cases 3. DOT 4. Monitoring treatment (SE) 5. Contact tracing 6. Missed dose, defaulter tracing mechanism	1 days

Mopping up trainings for concerned BHS from decentralized township health department

When a township health department identifies newly diagnosed MDR-TB patients, BHS will contact patient and family, conduct counseling for enrolment and refer to MDR-TB Center. The MDR TB Center (district/township NTP team) will initiate MDR-TB treatment and provide mopping up trainings towards BHSs from decentralized sites. Similar training will be provided to responsible BHSs if MDR-TB patients regardless of initiating MDR-TB Center are referred to the township health department of concerned BHS.

The courses must be in line with the teaching methodology and principles described in the facilitator manual for teaching tuberculosis control (WHO/NTP Myanmar 2011). The participants attending the course should receive an MDR-TB training manual developed by WHO/NTP Myanmar to keep and study after the course has ended.

After the training courses have been completed, on-the-job training must be used for follow-up and refresher training by the MO from the R/S/D TBC, R/S/D TBO and MO in-charge of the hospital, in collaboration with the MS. They are also responsible for training of any new health-care staff who is employed later after completion of the training.

The monitoring and evaluation of the training activities must be conducted regularly by the NTP Central Office as part of the supervisory visits.

Chapter
20

SUPERVISION, MONITORING AND EVALUATION

20.1 Supervision

Supervision is the observation of health workers in their workplace, performed on a regular basis, with the aim of developing their knowledge, perfecting their skills, solving problems, correcting errors, improving attitudes towards their work and increasing staff motivation. Ultimate aim is improved efficiency in their job. Supervision should be educative, supportive and corrective, **not punitive.**

Internal supervision

The quality of DR-TB management is ensured through regular internal supervision at all levels. The NTP has set up the following annual targets for on-site specific supervision for DR-TB management:

- At least one supervisory visit per year to Regions/States implementing DR-TB management, by the National Expert DR-TB Committee
- At least one supervisory visit per year to Regions/States implementing DR-TB management, by central NTP staff including central NTP microbiologist as well as WHO
- At least one joint supervisory visit per year to townships implementing DR-TB management activities, by central NTP Level / Region/State Level and WHO
- At least one joint supervisory visit to the TB reference laboratories, by the National Health Laboratory with NTP and WHO
- At least one joint supervision to DR-TB sites jointly implemented with NGOs and other partners

In addition, DR-TB management will be routinely supervised as part of the general annual

supervision scheme of TB control activities, as follows:

- Two supervisory visits per year to districts and townships by Region/State-level staff
- Four supervisory visits per year to townships by district-level staff
- Four supervisory visits per month to DR-TB patients' home by Health Assistants, Lady Health Visitor and Public Health Supervisor I.
- Four visits per year by the central level NTP to ensure anti-TB drug management supervision to Regions/States
- Four visits per year by Region/State level to ensure anti-TB drug management supervision to District/Townships

Standardized supervision checklists are available for all levels for basic TB control activities.

In addition, a checklist has been developed for townships managing MDR-TB (Annex 5).

The supervisory teams should develop a report during the visit and provide it to the TB staff responsible for immediate action. The main recommendations should be discussed and, if possible, agreed upon during the visit. The report should be short and should include: actions taken since the last visit, main achievements and constraints observed during the visit, recommendations and proposed next steps before the next visit to overcome problems and improve programme performance. Supervisory visit plans are developed every year and refined during the development of the NTP quarterly activity work plans at central and Region/State level.

External supervision

Technical assistance plans by external experts are to be managed by the NTP and WHO. WHO ensures annual missions as follows:

- Technical assistance on MDR-TB and XDR-TB clinical and programmatic aspects
- Supervision and technical support from the SNRL for support to DR-TB and XDR-TB diagnosis
- Annual GLC mission for PMDT management
- Mission by the Global Drug Facility to monitor progress on first- and second-line anti-TB drug management

Ad hoc missions are to be organized based on needs to cover specific aspects of DR-TB control, including data management, infection control, diagnosis, etc. Every three years, the NTP and WHO organize external comprehensive reviews of TB control efforts in Myanmar. In these review missions, DR-TB experts are always included.

20.2 Monitoring and evaluation

Monitoring and evaluating the performance of the DR-TB control programme involves assessing activities, monitoring costs and expenditure, determining the extent of programme coverage and evaluating treatment outcomes, as well as the epidemiological impact of the programme. Important factors include:

- Ensuring that training, supervision, logistics and communication activities are being carried out effectively at each level from the national level to the peripheral clinics
- Deciding whether health units are collecting the data needed to assess case notification rates and treatment outcomes
- Identifying technical and operational problems, specifying the reasons for the problems and taking the necessary corrective actions
- Assisting staff to improve standards of practice
- Improving patient care and support, and the quality of information.

Indicators

The Five Year National Strategic Plan for TB Control, 2016-2020 includes the impact, outcomes, output and programmatic indicators specific for DR-TB shown in Table 18.1.

Table 20.1 Indicators for DR-TB management in Myanmar in the 2016-2020 National Strategic Plan

	Description	Baseline			Target 2020
		Value	Year	Source	
Impact indicator	Prevalence of MDR-TB among new smear-positive TB patients	5%	2013	3rd National Drug Resistance Survey	4%
Outcome indicator	Treatment success rate among MDR-TB cases	79%	2012	Cohort analysis	82%
Programmatic indicator	Number of laboratory-confirmed MDR-TB patients to be notified in DR-TB treatment programme	2793	2015	NTP data	5115
	Number of treated MDR-TB patients	2207	2015	NTP data	3580

Cohort analysis

Cohort analysis is the key management tool used to evaluate the effectiveness of the DR-TB control activities in any given area. It is used to identify the quarterly and annual MDR-TB treatment success rates and provide middle or higher level managers with timely, concrete indicators of achievement. The quarterly smear and culture conversion reports and treatment outcomes enable the identification of problems, so that appropriate action may be taken to improve programme performance (e.g. low cure rate, high default rate, and high death rate, lower than expected case-detection rate).

Measurement of impact

Three nationwide DRS were conducted in 2002-2003, 2007-2008 and 2012-2013.

These surveys are important to provide an estimation of the magnitude of the DR-TB problem and can detect general trends overtime. The data from the DRS are linked to the overall WHO-estimated TB disease burden which in turn is based on data from annual TB surveillance as well as periodic national prevalence surveys.

Recording and reporting

The recording and reporting system allows for targeted, individualized follow-up to help patients who may not be making satisfactory progress, and for a rapid managerial assessment of the overall performance of each township, district, Region/State (R/S). This strong system of accountability and crosschecks avoids false reporting of data.

The NTP utilizes the following standardized recording and reporting forms, booklets and

registers in DR-TB implementation (see Annex 3):

- DR-TB Treatment Card (Form 01)
- DR-TB Register (Form 02)
- Patient Identity Booklet (Form 03)
- Laboratory Requisition Form for Smear, Culture, DST and Xpert MTB/RIF (TB 05)
- Laboratory Register for MTB/RIF, Culture and DST (Form 05)
- Notified DR-TB Register (Form 06)
- Quarterly Report on DR-TB Case Detection (Form 07)
- Nine-month Interim Outcome Assessment (Form 08)
- DR-TB Treatment 12-Month Culture Conversion Report (Form 09)
- Annual Report of Treatment Outcomes of DR-TB Cases (Form 10)
- Quarterly Laboratory DR-TB Report (Form 11)
- Register for Missed Dose Tracing (Form 12)
- List of Directly Observed Treatment (Form 13)
- Patient's Informed Consent Form for DR-TB treatment (Form 14)
- DR-TB Referral Form (Form 15)
- Quarterly Drug Stock Report (Form 16)
- The steps involved in the quarterly DR-TB data management are:
- DR-TB notification and cohort analysis of treatment outcomes are compiled by the R/S TBO every quarter, and at the end of every year the R/S TBO ensures that DR-TB management data from NGOs are included.
- Township quarterly reports on DR-TB notifications and treatment outcome are forwarded to the R/S TBC for verification and compilation of R/S DR-TB management report.
- The Region/State TBC verifies that township reports are correct, complete, dated, signed and consistent, and compiles cohort analysis reports on all patients in the Region/State.
- The Region/State TBC submits quarterly and annual reports to the central unit of the NTP.
- The central unit of the NTP compiles the DR-TB notification and cohort analysis reports on all DR-TB patients registered nationally and report to GF and WHO respectively.

R/S TB Officers are responsible to report on DR-TB patients who are treated outside the DR-TB management programme or in the private sector. Mandatory reporting from private sector will be initiated if new policy is approved by Ministry of Health and Sports.

The quarterly reporting at the Regional/State level is linked with the quarterly collection of drugs and supplies from the Central and Lower Myanmar TB Centre/Upper Myanmar TB Centre of NTP. The TB Offices at Region/State level compile the reports and forward them as

Region/State quarterly reports to the central level of the NTP.

The NTP is also implementing case-based electronic recording and reporting system with OpenMRS and will scale-up in all DR-TB diagnostic and treatment initiation centers by phase wise manner in 2017-2020.

Internal reviews and coordination with implementing partners

Quarterly meetings by the District/Township DR-TB Committee focus on issues and challenges of DR-TB control activities, while quarterly meetings of the Regional/State Committee for DR-TB Management focus on activity outcomes and achievements, including data on cohorts of cases notified and treated. Each year the NTP conducts annual evaluation meetings which all Region/State Public Health Directors, R/S TB Officers and implementing partners. DR-TB management is one of many topics discussed. Separate annual meetings on DR-TB activities are held, including meetings of the National Committee of DR-TB Management and the National Expert DR-TB Committee. The NTP also participates in annual evaluation meetings of partners.

ANNEX 1: Sputum Collection and Transportation

SPUTUM COLLECTION

Instruction for sputum collection

Good sputum means sputum containing purulent or mucopurulent particles.

Place to collect the sample

- Sputum collection place must be away from other people, in open air
- No one should be standing in front of the patient during collection

Collection procedure

- Rinse the mouth with water before producing sputum
- Take two deep breaths, holding the breath for a few seconds after each inhalation and then exhaling slowly
- Breath a third time and then forcefully blow the air out
- Hold the container close to the lip and spit into it gently after a productive cough
- Tightly close the lid of the container

After sputum collection

- Ask the patient to wash the hands with soap and water.

PACKING AND TRANSPORTATION

Packaging of specimens/culture

The culture bottles must be wrapped separately with tissue paper or other absorbent materials (to prevent breakage) and then placed in plastic boxes.

Transportation of specimen/culture

The plastic bags/culture bottles containing specimens must be placed in transport box (fibreboard box) containing absorbent materials – tissues or cotton wool – between, above and below the containers to prevent leakage during transportation.

During transportation if the weather is hot (temperature above 37 °C) the transport boxes must be sent with cold chain. Copies of questionnaire and requisition forms must be sent along with the specimens. It is important to write down the name and signature of sender/ receiver in the dispatch book.

If the specimen transport is going to be longer then 3 days, cetylpyridinium chloride (CPC) or cetylpyridinium bromide (CPB) is required. Specimens with CPC cannot be used with liquid culture and cannot be refrigerated (they will crystalize and ruin the

specimen). CPC can be used with Xpert MTB/RIF instruments.

Cold Chain Method for transport (preferred method for short transport times, less than 3 days, as MGIT can be used with the same specimen for confirmation)

- At township TB workers will collect sputum from all DR TB suspects/patients.
- Refrigerate at +4-+8 °C until transport.

Put the sputum container in the cold box to maintain the cold chain and send to a laboratory facility with Xpert MTB/RIF and or culture/DST.

CPC Method for transport (preferred for long transport times, longer than 3 days. MGIT cannot be used in a specimen wth CPC)

- Falcon tubes containing 5ml of CPC sol. will be made available at the townships.
- At township TB workers will collect sputum from all DR TB suspects/ patients.
- About 5 ml sputum will be transferred to the CPC-containing falcon tube, and the tube then closed tightly.
- Sputum sample in the falcon tube will be sent to the nearest facility with Xpert MTB/ RIF.
- DST result will be sent to periphery in vice-versa via e-mail to the Outpatient DR-TB Team and to the UHC that sent the results.

ANNEX 2: Forms for Management of Second-line Anti-TB Drugs

Drug management Form 01: UNPACKING and CHECKING FORM

Date received _____

Consignee (Name of health unit) _____

Unpacking/checking date _____

Consignor _____

Issue voucher no./date _____

Total No. of packages _____

SN	Package N0.	Packing Condition/ Weight of Package	Content (Commodity with specification)	A/U	Invoice/ Packing List Qty.	Actual received Qty.	Surplus Qty.	Shortage Qty.	Damage	Remark

Receiving checking team signature and remarks:

1 _____

Designation _____

2 _____

Designation _____

3 _____

Designation _____

Drug management Form 02: DRUG INVENTORY

Description _____

Strength _____

Stock No _____

Packing Size _____

Accounting Unit _____

Location _____

SN	Date	I/V No (Received)	Source of Supply	Batch No	Expiry Date	Quantity Received	I/V No (Issued)	Issue to	Quantity Issued	Balance	Remark	Signature

Drug management Form 03: INDENT/REQUISITION FORM

Indent of _____

Indent for _____ Quarter/Year _____

Indent number _____

Date _____

Sr. No.	Nomenclature	Packing size	A/U	Qty. received last qtr.	Amount available	Qty. needed	Remark

Signature _____

Name _____

Designation _____

Drug management Form 04: ISSUE VOUCHER FORM

Original _____ IV No _____

Issuing department _____

Date _____

Issued to _____

Sr. No.	Nomenclature	A/U	Issued Quantity	Expiry Date	Remarks

( ) Items only

Signature of Store Officer

Signature of Officer in-charge

Received correctly and completely

Signature

Drug management Form 05: SECOND-LINE DRUG REQUISITION FORM

(For use by the TB or S/R Hospital ward/OPD/Township Hospital)

Indent/Requisition of _____ Ward/Unit

Indent/Requisition number _____

Hospital/R/S TBC/ Township _____

Date _____

SN	MDR-TB patient name	Patient reg. no.	Age	Body Weight (Kg)	Treatment regimen	Drugs(vial/amp/cap/tab)									
						1		2		3		4		5	
						Bal	Req	Bal	Req	Bal	Req	Bal	Req	Bal	Req
Total															

Drug management Form 06: SECOND-LINE DRUG ISSUE VOUCHER (HEALTH FACILITY)

Issued from _____

Issued to _____

Issued date _____

IV Number _____

SN	MDR-TB patient name	Patient reg. no.	Age	Body weight (kg)	Treatment regimen	Quantity of drugs issued (vial/amp/cap/tab)				
						1 E/D	2 E/D	3 E/D	4 E/D	5 E/D

Signature of Store MO _____

Countersigned by MS /R//S TBO _____

Received correctly and completely _____

Signature _____

ANNEX 3: Recording and Reporting Forms

1. DR-TB Treatment Card
2. DR-TB Register
3. DR-TB Patient Identity Booklet
4. Laboratory Register for Xpert MTB/RIF, Culture and DST
5. Laboratory Requisition Form for Culture, DST and Xpert MTB/RIF
6. DR-TB Notified Register
7. Quarterly Report DR-TB Case Detection
8. 8, 9-month Interim Progress Assessment Report
9. 12-month Progress Assessment Report
10. Annual Report of Treatment Outcomes of MDR-TB Cases
11. Quarterly Laboratory Report on Culture & DST
12. Register for Missed Dose Tracing
13. Directly Observed Treatment (DOT) Card
14. Patient's Informed Consent Form for MDR-TB Treatment
15. MDR-TB Referral Form
16. Quarterly Drug Report Form

National Tuberculosis Program

Drug management Form 07 : Quarterly Drug Report Form (MDR-TB FORM 16)

Hospital/Township _____

State/Region _____

Month _____ Year _____

Drug Name										
	1	2	3	4	5	6	7	8	9	10
Expiry Date: Month										
Expiry Date: Year										
Balance										
Issued										
Received										

Signature _____

Designation _____

Countersigned _____

Designation _____

NATIONAL TUBERCULOSIS PROGRAMME (DR-TB Form 01)

MDR-TB Treatment Card

Name: _____

Sex: ☐ M ☐ F

Age: _____ Date of birth: ____/_____/_____

Initial weight (kg): _____ Height (cm): _____

Site: ☐ Pulmonary ☐ Extra-pulmonary ☐ Both

If extra-pulmonary, specific site: _____

Address: _____

_____

_____

phone: _____

_____

MDR-TB Initiation Center:: _____

DC Site/Center: _____

Name of DOT Provider: _____

DOT Supervisor: _____

Date of X-pert Result : _____

No	Registration group
1	New
2	Non-converter ☐IR ☐RR
3	Treatment after loss to follow up ☐IR ☐RR
4	Treatment after failure of treatment ☐IR ☐RR
5	Relapse ☐IR ☐RR
6	Treatment after MDR-TB treatment 6.1 Standard Regimen ☐LFU ☐Failure ☐Relapse 6.2 Other Regimen ☐LFU ☐Failure ☐Relapse
7	Others (a. Unknown regimen/outcome of previously treated TB b. patient who does not fit in registration group 1-6)

HIV information
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

Diabetes Mellitus	☐Yes	☐No

X-pert result:	N	I	T	RR	TI

N = No MTB, **I** = Invalid / No result, **T** = MTB detected, **RR** = Rif resistant,
TI = MTB (+)/but Rif resistant is invalid or No result

Date	S	H	R	E	Pto/ Eto	Km/ Amk	Cm	Fq	Other	Other	Other

R=resistant, S=susceptible, C=contaminated

MDR TB registration number:_____

Date of registration: ___/___/____

Previous tuberculosis treatment episodes

Previous Township TB No./ township	Start date (if unknown, put year)	Regimen (in drug abbre -viations)	Outcome

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= Thioacetazone)

Second-line drugs

Am= Amikacin
Km= Kanamycin
Cm= Capreomycin
Cfx= Ciprofloxacin
Ofx= Ofloxacin
Lfx= Levofloxacin
Mfx= Moxifloxacin
Gfx= Gatifloxacin
Pto= Prothionamide
Eto= Ethionamide
Cs= Cycloserine
PAS= P-aminosalicylic Na

Standard Treatment Regimen

☐ 6-8 (Amk Z Lfx Eto Cs)/ 12-14 (Z Lfx Eto Cs)

☐ 6-8 (Amk Z Lfx Eto Cs PAS)/ 12-14 (Z Lfx Eto Cs PAS)

Other Regimen

(Specify…….....……)

MDR-TB REGIMEN (date treatment started and dosage (mg), frequency of dose, change of dosage, and cessation of drugs):

Date	H	R	Z	E	S	Km	Am	Cm	FQ	Pto/Eto	Cs	PAS	Other	Comments

(od = Once a day, bd = 12 hourly: morning and evening doses)

ADMINISTRATION OF DRUGS (one line per month):

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

Mark in the boxes: √ = directly observed x = not supervised 0 = drugs not taken

Moved to XDR TB		
Not evaluated		
Lost to follow up		
Died		
Failed		
Completed		
Cured		
Outcome	**Mark one**	**Date**

Comments

_____

_____

_____

_____

_____

Mark in the boxes: √ = directly observed

N = not supervised

Ø = drugs not taken

ADMINISTRATION OF DRUGS (continued):

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

TB PROGRAMME MDR-TB Treatment Register (DR-TB FORM 02)

Serial No	Name in (Full)	Sex M or F	Age	Address	Previous Township TB No.	MDR-TB Register Number	Registration group*	Transfer in	X-pert result (N,I,T, RR,TI)	Date sample taken for DST	Result of drug susceptibility testing (DST) (Enter the DST that resulted in the patient being registered as a DR TB patient. If the DST is pending it should be filled in when the results are known. See treatment card for full history of DST data) R = resistant S = susceptible C = contaminated											
			Date of Birth d/m/y		Treatment Regimen	Date of registration			Date of result		R	H	E	S	Am	Z	Cm	Fq	Pto/Eto	Other	Other	Date sample taken for DST
1																						
2																						
3																						
4																						
5																						
6																						
7																						
8																						
9																						
10																						

Guidelines for the Manangement of DR-TB in Myanmar

MDR-TB treatment	Start of treatment month 0		Month 1		Month 2		Month 3		Month 4		Month 5		Month 6		Month 7		Month 8		Month 9		Month 10		Month 11		Month 12		Month 13		Month 14	
Regimen (in drug initials) Date started	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C
	D/M/Y		D/M/Y		D/M/Y		D/M/Y		D/M/Y		D/M/Y		D/M/Y		D/M/Y		D/M/Y		D/M/Y		D/M/Y		D/M/Y		D/M/Y		D/M/Y		D/M/Y	
	+		+		+		+	+	-		-	-	-	-				-								-				-
Date																														
Date																														
	+		+		+		+	+	-		-	-	-	-				-								-				-
Date																														
Date																														
	+		+		+		+	+	-		-	-	-	-				-								-				-
Date																														
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Date																														
Date																														
Date																														
Date																														

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)

Month 15		Month 16		Month 17		Month 18		Month 19		Month 20		Month 21		Month 22		Month 23		Month 24		Month 25		Month 26		Month 27		Month 28		Month 29		Month 30		Month 31		Month 32	
S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C
D/M/Y		D/M/Y		D/M/Y		D/M/Y		D/M/Y		D/M/Y		D/M/Y		D/M/Y		D/M/Y		D/M/Y		D/M/Y		D/M/Y		D/M/Y		D/M/Y		D/M/Y		D/M/Y		D/M/Y		D/M/Y	

Guidelines for the Manangement of DR-TB in Myanmar

Month 33		Month 34		Outcome Cured Completed Failed Died LFU Not evaluated Moved to XDR	TB/HIV activities					Comments
					HIV Testing					
S	C	S	C	Date outcome given	Test done (Y/N/Unknown)	Date of test	Result	ART Y/N start date	CPT Y/N start date	
D/M/Y		D/M/Y								
+		+								
+		+								
+		+								

NATIONAL TUBERCULOSIS PROGRAMME

Patient Identity Booklet (DR-TB FORM 03)

MDR-TB Registration No: ______________

MDR-TB Treatment No: ______________

Patient name: ____

Address : ____

Phone no: ____

Sex : ☐M ☐F Age: ______ Date of birth: ___/___/___

Township TB unit: ____________________

Health unit: ________________________

Lab result		Date
DST		
X pert		

Treatment Regimen/Type of Disease **Date treatment started**

☐ IR ☐ RR ☐ CR ☐ Pul ☐ EP ☐ Both Site: ____________________	___/___/___

DR Registration group

1. New [ ] 2. Non Converter (IR) (RR) [ ] 3. Treatment after loss to follow up (IR) (RR) [ ] 4.Treatment after failure of treatment (IR)(RR) [ ]	5. Relapse (IR) (RR) [ ] 6. Treatment after failure with the Standard MDR-TB treatment [ ] 7. Other [ ]

Treatment	**Intensive phase**	**Continuation phase**

Change in treatment	**Intensive phase**	**Continuation phase**

Allergies: ____

Severe adverse reactions: ______________________________

Remarks: ____

Guidelines for the Manangement of DR-TB in Myanmar

Appointment date	**Progress**		
	Weight	**Smear**	**Culture**

REMEMBER

1. Take care of your card.
2. You can be cured if you follow your treatment regimen by taking your prescribed drugs regularly.
3. Tuberculosis can spread to other people if you do not take your medication regularly.
4. Report any side effects to your DOT provider at once.
5. Remember to report to the health facility on appointment date given to you.

NATIONAL TUBERCULOSIS PROGRAMME

Laboratory Register for DR-TB

(DR-TB FORM 04)

SN. No.	Date	Name	Age/ Sex	Township TB/MDR TB No.	Type of patient	Smear result	Type of specimen	Culture No.	Culture result (Week) 1	2	3	4	5	6	7	8	Final result	Xpert MTB/RIF result	Date recorded	Remark (indicate Dx or F/U)

Guidelines for the Manangement of DR-TB in Myanmar

Request for examination of biological specimen for TB (TB - 05)

Treatment unit: ______________________ Date of request: ________________

Patient name: ______________________

Age (years): Date of birth: Sex: ☐ Male ☐ Female

Patient address: ____

_____________________________________Telephone: ____________________

Previously treated for TB: ☐ Yes ☐ No ☐ Unknown

HIV Status ☐ Positive ☐ Negative ☐ Unknown

Diabetes Status ☐ Yes ☐ No ☐ Unknown

Reason for examination: ______________________

☐ Diagnosis Presumptive TB Reg. / OPD No./TB No./MDR-TB No. ( )

☐ Follow-up Township TB No/MDR-TB No.____________ Month of treatment (__)

Specimen type: ☐ Sputum ☐ Other (specify): ______________________

Test(s) requested: ☐ Microscopy ☐ Xpert MTB/RIF

☐ Culture ☐ Drug susceptibility ☐ Line probe assay

Requested by Signature: ______________________

Name: ______________________

Designation: ______________________

Contact phone no. : ______________________

Microscopy results (to be completed in laboratory) Auramin ZN

Date of specimen received	Laboratory serial number (s)	Specimen type	Visual appearance (blood-stained, mucopurulent or saliva)	Result (tick one)				
				Negative	Scanty	+	++	+++

Examined by Signature: ______________________

Name: ______________________

Designation: ______________________

Date of result: ______________________

X-pert MTB/RIF test result (to be completed in the laboratory)

Date specimen collected:_____ X-pert Lab No:_____ Township: _____

X-pert result:	N	I	T	RR	TI

N = No MTB, **I** = Invalid / No result, **T** = MTB detected, **RR** = Rif resistant, **TI** = MTB (+)/but Rif resistant is invalid or No result

Examined by Signature: _____

Name: _____

Designation: _____

Date of result: _____

Date of Specimen Collected _____

Culture results (to be completed in the laboratory)

Media used	Date of specimen received	Laboratory serial No.	Results (tick one)						
			Negative	scanty	+	++	+++	NTM	Contaminated
L-J									
MGIT									

Signature of Microbiologist: _____

Name: _____

Designation: _____

Date of result: _____

Drug susceptibility test (DST) and line probe assay (LPA) results (to be completed in the laboratory)

Date sample received	Method[a]	Laboratory serial number(s)	**Results**[b] (mark for each drug)											
			H	R	E	S	Amk	Km	Cm	FQ				

[a] Specify: solid media DST; liquid media DST; direct LPA; indirect LPA

[b] Results codes: **R** = Resistant; **S** = Susceptible; **C** = Contaminated; — = Not done

Signature of Microbiologist: _____

Name: _____

Designation: _____

Date of result: _____

NATIONAL TUBERCULOSIS PROGRAMME (DR-TB FORM 06)

Notified DR TB register

Sr. No./ date	Name	Sex Age	Address	Town-ship TB No.	Name of treatment center	Regist-ration Group	Date specimen collected	X-pert result	Culture result	DST results for culture + specimen									
										S	H	R	E	Z	Am	Cm	Fq	Pto/Eto	Other	Other	Other

Registration Group: 1) New ; 2 Non Converter (IR) (RR)3) Treatment after loss to follow up (IR) (RR); 4) Treatment after failure of treatment (IR)(RR); 5) Relapse (IR) (RR); 6) Treatment after the MDR-TB treatment 7) Other

Culture results reported as follows:

No growth reported	0
Fewer than 10 colonies	Report number of colonies
10-100 colonies	+
More than 100 colonies	++
Innumerable or confluent growth	+++

DST results reported as follows: R= resistant; S= susceptible; C= contaminated

Xpert MTB/RIF results reported as follows: : N=No MTB, I =Invalid / No result, T = MTB detected, RR = Rif resistant, TI = MTB (+)/but Rif resistant is invalid or No result

Died before started DR-Treatment (Date)	SLD treatment at private sector (Date)	Refused (Date)	Lost to follow up. (Date)	MDR-TB treatment Started date and MDR-TB Reg. No.	Remarks

NATIONAL TB PROGRAMME
Quarterly Report on MDR-TB Case Registration

(DR-TB FORM 07)

(To be filled out one quarter after)

MDR-TB Township: _____

Patients registered in the MDR-TB Registerduring quarter _____ of year _____

Name and signature:_____ Date of completing this form: _____

Block 1: Confirmed MDR-TB registered during the quarter

Pulmonary												**Other***		**Total**	
New		**Previously treated patients**													
New MDR-TB case		Non Converter (IR,RR)		Treatment after LFU (IR,RR)		Treatment after failure of treatment (IR,RR)		Relapse (IR) (RR)		Treatment after failure with the Standard MDR-TB treatment					
M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F

* Other mean (a) previously treated EP,(b) Unknown outcome of previously treated Pul:TB (c) Previously treated with SLD

	<15	≥15
Total MDR TB Cases		

Remark :

Transfer in : _____

NATIONAL TB PROGRAMME

MDR-TB Treatment 12-month Progress Report

(DR-TB FORM 09)

(To be filled out 15 months later)

MDR-TB Township:_____

Patients registered in MDR-TB Registerduring quarter _____ of year _____

Name and signature: _____ Date of completing this form:_____

	Number started on treatment in the quarter	Smear and culture results at 8 months of treatment (of patients still on treatment)									No longer on treatment		
		Culture negative			Culture positive			Culture unknown			Died	Lost to Follow up	Not evaluated (transferred out)
		Smear negative	Smear positive	Smear unknown	Smear negative	Smear positive	Smear unknown	Smear negative	Smear positive	Smear unknown			
MDR-TB Cases													

Remark : _____

_____

Transfer in : _____

Confirmed by

Name: and Signature: _____

Designation: _____

Guidelines for the Manangement of DR-TB in Myanmar

NATIONAL TB PROGRAMME

9-month interim progress assessment Report

(DR-TB FORM 08)

(to be filled out 12 months after treatment initiation)

MDR-TB Township:_____

Patients registered in MDR-TB Registerduring quarter _____ of year _____

Name and signature: _____ Date of completing this form:_____

	Number started on treatment in the quarter	Smear and culture results at 8 months of treatment (of patients still on treatment)									No longer on treatment		
		Culture negative			Culture positive			Culture unknown			Died	Lost to Follow up	Not evaluated (transferred out)
		Smear negative	Smear positive	Smear unknown	Smear negative	Smear positive	Smear unknown	Smear negative	Smear positive	Smear unknown			
MDR-TB Cases													

Remark : _____

_____

Transfer in : _____

Confirmed by

Name: and Signature: _____

Designation: _____

NATIONAL TB PROGRAMME

ANNUAL REPORT OF TREATMENT OUTCOMES OF MDR-TB CASES

(DR-TB FORM 10)

(To be filled in 24 and 36 months after the starting date of treatment)

MDR-TB Township:_____ Date of completion of the report: _____

Patients registered in MDR-TB Registerduring quarter _____ of year _____

MDR-TB treatment site coordinator: _____ Signature: _____

Registration group	Cured	Completed	Failed	Lost to follow-up	Died	Still on treatment	Move to XDR	Total
New								
Non Converter (IR) (RR)								
Treatment after loss to follow up (IR,RR)								
Treatment after failure of treatment (IR,RR)								
Treatment after the Standard MDR-TB treatment								
Relapse (IR) (RR)								
Other*								
Total								

Other* mean (a) previously treated EP,(b) Unknown outcome of previously treated Pul:TB (c) Previously treated with SLD

Confirmed by

Name: and Signature: _____

Designation: _____

NATIONAL TB PROGRAMME

Quarterly Lab. Report on Culture & DST (first line drugs)

(DR-TB FORM 11)

Date of reporting : _____ Quarter reported: _____ of Year_____

Laboratory's name : _____

Laboratory Supervisor's name: _____

No. of DR-TB suspect investigated with culture: _____

No. of DR-TB suspects with culture positive investigated with DST: _____

DR-TB patterns reported:

Category of DR-TB suspects investigated with DST	No. of DR-TB suspects	No. of All sensitive	No. of Mono resistant	No. of Poly resistant (but not MDR-TB)	MDR-TB				Total No. of MDR-TB	Total No: of DST	Remark
					SHRE	SHR	HRE	HR			
New (MDR contact) (PLHIV)											
Non Converter (IR) (RR)											
Treatment after loss to follow up (IR,RR)											
Treatment after failure of treatment (IR,RR)											
Treatment after the Standard MDR-TB treatment											
Relapse (IR) (RR)											
Other*											
Total											
Unspecified											

Other* mean (a) previously treated EP,(b) Unknown outcome of previously treated Pul:TB (c) Previously treated with SLD

NATIONAL TB PROGRAMME
REGISTER FOR MISSED DOSE TRACING

(DR-TB FORM 12)

Date of reporting : _____ Quarter reported: _____ of Year_____

Laboratory's name : _____

Laboratory Supervisor's name: _____

No. of DR-TB suspect investigated with culture: _____

No. of DR-TB suspects with culture positive investigated with DST: _____

DR-TB patterns reported:

Dates of treatment interruption	Number of doses (-)	Reasons (according to patient)	Conclusion and decision	Date of meeting	MO/TMO signature	Patient signature
from…./…. to…./….						
from…./…. to…./….						
from…./…. to…./….						
from…./…. to…./….						
from…./…. to…./….						
from…./…. to…./….						
from…./…. to…./….						
from…./…. to…./….						
from…./…. to…./….						
from…./…. to…./….						

NATIONAL TUBERCULOSIS PROGRAMME

PATIENT'S INFORMED CONSENT FORM FOR MDR-TB TREATMENT

(DR-TBFORM 14)

Patient:

I (Name of patient) _____ fully understand that treatment of this form of Tuberculosis requires me to take the medicines provided daily for the next 20 months without interruption. If I do not take these medicines daily I am putting my own health at risk and I may spread this form of TB to my family and neighbors. I am committed to take these drugs for the full period at this Regimen_____/_____ for the next 20 months. I also understand that the MDR-TB treatment has some serious side effects.

(If patient is pregnant this treatment has some serious side effect on pregnancy.)

Signature _____

Name _____

Date _____ Age _____

Address _____

_____

MS/S/R TO/TMO:

I (Name of MS/DTO/TMO) _____ have explained the importance and difficulties of taking these medicines to (DOT Provider)_____ and I will do my best to support (Patient) _____ in completing a full course of treatment and getting cured.

Signature _____

Date _____ Name _____

Designation _____

DOT Provider:

I (Name of DOT Provider) _____ am committed to support (Name of patient) _____ in taking his/her full course of treatment at least for 20 months. I will do my best to encourage him/ her to return for treatment if he/she ever misses a dose, and committed to inform the Township TB Centre if he/she ever fails to take the prescribed medications. I am committed to help look for solutions to problems that might arise during treatment.

Signature _____

Date _____ Name _____

Address _____

_____

NATIONAL TUBERCULOSIS PROGRAMME

DR-TB Referral Form (FORM 15)

(Fill in duplicate. Send one copy to the respective facility receiving the patient, and keep the duplicate copy on file.)

Name and address of referring health facility _____

Name of health facility to which the patient is being transferred _____

Name of patient _____ Age _____ Sex ☐M ☐F

Complete address _____

Disease classification	Detail of Retreatment Regimen
☐ Pulmonary	Township and TB number _____
☐ Extra-pulmonary (Site _____)	Date of starting Retreatment Regimen
☐ Both	_____

Registration Group	Sputum, culture and DST details and X pert
☐ New (MDR contact) (PLHIV)	Date of culture collection _____
☐ Non Converter (IR) (RR)	Date of culture result _____
☐ Treatment after loss to follow up (IR,RR)	Date of DST result _____
☐ Treatment after failure (IR,RR)	DST result (resistance pattern only)
☐ Relapse (IR) (RR)	_____
☐ Treatment after failure with the Standard	
☐ MDR-TB treatment	X pert result_____
☐ Other	Date of X pert result_____

Details of MDR-TB patient	Refer for side effects
MDR-TB reg no. _____	☐ Psychosis
Name of MDR TB center _____	☐ Depression
Date of MDR-TB treatment start _____	☐ Seizures
Number of doses taken _____	☐ Other _____

Date of referral for MDR-TB treatment _____

Referred for ☐ In-door treatment ☐ Ambulatory treatment ☐ Transfer

Remarks _____

_____

Signature _____ Designation _____

Reminder for the health facility where the patient is being referred to: please send an e-mail to the referring unit, informing the referring doctor of the date that the above-mentioned patient reported at the receiving health facility.

ANNEX 4: Management of Electrolyte Disturbances

Although often asymptomatic, low serum potassium and magnesium may present as fatigue, myalgias, cramps, paraesthesias, lower extremity weakness, behaviour or mood changes, somnolence, and confusion. More severe disturbances can lead to tetany, paralysis, and life-threatening cardiac arrhythmias. The magnitude of total body depletion of potassium (K+) and magnesium (Mg++) may be far lower than that which is reflected in serum levels.

Warning: Coadministration of oral divalent or trivalent cation-containing compounds (i.e. Mg++ and Ca++) with oral fluoroquinolones may impair fluoroquinolone absorption. They must be dosed at least 2 hours before and three hours after the fluoroquinolone.

Hypokalaemia (defined as a serum potassium less than 3.5 mEq/L) and hypomagnesaemia (defined as a serum magnesium less than 1.8 mEq/L) are common in patients receiving MDR-TB therapy and are caused by the following:

- Direct renal tubular effect of aminoglycosides and capreomycin
- Vomiting and diarrhoea.

Once hypomagnesaemia or hypokalaemia is diagnosed:

- Underlying causes such as vomiting and diarrhoea should be treated.
- Arrhythmogenic medications (such as digoxin, tricyclic anti-depressants) should be discontinued if possible.
- An electrocardiogram should be performed in patients with significant electrolyte disturbances; if the QT segment is prolonged, any drugs contributing to QT prolongation— including certain fluoroquinolones, haloperidol, fluconazole, and cisapride— should be held.

Treatment of hypokalaemia and hypomagnesaemia:

- Should be administered orally if electrolyte disturbance is not severe (it is safer to give electrolytes, especially potassium, orally than intravenous). Intravenous treatment is required for patients with gastrointestinal disorders or when the potassium deficiency is severe and life-threatening.
- If severe, hold the injectable agent until potassium is in a safe range.
- Replacement may be needed during the whole time during the use of the aminogly-coside or capreomycin.
- The electrolyte abnormalities will correct after suspension of the injectable in the intensive phase. If electrolyte abnormalities do not correct once the injectable is suspended, suspect another aetiology.
- Preliminary antidotal observations indicate that capreomycin may cause

electrolyte abnormalities more frequently than other injectables. Consider changing CM to AMK or KM if the strain is susceptible.

- Hypokalaemia will be refractory to treatment unless hypomagnesaemia is also treated (it is acceptable to screen electrolyte disturbances with a serum potassium. If low obtain a serum magnesium and calcium. (If unable to screen for magnesium, empiric magnesium replacement with the potassium replacement is often essential, since potassium wasting will continue in hypomagnesaemic states).
- Normal renal function should be confirmed prior to instituting repletion, although even patients with renal failure should receive repletion in smaller doses.
- In cases of refractory electrolyte abnormalities, amiloride or spironolactone may be used to decrease potassium and magnesium wasting in the renal tubules (amiloride 5-10 mg once daily or sprionolactone 25 mg once daily). Frequent potassium monitoring must be used when potassium-sparing diuretics are given in conjunction with potassium supplements, as hyperkalaemia may result. Continue with potassium and magnesium supplements, but often can use lesser quantity.

The following are general recommendations for electrolyte replacement. Optimal replacement schedules have not been determined and individual programmes may vary:

Potassium

Oral Supplementation

- Occasional gastric intolerance.
- May dilute KCl tablets in water or take as pills.
- May split dose and give two or three times per day.
- Supplement diet with banana, orange/tomato/grapefruit juice.

IV Supplementation

- May produce burning at infusion site.
- Should NOT exceed more than 20 meq/h of KCl.
- Normal preparation is 40 meq in 1 litre of NaCl 0.9%, maximum preparation is 60 meq/L.

Potassium Level	Quantity of KCl	When to do next control (sooner if pt has vomiting or diarrhoea)
4.0 or more	None	Monthly
3.7 – 4.0	None	Monthly
3.4 – 3.6	20 - 40 meq	Monthly
3.0 – 3.3	60 meq	Two weeks
2.7 – 2.9	80 meq	One week
2.4 – 2.6	80-120 meq	1-2 days
2.0 – 2.3	60 meq IV and 80 meq PO	Every 6 to 24 hrs
<2.0	60 meq IV and 100 meq PO	Every 6 hrs with aggressive IV replacement. Consider holding injectable until >2.4

Notes on dosing potassium: The dosage of potassium supplements is usually expressed as mEq of potassium. Forty mEq of potassium is provided by approximately the following quantities:

3.9 g of potassium acetate

4.0 g of potassium bicarbonate

3.0 g of potassium chloride

4.3 g of potassium citrate

9.4 g of potassium gluconate

The acetate, bicarbonate, chloride, citrate, and gluconate salts of potassium can all be administered orally. Potassium chloride and potassium acetate may be administered by IV infusion.

Intravenous vials often come with a percentage of potassium. For example, a 10 ml vial of 10% potassium chloride is 1 gram of potassium chloride and would be 13.3 mEq of potassium.

Magnesium

<u>Oral Supplementation</u>

- Presentations:
  - Magnesium citrate
  - Magnesium lactate
  - Magnesium glycinate
  - Magnesimum gluconate
  - Magnesium chloride
  - Magnesium oxide
- Different preparations have different amounts of elemental magnesium.

- Recommended types include magnesium citrate, magnesium gluconate and magnesium lactate, all of which are more easily absorbed into the body than other forms.
- While magnesium oxide is probably the most common form given for replacement because of its low cost, Mg oxide does not have high bioavailability (i.e. the body does not absorb Mg oxide that well). For example, magnesium chloride, lactate, citrate and glycinate each have around the bioavailability 4 times greater than the oxide form. Magnesium citrate is probably the best in terms of absorption. (Patients with hypomagnesaemia will benefit from Mg oxide, so if other formulas are not affordable Mg oxide can be used. Other forms (chloride, lactate, citrate or glycinate) in tablet form are preferable.
- Quantities greater than 2000 mg are often more easily given IV or IM.

<u>IV Supplementation</u>

- Maximum concentration: 5 g or 40 meq $MgSO_4$ in 1 liter of NaCl 0.9% or Dextrose 5%.
- Do not exceed 150 mg per minute.
- If not emergency:
  - 2 g in 100 ml administered over 1–2 hours
  - 4 g in 250 ml administered over 2–4 hours

<u>Intramuscular Supplementation</u>

- 1 g (or up to 250 mg/kg) of $MgSO_4$ without dilution IM every 6 hours.
- No advantage over IV magnesium.
- Indicated if supplementation cannot be received PO or IV.
- Potassium sparing diuretics may also help with magnesium wasting.

Table 2. Frequency and replacement table for magnesium

Magnesium level	Quantity of Mg (Total daily dose)	When to do next control
2.0 or more	None	Monthly
1.5 – 1.9	1000 mg – 1200 mg	Monthly
1.0 – 1.4	2000 mg (consider IM)	1–2 weeks
<1.0	3000 mg – 6000 mg (give IV or IM)	1–6 days

Calcium

- Symptomatic hypocalcaemia should be treated on an emergency basis with 2 grams of calcium gluconate (180 mg elemental calcium or 20 ml 10% calcium gluconate) IV over 10 minutes, followed by infusion of 6 grams calcium gluconate in 500 ml D5W over 4–6 hrs. The IV infusion should be tapered. The initial oral dose during the transition from IV to oral therapy is 1–2 g elemental calcium three times a day.
- For long-term therapy the typical dose is 0.5–1.0 g PO three times a day.
- Hypomagnesaemia must be treated if present.
- Total serum calcium levels need to be adjusted for low albumin (if the laboratory tests for serum ionized levels of calcium, theses do not need to be adjusted). The total serum calcium can be corrected by adding 0.8 mg/dl for every 1 g/dl decrease of serum albumin below 4 g/dl. By doing this calculation one can determine if true hypocalcaemia is present:

Corrected calcium = 0.8 (4.0 – measured albumin) + reported calcium

Table 3. Frequency and replacement table for calcium

Calcium level (total calcium adjusted for low albumin)	Dose of calcium	When to do next control
>8.5 mg/dl (>4.2 meq/L)	None	
7.5 – 8.4	500 mg three times a day	Monthly
7.0 – 7.4	1000 mg three times a day	1–2 weeks
<7.0	Consider IV and taper to 1000 mg three times a day	1–4 days

Repeat warning: Always give any electrolyte replacement a few hours apart from the fluoroquinolones and the cations Mg++, and Ca++ can combine with the anions of the fluoroquinolones and decrease absorption.

ANNEX 5: Supervisory checklist for township health facility implementing MDR-TB management

Name of township: _____Date of visit: _____

Name of TMO: _____ Name of TB coordinator: _____

Name of Supervisors:_____

Please write "Yes" or "No" in the "Observation" column and write brief explanations if necessary

A.	Township TB centre	Observation
1	Does the TB clinic have good lighting, ventilation and adequate counselling	
2	Are smear-positive MDR-TB patients sharing waiting areas with other patients?	
3	Is there any area-wise MDR-TB patient mapping?	
4	Have township staff been trained on MDR-TB management? If yes, when was the last training?	
5	Are there IEC materials easily available for MDR-TB patients?	
6	Is there an DR-TB suspect register? If yes, is it properly filled in and up to date?	
7	Has any action been taken on recommendations of previous MDR-TB supervisory visits? If not, why?	

B.	Laboratory	Observation
1	Is the laboratory register filled in correctly? Is it up to date?	
2	What is the number of patients that are still smear-positive at the end of the initial phase of treatment and smear-positive at month 5, 6 and 8?	
3	Is there a system for transportation of specimens to laboratories performing Xpert MTB/RIF, LIPA, culture and DST? If yes, how often are samples sent to the next level laboratory services?	
4	Is the Quality Control schedule for microscopy followed? If yes, check the EQA feedback from R/STBC?	
5	Logistics: Are there sufficient amount (to last approximately one quarter) of: • Sputum cups • Slides • Slide boxes • Staining reagents	
6	How is waste disposed of? • burning • burial • boiling • Is the waste immersed in disinfectants before disposal?	

C.	Review MDR-TB treatment cards	Observation
1	Are MDR-TB treatment cards kept in order and up to date (according to MDR-TB numbers, yearly)?	
2	Is patient information filled in correctly on the MDR-TB treatment cards especially the past anti-TB history? Are the regimens chosen appropriate with the MDR-TB patient category?	
3	Are laboratory results (smear, culture, Xpert MTB/RIF, and DST) and body weight recorded correctly and updated?	
4	Is the information on the MDR- TB treatment card sufficient to determine the treat- ment outcome such as cured/completed/treatment failure?	
5	Are follow-up sputum and culture requisition forms attached to the MDR-TB treat ment cards?	
6	Is the treatment outcome and special situation filled up in the remarks space?	

D.	Review Township MDR-TB Register	Observation
1	Is it up to date?	
2	Are there any discrepancies, when you check correctness, completeness and consistency with: MDR-TB treatment cards: Laboratory register:	
3	Is there any report on treatment outcomes of patients transferred to other townships?	

E.	Drug Store	Observation
1	Are second-line anti-TB drugs kept under lock and key in main store?	
2	Do they have main, sub- and daily stock books?	
3	Are they filled up to date in main store?	
4	Is a FEFO (First Expiry First Out) system used?	
5	Are bin cards kept up to date, check with the ground balance? Check any surplus drugs and how they are used?	
6	Are ancillary drugs available to manage side-effects? Are there any shortages of ancillary drugs, and if so, which drugs?	

Drugs	Remaining amount	Expiry dates	If expired, amount of drugs
Amikacin			
Levofloxacin			
Pyrazinamide			
Ethionamide			
Cycloserine			
PAS			
B6			
Other			

F.	Interview with TB coordinator	Observation
1	Has the TB coordinator been trained on MDR-TB management by the NTP? If yes, when: If yes, type of training:	
2	Does the TB coordinator have a copy of the MDR-TB guidelines?	
3	Does the TB coordinator counsel MDR-TB patients at the time of registration?	
4	Does the TB coordinator have a list of MDR-TB patients with missed doses? Any action, and when does it start? Who checks if there are any MDR-TB patients who are not getting DOT?	
5	Is there a list of defaulters? Any action, and when does it start?	
6	How many defaulters return and continue the treatment?	
7	Does TB coordinator assign DOT providers to all MDR-TB patients?	
8	Does TB coordinator regularly go for supervision according to plan?	
9	and treatment? If yes, from GPs _____ Is this recorded? from NGOs _____ Is this recorded?	
10	Are second-line, anti-TB drugs supplied to BHS? How frequent?	
11	Do you have enough N95 respirators?	
12	Do you have a system for initial home visit and contact tracing just after a new MDR-TB patient has registered?	
13	Do you have enough stock of respirators for health care staff in contact with MDR-TB patients?	
14	Do you have any specific and urgent problems?	

G.	Interview with BHS	Observation
1	Have BHS received training on MDR-TB Management from NTP? If yes, when: If yes, what type of training:	
2	Does BHS have NTP guidelines for DOT providers?	
3	Does BHS have sub-centre MDR-TB sub-register?	
4	Does BHS make initial visit to MDR-TB patient's home for contact tracing and information about infection control?	
5	Does BHS assign a suitable DOT provider for each MDR-TB patient?	
6	Does BHS supervise the DOT providers? If yes, how frequent? What does BHS usually check during the supervision?	
7	Is there any DOT by BHS? No. of patients:	
8	Does BHS supply second-line anti-TB drugs to the DOT providers/MDR-TB patients? If yes, how frequently? (Need to check who gives the injection if community volunteers are acting as DOT provider)	
9	Does BHS give health education to their MDR-TB patients?	
10	Does BHS check any patients with missed doses? How does BHS take action?	
11	Does BHS know what action to take for side effects of second-line anti-TB drugs?	
12	When was the last supervision make by Region/State/District/Township?	

H.	Interview with TB patients (tick box is correct answer)	Observation				
		P1	P2	P3	P4	P5
1	Are you aware that you are undergoing treatment for MDR-TB?					
2	Do you know how MDR-TB is spread? How to prevent spread?					
3	Do you know the duration of MDR-TB treatment?					
4	How many tablets are you taking every day? When do you take the medicines? When do you get injection, by whom?					
5	Does anyone observe you when you are taking the medicines (BHS in morning, volunteer or family member)?					
6	Do you know when to do sputum follow-up examinations?					
7	Are drugs given to you in advance for treatment? How many doses?					
8	Do you have to pay for the second-line anti-TB drugs?					
9	Do you have to pay for drugs to manage side-effects?					
10	Do you have to pay for laboratory investigations or X-rays?					

H.	Interview with TB patients (tick box is correct answer)	Observation				
		P1	P2	P3	P4	P5
11	Do you know the name of your DOT supervisor?					
12	Do you have any problem with treatment? (time, travel cost, clinic hours, suffering side effects)?					
13	Do you receive any socioeconomic support during your MDR-TB treatment?					
14	Do you know what to do for getting continuous second-line anti-TB drugs if you move out of the area?					

I.	Interview with DOT provider/Community TB treatment supporter	Observation
1	Did you get any training for your task? If yes, when, and where?	
2	How many MDR-TB patients are you currently supporting?	
3	Do you receive anti-TB drugs regularly from BHS? Do you have enough N95 respirators?	
4	Do you watch your patients swallowing second-line anti-TB drugs daily? Who gives the daily injection? Is the injection given at the same time as the other drugs or not?	
5	Do you fill in the list of DOT at the same time when DOT is given?	
6	How frequently does your DOT supervisor visit to you? When was the last visit?	
7	What will you do when patients interrupt the treatment?	
8	What will you do if patients complain of side effects?	
9	Do you know the schedule for follow-up sputum examinations?	
10	What will you do when patients want to move to another place?	
11	Do you get reimbursement for travel costs during home visits to patients?	

J.	Interview with local GPs or NGOs	Observation
1	Do you refer MDR-TB suspects to the township TB clinic?	
2	Do you refer sputum samples of MDR-TB suspects to the NTP for DST?	
3	Are you prescribing second-line anti-TB drugs to your patients?	
4	Does your clinic support DOT of MDR-TB patients in collaboration with the NTP?	
5	Do you know that the MDR-TB treatment is provided free of charge by the NTP?	
6	Do you know current MDR-TB treatment guidelines?	
7	Would you like to have a more active role in MDR-TB management?	

Signature: _____

Name of Supervisor: _____

Designation: _____

Date: _____

ANNEX 6: Form for Reporting of Serious Adverse Event (NTP)

Form for Reporting of Serious Adverse Event

Date of Report (/ /) All dates must be filled in as (dd/mmm/yyyy)

Is this report a new event? ☐ Yes ☐ No Give date when previous SAE form sent (/ /)

1. Patient Details

Full Name _____ Age(yrs)_____ Date of Birth(/ /)

pre/XDR/MDR TB registration number _____ Sex ☐M ☐F Is patient pregnant ☐Yes ☐No

Treatment Center_____ Weight (Kg)_____ Height (cm)_____

Address and Phone Number _____

_____

2. Suspected Medicine (s)

Name (Generic name)	Total daily dose	Date started	Date stopped	Continues √

3. Details of Serious Adverse Event

Date Event Started	Date Event Stopped
Description of Event	

Why is the event considered serious?

○Death ○Life Threatening ○Hospitalization OR prolongation of hospitalization OR ICU/HDU

○Persistent/ Significant disability ○Congenital Abnormality ○ Others(spacify)……

4. Action Taken		**5. Outcome of Serious Adverse Event**	
○ Medicine withdrawn		○ Recovered/ resolved	
○ Dose reduced		○ Recovering/ resolving	
○ Dose not changed		○ Recovered with sequelae	
○ Dose interupped		○ Not recovered/ not resolved	
○ Unknown		○Died	
		○ Unknown	
6. Details of suspected drug	Drug 1	Drug 2	Drug 3
Brand Name			
Generic Name			
Batch No			
MM FDA no			
Expiry Date			

7. Relevant Medical Histories
Co-morbidities HIV DM Liver disease ○Renal disease ○ IHD ○ Hypertension ○ Other (specify) _____

8. Concomitant Medicine (s)				
Name (Generic name)	Total daily dose	Date started	Date stopped	Continues √

9. SOURCE OF REPORT
Name of Reporter _____ Address _____ Designation _____ email _____ Signature _____Date _____Tel no. _____

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