

GUIDELINES FOR THE MANAGEMENT OF MULTIDRUG-RESISTANT TUBERCULOSIS (MDR-TB) IN MYANMAR

Myanmar, May 2013



**Ministry of Health
Department of Health
National Tuberculosis Programme**

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LIST OF ABBREVIATIONS

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
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-inflammatory 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-TB	Rifampicin-resistant TB
R/S	Regional/State
R/S TBC	Regional/State Tuberculosis Centre
R/S TBO	Regional/State TB Officer
SNRL	Supranational Reference Laboratory
TAD	Treatment after default
TAF	Treatment after failure
THNO	Township Health Nurse Officer
TB	Tuberculosis
TMO	Township Medical 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
Capreomycin	Cm
Clarithromycin	Clr
Clofazimine	Cfz
Cycloserine	Cs
Ethambutol	E
Ethionamide	Eto
Imipenem/Cilastatin	Ipm
Isoniazid	H
Kanamycin	Km
Levofloxacin	Lfx
Linezolid	Lzd
Moxifloxacin	Mfx
Ofloxacin	Ofx
<i>p</i> -aminosalicylic acid	PAS
protionamide	Pto
Pyrazinamide	Z
Rifabutin	Rfb
Rifampicin	R
Streptomycin	S
Thioacetazone	Thz

INTRODUCTION

The World Health Organization (WHO) estimates that 5,500 cases of multidrug-resistant tuberculosis (MDR-TB) occurred among notified pulmonary TB cases in Myanmar in 2011. Extensively drug-resistant TB (XDR-TB) has been reported since 2007. Two nationwide drug resistance surveys have been carried out, and a third will be completed in 2013. The first survey, 2003-2004, showed an MDR-TB rate of 4% among new cases and 15.5% among previously treated cases. In the second survey, 2007-2008, the proportion of MDR-TB was 4.2% among new cases and 10.0% among previously treated cases.

Myanmar's Ministry of Health established a National Drug-Resistant TB Committee in September 2006, and by the end of 2007 the Green Light Committee approved an MDR-TB pilot project. In March 2009, the National Tuberculosis Programme (NTP) and WHO published *Operational Procedures for the DOTS-Plus Pilot Sites for Multidrug Resistant TB Management in Yangon and Mandalay Divisions*. In July 2009, the DOTS-Plus pilot project was launched in 10 townships in Yangon and Mandalay Regions, in close collaboration with WHO and Médecins Sans Frontières (MSF). The plan was to enroll 275 MDR-TB patients on a standardized second-line anti-TB drug regimen during a two-year period. Only Category II treatment failures with drug susceptibility testing (DST) results confirming MDR-TB were included in the pilot project. Two years later, 275 MDR-TB patients had been enrolled, and by December 2012 treatment outcomes were available for the first 184 MDR-TB patients enrolled between July 2009 and December 2010. The final outcomes of these 184 patients are considered good compared to other countries, despite protracted and severe diseases among all patients: 131 (71.2%) were cured, 31 (16.8%) died, 20 (10.9%) defaulted and 2 (1.1%) failed.

Following the encouraging initial results of the pilot project, the Ministry of Health is committed to increasing access to MDR-TB diagnosis, treatment and care. An expansion plan for the programmatic management of drug-resistant TB has been developed and forms part of the Five Year National Strategic Plan for TB Control, 2011-2015. The long-term goals of the MDR-TB expansion plan are threefold:

1. Diagnosis of MDR-TB in all groups of patients at risk for MDR-TB
2. Diagnosis of MDR-TB in all HIV-infected TB patients
3. MDR-TB treatment for all patients diagnosed with MDR-TB under WHO-endorsed treatment protocols

In 2011, MDR-TB management expanded from 10 to 22 townships in Yangon and Mandalay Regions. By the end of 2012, diagnosis, treatment and care for MDR-TB expanded to another 16 townships in Magway, Sagaing and Yangon Regions as well as in Mon, Shan North and Shan South States. The 2011-2015 MDR-TB expansion plan will enable treatment of nearly 10 000 MDR-TB patients in 100 townships of the country, should adequate human and financial resources be available.

These guidelines have been prepared principally for use by NTP managers and staff, as well as partner organizations and professionals involved in delivering TB and MDR-TB care and implementing MDR-TB control activities in Myanmar. They are an updated version

of the *Operational Procedures for the DOTS-Plus Pilot Sites for Multidrug Resistant TB Management in Yangon and Mandalay Divisions*. They incorporate the wealth of experience gained from the DOTS-Plus pilot project and from more than three and a half years of MDR-TB management according to Green Light Committee and WHO standards, including the treatment and care of close to 800 MDR-TB patients.

Furthermore, these updated guidelines take into account recent advances in laboratory diagnostics and MDR-TB management, including the WHO publications *Guidelines for the programmatic management of drug-resistant tuberculosis - 2011 update* (WHO/HTM/TB/2011.6), *Guidelines for the programmatic management of drug-resistant tuberculosis* (WHO/HTM/TB/2008.402) and *Policy statement: Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system* (WHO/HTM.2011.4).

The following major updates are incorporated into this version:

- MDR-TB testing has expanded from only chronic TB patients to include all previously treated cases, contacts of MDR-TB patients and TB patients living with HIV.
- The use of rapid molecular diagnostic techniques has been incorporated, including the use of Xpert MTB/RIF, with new diagnostic algorithms defined.
- The strict MDR-TB treatment inclusion criteria used during the pilot phase have been relaxed (such as exclusion of patients abusing drugs or alcohol or patients without family member support).
- The composition of the second-line anti-TB drug regimen has been revised taking into account the 2011 WHO policy recommendations.
- The model of care has changed from compulsory initial hospitalization of all MDR-TB patients to community-based care, with option for hospitalization only for severely ill patients and/or for patients with social problems.

The recommendations contained in these guidelines will ensure the wider use of rapid DST with molecular techniques to detect MDR-TB patients earlier and provide adequate patient-centered treatment and care. It is hoped that the occurrence of new MDR-TB cases will be prevented by sound TB control practices and early detection and treatment of MDR-TB cases. Moreover, it is expected that MDR-TB treatment outcomes will improve since MDR-TB patients will be detected and treated earlier, rather than only after failing two treatment courses. Finally, the availability of high-quality and free-of-charge MDR-TB diagnosis, treatment and care in the public sector will prevent irrational use of second-line anti-TB drugs in the private sector leading to additional suffering by patients, catastrophic health expenditures and further development of resistance to second-line anti-TB drugs.

ACKNOWLEDGEMENTS

These guidelines were developed by the National Expert MDR-TB Committee and are based on the 2009 *Operational Procedures for the DOTS-Plus Pilot Sites for Multidrug Resistant TB Management in Yangon and Mandalay Divisions*. The core team revising the technical contents of the guidelines includes, in alphabetical order: Dr Htin Aung Saw, Dr Khin Nyein Chan (MSF), Dr Khin Zaw Latt, Dr Moe Zaw, Dr Ne Win, Dr Phyu Noe, Dr Saw Thein, Dr Si Thu Aung, Dr Thandar Hmum, Dr Thandar Lwin, Dr Ti Ti, Professor Tin Maung Cho, Dr Tin Mi Mi Khaing, Dr Win Maung, Professor Win Naing, Dr Wint Wint Nyunt, Professor Yadanar Kyaw and Professor Ye Htun. The team was led by Professor Tin Maung Cho as chair of the National Expert MDR-TB Committee, while guidance on programmatic management were provided by Dr Win Maung, Dr Thandar Lwin and Dr Moe Zaw.

Invaluable support was given by Dr Michael L. Rich and Ms Minda Nicolas of Partners in Health, Boston, USA, as consultants to WHO. Technical guidance and coordination was also supported by WHO Myanmar colleagues Dr Erwin Cooreman, Ms Eva Nathanson and Dr Myo Zaw.

The principal source of financial support for the development and publication of these guidelines was the United States Agency for International Development.

We are grateful to the following technical and financial partners that support the fight against MDR-TB in Myanmar: FHI360, Foundation for Innovative New Diagnostics, Global Drug Facility, Global Fund to Fight AIDS, Tuberculosis and Malaria, Japan International Cooperation Agency, Médecins Sans Frontières, the Union, Three Diseases/Three Millennium Development Goals Fund, UNITAID and United States Agency for International Development.

CHAPTER 1

MDR-TB COMMITTEES

The National MDR-TB Programme has established a number of committees to plan, implement and monitor the MDR-TB Programme. The committees have other ministerial representatives (as needed) and exist on national, Regional/State and district/township levels. The Regional/State Committees for MDR-TB Management oversee direct enrolment and care of MDR-TB patients.

1.1 National Committee for MDR-TB Management

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

Terms of reference:

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

Frequency of meeting: biannual

Members:

1. Deputy Director General (Disease Control), DOH (Chairperson)
2. Professor/Head, Department of Medicine, University of Medicine (1), Yangon
3. Professor/Head, Department of Child Health, University of Medicine (1), Yangon
4. Professor Tin Maung Cho
5. Professor/Head, Department of Respiratory Medicine, Yangon General 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. Associate Professor, Special Infectious Disease Hospital, Mingalardon
9. Director (Disease Control), DOH
10. Director, National Health Laboratory, DOH
11. Director, Food & Drug Administration, DOH
12. Medical Superintendent (MS), Aung San TB Hospital
13. Medical Superintendent (MS), Patheingyi TB Hospital
14. Regional TB Officer, Yangon Region & Lower Myanmar TB Office
15. Regional TB Officer, Mandalay Region & Upper Myanmar TB Office
16. Senior Consultant Microbiologist, NTP
17. Assistant Director, NTP, DOH
18. Medical Officer – TB, WHO
19. Representative from MSF-Holland

20. Representative from Populations Services International
21. Representative from Japan International Cooperation Agency
22. Representative from Myanmar Medical Association
23. Programme Manager, NTP (Secretary)
24. Senior Consultant Physician, Aung San TB Hospital (1st Joint Secretary)
25. Technical Officer – TB, WHO (2nd Joint Secretary)

1.2 National Expert MDR-TB Committee

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

Terms of reference:

1. To advise the National Committee for MDR-TB Management on technical policies
2. To oversee Regional/State Committees for MDR-TB Management on all aspects of programmatic management of MDR-TB including clinical management
3. To advise the National Tuberculosis Programme on MDR-TB Management township expansion based on the MDR-TB waiting list
4. To advise the Regional/State Committees for MDR-TB Management on infection control

Frequency of meeting: biannual

Members:

1. Professor Tin Maung Cho (Chairperson)
2. Professor/Head, Department of Medicine, University of Medicine (1), Yangon
3. Professor/Head, Department of Child Health, University of Medicine (1), Yangon
4. Professor/Head, Department of Respiratory Medicine, Yangon General Hospital, University of Medicine (1)
5. Professor/Head, Department of Respiratory Medicine, Mandalay General Hospital, University of Medicine, Mandalay
6. Professor/Head, Department of Respiratory Medicine, Thingungyun San Pya General Hospital, University of Medicine (2)
7. Associate Professor, Special Infectious Disease Hospital, Mingalardon
8. Director (Disease Control), DOH
9. Director, National Health Laboratory, DOH
10. Medical Superintendent, Aung San TB Hospital
11. Medical Superintendent, Patheingyi TB Hospital
12. Regional TB Officer, Yangon Region & Lower Myanmar
13. Regional TB Officer, Mandalay Region & Upper Myanmar
14. Senior Consultant Microbiologist/Consultant Microbiologist, NTP
15. Assistant Director, NTP, DOH
16. Medical Officer – TB, WHO
17. Programme Manager, NTP (Secretary)
18. Senior Consultant Physician, Aung San TB Hospital (1st Joint Secretary)
19. Technical Officer – TB, WHO (2nd Joint Secretary)

1.3 Regional/State Committee for MDR-TB Management

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

Terms of Reference:

1. Plan and oversee operational steps in implementing, monitoring, and evaluating MDR-TB management at Regional/State level
2. Supervise all aspects of programmatic management of MDR-TB (including drug and supply management chain related to MDR-TB) at district/township levels
3. Oversee interministerial and interdepartmental coordination and collaboration on MDR-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
5. Compile and analyse quarterly reports on MDR-TB management including on laboratory quality control
6. Give feedback to the National Expert MDR-TB Committee on the progress of MDR-TB management
7. Oversee the enrolment of MDR-TB patients
8. Support medical management of complicated cases, including patients with concomitant diseases (e.g. HIV/AIDS, diabetes) and patients suffering from severe adverse events

Frequency of meeting: quarterly

Members:

1. Regional/State Health Director (Chairperson)
2. Medical Superintendent of hospitals
3. Senior Consultant Physician, Hospital
4. Physician
5. Paediatrician
6. Psychiatrist
7. Physician (HIV/AIDS)
8. Microbiologist/Pathologist
9. Medico-social workers
10. District Medical Officer
11. District TB Team Leader
12. Township Medical Officers (TMOs) (related MDR-TB townships)
13. Nongovernmental organizations (NGOs) involved in MDR-TB management at

- Regional/State level
14. Regional/State TB Officer (Secretary)

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

1.4 District/Township MDR-TB Committee

The District/Township MDR-TB Committee (formally known as the Hospital MDR-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 enrol MDR-TB patients
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 monitor data management, recording and reporting to R/S and central levels
7. To periodically supervise all aspects of programmatic management of MDR-TB at Township Health Centres

Frequency of committee meeting: monthly (at first)

Members:

1. District Medical Officer/Township Medical Officer (Chairperson)
2. Township Medical Officer (TMO)
3. NGOs involved in MDR-TB management at district/township level
4. Physician
5. Paediatrician
6. Counsellor
7. Laboratory Technician
8. Community DOT Provider
9. Pharmacist/Compounder
10. District/Township TB team leader (Secretary)
11. Township TB Coordinator (Joint Secretary)

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

1. Enrolment of MDR-TB patients to be presented by Regional/State TB Officer or Township TB Coordinator
2. Patient progress: Medical management, logistics/drugs to be presented by con-

- sultant physician, R/S TBO or TMO
3. Community programme progress to be presented by TMO
 4. Programme progress to be presented by R/S TBO or TMO
 5. Linkage between community DOT action plan to be presented by trained socio medical workers, TMOs and NGOs

Six main forms will be presented:

I. Forms for enrolment

- 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 MDR-TB treatment by the Team

- Agree to put up the treatment.
- Signed by at least three team members (Chair, Physician, District/Township TB Team Leader or relevant TMO).

III. Forms for patient's progress

- Present all patients on MDR-TB treatment, summarizing according to smear status, culture status, DST status, X-ray finding, weight and general condition.
- MDR-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 TBO or relevant TMO (current NTP report on logistic/drug stocks will be used).

IV. Community programme progress

- TMO and NGOs should present the number of patients on MDR-TB drugs, any side-effects, any missed doses, drug stocks, number of supervisory visits by DOT Supervisors and any problems.

V. Programme progress

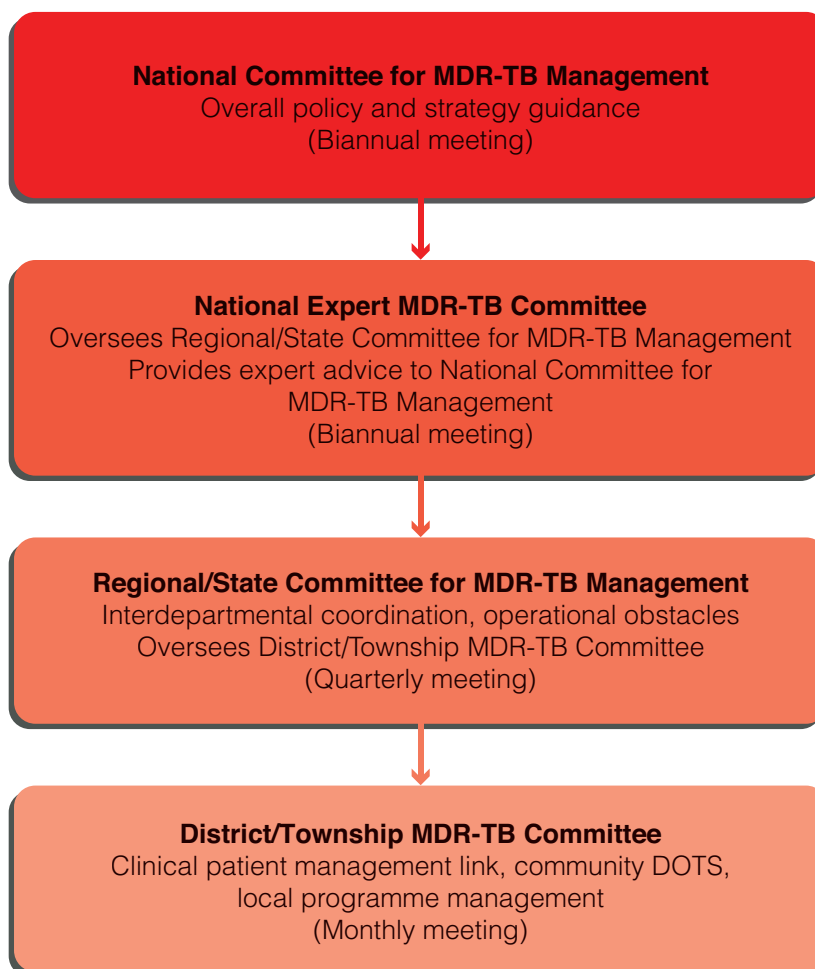
- Cohort analysis
- Programme performance details such as: DOT Provider training, number of supervisory visits, number of meetings conducted and waiting list, drug balance in stock, lab quality control (QC) internally and externally, turnaround time at laboratory to get

treatment, any problems; to be presented by R/S TBO.

VI. Linkage between community DOT

- To be presented by TMO, 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.

Figure 1.1 Hierarchy of MDR-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 a certain drug (or drugs) is no longer effective against the bacteria. DR-TB is confirmed through laboratory tests (see Chapter 3) that demonstrate growth in-vitro 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 and rifampicin.
- **Multidrug-resistant TB (MDR-TB):** Resistance to at least isoniazid and rifampicin, the two most potent anti-TB agents.
- **Rifampicin-resistant TB (RR-TB):** Resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, including mono-resistance, multi-drug resistance and poly-resistance.
- **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. WHO has stopped using the terms “DOTS-Plus” or “Category IV” to categorize these patients. These guidelines therefore no longer use these terms. Moreover, as these guidelines focus on the programmatic management of MDR-TB, the term MDR-TB is mainly used, rather than DR-TB.

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 isoniazid and rifampicin DST, or rifampicin alone, at the start of TB treatment:

1. Retreatment cases including Category II failure, Category I failure, relapse and return after default and other
2. Close contacts of MDR-TB patients who develop active TB
3. All TB patients living with HIV/AIDS
4. Other cases to be considered individually by MDR-TB committee

The R/S TBO is responsible for reporting to the Regional/State Committee for MDR-TB Management on all MDR-TB suspects who have undergone DST. Figure 2.1 illustrates the case-finding referral algorithm for MDR-TB management.

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 on an MDR-TB regimen (see Chapter 5 for the standardized MDR-TB regimens to be used). The enrollment of the patient based on Xpert MTB/RIF testing and confirmation DST is described in Table 2.1.

Table 2.1 Enrollment in MDR-TB treatment based on Xpert MTB/RIF testing and confirmation DST

Initial R-resistance Xpert MTB/RIF result	1 st confirmation test*	2 nd confirmation test**	Enrollment in MDR-TB Programme
	LPA (H and R DST)	Liquid culture	
Negative	Not indicated	Not indicated	Do not enroll. Consider repeat Xpert MTB/RIF or additional DST testing if MDR-TB is highly suspected.
Positive	Positive (H and R resistance, or R resistance only)	Not indicated	Enroll in MDR-TB Programme.
Positive	Negative (or H resistance only)	Positive (H and R resistance, or R resistance only)	Enroll in MDR-TB Programme.
Positive	Negative (or H resistance only)	Negative (or H resistance only)	Do not enroll. Consider repeat Xpert MTB/RIF or additional DST testing if MDR-TB is highly suspected.

* LPA is the confirmation test of choice because of its quick turn-around time. If LPA is not available use liquid or solid DST. Once greater than 95% concordance between the Xpert RIF/MTB and LPA tests is demonstrated for rifampicin resistance, routine confirmation testing is no longer required.

** Liquid culture is the preferred second confirmation DST when discordant results are seen between the Xpert MTB/RIF and the LPA.

Patients with an Xpert MTB/RIF test showing rifampicin resistance who are (1) failures of category II or (2) close contacts of MDR-TB patients should start on the standardized MDR-TB regimen while waiting for confirmation DST. If the first and second confirmation tests confirm no MDR-TB, the patient can be switched to a standard (first-line) TB regimen. Direct enrolment on second-line anti-TB drugs following a positive rifampicin resistance screening test (Xpert MTB/RIF) among high-risk patients is however only possible if there is no waiting list for second-line anti-TB drug treatment. Figures 2.2 – 2.4 illustrate the diagnostic algorithms when Xpert MTB/RIF is available to a facility.

There are 7 registration categories for MDR-TB:

1. New
2. Relapse
3. Treatment after default
4. Treatment after failure of Category I treatment
5. Treatment after failure of Category II treatment
6. Treatment after failure with the Standard MDR-TB regimen
7. Other (TB treatment with unknown regimen or unknown outcome, or treatment in the private sector with unconventional regimen).

Special considerations for MDR-TB programme enrolment. While not common, there are some exclusion criteria for MDR-TB regimens. The R/S TBO is responsible for identifying any treatment exclusion criteria of MDR-TB patients and reporting them to the R/S MDR-TB Committee. Any decision to exclude a patient from treatment should be done by the R/S MDR-TB Committee. The criteria are listed in Table 2.1 and should be decided on a case-by-case basis (exceptions can be made by the R/S Committee for MDR-TB Management).

Table 2.2 Special considerations for MDR-TB programme enrolment

Criteria	Reason for special consideration on MDR-TB enrolment
Willingness to consent to treatment	Any patient refusing treatment including the refusal of DOT will not be included in the programme.
Residency	Form 10 available or guest Form for greater than 1 month duration should be present. Exceptions are allowed for patients who come from districts where there is no MDR-TB treatment and who are willing to move to a township with treatment, and approval for residency is pending. Continuously migrant persons should be excluded.
Alcohol	When alcohol use is heavy or gets in the way of safe treatment the patient may be excluded from 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 is not tolerated and safe MDR-TB treatment cannot be given. Efforts to help the patient with their drug addiction should be made before exclusion. A history of illicit drug use 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, if the patient is not expected to survive due for example to liver or kidney disease, is considered criterion for exclusion.
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, exclusion can be considered.

2.4 Case-finding of MDR-TB in children

The indications for screening for MDR-TB are the same for children as adults (see Section 2.2). MDR-TB in children can be harder to diagnose because bacterial load is usually lower and getting a specimen for DST is difficult. Xpert MTB/RIF can be used in sputum specimens from children including induced sputum. Studies on sensitivity and specificity of using Xpert MTB/RIF on non-sputum specimens in children (as well as in adults) are ongoing. Children will be selected for enrolment for MDR-TB by paediatricians trained in 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 of the utmost importance to diagnose MDR-TB in HIV-positive patients, because untreated MDR-TB in an HIV-infected patient carries a high mortality. WHO recommends that all HIV-infected patients with active TB be tested for MDR-TB. Currently resources are not available to test all HIV-infected patients, but the MDR-TB programme will continue to seek resources so that all HIV-infected patients with TB will have a rapid DST (with Xpert MTB/RIF) at the start of TB treatment. Until then, any HIV-infected patient at risk for MDR-TB (contact with MDR-TB or even contact with a patient with possible MDR-TB, history of previous TB treatment or failure to convert by Month 2 of TB treatment) should have a rapid molecular DST. In short, Xpert MTB/RIF should be used in any HIV patient with a risk factor for resistance (Figure 2.4). When Xpert MTB/RIF is more readily available it should also be used in as illustrated in Figure 2.3, which will both diagnose more TB in HIV-infected individuals and screen for rifampicin resistance in all HIV-infected patients with TB.

2.6 Case-finding of XDR-TB

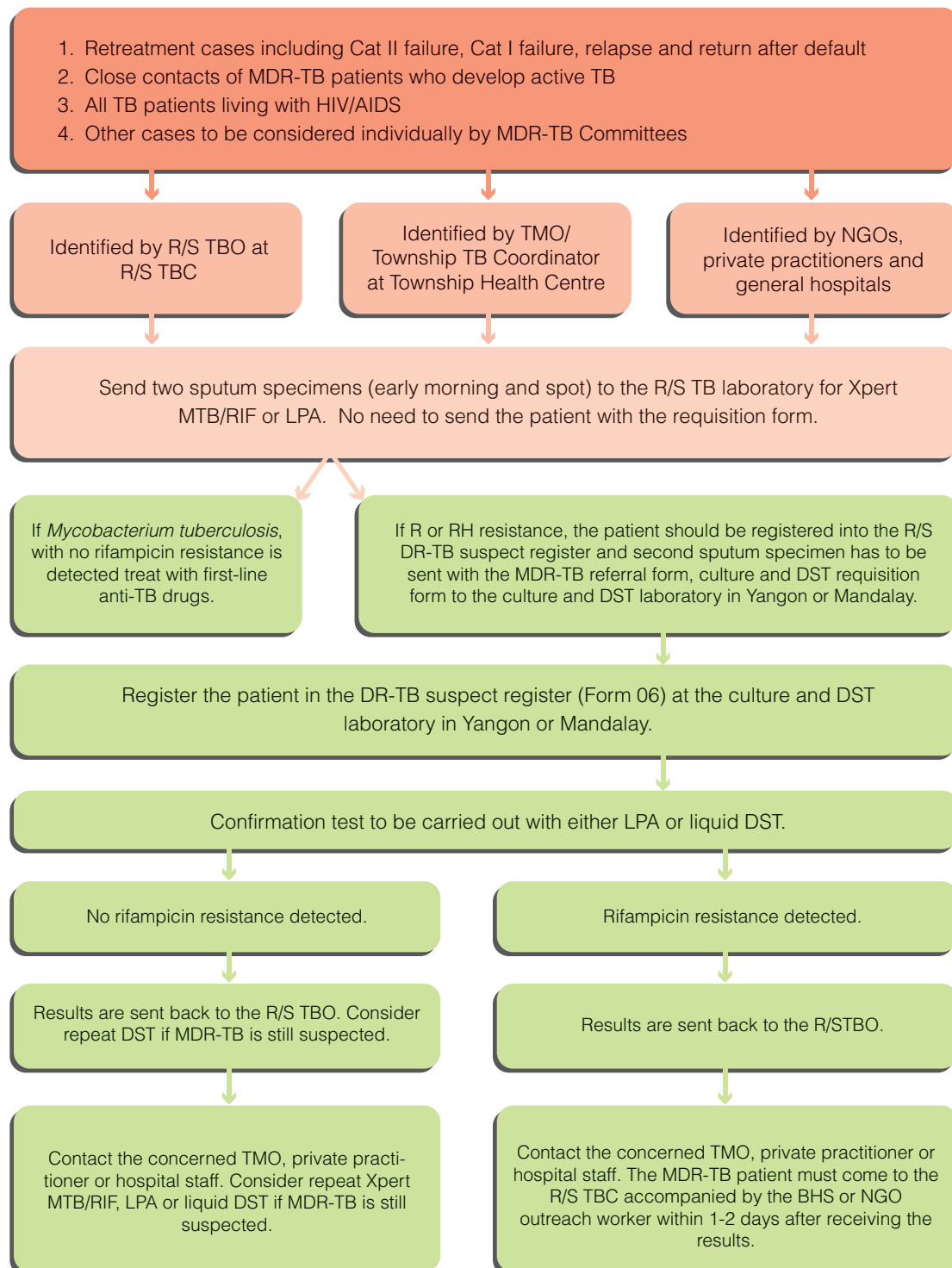
Any patient who falls into one of the following categories will be targeted for DST to second-line drugs to determine if the patient has XDR-TB:

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.

2.7 Summary of MDR-TB case-finding

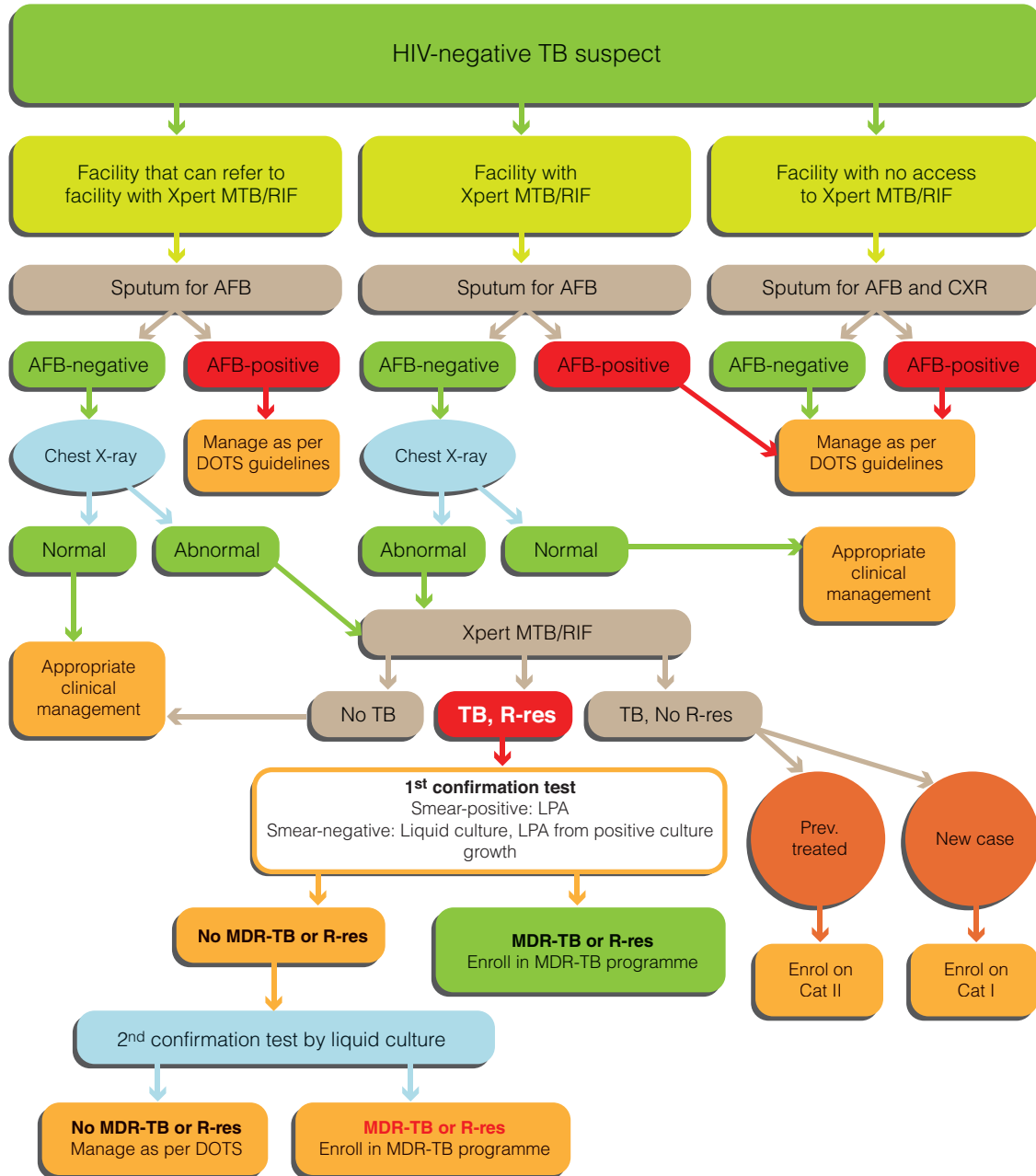
The introduction of Xpert MTB/RIF can improve both drug-sensitive and MDR-TB case detection. This section summarizes the case-finding strategies for both categories, when a facility has access to Xpert MTB/RIF. Diagnostic algorithms include:

- Figure 2.1 Case-finding and referral algorithm for MDR-TB management
- Figure 2.2 Diagnosis of TB in HIV-negative patients with no significant risk for MDR-TB
- Figure 2.3 Diagnosis of TB/MDR-TB in HIV-positive patients
- Figure 2.4 Diagnosis of MDR-TB in patients with risk factor for resistance

Figure 2.1 Case-finding and referral algorithm for MDR-TB management

Every MDR-TB suspect, regardless of the category, must be entered into the DR-TB Suspect Register kept by the R/S TBC. Only laboratory-confirmed MDR-TB patients will be routinely enrolled on second-line anti-TB drug treatment. (Section 2.3, Table 2.1 describes exceptions for some patient categories to be enrolled).

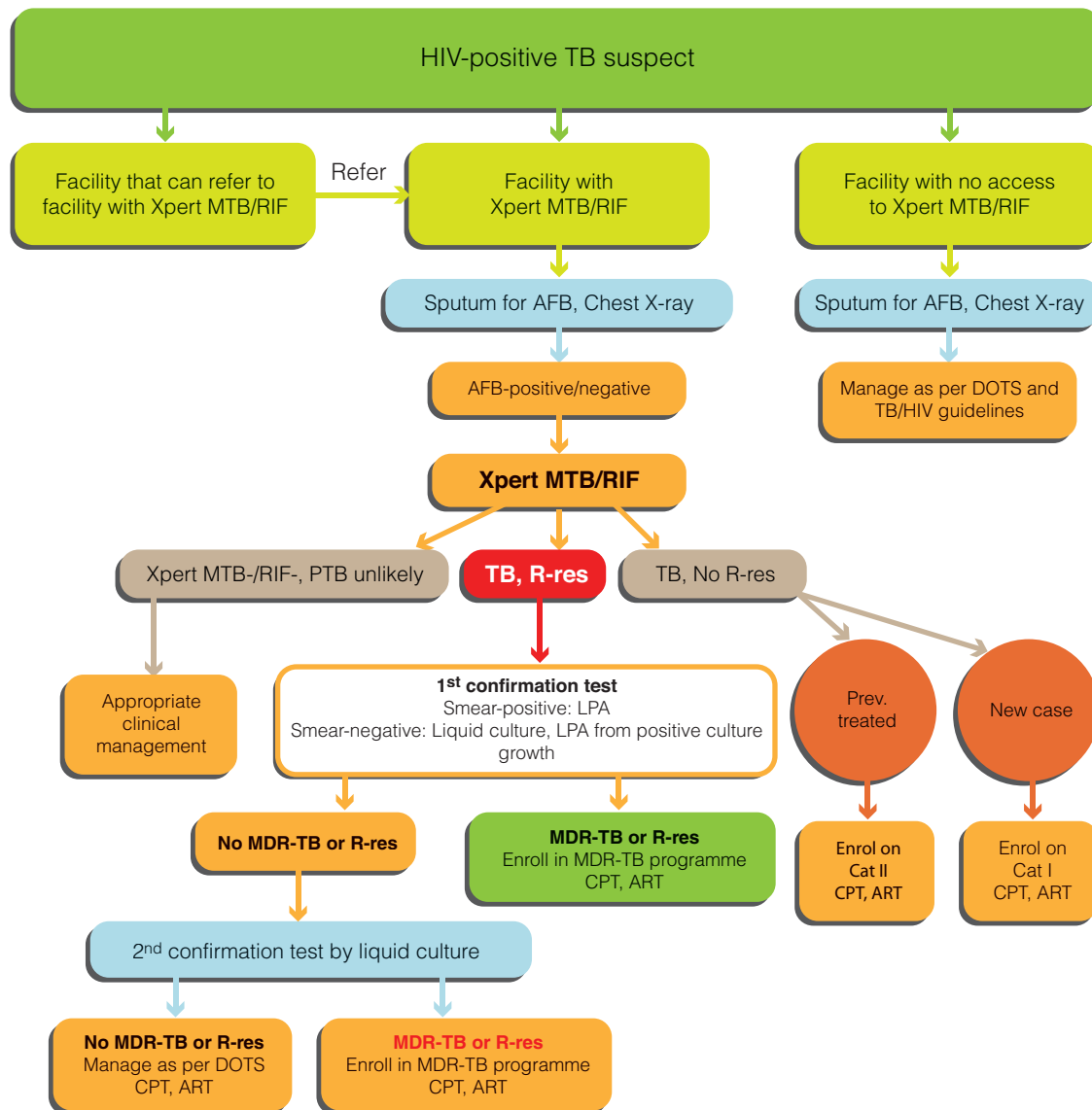
Figure 2.2 Diagnosis of TB in HIV-negative patients with no significant risk for MDR-TB



Abbreviations for Figure 2.2

AFB	Acid-fast bacilli
R-res	Rifampicin resistance
Cat II	Retreatment regimen with first-line drugs (2SHREZ/1HREZ/3HRE)
Cat I	Treatment for new patients with first-line anti-TB drugs (2HREZ/4HR)
LPA	Line probe assay

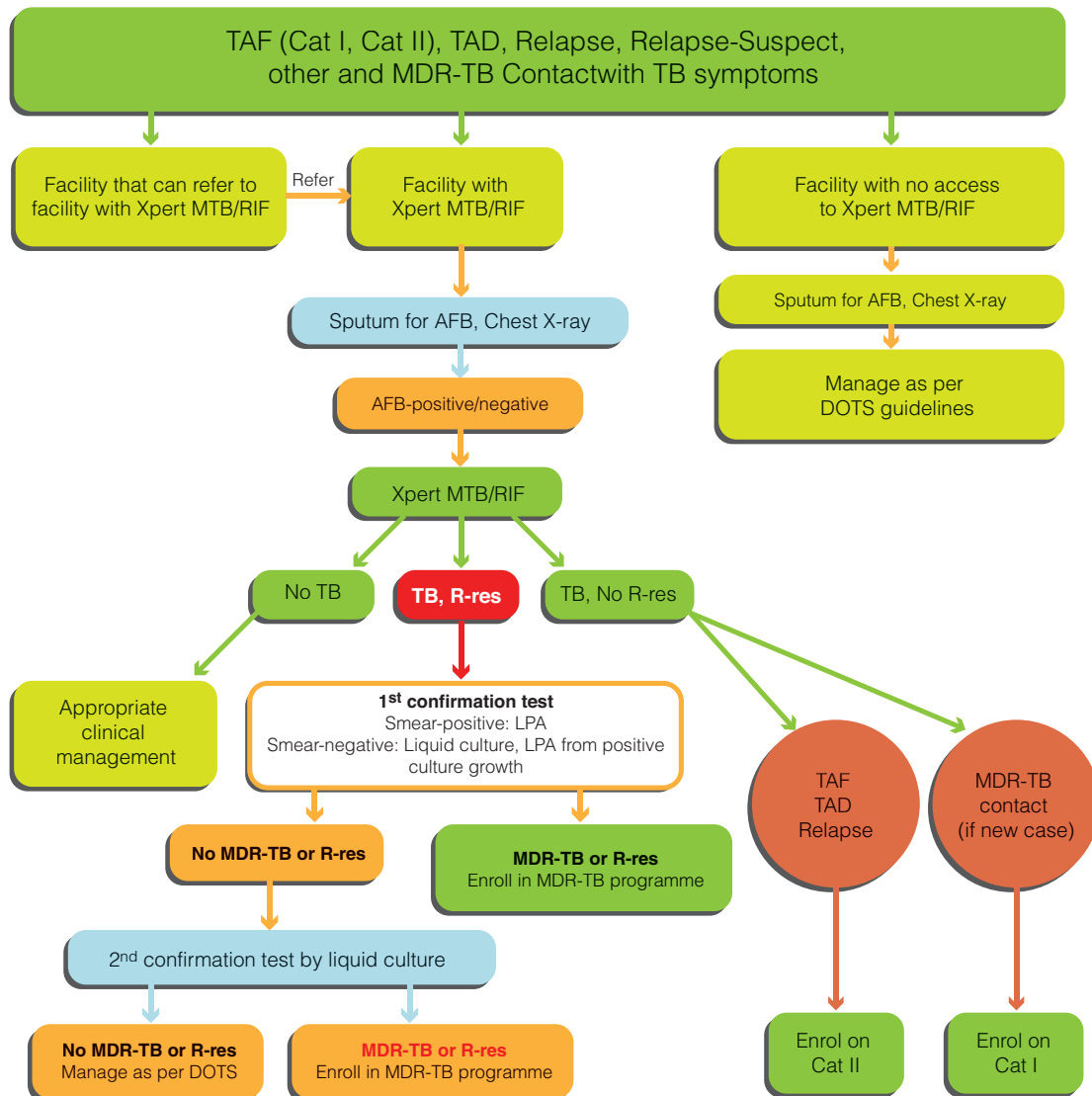
Figure 2.3 Diagnosis of TB/MDR-TB in HIV-positive patients



Abbreviations for Figure 2.3

AFB	Acid-fast bacillus
R-res	Rifampicin resistance
Cat II	Retreatment regimen with first-line drugs (2SHREZ/1HREZ/3HRE)
Cat I	Treatment for new patients with first-line anti-TB drugs (2HREZ/4HR)
PTB	Pulmonary tuberculosis
LPA	Line probe assay
CPT	Cotrimoxazole therapy
ART	Antiretroviral therapy

Figure 2.4 Diagnosis of MDR-TB in patients with risk factor for resistance



Abbreviations for Figure 2.4

R-res	Rifampicin Resistance
Cat II	Retreatment regimen with first-line drugs (2SHREZ/1HREZ/3HRE)
Cat I	Treatment for new patients with first-line anti-TB drugs (2HREZ/4HR)
TAF-I	Treatment after Failure Category I
TAF-II	Treatment after Failure Category II
TAD	Treatment after Default
LPA	Line probe assay

CHAPTER 3

LABORATORY ASPECTS OF MDR-TB

Since MDR-TB is based on microbiological and molecular diagnosis, the quality-assured laboratory results play an essential role in the management of MDR-TB patients. Much of the laboratory support has been an international initiative with Expand TB Project, a collaborative effort between UNITAID, Global Laboratory Initiative, Global Drug Facility (GDF) and Foundation for Innovative New Diagnostics. National TB Reference Laboratories (NTRLs) have been established at Yangon and Mandalay with Regional TB Reference Laboratories planned for the future.

The full monitoring requirements of patients clinically, bacteriologically, and for adverse effects are described in Chapter 10. This chapter addresses only laboratory aspects of diagnosis of MDR-TB, monitoring MDR-TB therapy, 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 the TB bacterium 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 specimen in a molecular test.
- **Indirect testing:** Indirect testing refers to testing performed on a culture of *M. tuberculosis* that has been grown from a clinical sample.

3.2 Sputum collection and transport system

Each MDR-TB suspect should have two specimens collected: one spot and one first 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 instrument** (this is the test of choice as it simple, inexpensive, 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

smear-negative and have the same appearance, use the first morning specimen. (Note: a RIF-positive specimen is usually a surrogate marker for MDR-TB; the patient can be started on an MDR-TB regimen and the specimen should be sent for confirmation 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.

Whenever possible, specimens should be collected outside, where air movement will rapidly dilute infectious droplets and ultraviolet (UV) rays from the sun will 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 sample requires that the patient be given clear instructions. Specimens should be collected in wide-mouthed containers that are sterile, 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 a refrigerator at a temperature of +4 °C. If travel 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%, or cetylpyridinium bromide (CPB) 1%, equal to the volume of the sputum, 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.

3.3 Procedures for smear, culture, and DST

All procedures for culture and DST of MDR-TB suspects must be handled in a Class II Biological Safety Cabinet. Xpert MTB/RIF does not require a Class II Biological Safety Cabinet and can be processed under the same infection control measures as smear microscopy.

Smear microscopy. The smear should be stained using the Ziehl-Neelsen method, examined with a good binocular microscope and graded according to the WHO grading chart for AFB microscopy. Fluorescence staining and microscopy can be used instead of

light microscopy, and can increase sensitivity by more than 10%.

Culture. For culture, pre-treatment procedures and inoculation to Lowenstein-Jensen (LJ) media bottles must be completed according to standard steps. 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”. Culture (and smear) is used to monitor the patient’s response to treatment.

Identification of *M. tuberculosis*. As antibiotic treatment varies according to the species of mycobacterium, the growth from any positive culture (including liquid culture) is tested for confirmation of *M. tuberculosis* with lateral flow assay test strips (these tests are not needed for LPA or Xpert MTB/RIF). The assay is based on the detection of the presence of the *M. tuberculosis* complex by detection of a specific protein, MPT64, in the culture isolates. The results are available within two hours. The products used are either of:

- Capilia TB rapid diagnostic test (Tauns Laboratories Inc., South Korea);
- TB Antigen MPT64 test (SD Bioline, South Korea).

Drug Susceptibility Testing (DST) on solid culture. DST on solid culture media is performed at baseline only for diagnosis of MDR-TB or for confirmation of an Xpert MTB/RIF rifampicin-positive test. DST on solid media can be performed at Yangon and Mandalay or in Regional/State TB laboratories using the proportion method. DST is done on a single sample. The solid drug media is the LJ media. DST result will be obtained in two and a half to three months after the original collection of the sputum as the culture is grown first and then DST is performed.

Resistance to isoniazid, rifampicin, amikacin, capreomycin and levofloxacin is tested. Resistance to streptomycin and ethambutol is only tested in special circumstances such as during drug resistance surveys. 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 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. Growth supplement and a combination of antimicrobial agents (PANTA) are added to suppress the growth of contaminants. The tubes of liquid are put in the machine and monitored. The machine can hold 960 tubes at one time. 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 discarded on the 42nd day. The DST is performed in the same MGIT machine, from an inoculum from liquid culture-positive tubes into the drug-containing tubes. The drugs tested for are isoniazid, rifampicin, amikacin,

capreomycin, and levofloxacin. Results are mostly available within 3 weeks from the inoculation. DST to the second-line anti-TB drugs amikacin, capreomycin and levofloxacin is under development at the NTRLs.

Genotypic testing (molecular tests). Nucleic acid amplification technologies, the most common genotypic DST, hold promise for significant gains in speed and performance for DST. The technologies can amplify either DNA or RNA; polymerase chain reaction (PCR) is the most common method of amplification. Two types of genotypic testing are used in the Myanmar MDR-TB Programme: the **Genotype MTBDR *plus* Test** and the **Cepheid Xpert® MTB/RIF assay**.

- In 2008, WHO endorsed the use of LPAs to detect both TB bacteria and mutations that indicate resistance. The Genotype MTBDR *plus* Test (Hain Life Sciences) is used at both NTRLs. One disadvantage of the test is that it must be performed with an AFB smear-positive sputum specimen having positive grading of 2+, 3+ or from isolates from solid or liquid culture growth. Results can be known in 3 days. Negative, scanty and 1+ specimens must first be grown in culture and then tested, but this adds a number of weeks to the turnaround time for results. One advantage of the Genotype MTBDR *plus* Test is that it tests for mutations that cause both rifampicin resistance (*rpoB* gene) and isoniazid resistance (*katG* and *inhA* genes). The detection of gene mutations to second-line anti-TB drugs is not yet validated.
- In 2010, WHO endorsed the Cepheid Xpert® MTB/RIF assay (Xpert MTB/RIF), an instrument that uses nested real-time PCR to identify TB bacteria and the common rifampicin resistance mutations. Xpert MTB/RIF is a fully automated molecular diagnostic test that can detect *M. tuberculosis* complex DNA and mutations associated with rifampicin resistance (*rpoB* gene mutation) directly from sputum specimens in less than two hours. The assay has similar sensitivity, specificity and accuracy as culture on solid media and can be used on smear-negative specimens. Only one specimen needs to be submitted. One disadvantage of the Xpert MTB/RIF is that it only tests for the presence of rifampicin resistance. 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. Another significant advantage of rapid rifampicin resistance testing with 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 confirmation culture and DST of choice for molecular testing is the MGIT liquid system, given that it is relatively quick and has high sensitivity and specificity. (Note: Genotype MTBDR *plus* Test can also be used for confirmation of rifampicin resistance with Xpert MTB/RIF but requires a positive smear, or the specimen to be taken from a culture.)

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 smear-positive 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	Gold standard for TB culture and test of choice for DST confirmation. Liquid culture systems. Fully automated systems exist with the MGIT 960. First- and second-line DST can be done.
Molecular Testing	Line Probe Assay (LPA)	1 day direct 21 days indirect	DNA targets are amplified by PCR and hybridized to immobilized oligonucleotide targets. Identifies <i>M. tuberculosis</i> , isoniazid resistance by detecting the <i>katG</i> and <i>inhA</i> gene mutations and rifampicin resistance by detecting the <i>rpoB</i> gene mutation. Can only be done directly on smear-positive 2+ or 3+ or a positive liquid or solid culture. Detection of gene mutations to second-line anti-TB drugs not yet validated.
	Xpert® MTB/RIF	2 hours	An instrument that uses nested real-time PCR to identify <i>M. tuberculosis</i> and rifampicin resistance by detecting the <i>rpoB</i> gene mutation. Can be done directly on 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. At baseline (or Month 0) the method of choice for culture and DST is the MGIT liquid. Smear is done monthly; 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. If smear and culture are still positive at Month 16, no laboratory monitoring will be continued. In most cases, it is highly likely that treatment failure has already been declared after 8 months of treatment if culture conversion has not been achieved by this time. In many cases, patients will have been switched to a

Table 3.2 Sputum and culture testing schedule for follow-up

Time of smear and culture conversion	Test	Timeframe (month)																																		
		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32		
Before Month 8	Smear	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Culture	✓		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓
Months 9-12	Smear							✓		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓
	Culture									✓		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓
Months 13-16	Smear										✓		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓	
	Culture											✓		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓
After Month 16	Smear															✓		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓
	Culture																✓		✓		✓		✓		✓		✓		✓		✓		✓		✓	
A new treatment regimen should be started in patients who fail to convert by the month of 16																																				

Red colored months require liquid culture and yellow colored months require solid culture. Follow-up smear examinations is done monthly throughout the course of treatment.

new treatment or an XDR-TB treatment before reaching Month 16. DST can be repeated if the patient remains positive after four months of treatment. The DST should repeat first-line DST and include DST to second-line drugs including Amk, Cm, and Lfx.

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 result 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 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 TBC or Hospital or at the NHL/MGH.

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

Sr. No.	Test	Reference range		Reference range (international units)	
1	Serum Creatinine	0.6–1.6	mg%	M 60–106	mmol/L
				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 Stimulating Hormone				
	T3			0.69–2.02	ng/ml
	T4			M–4.4–10.8	ug/dl
	T4			F–4.8–11–6	ug/dl
	TSH			0.3–6.2	ml u/l

3.6 Infection control and bio-safety in the laboratory

Transmission of MDR-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/TB specimens can be with the same conditions as smear microscopy 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, Class 3 Biological Safety 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.

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. The Supra-national Reference Laboratory (SNRL) in Bangkok, Thailand assesses proficiency of DST annually with specific QA protocols for MGIT. 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 the results. In addition, ongoing surveillance can be done for the different groups such as failures of Category II, failures of Category I, close contacts, relapse, return after default. The third DRS will be completed in 2013.

3.9 Organizational structure of laboratories in TB control

Figure 3.1 provides the organizational structure and the relationships between the National Health Laboratories, the NTRLs and all TB support laboratories down to the township level.

CHAPTER 4

MDR-TB PATIENT EDUCATION

All patients and their families should receive education and counselling about MDR-TB, its treatment, duration, adverse drug effects and the importance of adherence to therapy. Education and counselling should commence at the beginning of therapy and continue throughout the course of treatment.

Patient education is an essential component of any MDR-TB control programme and is possible when there is trusting interpersonal communication between patients and medical personnel. It influences treatment adherence and, as a result, successful treatment outcomes. Just as important, education 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. Moreover, well-informed and cured patients can 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), nurses, voluntary health workers, DOT providers and NGO members. Counselling must 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, 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 with economic challenges to receive monthly financial support. This support is subject to availability and because of financial restrictions can vary in amount.

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.

4.3 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 prevention
- What resistance is and how it develops
- The main symptoms of TB
- Reasons for performing a sputum examination
- What adequate TB and MDR-TB treatment is
- Why DOT is important
- Possible side-effects of treatment with second-line drugs and other drugs
- 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

In particular, at the initiation of the intensive phase of treatment, the following topics should be delivered:

- Rules of personal hygiene and prevention techniques for a patient with TB and MDR-TB to avoid transmitting TB to relatives
- How to protect oneself from re-infection within the TB hospital and in the community
- How to inform contacts and family members about the diagnosis
- How, and how often, sputum should be collected, and frequency of other diagnostic procedures
- The anti-TB drugs prescribed: the names of drugs, how to identify the drugs, the quantity and dosages of drugs, intake frequency
- Recognizing side-effects of treatment
- Principles of treatment and required rules for behaviour during continuation phase

4.4 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 and diagnostics, drug supply, etc.) 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 selection. Signing the Patient Informed Consent Form should not be considered simply a bureaucratic precondition 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, Form 14.

The patient education 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.

4.5 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 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 analysed:

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

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 4.1 Questionnaire on MDR-TB knowledge and attitudes

အဖြေမှန်များကို အနီရောင်ဖြင့်ဖော်ပြထားသည်။ မေးခွန်းတိုင်းအတွက် အဖြေမှန်သည် တစ်ခုမက ဖြစ်နိုင်သည်။

- (၁) တီဘီရောဂါနှင့်ပတ်သက်၍ မည်သည့်အကြောင်းအရာများသည် မှန်ကန်ပါသနည်း။
- တီဘီရောဂါသည် *Mycobacterium tuberculosis* ခေါ်သော တီဘီရောဂါပိုးကြောင့်ဖြစ်သည်။
 - လူတစ်ဦးမှတစ်ဦးသို့ကူးစက်တတ်သောရောဂါဖြစ်သည်။
 - အဆုတ်တွင်အများဆုံးဖြစ်ပွားသည်။
 - သေသေချာချာကုလျှင် ရောဂါပျောက်ကင်းနိုင်သည်။
 - လူတစ်ဦးမှ တစ်ဦးသို့ မကူးစက်နိုင်ပါ။

- (၂) တီဘီရောဂါ၏ အဓိကလက္ခဏာများမှာ
- ချောင်းဆိုးခြင်း။
 - ချောင်းဆိုး၍ သလိပ်၊ သလိပ်ခဲများထွက်ခြင်း။
 - ချောင်းဆိုးသွေးပါခြင်း။
 - ကိုယ်အလေးချိန်လျော့ကျခြင်း။
 - ဆီးအမည်းရောင်သွားခြင်း။

- (၃) တီဘီရောဂါမည်သို့ ကူးစက်နိုင်သနည်း။
- လေမှ တဆင့်(ချောင်ဆိုးခြင်း၊ နှာချေခြင်း၊ ရယ်မောခြင်းနှင့် စကားပြောခြင်း) ကူးစက်နိုင်သည်။
 - မသန့်ရှင်းသော အစားအစာကို စားသုံးမိသောကြောင့်ကူးစက်နိုင်သည်။
 - မသန့်ရှင်းသောရေကို သောက်သုံးမိသောကြောင့် ကူးစက်နိုင်သည်။
 - လူတို့၏အရေပြားအချင်းချင်း ထိမိခြင်းကြောင့် လည်းကူးစက်နိုင်သည်။
 - သိပ္ပံနည်းကျ မဖော်ထုတ်နိုင်သေးပါ။

- (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 တစ်မျိုး ဖြစ်သည်။

(၅) တီဘီရောဂါမကူးစက်အောင် မည်သို့ကာကွယ်နိုင်သနည်း။

- တီဘီလူနာများအားလုံးကို ဆေးကုသပေးခြင်း။ (အထူးသဖြင့် သလိပ်ပိုးတွေ့လူနာများ)
- ချောင်ဆိုးခြင်း၊ နှာချေခြင်း၊ ရယ်မောခြင်းနှင့် စကားပြောခြင်း တို့တွင် ပါးစပ်နှင့် နှာခေါင်းတို့ကို လုံအောင်ပိတ်ခြင်း။
- အိမ်ရှိတံခါးနှင့် ပြတင်းပေါက်များကို ပိတ်ထားခြင်း။
- သဘာဝအလင်းရောင် ကောင်းစွာရရှိခြင်း။
- အထူးဈေးကြီးသော 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။

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 availability of both first- and second-line anti-TB drugs, 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 default and other cases).

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. An alternative is to group the drugs in the following five groups based on potency, evidence of efficacy, experience of use and drug class (Table 5.1):

Table 5.1 Anti-TB drug groups

Group name	Anti-TB agent	Abbreviation
Group 1. First-line oral agents	Isoniazid Rifampicin Ethambutol Pyrazinamide Rifabutin ^a	H R E Z Rfb
Group 2. Injectable anti-TB drugs (injectable agents or parenteral agents)	Streptomycin Kanamycin Amikacin Capreomycin	S Km Am Cm
Group 3. Fluoroquinolones (FQs)	Levofloxacin Moxifloxacin Ofloxacin	Lfx Mfx Ofx
Group 4. Oral bacteriostatic second-line anti-TB drugs	Ethionamide Prothionamide Cycloserine <i>p</i> -aminosalicylic acid <i>p</i> -aminosalicylate sodium	Eto Pto Cs PAS PAS-Na
Group 5. Anti-TB drugs with unclear efficacy or unclear role in MDR-TB treatment	Clofazimine Amoxicillin/Clavulanate Linezolid Imipenem/Cilastatin High-dose isoniazid ^b Thioacetazone ^c Clarithromycin	Cfz Amx/Clv Lzd Ipm/Cln High-dose H T Clr

- a Rifabutin is not on the WHO List of Essential Medicines, but it is included here as it is used routinely in patients on protease inhibitors in many settings.
- b High-dose H is defined as 16-20 mg/kg/day.
- c Thioacetazone is a drug with known efficacy against TB; however, it is placed in Group 5 because the experience of its use in MDR-TB regimens has been limited, there is known cross-resistance to ethionamide, and toxicity is common (and can be fatal in HIV, so thioacetazone should not be used in HIV-infected patients).

- **Group 1 – First-line oral agents.** Group 1 anti-TB drugs, the most potent and best tolerated, should be used if there is good laboratory evidence and clinical history suggests that a drug from this group is effective. If a Group 1 drug was used in a previous regimen that failed, its efficacy should be questioned even if the DST result suggests susceptibility. For patients with strains resistant to low concentrations of isoniazid but susceptible to higher concentrations, the use of high-dose isoniazid may have some benefit (since the benefit is probably small, when isoniazid is used in this manner it is considered a Group 5 drug, see below). The newer rifamycins, such as rifabutin, have very high cross-resistance to rifampicin. **Pyrazinamide is added routinely to MDR regimens if the DST is documented to be susceptible or if DST is unknown.** Ethambutol should **not** be routinely added to MDR regimens; however it can be added if the criteria of it being a likely effective drug are met (see Section 5.4 for criteria of a “likely effective” drug).
- **Group 2 – Injectable anti-TB drugs.** A Group 2 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 resistance in patients with MDR-TB (greater than 50% in some countries) and extensive use of streptomycin, it is not recommended even if DST is susceptible. 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 two¹ (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 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, streptomycin 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 2 drugs can also be given intravenously (IV) but must be given slowly, over 60 minutes.
- **Group 3 – Fluoroquinolones.** FQs are often the **most effective anti-TB drugs in an MDR-TB regimen.** Currently, the most potent available FQs, in descending

1 Dooley KE, Mitnick CD, DeGroot 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.

order based on in vitro activity and animal studies, are: moxifloxacin = gatifloxacin > levofloxacin > ofloxacin.^{2,3} 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 has not been listed in the WHO classification of Group 2 drugs of FQs. In summary, moxifloxacin or levofloxacin are the FQs of choice.

- Group 4 - Oral bacteriostatic 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.⁴ 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 can be included in a MDR regimen but should 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 three Group 4 agents are needed. The drugs in Group 4 may be started at a low dose and escalated over 3 to 10 days to reduce side-effects (this is known as dose-ramping).⁵
- Group 5 - Anti-TB drugs with unclear efficacy or unclear role in MDR-TB treatment.** Group 5 drugs are not recommended by the WHO for routine use in MDR-TB treatment because their contribution to the efficacy of MDR-TB regimens is unclear. Although they have demonstrated some activity in vitro or in animal models there is little or no 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 1-4. They should be used in consultation with an expert in the treatment of MDR-TB. If a situation requires the use of Group 5 drugs, often experts will recommend using two to three drugs from the group, given the limited knowledge about their efficacy.

2 Alvarez-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.

3 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.

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

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

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 second-line drugs 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 2 and 3 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 2 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 5.2. 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 4 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(Amk Z Lfx Eto Cs)/18(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 will be added to the Standard MDR-TB Regimen for patients with the following conditions:

1. Failures of Category II;
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 with a known history of resistance to second-line drugs.

PAS can also be used in the following situations:

- If the patient cannot tolerate cycloserine in Standard MDR-TB Regimen, then PAS can be substituted for cycloserine;
- If the patient cannot tolerate ethionamide in Standard MDR-TB Regimen, then PAS 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.

Note: *The above Standard MDR-TB Regimen should not be used for XDR-TB or when XDR-TB is strongly suspected. Special XDR-TB regimens will be designed by the National Expert MDR-TB Committee. Likewise the management of mono- and poly-resistant strains is not covered in these guidelines. The likelihood of poor outcomes is relatively low with many types of mono- and poly-resistant strains as the majority of patients will be cured with basic DOTS. Exceptional cases will be managed individually following advice from the National Expert MDR-TB Committee.*

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. The injectable agent should be continued for at least six months and at least four months after the patient becomes culture-negative, whichever is longer.

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 a minimum of 24 months and at least 18 months after the patient becomes culture-negative. Extension of therapy to 32 months may be indicated in chronic cases with extensive pulmonary damage.

5.7 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, protionamide/ethionamide and cycloserine have good penetration; kanamycin, amikacin and capreomycin penetrate effectively only in the presence of meningeal inflammation; PAS and ethambutol have poor or no penetration.

5.8 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 to maximize the likelihood of cure. Surgery for TB requires highly experienced surgeons as well as 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 (removing part of the lung or one whole lung). It is considered to be an adjunct to chemotherapy. 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 lung lobe. Generally, at least two months of therapy should be given 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, an additional 12–24 months of chemotherapy should be given.

General indications for surgical resection include patients who remain sputum smear-positive, 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.

5.9 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.

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 5.2 Weight-based dosing of anti-TB drugs

MEDICATION (DRUG ABBREVIATION), (COMMON PRESENTATION)	WEIGHT CLASS			
	<33 kg	33–50 kg	51–70 kg	>70 kg (ALSO MAXI- MUM DOSE)
GROUP 1: FIRST-LINE ORAL ANTI-TB DRUGS				
Isoniazid (H) (100, 300 mg)	4–6 mg/kg daily	200–300 mg daily	300 mg daily	300 mg daily
Rifampicin (R) (150, 300 mg)	10–20 mg/kg daily	450–600 mg	600 mg	600 mg
Ethambutol (E) (100, 400 mg)	25 mg/kg daily	800–1200 mg	1200–1600 mg	1600–2000 mg
Pyrazinamide (Z) (500 mg)	30–40 mg/kg daily	1000–1750 mg	1750–2000 mg	2000–2500 mg
GROUP 2: INJECTABLE ANTI-TB DRUGS				
Streptomycin (S) (1 g vial)	15–20 mg/kg daily	500–750 mg	1000 mg	1000 mg
Kanamycin (Km) (1 g vial)	15–20 mg/kg daily	500–750 mg	1000 mg	1000 mg
Amikacin (Am) (1 g vial)	15–20 mg/kg daily	500–750 mg	1000 mg	1000 mg
Capreomycin (Cm) (1 g vial)	15–20 mg/kg daily	500–750 mg	1000 mg	1000 mg
GROUP 3: FLUOROQUINOLONES				
Ofloxacin (Ofx) (200, 300, 400 mg)	Usual adult dose for MDR-TB is 800 mg	800 mg	800 mg	800–1000 mg
Levofloxacin (Lfx) (250, 500 mg)	Usual adult dose for MDR-TB is 750–1000 mg	750 mg	750–1000 mg	1000 mg
Moxifloxacin (Mfx) (400 mg)	Usual adult dose for MDR-TB is 400 mg	400 mg	400 mg	400 mg
Gatifloxacin (Gfx) (400 mg)	Usual adult dose for MDR-TB is 400 mg	400 mg	400 mg	400 mg
GROUP 4: ORAL BACTERIOSTATIC SECOND-LINE ANTI-TB DRUGS				
Ethionamide (Eto) (250 mg)	15–20 mg/kg daily	500 mg	750 mg	750–1000 mg
Protonamide (Pto) (250 mg)	15–20 mg/kg daily	500 mg	750 mg	750–1000 mg
Cycloserine (Cs) (250 mg)	15–20 mg/kg daily	500 mg	750 mg	750–1000 mg
<i>p</i> -aminosalicylic acid (PAS) (4 g sachets)	150 mg/kg daily	8 g	8 g	12 g
Sodium PAS	Dosing can vary with manufacture and preparation: check dose recommended by the manufacturer.			

MEDICATION (DRUG ABBREVIATION), (COMMON PRESENTATION)	WEIGHT CLASS			
	<33 kg	33–50 kg	51–70 kg	>70 kg (ALSO MAXI- MUM DOSE)
GROUP 5: AGENTS WITH UNCLEAR EFFICACY (NOT RECOMMENDED FOR ROUTINE USE IN MDR-TB PATIENTS)				
Clofazimine (Cfz)	5 mg/kg or 200 mg daily for 2 months, then 100 mg daily (limited data).			
Linezolid (Lzd)	600 mg once a day for adults. May need to stop after a few months of therapy due to adverse effects.			
Amoxicillin/Clavulanate (Amx/Clv)	Dosages for MDR-TB not well defined. These guidelines suggest a dose of 500/125 mg tablets three times a day plus 500 mg of amoxicillin three times a day.			
Imipenem/cilastatin (Ipm/Cln)	Usual adult dose is 500–1000 mg IV every 6 hours.			
Clarithromycin (Clr)	Usual adult dose is 500 mg twice daily.			
High-dose isoniazid (High-dose H)	16-20 mg/kg daily.			

* See page 57 for paediatric dosing

Source: *Guidelines for the programmatic management of drug-resistant tuberculosis, WHO 2006*

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 counselling and education of the patient, treatment delivery settings, the provision of DOT and techniques to prevent default.

6.1 Counselling and health education

The patient must receive three adherence counselling sessions before treatment. A trained counsellor (any health staff – BHS, TB coordinator, Medical Officer or medical social worker from hospitals, NTP, townships or NGOs – who has received proper training on counselling will be considered as a counsellor) from the Regional/State/District/Township TB centre, hospital or INGOs conducts the sessions. Each counselling session is noted in the counselling register.

The adherence counselling sessions have three steps (also see Chapter 4 on MDR-TB patient education):

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

The counselling sessions must give the patient (and family) a full overview of what treatment consists of and also help ensure that the patient gets all the necessary evaluations during care. The counselling covers the following issues:

1. An explanation of the nature of the disease and infectiousness.
2. Baseline and monthly laboratory investigations are required.
3. The treatment requires full DOT and adherence (DOT Provider will observe all doses).
4. The patient may require hospital admission.
5. The treatment may result in side-effects and early and effective management will help minimize these.
6. There is a system for the DOT Provider to collect the drugs.
7. Follow-up examinations are required.

During counselling sessions, particular attention must be given to:

- Previously defaulted patients
- Military persons
- 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 from non MDR-TB project sites
- Patients with addictions to alcohol or other drugs

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

Health education must be provided by the MO, nurses, BHS and/or medical social worker. It can be provided to patients through a variety of media, including pamphlets, posters and videos, where available. Health education can be delivered individually or in a group at the patient's home with their family involved, or in a clinic room at the Township Health Department, Regional TB Centre or TB Hospital. In addition, health education is done by the DOT Provider on a daily basis and by the DOT Supervisor during any follow-up visits. NGOs supporting community MDR-TB care have a vital role in health education as well as in counselling.

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

6.2 Treatment delivery setting

The Myanmar MDR-TB Programme will principally utilize an ambulatory treatment delivery with home-based DOT (a DOT Provider going to the home each day).

Initial care and baseline investigations. After the decision is made by the Regional/State MDR-TB Committee, selected patients will be informed by BHS through the TMO and TB Coordinator. Those patients approved for either ambulatory or hospitalized treatment will be brought by their family member to the R/S TBC. Those requiring hospitalization will be registered at the R/S TBC and sent to the hospital with MDR-TB inpatient facilities. For ambulatory treatment, baseline investigations will be done at the R/S TBC. At any level, the **MDR-TB referral form** must be used (Annex 3, Form 15).

Ambulatory care. For a patient to receive ambulatory care from the start of treatment (or if being transferred from hospital care to ambulatory care) the following must be in place:

- Patient's household is ready to receive the patient and has been educated in how to reduce the risk of transmission.
- A DOT provider is identified and educated on MDR-TB care and follow-up (most often this is a BHS).
- The place of follow-up care (often the Township Health Centre trained in MDR-TB care) has been designated and is ready to receive the patient.
- Transportation for monthly follow-up care is in place.
- A link between the Township Health Centre and the R/S TBC is established.
- Any socioeconomic support that the patient qualifies for has been arranged.

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** regardless 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 supply of medicines will be ensured to all patients free of charge, to be taken with DOT support. Consistent monthly clinical and laboratory follow-up is also free of charge and is described in Chapter 10.

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. After discharge, or if starting treatment in the ambulatory setting, the team at township level is composed of the TMO, township TB Coordinator, BHS (or DOT provider) and possibly NGO staff. DOT must be daily over the course of treatment, regardless of the treatment delivery setting. There will be circumstances where an initial period of hospital-based care may be needed.

The criteria for admission to the hospital are as follows:

- Patient is very sick, 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 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 Mingalardon or Tharketa specialist hospitals should have an Xpert MTB/RIF test. If the test shows rifampicin resistance, the patient should be separated from other patients. All confirmed or suspected XDR-TB cases should be isolated or treated in single occupancy rooms. Hospitals should have good infection control and allow for family socialization 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).

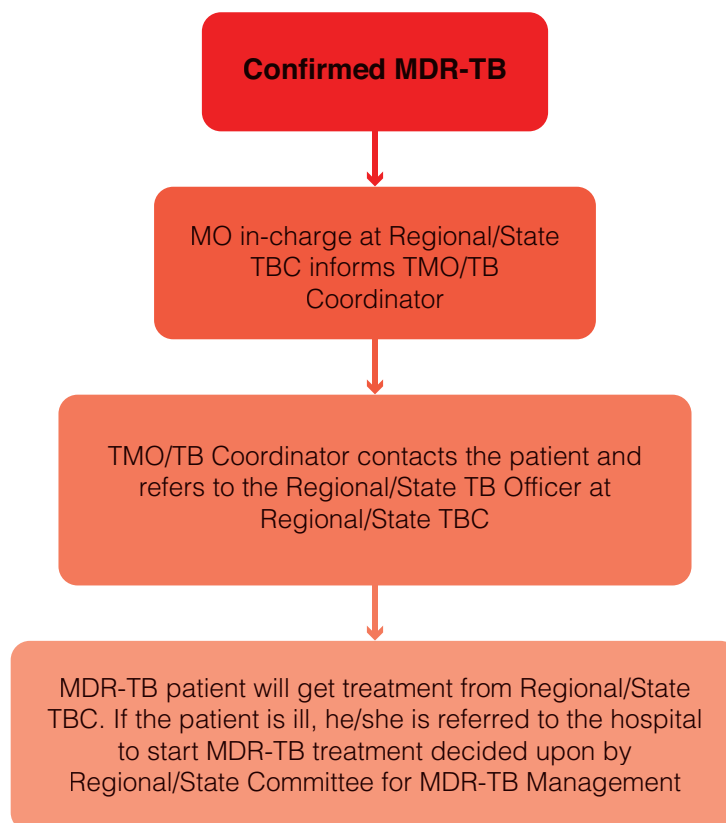
Arrangements for discharge from the hospital to ambulatory care setting should be made as soon as possible. Upon discharge, a transfer note should be written to the TMO and TB Coordinator.

6.3 Flow of MDR-TB patients into treatment

Once a patient is suspected of having MDR-TB, he or she is registered in the township DR-TB suspect register and referred to and registered in the R/S DR-TB suspect register. Sputum specimens of MDR-TB suspected patients are sent to a reference laboratory for culture and DST. When DST results are sent back to the R/S TBC, the Regional/State TB Officer must contact the TMO/TB coordinator. The TMO/TB coordinator contacts the MDR-TB patients through BHS. Initial home visits to MDR-TB patients and necessary counselling sessions will be provided by BHS and TMOs.

The MDR-TB patients will be assessed by the District/Township MDR-TB Committee and, when ready for treatment, referred to the R/S TBC. The Regional/State Committee for MDR-TB Management assesses and approves the selection of patients to initiate MDR-TB treatment. Follow-up will be continued at the R/S TBC. MDR-TB patients must also be included in the township MDR-TB register. If the patient is ill, he or she should be referred to the hospital to start MDR-TB treatment as decided upon by the Regional/State Committee for MDR-TB Management. At any level of referral, the MDR-TB referral forms will be used (Annex 3, Form 15). (In future, and when district/township level is ready to decentralize the enrollment of MDR-TB patients, the enrollment will take place following a decision of the District/Township MDR-TB Committee.)

Figure 6.1 Flow of MDR-TB patients into treatment process



6.4 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 TMO, the DOT Provider, and NGO staff if relevant. It is the responsibility of the clinical staff to supervise the fulfilment 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 counsellor 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 complicated for the MDR-TB patient; a family member could be subject to subtle manipulation by the patient, relatives, employer, etc (however, a family member may be a DOT provider if no other person can be identified as a last resort).

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 so that DOT can still be given on the primary DOT provider's day off. The secondary DOT Provider can also be used to observe an afternoon dose if the dosing is split up daily to lessen side-effects, allowing the primary DOT Provider to go to the patient's house only once per day.

At the clinic/health center, 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 FQs 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, and only after that give them to the patient. 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 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 a mark in the **MDR-TB Treatment Card** (Annex 3, Form 01) and mark the **List of Directly Observed Treatment** (Annex 3, 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.

6.5 Ambulatory treatment

When transitioning from the hospital to ambulatory care, at discharge the patient must be provided with a 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 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.

The R/S TBO assesses the patient's condition, reviews the MDR-TB Treatment Card and registers the patient in the R/S MDR-TB Register. Then the patient must be referred to the TMO or Township TB Coordinator at the Township Health Centre and be recorded into 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/counselling 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 investigation and assessment will be done at township level.

The TMO or Township TB Coordinator must refer the MDR-TB patient to the R/S 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 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 centre 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 emotional support to the patient, encouraging the patient to complete the full course of treatment and give additional health education/counselling 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.

6.6 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:

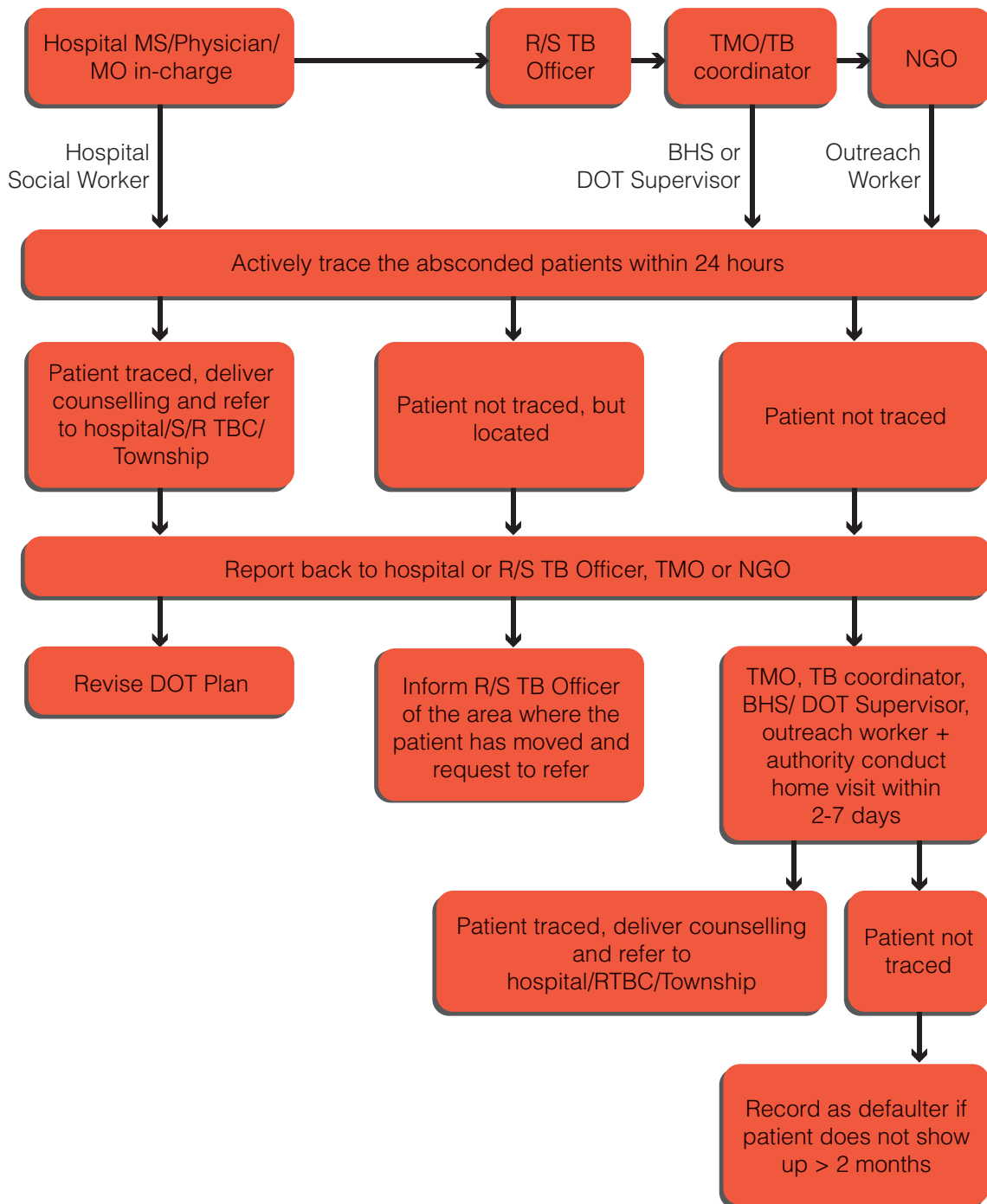
Table 6.1 Adherence approaches

Action	Responsible
Education, psychological preparation and regular support, counselling	MO/nurse/social worker/BHS/DOT Provider and Supervisor/TMO/INGO (ideally the educator/counsellor 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. If patient moves elsewhere, is considered a defaulter)
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.

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 reminding 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 personal role in treatment success (see Chapter 4).
- Training and psychological preparation of the patient for treatment and possible 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.

CHAPTER 7

ROLE OF OTHER PROVIDERS IN MDR-TB MANAGEMENT

Private providers are engaged in TB control on a nationwide scale through a successful partnership with the Myanmar Medical Association (MMA) and Population Services International (PSI). In 2011, more than 15% of TB case-finding was accounted for by MMA- and PSI-affiliated private practitioners. There are three schemes available for engagement of private providers in TB control: 1) referral of suspects and cases, 2) referral and treatment provision and 3) referral, diagnosis and treatment provision.

By November 2012, there were 15 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 NGOs support basic TB control in Myanmar, including referral, diagnosis, treatment and care. At present, only MSF is involved in MDR-TB control. MSF supports most clinical tasks of MDR-TB management except for MDR-TB diagnosis and laboratory monitoring of treatment progress, which are carried out at the NTRLs and in the future also at Regional/ State TB laboratories with liquid and 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.

Table 7.1 MDR-TB management task mix for different provider categories

(Shaded cells correspond to tasks that are carried out by respective provider type)

Providers	Tasks	Providers					
		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 MDR-TB suspects						
	Collect sputum samples						
	Refer MDR-TB suspects						
	Screen by Xpert MTB/RIF						
	Diagnose MDR-TB						
	Notify/record MDR-TB cases*						
	Initiate MDR-TB treatment						
	Provide DOT during initial phase (injectable second-line 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						

	Tasks	Providers					
		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
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						
	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.

CHAPTER 8

MDR-TB TREATMENT IN SPECIAL SITUATIONS

Some special situations can make the treatment of MDR-TB more complex, but it can nonetheless 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.

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 them 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.

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.

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 5.2) 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 2012*.

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 second-line anti-tuberculosis medications

Group	Drug	Daily dose	Maximum daily dose
1	isoniazid (H)	10-15 mg/kg once daily	300 mg
	rifampicin (R)	10-20 mg/kg once daily	600 mg
	ethambutol (E)	15-25 mg/kg once daily	2000 mg
	pyrazinamide (Z)	30-40 mg/kg once daily	2500 mg
2	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
3	ofloxacin (Ofx)	15-20 mg/kg in 2 divided doses	800 mg
	levofloxacin (Lfx)	< 5 years 5-10 mg/kg twice daily > 5 years 10 mg/kg twice daily	1000 mg
	moxifloxacin (Mfx)	7.5-10 mg/kg once daily	400 mg
4	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)	300 mg two or three times daily	12 g
5	clofazimine (Cfz)	1 mg/kg once daily	200 mg
	co-amoxiclav (Amx/Clv)	80 mg/kg in 2 divided doses	4000 mg of Amx and 500 mg Clv

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 previous use of aminoglycosides is not uncommon. Great care should be taken in the administration of second-line drugs in patients with renal insufficiency, and the dose and/or the interval between dosing should be adjusted according to Table 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
protionamide	No change	250–500 mg per dose daily
ethionamide	No change	250–500 mg per dose daily
<i>p</i> -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

- a Source: *Guidelines for the programmatic management of drug-resistant tuberculosis* (WHO 2008)
- 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

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

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 $\mu\text{mol/L}$ (about 0.5 to 1.0 mg/dl)

For men: 60-110 $\mu\text{mol/L}$ (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 ($\mu\text{mol/L}$) by multiplying by 88.4.

(For example a creatinine = 1.2 mg/dl is equivalent to $(88.4 \times 1.2) = 106.1 \mu\text{mol/L}$.)

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 $\mu\text{mol/L}$, age = 46, ideal body weight = 50 kg. What is the creatinine clearance?

Calculate the creatinine clearance:

$$\begin{aligned} & \text{Weight (kg)} \times (140 - \text{age}) \times (\text{constant}) / \text{Serum Creatinine} = \\ & 50 \times (140 - 46) \times (1.04 \text{ for women}) / 212 = \\ & 23.0 \text{ ml/min} \end{aligned}$$

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 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Peripheral neuropathy maybe 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.
Monitoring of drug-resistant TB and HIV in co-infected patients	<ul style="list-style-type: none"> • 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.

Issue	Comment
Implications of HIV for MDR-TB infection control	<ul style="list-style-type: none">• 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 Hospitals 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 PATIENTS

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 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	<ol style="list-style-type: none"> For serious allergic reactions, stop all therapy pending resolution of reaction. In the case of anaphylaxis manage with standard emergency protocols. Eliminate other potential causes of allergic skin reaction (like scabies or other environmental agents). For minor dermatologic reactions, various agents may be helpful and allow continuation of the medication. They include: <ul style="list-style-type: none"> 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. 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. Suspend permanently any drug identified to be the cause of a serious reaction. 	<ol style="list-style-type: none"> History of previous drug allergies should be carefully reviewed. Any known drug allergies should be noted on the treatment card. 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. 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. 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	<p>Eto, Pto, PAS, H, E, Z, Amx/ Clv, Cfz</p>	<p>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.</p> <p>2. Initiate stepwise approach to nausea and vomiting.</p> <ul style="list-style-type: none"> • Phase 1: Adjust medications and conditions without lowering overall dose: <ul style="list-style-type: none"> • 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): <ul style="list-style-type: none"> • 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. 	<p>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.</p> <p>2. Creatinine and electrolytes should be checked if vomiting is severe. Give IV fluids and replace electrolytes as needed.</p> <p>3. Another strategy is to stop a responsible medicine for two or three days and then add it back, gradually increasing the dose (advise the patient the medicine will be increased back to a therapeutic dose in a manner that will be better tolerated).</p> <p>4. Ondansetron 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.</p> <p>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.</p>

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

Adverse effect	Suspected agent(s)**	Suggested management strategies	Comments
Gastritis and abdominal pain	PAS, Eto, Pto, Cfz, FQs, H, E, and Z	<ol style="list-style-type: none"> 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. 	<ol style="list-style-type: none"> 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 nonsteroidal anti-inflammatory drugs (NSAIDs) the patient may be taking. 4. Diagnose and treat <i>Helicobacter pylori</i> 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 flatulence	PAS, Eto/Pto	<ol style="list-style-type: none"> 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. 	<ol style="list-style-type: none"> 1. Consider other causes of diarrhoea: <ul style="list-style-type: none"> • 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 pseudo-membranous colitis. • Parasites and common water-borne pathogens in the area should be looked for in the patient and treated if present. • Lactose intolerance, especially 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	<p>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.</p> <p>2. Eliminate other potential causes of hepatitis (viral hepatitis and alcohol-induced hepatitis being the two most common causes) and treat any identified.</p> <p>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.</p>	<p>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.</p> <p>2. Viral serology should be done to rule out other etiologies of the hepatitis if available, especially to A, B, and C.</p> <p>3. Alcohol use should be investigated and alcoholism addressed if found.</p> <p>4. Generally, hepatitis due to medications resolves upon discontinuation of suspected drug.</p>
Hypothyroidism	Eto/Pto, PAS	<p>1. Most adults will require 100 to 150 mcg of levothyroxine daily. Start levothyroxine in the following manner:</p> <ul style="list-style-type: none"> • 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. <p>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.</p>	<p>1. Symptoms of hypothyroidism include fatigue, somnolence, cold intolerance, dry skin, coarse hair, and constipation, as well as occasional depression and inability to concentrate.</p> <p>2. Do not start treatment unless TSH is above 1.5 to 2.0 times upper normal limit.</p> <p>3. Completely reversible upon discontinuation of PAS and/or ethionamide/protonamide.</p> <p>3. The combination of ethionamide/protonamide with PAS is more frequently associated with hypothyroidism than is the individual use of each drug.</p>

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

Adverse effect	Suspected agent(s)**	Suggested management strategies	Comments
Arthralgias	Z , Fluoroquinolones	<ol style="list-style-type: none"> 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. 	<ol style="list-style-type: none"> 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		<ol style="list-style-type: none"> 1. If significant inflammation of tendons or tendon sheaths occurs: <ul style="list-style-type: none"> • Consider stopping FQs • Give an NSAID (ibuprofen 400 mg four times daily) • Rest the joint 2. If treatment failure is likely without the fluoroquinolone <ul style="list-style-type: none"> • 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. 	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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. <p>ALSO SEE ANNEX 4 - MANAGEMENT OF ELECTROLYTE DISTURBANCES</p>	<ol style="list-style-type: none"> 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.

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

Adverse effect	Suspected agent(s)**	Suggested management strategies	Comments
Nephrotoxicity (Renal toxicity)	S, Km, Am, Cm	<ol style="list-style-type: none"> 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. 5. Adjust all TB medications according to the creatinine clearance (Table 8.2). 	<ol style="list-style-type: none"> 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 7.2. 3. Renal impairment may be permanent.
Vestibular Toxicity (tinnitus and dizziness)	S, Km, Am, Cm, Cs, FQs, H Eto, Lzd	<ol style="list-style-type: none"> 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. 3. 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. 	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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. 	<ol style="list-style-type: none"> 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.

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

Adverse effect	Suspected agent(s)**	Suggested management strategies	Comments
Peripheral neuropathy	Cs, Lzd, H, S, Km, Cm, H , Fluoroquinolones, rarely Pto/Eto, E	<ol style="list-style-type: none"> 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: <ul style="list-style-type: none"> • 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) antidepressant 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. 	<ol style="list-style-type: none"> 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 , fluoroquinolones, H, Eto/Pto	<ol style="list-style-type: none"> 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 (amitriptyline, 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. 	<ol style="list-style-type: none"> 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.

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

Adverse effect	Suspected agent(s)**	Suggested management strategies	Comments
Suicidal ideation	CS , H, Eto/Pto	<ol style="list-style-type: none"> 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. 	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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. 	<ol style="list-style-type: none"> 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.

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

Adverse effect	Suspected agent(s)**	Suggested management strategies	Comments
Seizures	Cs, H, fluoroquinolones	<ol style="list-style-type: none"> 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. 	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 1. Stop ethambutol. Do not restart. 2. Refer patient to an ophthalmologist. 	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 1. Encourage the patient to tolerate this side-effect. 2. Sucking hard candy or chewing gum can be helpful. 	<ol style="list-style-type: none"> 1. Normal taste returns when treatment is stopped.
Gynecomastia	Eto/Pto	<ol style="list-style-type: none"> 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. 	<ol style="list-style-type: none"> 1. Resolution occurs after treatment is stopped.

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

Adverse effect	Suspected agent(s)**	Suggested management strategies	Comments
Alopecia	H, Eto/Pto	<ol style="list-style-type: none"> 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. 	<ol style="list-style-type: none"> 1. Significant cosmetic change has not been reported.
Superficial fungal infection and thrush	FQs and other antibiotics	<ol style="list-style-type: none"> 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). 	<ol style="list-style-type: none"> 1. Vaginal or penile candidiasis, oral thrush or cutaneous candidiasis in skin folds may occur with antibiotic treatment.
Lactic Acidosis		<ol style="list-style-type: none"> 1. Stop linezolid if lactic acidosis occurs. 	<ol style="list-style-type: none"> 1. Lactic acidosis can be monitored with a blood test to measure lactic acid.
Dysglycaemia and Hyperglycaemia	Gfx, Eto/Pto	<ol style="list-style-type: none"> 1. Stop gatifloxacin and replace with different later-generation FQ like moxifloxacin. 2. Treat diabetes as needed. Good glucose control is important during treatment. 	<ol style="list-style-type: none"> 1. These guidelines do not recommend the routine use of gatifloxacin in MDR-TB treatment.
QT prolongation	FQs	<ol style="list-style-type: none"> 1. Values of QT greater than 500 ms should cause concern. For any patient found to have a value greater than 500 ms: <ul style="list-style-type: none"> • 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. 	<ol style="list-style-type: none"> 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 torsades 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.

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

Adverse effect	Suspected agent(s)**	Suggested management strategies	Comments
Haematological abnormalities	linezolid	<ol style="list-style-type: none"> 1. Stop linezolid if myelosuppression (suppression of white blood cells, red blood cells or platelets) occurs. 2. Consider blood transfusion for severe anaemia. 	<ol style="list-style-type: none"> 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 linezolid.

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

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 9.3 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 complication

Side-effect	Referral to specialist
<ul style="list-style-type: none"> • Difficult to control with Oral Hypoglycaemic Agent • Brittle diabetes • Problems of hypo-/hyperglycaemia • Thyroid problems 	Endocrinologist
<ul style="list-style-type: none"> • Treatment complications with underlying liver disease like Hepatitis B/C infection • Cirrhosis of liver 	Hepatologist
<ul style="list-style-type: none"> • Complication of haematemesis and melaena 	Gastroenterologist
<ul style="list-style-type: none"> • Severe psychiatric problems, e.g. severe depression, anxiety or neurosis • Major psychiatric disorders, e.g. schizophrenia or new-onset psychosis 	Psychiatrist
<ul style="list-style-type: none"> • Progressive renal impairment • Severe enough for renal replacement therapy 	Nephrologist
<ul style="list-style-type: none"> • 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 programme treatment depends on the intensity and quality of monitoring and supervision activities. 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	<ul style="list-style-type: none">• At baseline• On monthly basis until conversion• Then every 2–3 months <i>In particular, clinical monitoring for hypothyroidism if receiving ethionamide/prothionamide and/or PAS; monitor for hepatitis if receiving pyrazinamide.</i>
Visual assessment by physician	<ul style="list-style-type: none">• On monthly basis <i>if receiving ethambutol</i>
Psychological assessment by psychiatrist	<ul style="list-style-type: none">• At baseline• Repeat if indicated
Weight assessment by physician or nurse	<ul style="list-style-type: none">• At baseline• Then monthly until conversion• Then every 2–3 months
Monitoring of side-effects by DOT Provider	<ul style="list-style-type: none">• Daily, at every DOT encounter
Sputum smear and cultures	<ul style="list-style-type: none">• Monthly until conversion• Then smears on monthly basis and cultures at two-month intervals
Drug susceptibility testing (DST)	<ul style="list-style-type: none">• At baseline for diagnosis of MDR-TB• DST can be repeated if the patient remains positive after 4 months of treatment (DST to first- and second-line anti-TB drugs)
Chest radiograph	<ul style="list-style-type: none">• At baseline• Then every 6 months
Serum creatinine	<ul style="list-style-type: none">• At baseline (patients with baseline renal insufficiency, diabetes or HIV should be monitored frequently)• Then monthly (while receiving an injectable drug)
Serum potassium	<ul style="list-style-type: none">• 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	<ul style="list-style-type: none">• At baseline• Repeat if indicated

Monitoring	Recommended frequency
Thyroid stimulating hormone (TSH)	<ul style="list-style-type: none"> At 3rd month, 6th month and repeat if indicated. TSH is sufficient for screening for hypothyroidism. It is not necessary to measure hormone thyroid level.
Liver serum enzymes	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> At baseline Repeat if clinically indicated
Pregnancy tests	<ul style="list-style-type: none"> At baseline for women of childbearing age (all women of child-bearing age should be provided with family planning counselling.) Repeat if indicated
Assessment by physician with expertise in HIV/AIDS for MDR-TB HIV co-infected patient	<ul style="list-style-type: none"> At baseline Repeated if indicated
Audiometry	<ul style="list-style-type: none"> At baseline and monthly while on the injectable agent.

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

11.2 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
2. Body weight
3. Chest X-ray
4. DST (if culture result is positive)

If the patient has stopped treatment before completing the recommended full treatment, the patient should still be assessed every 6 months for at least 2 years. The assessment should include the following examination:

1. Body weight and clinical examination
2. Sputum smear and culture examination
3. DST (if culture result is positive)

If during any post-treatment examination the patient shows evidence of active TB, a full course of treatment must be restarted.

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 six 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	A patient who has completed MDR-TB treatment, is culture-negative in the last month of treatment, and has been culture-negative during the preceding 11 months of treatment. A minimum of five cultures must be performed within the last 12 months of treatment. To allow for the possibility of contamination, a patient may still be considered cured if one positive culture is reported during that time. However in order to meet the criteria for cure, a positive culture must be followed by a minimum of three consecutive negative cultures.
Treatment completed	A patient who has completed MDR-TB treatment but does not meet the definition for cure or failure due to lack of bacteriologic results.
Treatment failed	Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of: <ul style="list-style-type: none">• lack of conversion by the end of the intensive phase, or• bacteriological reversion in the continuation phase after conversion to negative, or• evidence of additional 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 2 consecutive months or more. (This category was previously known as defaulted.)
Not evaluated	A patient for whom no treatment outcome is assigned. (This includes cases “transferred out” to another treatment unit and whose treatment outcome is unknown).
Treatment success	The sum of cured and treatment completed.

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 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 phase, a cut-off 8 months after the start of treatment is suggested to determine when the criteria for *Cured*, *Treatment completed* and *Treatment failed* start to apply.

Patients who have **transferred in** should have their outcome reported back to the treatment centre at which they were originally registered. The responsibility for reporting their final outcomes rests with the original treatment centre. Note that the category “Transferred out” (referring to a patient who moved to another treatment centre but whose definitive outcome at the end of treatment was not established) may inform the programme 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, three 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 quarter of July 1, 2008–Sept 31, 2008 will have cohort analyses on:

- Oct 1, 2010 for the 24th month analysis (preliminary analysis)
- Oct 1, 2011 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 Category I/II” or “regimen modified for mono- or poly-drug resistance” should be incorporated into the comment section of the register.

Patients will not be analysed in the cohort of MDR-TB patients if they are proven by DST not to have MDR-TB.

The analysis is conducted at 24 months 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 desig-

nated 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 kanamycin or capreomycin and an FQ. The XDR-TB cases will be analyzed as part of the cohort of MDR-TB patients and 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 past 8 months;
 - After culture conversion, two consecutive positive cultures at least 1 month apart (reversion);
 - 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, vertigo and deafness);
- No signs of improvement after 8 months of treatment;
- 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 defaulters:

- 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.

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 used. 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 present treatment should be declared a failure for the patient 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 counselling 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

LOGISTICS MANAGEMENT OF SECOND-LINE ANTI-TB DRUGS

Proper management of second-line anti-TB drugs is critical to the success of the MDR-TB programme. This includes placing the drug order, arranging for its arrival, timely distribution to the appropriate drug stores, and monitoring the drug stock to avoid stock-outs and ensure the use of the drugs well before their expiration date. The management is overseen by the NTP, but health-care staff and non-health-care staff at all levels must participate in the management of these drugs.

14.1 Ordering and arrival of second-line drugs

Second-line anti-TB drugs not registered in the country will be exempted from registration by the Ministry of Health and all customs duties for importation will be waived by relevant authorities. A joint annual order is made to GDF for shipment and import of second-line TB drugs for NTP and NGOs. NTP will receive all drugs in the Central TB Store, after which the drug stock for NGO patients will be dispatched to the NGO drug store.

Drugs arriving at the airport will be cleared with a Special Order as fast as possible and delivered directly to the Central TB Store.

14.2 Storage and distribution

At the central level

Drugs delivered to the Central TB Store will be checked. If any carton is damaged, it will be unpacked and checked promptly in the presence of the MO in-charge of the Central TB Store, one staff member who is involved in the drug management and the person who delivered the drugs. If there is any discrepancy or damage, the MO in-charge of the Central TB Store must report to National TB Programme (NTP Headquarters), Central Medical Stores Depot, GDF, WHO and other relevant partners/funding agencies.

If the packing is intact, the drug cartons are placed in the store securely for unpacking and checking to be done within a week in the presence of the above persons plus one person from Myanmar Inspection and Testing Service. The findings are recorded on an **Unpacking and Checking form** (Annex 2, Form 01). If everything is correct and complete, drugs are recorded in the stock book and on the **Drug Inventory cards** (Annex 2, Form 02). Findings must be reported with the signed unpacking and checking form to the same departments mentioned above.

The responsible person from Central TB Store will distribute SLD to Lower and Upper Myanmar TB Stores based on the number of MDR-TB cases to be enrolled. In the expansion phase, Lower and Upper Myanmar TB Stores are responsible for distributing SLD to R/S TB

stores. The R/S TB stores will distribute SLD to District and Township Health Centres based on the number of MDR-TB cases to be enrolled.

TB Hospital (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 TB 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.

Outpatient level

When the patient is discharged from the hospital, the MO of the TB or general hospital MDR-TB ward, countersigned by the Physician, must refer to the R/S TBC. For those referred cases and fully ambulatory patients, a TB specialist from the R/S TB outpatient departments (OPDs) must request drugs from the R/S TB Drug Store monthly for the patients, using the **Second-Line Drug Requisition Form** (Annex 2, Form 05). After receiving authorization for release of second-line drugs for the listed patients from the R/S Committee for MDR-TB Management, R/S TB Drug Store can issue the drugs to TB OPDs by using the **Second-Line Drug Issue Voucher** (Annex 2, Form 06).

Second-line drugs must be recorded in a separate Sub-stock book. The MO of the TB OPD with the approval of the TB specialist will issue the drugs to the TMO monthly, and the TMO will issue the drugs to the DOT Provider and NGO 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.

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.

14.3 Monitoring

Monitoring of the drug management must be done throughout the project by 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 TBO in the Region/State of the implementing Hospitals, TB OPDs and Townships.

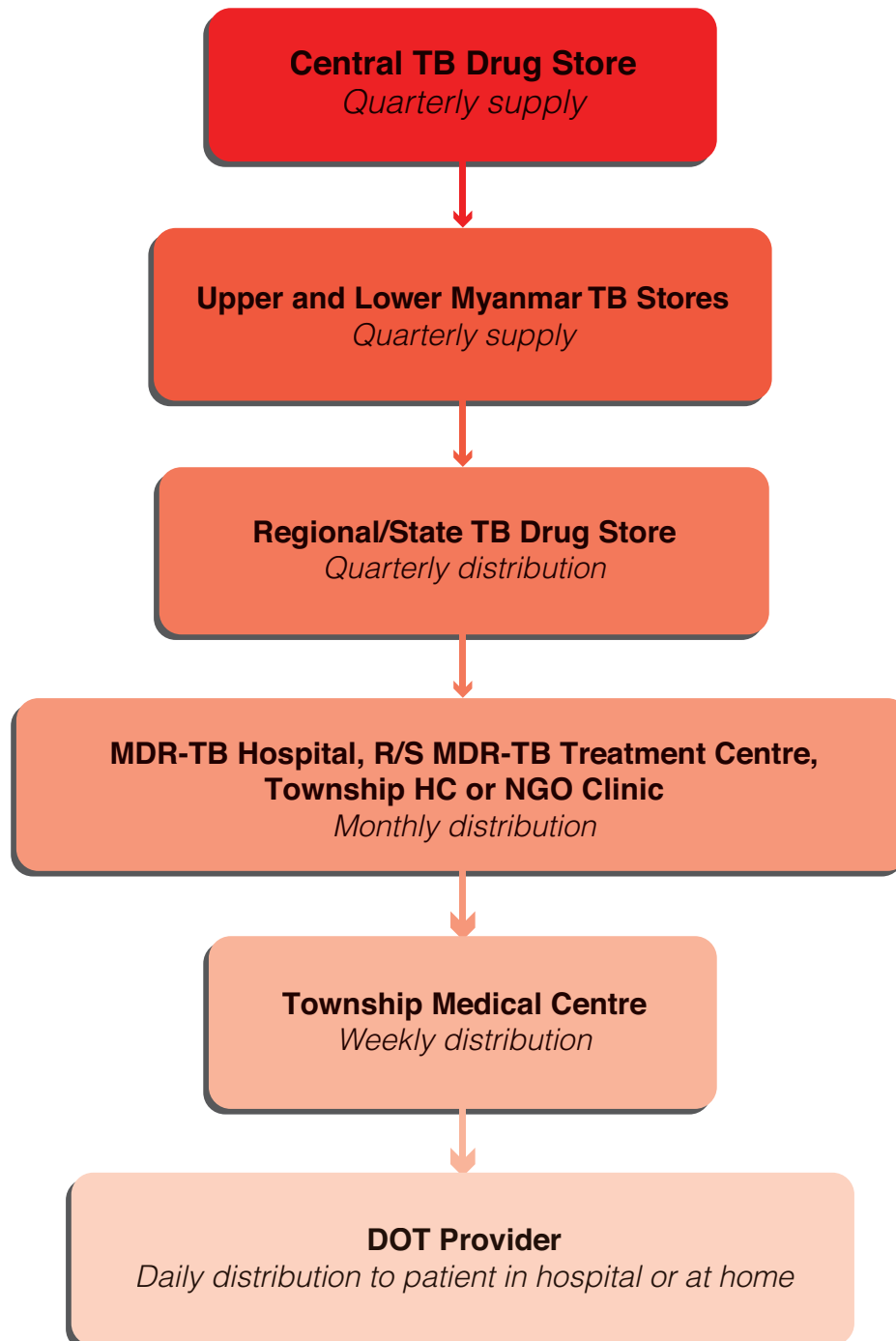
14.4 Reporting

Implementing R/S TBCs/Hospitals must report quarterly to NTP with copies to respective R/S TBC using the **Quarterly Drug Report Form** (Annex 3, Form 16).

14.5 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.

Figure 14.1 Drug flow of second-line anti-TB drugs

CHAPTER 15

INFORMATION SYSTEM AND DATA MANAGEMENT FOR MDR-TB

The aim of the information system for MDR-TB patients, both registered and not registered under the MDR-TB programme, is to monitor the trend of drug resistance and the overall programme performance in controlling MDR-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 within the MDR-TB Programme.

Table 15.1 List of records 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	A copy at INGO clinic	INGO staff
		Hospital/TB OPD sites, R/S TBC	MO in-charge
		A copy at township Health Centre (HC)	TMO/TB coordinator
02	MDR-TB Register	INGO clinic	INGO staff
		TB Hospital	MO in-charge
		R/S TBC	R/S TBO
		Township HC	TMO/TB coordinator
03	MDR-TB Patient's Identity booklet	To be kept by patient	MO in-charge of hospital/TB OPD
04	Laboratory requisition form for Xpert MTB/RIF, culture and DST	R/S TBC	R/S TBO or assigned MO
		TB Hospital	MO in-charge
		Township HC	TMO/TB coordinator
		PPM partners	Respective R/S TBO or assigned MO or TMO
TB 04	Laboratory register for sputum microscopy	NTRL/Upper Myangmar TB Laboratory (UMTBL) & R/S Township Lab	Laboratory technician in-charge
05	Laboratory register for culture and DST	NTRL/UMTBL & R/S Lab	Laboratory technician in-charge
06	DR-TB Suspects Register	R/S TBC	R/S TBO
		Township HC	TMO/TB coordinator
		NGO clinic	NGO staff

MDR-TB Form No.	Recording and reporting forms	Where to be kept	Responsible for filling in the form
07	Quarterly report on MDR-TB case detection	R/S TBC	R/S TBO
08	Six-month interim outcome assessment	R/S TBC, to be sent to NTP central office, copy to the Hospital and WHO	MO/TB key person in charge at R/S TBC
09	MDR-TB treatment 12-month culture conversion report		Microbiologists of NTRL/UMTBL and R/S Lab
10	Annual report of MDR-TB treatment outcome		
11	Quarterly MDR-TB laboratory report		
12	Register for missed dose tracing	Hospital/TB OPD	MO
		R/S TB Center, Township HC	TMO/TB coordinator
13	List of directly observed treatment	By the patient	DOT Provider
14	Patient's informed consent for treatment	Hospital/R/S TB Center	MS/MO in-charge
15	MDR-TB Referral Form	Hospital	MO in-charge
		R/S TBC	R/S TBO
		Township HC	TMO/TB coordinator
		PPM partners	Focal person
16	Quarterly Drug Report	Hospital/ R/S TBC	MO in-charge

15.1 Recording and reporting system

MDR-TB Form 01: MDR-TB Treatment Card

This card is a key instrument for health staff who administer 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 R/S TBC or hospital. 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 site and a duplicate must be given to the 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 numbers for each R/S in the first 1-2 years before complete decentralization of MDR-TB treatment at township level.

- Date of registration.
- Township TB Number: this number is assigned to the patient at R/S Township TBC, after discharge from the hospital (if hospitalized).
- Date of TB registration at township.
- Patient registration category: one of seven possible groups must be assigned to each patient upon registration.
- 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.
- Record any remark from the R/S 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 DST, including DST for second-line anti-TB drugs.
- 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 List of DOT Form: 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 hospital, R/S TBC and Township Health Centre. At the R/S and township level, enrolled patients must be registered in the R/S TBC and township register in addition to the central hospital MDR-TB Register. The hospitalized inpatients will only be registered in the R/S TBC and township registers after discharge from the hospital.

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:

- Date of registration.
- Township TB number.
- MDR-TB Register number.
- 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 04: Laboratory Requisition Form for Culture, DST and Xpert MTB/RIF

This form is used to request examination of biological specimens for culture, DST and Xpert MTB/RIF. The top portion includes patient demographic information as well as the reason for the request, the patient registration category, the specimen type and examination requested, and whether or not the patient is believed to have RR-TB or MDR-TB. The middle portion is for reporting smear, culture and Xpert MTB/RIF results, while the bottom portion is for reporting the DST results, including DST to second-line anti-TB drugs. The requisition form must be sent back to the treatment unit with the results by the laboratory technician. Requisition forms are to be attached to the MDR-TB Treatment Card.

Note: Laboratory Register for Sputum Microscopy. This standard sputum microscopy register is to be kept at all TB laboratories that are part of the NTP network. The register should be maintained by the laboratory personnel. All sputum microscopy results for MDR-TB patients are kept in this register, regardless of their registration category.

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 suspects.

The Culture and DST Register 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 category of any confirmed MDR-TB case must be specified in the Remarks column of the register.

MDR-TB Form 06: DR-TB Suspect Register

This register is kept at the R/S TBC, Township HC and INGO clinic by the R/S TBO, the TMO/Township TB Coordinator and the INGO staff, respectively. All MDR-TB suspects must be entered in this register and then referred to the R/S TBO who is responsible for requesting culture, DST and/or Xpert MTB/RIF. As soon as the MDR-TB case matches the selection criteria for programme enrolment, he/she must be entered in the MDR-TB Register at the R/S TBC or hospital upon admission, and then registered again in the MDR-TB Register kept at R/S TBC/Township HC/INGO clinic when discharged from the hospital and referred for continued care.

MDR-TB Form 07: Quarterly Report on MDR-TB Case Detection (to be completed at the end of the quarter)

This report is completed with data from the Laboratory Register for Culture and DST kept at the NTRL, UMTBL, or R/S Laboratory, as well as data from the MDR-TB Register kept at R/S TBC. This quarterly report records how many "suspect MDR-TB" patients were tested at the NTRL and how many confirmed MDR-TB cases (or confirmed RR-TB) were registered in the MDR-TB Programme. This report is completed quarterly for the previous quarter by the MO in-charge at the R/S TBC. The report must be submitted on a regular basis to the NTP Central Office, from R/S TBC. For townships, the report must be sent to central NTP and copied to R/S TBC.

Example

TB patients with positive culture and DST results for MDR-TB who started treatment during the 1st quarter (01 January to 31 March) of 2012 must be reported in the Quarterly Report 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: Six-Month Interim Outcome Assessment (to be completed 9 months after treatment initiation)

This biannual report evaluates the interim outcomes after six 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 R/S TBC. The MO in-charge at the R/S TBC or township TB center is responsible for the timely and regular submission of the report to the central NTP office, from the R/S TBC. For townships, the report must be sent to the central NTP office with a copy to the R/S TBC.

The interim results will be reported nine months past the closing date of the reported cohort (e.g. cohort of March 2012 is reported in January 2013). Reporting nine months after the closing date allows for complete culture results for the first six months of treatment.

Example

TB patients registered during the 1st quarter (01 January to 31 March) of year 2012 must be reported in the Six-Month Interim Outcome Report of January 2013.

The number of patients who have negative smears/cultures at Months 4, 5 and 6 (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 Culture Conversion Report (to be completed 15 months after cohort closing date)

Each quarterly cohort defined by the date of MDR-TB registration should have a culture conversion report submitted after 12 months of treatment. This report should be completed by the R/S TBC Coordinator or township TB coordinator, based on information recorded in the MDR-TB Register. Since reporting at the end of treatment is very late (after two or even three years), preliminary results are desirable for all cohorts.

The conversion results will be reported 15 months past the closing date of the cohort being reported on. This allows complete culture results for the first 12 months of treatment to be included for all patients in the cohort.

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

This report shows the final treatment outcomes for patients enrolled 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 last patient in the cohort starts treatment. Most of the patients will have finished treatment by 24 months and this allows preliminary assessment of cure rates. Since a few patients may be on treatment for longer than 24 months, the form is completed again at 36 months after the last patient in the cohort starts treatment. The 36-month evaluation is considered the final “treatment cohort analysis” (see Box 15.1).

The annual report is completed by using data from MDR-TB Register kept at R/S TBC or township TBC. The MO in-charge at the R/S TBC or Township TB Coordinator is responsible for the timely and regular submission of the report to the NTP Central Office, sending one additional copy to the Hospital.

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.

Box 15.1 Cohort analysis

An MDR-TB treatment cohort is defined as a group of patients who started second-line anti-TB treatment during a defined time period. The MDR-TB treatment cohort will consist of a subset of patients recorded in the MDR-TB Register. **Note: Patients with either confirmed MDR-TB by conventional testing or RR-TB by Xpert MTB/RIF are included in all interim analysis and treatment cohort analysis.**

To allow adequate analysis of all MDR-TB patients, the following dates are to be recorded:

1. Date of initial registration as a TB case (most commonly obtained from the Township TB Register).
2. Date of registration as MDR-TB case.
3. Date of starting second-line treatment.

The treatment cohort analysis focuses on treatment outcomes among patients who actually started second-line anti-TB treatment. Registration cohort analysis focuses on the number of patients identified and the number who are placed on treatment.

The recommended timeframe for MDR-TB treatment cohort analysis reflects the long duration of MDR-TB regimens. Cohort analysis should be carried out at 24 months and repeated at 36 months after the last patient starts treatment. The 36-month evaluation is considered the final treatment cohort analysis result.

For recording and reporting purposes all patients should be assigned the first outcome they experience. The NTP may have to record subsequent outcomes among patients followed systematically. Patients who remain on treatment at the end of a designed cohort treatment period must be identified as “still on treatment”.

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

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, hospital 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 R/S TBC, hospital or the TMO at township level must specify the number of missed dose(s), the reasons for missing treatment, the decision taken and then sign the register in agreement with the patient.

MDR-TB Form 13: List of Directly Observed Treatment

This form allows to the DOT Provider to record the patient's drug intake on a daily basis, by ticking the appropriate month and day. This form is kept by the MDR-TB patient and filled in by the DOT Provider. 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 for MDR-TB Treatment Form

This form formalizes the contract between the patient and the clinic to encourage compliance with treatment. This form must be read aloud to the patient by the counsellor at the R/S TBC or hospital after the three adherence counselling sessions have been successfully conducted. The R/S TB Coordinator or MS of the hospital must read and explain the content of the consent form to the patient. The form must be signed by the patient, the MS of the R/S TBC or the TMO of the township, as well as the DOT Provider before starting the treatment. If the patient is discharged from the R/S TBC and referred to a township treatment centre, or if the patient is transferred to a different treatment centre entirely, a new Patient Consent Form must be filled out. The form must be kept at the R/S TBC, and upon discharge or transfer, a copy must be sent with the patient to the new treatment centre.

MDR-TB Form 15: MDR-TB Referral Form

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

MDR-TB Form 16: Quarterly Drug Report Form

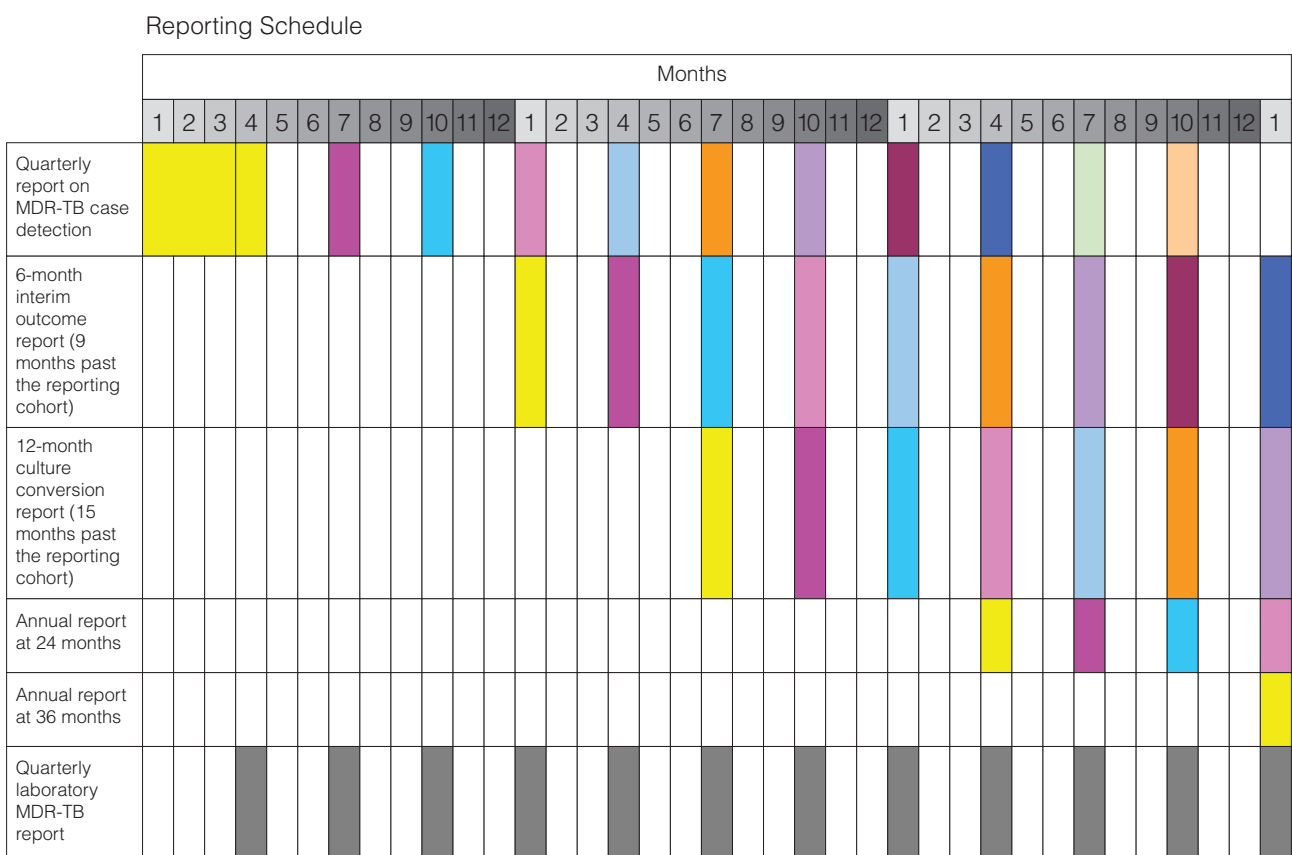
This form is used to report the current drug stock at the Central TB Drug Store, the R/S TBC, the TB Treatment Centre, the MDR-TB hospital ward and the NGO clinic. This report should be completed on a quarterly basis and sent to the NTP Central Office. More information

on the use of this form can be found in Chapter 13, *Management of Second-line Anti-TB Drugs*.

15.2 Computerized system

Presently, 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 for MDR-TB.

Figure 15.1 Reporting schedule for MDR-TB programme



Note: Each colour represents the reporting schedule for a particular cohort. 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 detection is due in April of Year 1, 6-month interim report is due in January of Year 2, 12-month culture conversion report is due in July of Year 2, 24-month annual report is due in April of Year 3, and 36-month annual report is due in January of Year 4.

Figure 15.2 Health centres and their responsibilities in MDR-TB management

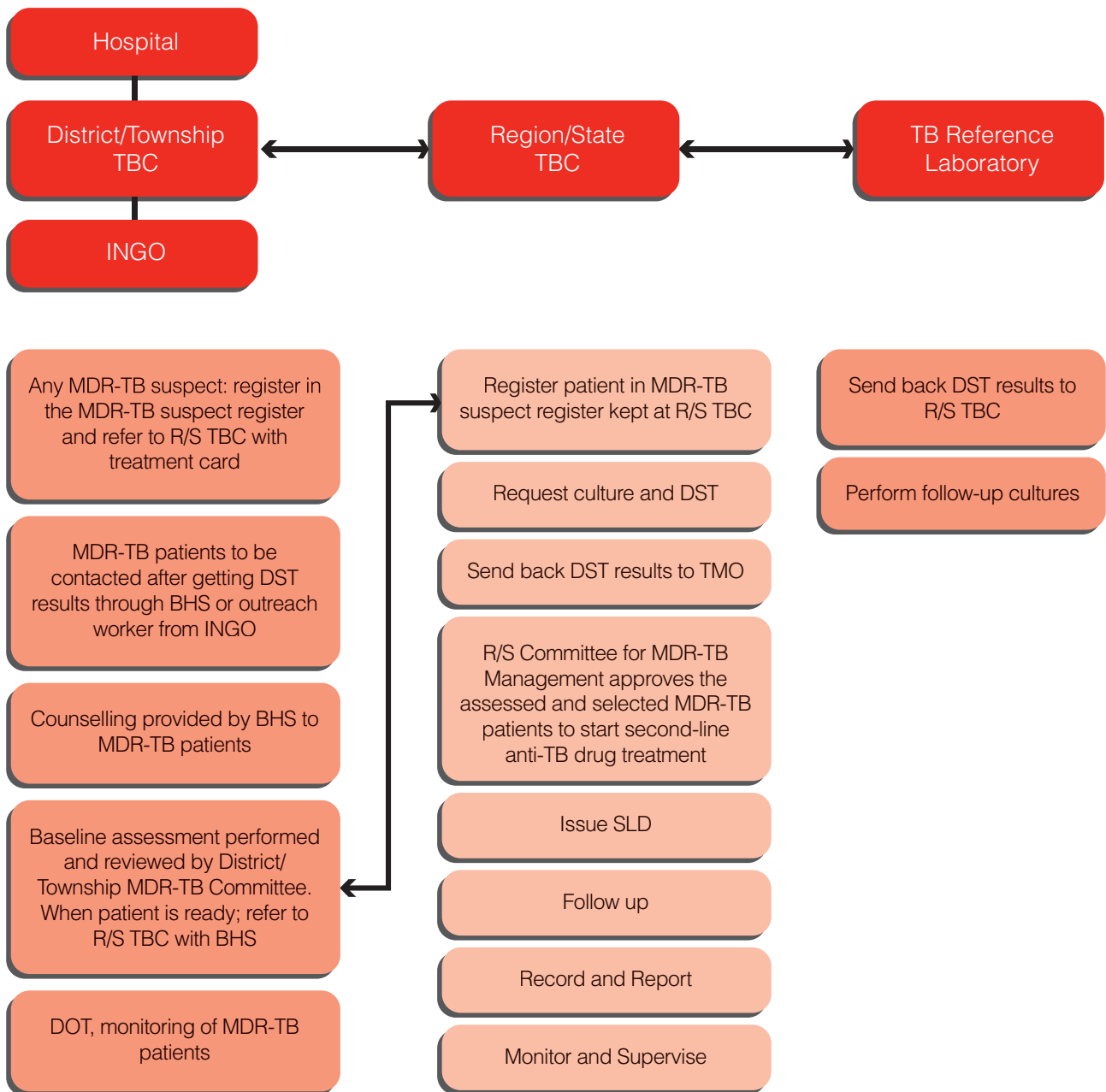
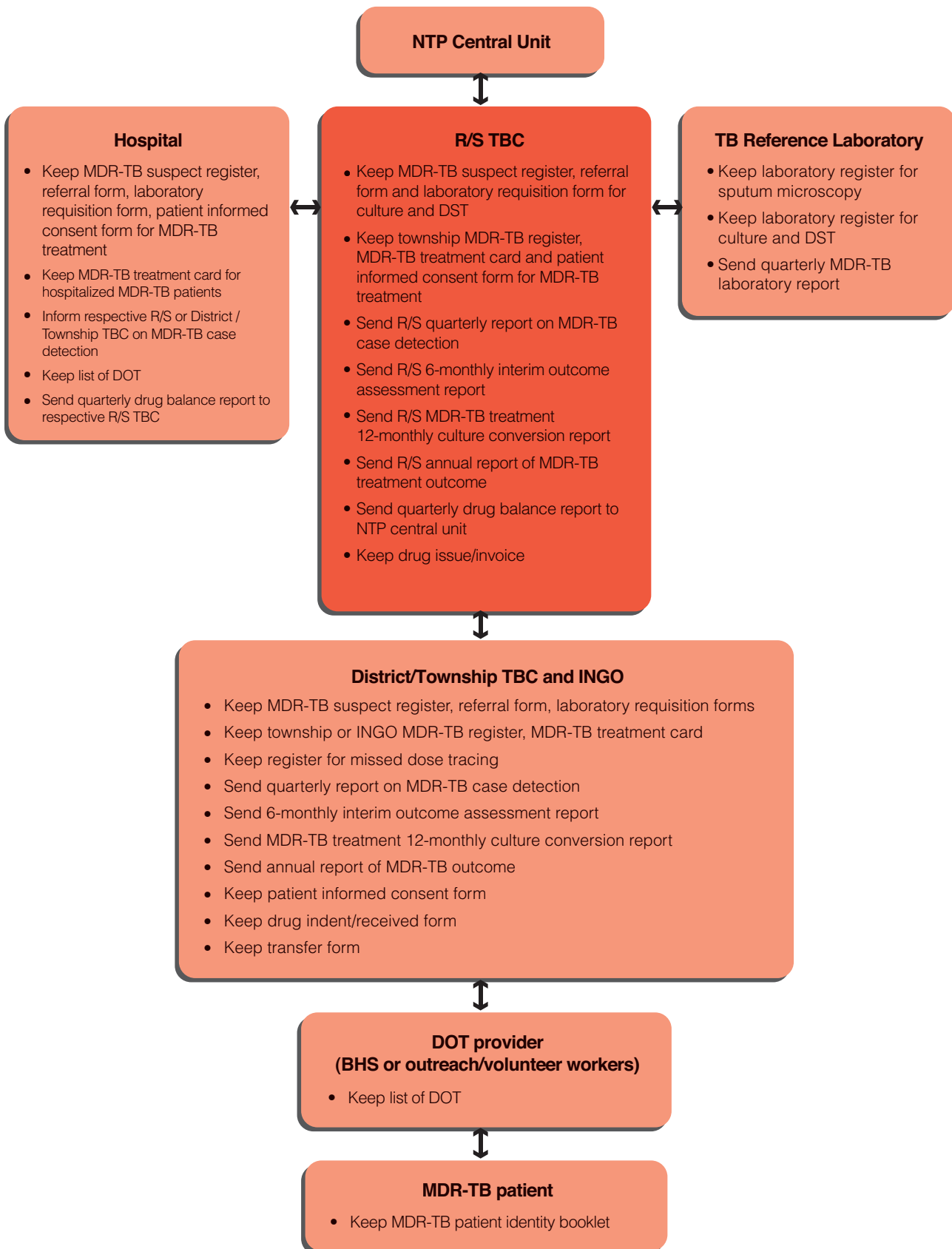


Figure 15.3 Algorithm for MDR-TB treatment programme recording and reporting



CHAPTER 16

INFECTION CONTROL OF MDR-TB

16.1 Introduction to infection control strategies

There are three levels of TB infection control (TB IC) measures: administrative (managerial), environmental, and personal respiratory protection. Administrative controls are the most important, since environmental controls and personal respiratory protection will not work in the absence of good administrative control measures. Each level operates at a different point in the transmission process:

- Administrative controls reduce *M. tuberculosis* exposure.
- Environmental controls reduce the concentration of infectious droplet nuclei.
- Personal respiratory protection protects health-care workers (HCWs) and other people in areas where the concentration of droplet nuclei cannot be adequately reduced by administrative and environmental controls.

16.2 Administrative (managerial) controls

The first and most important level of control is the use of administrative controls to prevent aerosol from being generated and thus reducing the exposure of all people to *M. tuberculosis*. Ideally, if the risk of exposure can be eliminated, no further controls are needed. Unfortunately, the risk usually cannot be eliminated, but it can be significantly reduced with proper administrative measures.

Important administrative measures include reduced/minimal waiting time at health facilities for TB suspects and patients, early diagnosis of potentially infectious TB patients, prompt separation or isolation of infectious TB patients, and the prompt initiation of appropriate anti-TB treatment.

Other important measures include an assessment of the risk of transmission in the facility, the development of a TB IC plan that details in writing the measures that should be taken in a given facility, and adequate training of HCWs to implement the plan. It is essential that one individual be assigned responsibility and accorded authority to monitor the implementation of the TB IC plan.

16.3 Environmental control measures

Since exposure to infectious nuclei usually cannot be fully eliminated, various environmental control methods can be used in high-risk areas to reduce the concentration of nuclei in the air. Such measures include maximizing natural ventilation and controlling the direction of airflow. Although many environmental control measures require resources that are not available in most situations (e.g. most township-level health facilities), some can be implemented in resource-limited settings (e.g. opening windows to increase natural ventilation, and use of fans to control the direction of air flow).

16.4 Personal respiratory protection

The third recommended control measure is the protection of the person from inhaling infectious droplets through the use of personal respiratory protective devices, which are designed to fit over the mouth and nose and filter out infectious TB particles. The type of surgical masks (cloth, paper) commonly used by HCWs do not filter out infectious droplet nuclei, although they may be of some use if placed on patients to prevent the generation of such nuclei. Personal respiratory protective devices for HCWs that are capable of adequately filtering out infectious particles are more expensive than surgical masks and are the least effective of the three TB IC measures.

16.5 Implementing infection control measures

The management or implementation of MDR-TB IC 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 centre (e.g. 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
- R/S TBCs
- Township Health Centres
- The MDR-TB patient's home
- HIV clinics

The primary measures for preventing infection 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*;
- Create mechanical barriers to prevent the spread of mycobacterium.

16.6 Infection control plan

16.6.1 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 Mingalardon and Tharketa 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 200 ml, sealable (if possible), non-sterile containers. Replace the containers daily. In Myanmar a spittoon with a cover is used (*Htwe gan*). A plastic bag is placed inside the spittoon. If spitting sputum, the patient must remove the lid and 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. Do not re-use. Do not fill the containers with chlorine 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 the ward, they must wear a cloth mask. Those masks must be washed with antiseptic solution on a daily basis and 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 their hands.

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 pigeonholes).⁶

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, 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.

⁶ 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)

16.6.2 Outpatient counselling rooms and X-ray room in the hospitals, R/STBC, 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.

16.6.3 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.

16.6.4 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.

16.6.5 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 HIV patients. 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.

- Patient's linen and clothes should not be shaken, to prevent aerosolization. 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 visiting with 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 when in contact with family members in areas that are poorly ventilated if the patient is culture-positive.
 - 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.

16.6.6 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.

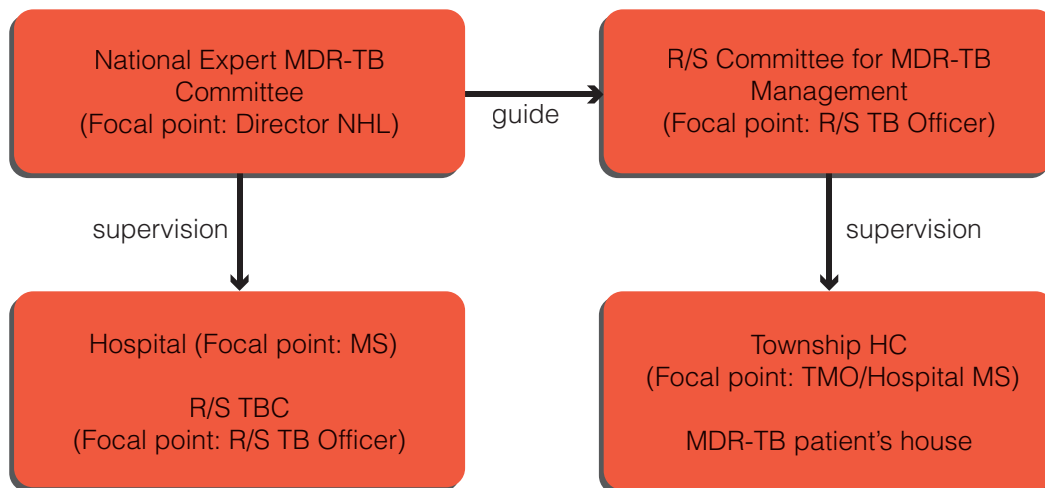
16.7 Monitoring and evaluation of infection control interventions

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 Centres, 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 16.1 Supervision of infection control at various levels



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

Table 16.1 Checklist for hospital supervision

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

Table 16.2 Checklist for regional TBC supervision

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

Table 16.3 Checklist for township HC supervision

Township		
Health staff use N95 respirators if MDR-TB patient is still smear-positive	<input type="checkbox"/> Yes	<input type="checkbox"/> No
OPD well ventilated and lighted	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Waiting room not overcrowded	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Patients using cloth masks	<input type="checkbox"/> Yes	<input type="checkbox"/> No

Table 16.4 Checklist for patient home supervision

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

CHAPTER 17

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 training 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, townships and NGO clinics, including support staff and treatment volunteers. The training programme is coordinated and delivered by staff from NTP central office in collaboration with the WHO.

Table 17.1 Targeted audience of MDR-TB training courses, divided by health facility level

Aung Sang TB Hospital, Yangon	8 MO, 50 nurses, 3 laboratory technicians, 2 medical social workers, 1 clerk
Pathengi TB Hospital, Mandalay	8 MO, 50 nurses, 4 laboratory technicians, 2 medical social workers, 1 clerk
R/S Hospital	8 MO, 50 nurses, 4 laboratory technicians, 2 medical social workers, 1 clerk per Region/State
Upper Myanmar TB Reference Laboratory, Mandalay	4 laboratory technicians, 1 assistant microbiologist
National TB Reference Laboratory, Yangon	7 laboratory technicians, 1 assistant microbiologist
1 R/S Laboratory	4 laboratory technicians, 1 assistant microbiologist or pathologist per R/S laboratory
Township level	1 TMO, 1 TB Coordinator and 50 BHS per township
R/S TBCs	2 MO, 2 nurses per township
NGOs	MOs, public health officers, nurses, counsellors, volunteers

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
- Treatment of MDR-TB in special conditions
- HIV infection and MDR-TB

- Monitoring of treatment
- Management of adverse effects
- Treatment adherence, missed-dose and defaulter tracing
- Counselling
- Management of patients after MDR-TB treatment failure
- Management of contacts of MDR-TB patients
- Recording and reporting system
- Supervision, monitoring and evaluation

However, depending on the level of health-care provider to be trained, the course must be modified to include relevant information on specific responsibilities and roles of each individual in MDR-TB control. Target audiences, topics, and course duration are outlined in Table 17.2.

Table 17.2 MDR-TB control management training topics for each health facility level

Health staff from NTP central office and states/regions		
Target	Topics	Course duration
Senior NTP staff from central office and Regions/States	The full curriculum of the training following these guidelines.	3 days
Medical Superintendents/ Senior Physicians		
Senior NGO staff		
Health staff from hospital		
Target	Topics	Course duration
Medical officers and physicians from Hospital	The full curriculum of the training following these guidelines.	3 days
Nurses, Social workers, Lab Technicians from Hospital	The full curriculum of the training following these guidelines with BHS manual (Myanmar language).	3 days
Store officers	1. Store management (On Job Training)	1 day
Office staff	1. R&R system and data management (On Job Training)	1 day
Menials	1. Basic information on MDR-TB (On Job Training) 2. Infection control	1 day

Health staff from regional/township level		
Target	Topics	Course duration
MO from R/S TBC; TMO; Township TB Coordinator	The full curriculum of the training following these guidelines.	3 days
Nurses from R/S TBC; BHS (DOT Supervisor)	The full curriculum of the training following these guidelines with BHS manual (Myanmar language).	3 days
NGO staff (DOT Provider)	<ol style="list-style-type: none"> 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 day
General private practitioners (PSI and Myanmar Medical Association)	The full curriculum of the training following these guidelines	2 days

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

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 after the course has ended.

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

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

CHAPTER 18

SUPERVISION, MONITORING AND EVALUATION

18.1 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. Supervision should be educative, supporting and corrective, not punitive.

Internal supervision

The quality of MDR-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 MDR-TB management:

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

In addition, MDR-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 visit per year to Station hospitals and rural health centres by TMOs
- Four supervisory visits per month to sub-centres 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 and 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 workplans at central and Region/State level.

External supervision

Technical assistance plans by external experts are to be managed by the NTP and WHO. For MDR-TB, WHO ensures three yearly missions as follows:

- Technical assistance on MDR-TB clinical and programmatic aspects
- Supervision and technical support from the SNRL in Bangkok for support to MDR-TB diagnosis
- 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 MDR-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, MDR-TB experts are always included.

18.2 Monitoring and evaluation

Monitoring and evaluating the performance of the MDR-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 clinic
- 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, 2011-2015 includes the impact, output and programmatic indicators specific for MDR-TB shown in Table 18.1.

Table 18.1 Indicators for MDR-TB management in Myanmar with 2015 targets as outlined in the 2011-2015 National Strategic Plan

	Description	Baseline			Target 2015
		Value	Year	Source	
Impact indicator	Prevalence of MDR-TB among new smear-positive TB patients	4.2%	2007	National Drug Resistance Survey	<4%
Outcome indicator	Treatment success rate among MDR-TB cases	N/A	N/A	N/A	≥ 75%
Programmatic indicator	Number of laboratory-confirmed MDR-TB patients enrolled in the MDR-TB treatment programme	64	2009	NTP data	3 395

Cohort analysis

Cohort analysis is the key management tool used to evaluate the effectiveness of the MDR-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, lower than expected case-detection rate).

Measurement of impact

Two nationwide DRS were conducted in 2002-2003 and 2007-2008. The third survey began in September 2012 and will be completed in 2013. These surveys are important to provide an estimation of the magnitude of the MDR-TB problem and can detect general trends over time. 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. 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 MDR-TB implementation (see Annex 3):

- MDR-TB Treatment Card (Form 01)
- MDR-TB Register (Form 02)
- Patient Identity Booklet (Form 03)
- Laboratory Requisition Form for Culture, DST and Xpert MTB/RIF (Form 04)

- Laboratory Register for Expert MTB/RIF, Culture and DST (Form 05)
- DR-TB Suspect Register (Form 06)
- Quarterly Report on MDR-TB Case Detection (Form 07)
- Six-month Interim Outcome Assessment (Form 08)
- MDR-TB Treatment 12-Month Culture Conversion Report (Form 09)
- Annual Report of Treatment Outcomes of MDR-TB Cases (Form 10)
- Quarterly Laboratory MDR-TB Report (Form 11)
- Register for Missed Dose Tracing (Form 12)
- List of Directly Observed Treatment (Form 13)
- Patient's Informed Consent for MDR-TB treatment Form (Form 14)
- MDR-TB Referral Form (Form 15)
- Quarterly Drug Report Management (Form 16)

The steps involved in the quarterly MDR-TB data management are:

- MDR-TB notification and cohort analysis of treatment outcome are compiled by the R/S TBO every quarter, and at the end of every year the R/S TBO ensures that MDR-TB management data from NGOs are included.
- Township quarterly reports on MDR-TB notifications and treatment outcome are forwarded to the R/S TBC for verification and compilation of R/S MDR-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 MDR-TB notification and cohort analysis reports on all MDR-TB patients registered nationally.

R/S TBOs are responsible to report on MDR-TB patients who are treated outside the MDR-TB management programme or in the private sector.

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.

Internal reviews and coordination with implementing partners

Monthly meetings by the District/Township MDR-TB Committee focus on issues and challenges of MDR-TB control activities, while quarterly meetings of the Regional/State Committee for MDR-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 Health Directors, R/S TBOs and implementing partners attend. MDR-TB management is one of many topics discussed. Separate annual meetings on MDR-TB activities are held, including meetings of the National Committee of MDR-TB Management and the National Expert MDR-TB Committee. The NTP also participates at 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
- Breathe 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 than 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 with 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 No.	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 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															

Signature of Ward MO/OPD MO/TMO _____

Countersigned by Ward In-charge Physician _____

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
Total										

Signature of Store MO _____

Countersigned by MS / R/S TBO _____

Received correctly and completely

Signature _____

Annex 3: Recording and Reporting Forms

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

NATIONAL TUBERCULOSIS PROGRAMME

(MDR-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: _____

MDR TB registration number: _____

Date of registration: ____/____/____

Township TB number: _____

Date of township TB registration: ____/____/____

Address: _____

Township/District: _____

Treatment/centre: _____

Name of DOT Provider: _____

DOT Supervisor: _____

*Backlog of cases who have waited with no or inadequate treatment for a period of time

Contact of MDR-TB case: [] Yes [] No

No	Registration group	Select one only
1	New	
2	Relapse	
3	Treatment after default	
4	Treatment after failure of Category I treatment	
5	Treatment after failure of Category II treatment	
6	Treatment after failure with the Standard MDR-TB regimen	
7	Other	

Previous tuberculosis treatment episodes

Previous Township TB No./township	Start date (if unknown, put year)	Regimen (in drug abbreviations)	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
Ofx= Ciprofloxacin
Ofx= Ofloxacin
Lfx= Levofloxacin
Mfx= Moxifloxacin
Gfx= Gatifloxacin
Pto= Prothionamide
Eto= Ethionamide
Cs= Cycloserine
PAS= P-aminosalicylic Na

HIV information

HIV testing done: [] Y [] N [] unknown

Date of test ____/____/____ Results: _____

Started on ART: [] Y [] N Date ____/____/____

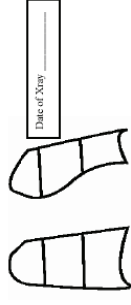
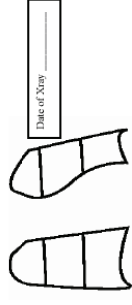
Started on CPT: [] Y [] N Date ____/____/____

ART= antiretroviral therapy; CPT = co-trimoxazole preventive therapy

District/Township MDR-TB Committee recommendation

Date	Decision	Next date

CXR Results



Month No.	Sputum Smear Microscopy			Culture			Urea	Serum Creatinine	LFT	CP	Serum Uric Acid	TSH	ECG	Electrolytes	Blood sugar
	Date	Sample No.	Grading	Date	Sample No.	Grading									
Diagnosis															
1															
2															
3															
4															
5															
6															
7															
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23															
24															
25															
26															

Drug susceptibility testing (DST) results

Date	S	H	R	E	Pto/Eto	Km/Amk	Cm	Fq	Other	Other	Other

R = resistant, S= susceptible, C = contaminated

NATIONAL TUBERCULOSIS PROGRAMME

Patient Identity Booklet

(MDR-TB FORM 03)

MDR-TB Registration No: _____

MDR-TB Treatment Site: _____

Patient name: _____

Address: _____

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

Township TB unit: _____

Health unit: _____

Disease classification	Date treatment started
<input type="checkbox"/> Pulmonary <input type="checkbox"/> Ex-pulmonary <input type="checkbox"/> Both Site: _____	____/____/____

Registration group	
1. New <input type="checkbox"/> 2. Relapse <input type="checkbox"/> 3. Treatment after default <input type="checkbox"/> 4. Treatment after failure of Category I treatment <input type="checkbox"/>	5. Treatment after failure of Category II treatment <input type="checkbox"/> 6. Treatment after failure with the Standard MDR-TB regimen <input type="checkbox"/> 7. Other <input type="checkbox"/>

Treatment	Intensive phase	Continuation phase

Change in treatment	Intensive phase	Continuation phase

Allergies: _____

Severe adverse reactions: _____

Remarks: _____

NATIONAL TUBERCULOSIS PROGRAMME

Lab Requisition Form for Culture, DST and Xpert MTB/RIF

(MDR-TB FORM 04)

Requisition form for lab to be filled in by treatment centre

Treatment unit: _____ Date: _____ Suspect/MDR-TB No. _____

Patient name: _____ Age: _____ Date of birth: _____ Sex: [] M [] F

Address: _____

Type of patient (if TB diagnosis or presumptive RR-TB/MDR-TB:	
1. New []	5. Treatment after failure of Category II treatment []
2. Relapse []	6. Treatment after failure with the Standard MDR-TB regimen []
3. Treatment after default []	7. Other []
4. Treatment after failure of Category I treatment []	

Reason for examination: [] TB Diagnosis [] Follow-up exam (Month of treatment ____ [] Presumptive RR-TB/MDR-TB

Specimen type: [] Sputum [] Other _____

Test requested: [] Smear [] Culture [] Xpert MTB/RIF [] DST (Specify: [] S [] R [] H [] E [] Other _____, _____, _____)

Name and signature of person requesting exam: _____

RESULTS (to be completed in laboratory)

Smear results

Date collected	Specimen type	Lab no./ Serial no.	Visual appearance (blood stained, mucopurulent, or saliva)	Result (check one)				
				Negative 0 AFB	scanty 1-9 AFB/100 HPF	+ 10-99 AFB/100 HPF	++ 10 AFB/HPF	+++ >10 AFB/HPF

Examined by (name and signature) _____ Date of result _____

Xpert MTB/RIF results

Date collected				
	No TB detected	TB confirmed, not Rifampicin-resistant	TB confirmed, Rifampicin-resistant	Indeterminate result
	No TB detected	TB confirmed, not Rifampicin-resistant	TB confirmed, Rifampicin-resistant	Indeterminate result

Examined by (name and signature) _____ Date of result _____

Culture results

Date collected	Specimen type	Lab no./ Serial no.	Result (check one)					Contaminated
			Negative 0 colonies	1-9 colonies	+ 10-100 colonies	++ >100 colonies	+++ Innumerable/confluent growth	

Examined by (name and signature) _____ Date of result _____

DST results

Date collected	Specimen type	Lab no./ Serial no.	H	R	E	S	Km	Cm	Fq	Pto/Eto	Other	Other	Other

R= resistant; S= susceptible; C=contaminated

Examined by (name and signature) _____ Date of result _____

NATIONAL TB PROGRAMME**Quarterly Report on MDR-TB Case Detection
(To be filled out one quarter after)****(MDR-TB FORM 07)**

MDR-TB treatment unit: _____

Patients registered in the MDR-TB Register

MDR-TB reg. no.: _____

during quarter _____ of year _____

Name of MDR-TB treatment site: _____

Name and signature: _____

Date of completing this form: _____

Block 1: Number of MDRTB patients registered

Patients	Confirmed MDR-TB (or RR-TB)	Other
Registered in MDR-TB diagnostic group		
Started on MDR-TB treatment during the quarter		

Block 2: Confirmed MDR-TB registered during the quarter

New	Pulmonary			Other*	Total
	Previously treated patients				
New MDR-TB case	Relapse	Treatment after default	Treatment after failure of Category I treatment	Treatment after failure of Category II treatment	Treatment after failure with the Standard MDR-TB regimen

Remark:

Transfer in: _____

* Other cases include previously treated pulmonary TB patients without known outcome status, and all previously treated extra-pulmonary TB patients.

NATIONAL TUBERCULOSIS PROGRAMME

(MDR-TB FORM 10)

ANNUAL REPORT OF TREATMENT OUTCOMES OF MDR-TB CASES
(To be filled in 24 and 36 months after the closing date of year of treatment)

Name of MDR-TB treatment site and state: _____ Date of completion of the report: _____

Patients registered in the MDR-TB register during Quarter _____ of Year _____

MDR-TB treatment site coordinator: _____ Signature: _____

Blocks 1 and 2 are for all patients who enter MDR-TB register (due to MDR-TB on conventional DST or RR-TB by Xpert MTB/RIF)

Block 1: Patients by smear and culture result at initiation of MDR-TB treatment (all patients)

	Cured	Completed	Failed	Lost to follow-up	Died	Still on treatment	Total
S+C+							
S-C+							
Total							

S = smear, C = culture

Block 2: Patients by registration category (for all patients entering MDR-TB register)

Registration group	Cured	Completed	Failed	Lost to follow-up	Died	Still on treatment	Total
New							
Relapse							
Treatment after default							
Treatment after failure of Category I treatment							
Treatment after failure of Category II treatment							
Treatment after failure with the Standard MDR-TB regimen							
Other							
Total							

Year of cohort of treatment: _____

Blocks 3 and 4 are for MDR-TB (RR-TB) patients only

Block 3: Patients by smear and culture result at initiation of MDR-TB treatment (for patients with documented MDR-TB)

	Cured	Completed	Failed	Lost to follow-up	Died	Still on treatment	Total
S+C+							
S-C+							
Total							

S= smear, C= culture

Block 4: Patients by registration category (for patients with documented MDR-TB)

Registration group	Cured	Completed	Failed	Lost to follow-up	Died	Still on treatment	Total
New							
Relapse							
Treatment after default							
Treatment after failure of Category I treatment							
Treatment after failure of Category II treatment							
Treatment after failure with the Standard MDR-TB regimen							
Other							
Total							

NATIONAL TUBERCULOSIS PROGRAMME
Quarterly Laboratory MDR-TB Report

(MDR-TB FORM 11)

Date of reporting: _____ of year _____

Quarter reported: _____ of year _____

Laboratory name: _____

Laboratory technician name: _____

No. of MDR-TB suspect investigated with culture: _____

No. of MDR-TB suspects with culture positive investigated with DST: _____

DR patterns reported:

	Mono-resistant				Poly-resistant Specify the type of resistance	MDR-TB
	H	S	R	E		
No. DR-TB suspects investigated with DST						
New						
Relapse						
Treatment after default						
Treatment after failure of Category I treatment						
Treatment after failure of Category II treatment						
Treatment after failure with the Standard MDR-TB regimen						
Other						
Total						

**NATIONAL TUBERCULOSIS PROGRAMME
PATIENT'S INFORMED CONSENT FOR MDR-TB TREATMENT FORM**

(MDR-TB FORM 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 24 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 24 months. If I default from this treatment I understand that I will not be able to get further treatment. 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.)

Date: _____	Signature _____
	Name _____
	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.

Date: _____	Signature _____
	Name _____
	Designation _____

DOT Provider:

I (Name of DOT Provider) _____ am committed to support (Name of patient) _____ in taking his/her full course of treatment for 24 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.

Date: _____	Signature _____
	Name _____
	Address _____

NATIONAL TUBERCULOSIS PROGRAMME
MDR-TB Referral Form

(MDR-TB 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 _____

<p>Disease classification</p> <p><input type="checkbox"/> Pulmonary</p> <p><input type="checkbox"/> Extra-pulmonary (Site _____)</p> <p><input type="checkbox"/> Both</p>	<p>Detail of treatment category</p> <p>Township and TB number _____</p> <p>Date of starting treatment _____</p>
--	--

<p>Type of TB patient</p> <p><input type="checkbox"/> New</p> <p><input type="checkbox"/> Relapse</p> <p><input type="checkbox"/> Treatment after default</p> <p><input type="checkbox"/> Treatment after failure to category I treatment</p> <p><input type="checkbox"/> Treatment after failure to category II treatment</p> <p><input type="checkbox"/> Treatment after failure with the Standard MDR-TB regimen</p> <p><input type="checkbox"/> Other _____</p>	<p>Sputum, culture and DST details</p> <p>Date of culture collection _____</p> <p>Date of culture result _____</p> <p>Date of DST result _____</p> <p>DST result (resistance pattern only)</p> <p>_____</p>
--	--

<p>Details of MDR-TB patient</p> <p>MDR-TB reg no. _____</p> <p>Name of S/R hospital _____</p> <p>Date of MDR-TB treatment start _____</p> <p>Number of doses taken _____</p>	<p>Refer for side effects</p> <p><input type="checkbox"/> Psychosis</p> <p><input type="checkbox"/> Depression</p> <p><input type="checkbox"/> Seizures</p> <p><input type="checkbox"/> Other _____</p>
--	--

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.

NATIONAL TUBERCULOSIS PROGRAMME
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
Received										
Issued										
Balance										
Expiry Date	Month									
	Year									

Signature _____

Designation _____

Countersigned _____

Designation _____

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 aminoglycoside 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 spironolactone 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

Oral Supplementation

- Presentations:
 - Magnesium citrate
 - Magnesium lactate
 - Magnesium glycinate
 - Magnesium 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.

IV Supplementation

- Maximum concentration: 5 g or 40 meq MgSO₄ 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

Intramuscular Supplementation

- 1 g (or up to 250 mg/kg) of MgSO₄ 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, these 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:

$$\text{Corrected calcium} = 0.8 (4.0 - \text{measured albumin}) + \text{reported calcium}$$

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 space?	
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: <ul style="list-style-type: none"> • Sputum cups • Slides • Slide boxes • Staining reagents 	
6	How is waste disposed of? <ul style="list-style-type: none"> • 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 treatment outcome such as cured/completed/treatment failure?	
5	Are follow-up sputum and culture requisition forms attached to the MDR-TB treatment 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?	

Drugs	Remaining amount	Expiry dates	If expired, amount of drugs
Amikacin			
Levofloxacin			
Pyrazinamide			
Ethionamide			
Cycloserine			
PAS			
B6			
Other			

6	Are ancillary drugs available to manage side-effects? Are there any shortages of ancillary drugs, and if so, which drugs?	
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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	Do GPs/NGOs refer suspect MDR-TB patients to health centre for early diagnosis 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: _____

GUIDELINES FOR THE MANAGEMENT OF
MULTIDRUG-RESISTANT TUBERCULOSIS
(MDR-TB) IN MYANMAR

Myanmar, May 2013