



THE GOVERNMENT OF THE KINGDOM OF SWAZILAND

MINISTRY OF HEALTH AND SOCIAL WELFARE

P. O. BOX 5

MBABANE

**DRUG RESISTANT TUBERCULOSIS MANAGEMENT GUIDELINES
AND MANUAL**

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FOREWORD

Swaziland has a population of about 1.1 million with an area of 17 373 Km². The country is divided into 4 regions which are Hhohho, Lubombo, Shiselweni and Manzini. The population is almost evenly distributed with the largest population of 30% in Manzini and the least 20.9% in Lubombo. According to the WHO Global TB Report of 2005, the incidence rate of TB in Swaziland is the highest in the world. The TB programme faces problems of poor diagnosis of cases, poor case holding and high defaulter rates

In recent times, the World Health Organization (WHO) has expressed concern over the emergence of TB strains that are resistant to first line anti TB drugs (MDR TB) and even second line drugs (XDRTB) and is calling for measures to be strengthened and implemented to prevent the global spread of these deadly TB strains. This follows research showing the extent of XDR-TB, a newly identified TB threat which leaves patients (including many people living with HIV) virtually untreatable using currently available anti-TB drugs. XDR-TB poses a grave public health threat, especially in populations with high rates of HIV and where there are few health care resources.

Swaziland started implementing an ambitious 5 year plan to combat TB, a major public health problem that has been declared an emergency in the SADC region in 2006. As Swaziland makes frantic efforts to identify additional financial resources for TB, there are efforts to strengthen health systems in the country. The country has focused on:

- **improving the quantity and quality of staff involved in TB control;**
- **increasing TB case detection and treatment success rates with expanded DOTS coverage at national and lower levels;**
- **reducing the combined TB patient default and transfer out rates;**
- **scaling up access to counseling and testing for HIV among TB patient**
- **scaling up interventions to manage TB and HIV together, including increased access to anti-retroviral therapy for TB patients who are co-infected with HIV;**
- **Expanding national TB partnerships, public-private collaboration and community participation in TB control activities.**
- **strengthening basic TB care to prevent the emergence of drug-resistance**
- **ensuring prompt diagnosis and treatment of drug resistant cases to cure existing cases and prevent further transmission**
- **Increasing investment in laboratory infrastructures to enable better detection and management of resistant cases.**

The outbreak of XDR TB in the KwaZulu-Natal province of South Africa made it imperative for the Swaziland National Tuberculosis Control Programme to devise plans to respond to the increasing threat of MDR and XDR-TB because Swaziland shares borders with the KwaZulu- Natal. Subsequently a short term plan was developed to address the short-term priorities in order to limit the negative impact of drug-resistant TB. In developing the plan, the NTCP did analyze the issues affecting MDR identification and management through a process of problem identification and analysis.

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- **Lesotho MDR-TB guidelines: Chronic Care for MDR-TB**
- **The PIH Guide to the Medical Management of Multidrug-Resistant Tuberculosis: International Edition**
- **National Tuberculosis Centre: Drug resistant Tuberculosis: a survival guide for clinicians 2nd edition**

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ACRONYMS AND ABBREVIATIONS

AFB acid-fast bacilli	ART antiretroviral therapy
CDC United States Centers for Disease Control and Prevention	CPT co-trimoxazole preventive therapy
DOT directly observed therapy	DOTS internationally recommended strategy for TB control
DRS drug resistance surveillance	DST drug susceptibility testing
FIND Foundation for Innovative New Diagnostics	GFATM Global Fund to Fight AIDS, Tuberculosis and Malaria
GLC Green Light Committee	HIV human immunodeficiency virus
HPF high-power field	HRD human resource development
IUATLD International Union Against Tuberculosis and Lung Disease	LFT liver function test
MDR-TB multidrug-resistant tuberculosis	NTM nontuberculous mycobacteria
PIH Partners In Health	PPD purified protein derivative
PPM public-private mix	SCC short-course chemotherapy
TB tuberculosis	TSH thyroid-stimulating hormone
UNAIDS Joint United Nations Programme on HIV/AIDS	UVGI ultraviolet germicidal irradiation
WHO World Health Organization	Z Pyrazinamide
Am Amikacin	Lfx Levofloxacin
Amx/Clv Amoxicillin/Clavulanate	Cfx Ciprofloxacin
Lzd Linezolid	Cfz Clofazimine
Mfx Moxifloxacin	Clr Clarithromycin PAS
Ofx Ofloxacin	Cm Capreomycin
P-aminosalicylic acid	Cs Cycloserine
Pto Protionamide	E Ethambutol
R Rifampicin	Eto Ethionamide
S Streptomycin	Gfx Gatifloxacin
Th Thioacetazone	H Isoniazid
Trd Terizidone	Km Kanamycin
Vi Viomycin	

**MANAGEMENT OF DRUG RESISTANT
TUBERCULOSIS:
MANAGEMENT AND COORDINATION**

1 Background information on Swaziland TB control programme and drug-resistant tuberculosis in Swaziland

1.1 Epidemiology of tuberculosis in Swaziland

Tuberculosis is one of the leading causes of morbidity and mortality among adults in Swaziland. The number of TB cases notified in Swaziland has increased 6 fold over the last 15 years and is among the highest in the world. Although Swaziland is not listed among the 9 Southern High TB Burden countries, nor among the 9 African High TB Burden countries, the highest TB incidence in the world is reported in Swaziland (WHO, Global TB Report 2008). The country also notified 2,539 sputum smear positive cases (224 per 100,000 population) out of an estimated 5,188, equivalent to 49% sputum smear positive case detection. With over 80% TB-HIV co-infection, Swaziland has one of the highest TB/HIV co-infection rates in the world. Treatment success among sputum smear positive TB cases enrolled in 2005 was 42%. Sputum smear positive TB cases transferred out or not evaluated represent 26% of the cases. Several causes can be appointed for these unsuccessful outcomes, but poor infrastructure – including an insufficient laboratory network and a critical shortage of human resources of all types – is certainly influencing the situation. Follow-up of patients enrolled on treatment is very inadequate. Approximately 60 multi-drug resistant (MDR) TB cases out of an estimated 249 (a rapid MDR TB survey conducted in July-August 2007 showed high rates of MDR-TB among re-treatment cases) are currently on MDR treatment. Because of challenges in the laboratory, often patients are started on second-line treatments without appropriate laboratory confirmation of diagnosis. In addition, the monitoring of MDR-TB patients is far from desirable. Four cases of extensively drug resistant (XDR) TB have been identified so far.

1.2 Causes of DR-TB

Although its causes are microbial, clinical and programmatic, DR-TB is essentially a man-made phenomenon. From a microbiological perspective, resistance is caused by a genetic mutation that makes a drug ineffective against the mutant bacilli. From a clinical and programmatic perspective, it is an inadequate or poorly administered treatment regimen that allows a drug-resistant strain to become the dominant strain in a patient infected with TB. Table 1.1 summarizes the common causes of inadequate treatment.

Short-course chemotherapy (SCC) for patients infected with drug-resistant strains may create even more resistance to the drugs in use. This has been termed the “amplifier effect” of SCC. Ongoing transmission of established drug-resistant strains in a population is also a significant source of new drug-resistant cases.

Table 1.1 Causes of inadequate antituberculosis treatment*

Health-care providers: inadequate regimens	Drugs: inadequate supply or quality	Patients: inadequate drug intake
Inappropriate guidelines Noncompliance with guidelines Absence of guidelines Poor training No monitoring of treatment Poorly organized or funded TB control programmes	Poor quality Unavailability of certain drugs (stock-outs or delivery disruptions) Poor storage conditions Wrong dose or combination	Poor adherence (or poor DOT) Lack of information Lack of money (no treatment available free of charge) Lack of transportation Adverse effects Social barriers Malabsorption Substance dependency disorders

*adapted from WHO programmatic management of DR guidelines 2006

1.3 Magnitude of the DR-TB problem

The incidence of drug resistance has increased since the first drug treatment for TB was introduced in 1943. The emergence of MDR-TB following the widespread use of rifampicin beginning in the 1970s led to the use of second-line drugs. Improper use of these drugs has fuelled the generation and subsequent transmission of highly resistant strains of TB termed extensively DR-TB, or XDR-TB. These strains are resistant to at least one of the fluoroquinolone drugs and an injectable agent in addition to isoniazid and rifampicin.

According to the data from a XDR/MDR-TB rapid survey conducted in July-Aug 2007 where the study population was the high risk groups for MDR/XDR-TB, resistance to first line and second line drugs is common in Swaziland.

Table 1.2: Resistance to first line and second anti-tuberculosis drugs in Swaziland from the Swaziland XDR-TB rapid survey, July-August 2007

Drug	Number Isolates tested (Denominator)	Resistant Strains		Sensitive Strains	
		Frequency	Percentage	Frequency	Percentage
Streptomycin	116	87	75.0	29	25.0
Isoniazid	115	96	83.5	19	16.5
Ethambutol	115	77	67.0	38	33.0
Pyrazinamide	89	63	70.8	26	29.2
Rifampicin	115	55	47.8	60	52.2
Amikacin	111	12	10.8	99	89.2
Kanamycin	111	9	3.5	102	91.9
Capreomycin (lower dose)	111	23	20.7	88	79.3
Capreomycin (higher dose)	111	15	13.5	96	86.5
Ofloxacin (lower dose)	111	14	12.6	97	87.4
Ofloxacin (higher dose)	111	9	3.5	102	91.9
Ethionamide	111	43	38.7	68	61.3

1.4 Coordination

Coordination needs to include the contributions of all the key stakeholders, organizations and external partners, as considered below.

TB Diagnostic health Units system and the National TB Hospital. Transfer from hospitals to outpatient settings requires care, advance planning and good communication. Given the type of care required during the treatment of DR-TB patients, a team of health workers including physicians, nurses and social workers is often used.

Community level. Community involvement and communication with community leaders will greatly facilitate implementation of treatment and respond to needs that cannot be met by medical services alone. Community education, involvement and organization around TB issues will foster community ownership of control programmes and reduce stigma. The NTCP will collaborate with communities to help address the interim needs of patients, including the provision of DOT, food and/or housing. Community health workers often play a critical role in ambulatory care of DR-TB patients, and the NTCP will ensure that they are properly selected, trained and screened for HIV and TB.

Coordination with prisons and other congregate and Institutional organizations. Transmission in prisons is an important source of spread of DR-TB and infection control measures will be put in place to reduce incidence substantially, ensure that arrangements for inmates released from prison before they finish treatment are made for them to complete their treatment. Close coordination and communication with the National TB control programme, advance planning, targeted social support and specific procedures for transferring care will help ensure that patients complete treatment after release from prison.

All health-care providers (both public and private). Private practitioners manage some cases of DR-TB in Swaziland. In these settings, it is important to involve the private sector in the design and technical aspects of the programme. Many PPM programmes have demonstrated effective and mutually beneficial cooperation for susceptible TB. In the PPM system, patients and information move in both directions. Similar PPM mixes will be established for treatment of patients with DR-TB, with exceptional coordination.

International level. International technical support through WHO, the GLC, SRLs, PEPFAR and other technical agencies like the University Research co., LLC, MSF will be made use of in the implementation of Drug Resistant TB management. The NTP will set up and lead an interagency body that ensures clear division of tasks and responsibilities.

PART 2: DRUG RESISTANCE TB MANAGEMENT MANUAL

2 Definitions: case registration, bacteriology and treatment outcomes

2.1 Definitions of drug resistance and diagnostic Category IV

DR-TB is **confirmed** through laboratory tests that show that the infecting isolates of *Mycobacterium tuberculosis* grow in vitro in the presence of one or more antituberculosis drugs (see Chapter 6 for further information on laboratory requirements). Four different categories of drug resistance have been established:

- **Mono-resistance:** resistance to one antituberculosis drug.
- **Poly-resistance:** resistance to more than one antituberculosis drug, other than both isoniazid and rifampicin.
- **Multidrug-resistance:** resistance to at least isoniazid and rifampicin.
- **Extensive drug-resistance:** resistance to any fluoroquinolone, and at least one of three injectable second-line drugs (capreomycin, kanamycin and amikacin), in addition to multidrug-resistance.

Diagnostic Category IV includes patients with:

- **Confirmed MDR-TB.**
- **Suspected MDR-TB.** This requires that the case management committee recommends that the patient should receive Category IV treatment. Patients may be entered in the Category IV register and started on Category IV treatment before MDR-TB is confirmed only if representative DST surveys or other epidemiologic data indicate a very high probability of MDR-TB (Swaziland has not yet carried out the representative DST survey)
- **Poly-resistant TB.** Some cases of poly-resistant TB will require Category IV treatments. These patients require prolonged treatment (18 months or more) with first-line drugs combined with two or more second-line drugs and should be entered into the Category IV register.

2.2 Site of drug-resistant TB disease (pulmonary and extrapulmonary)

In general, recommended treatment regimens for drug-resistant forms of TB are similar, irrespective of site. The importance of defining site is primarily for recording and reporting purposes.

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

Patients with both pulmonary and extrapulmonary TB should be classified as a case of pulmonary TB.

2.3 Sputum conversion

Sputum conversion is defined as two sets of consecutive negative smears and cultures, from samples collected at least 30 days apart. Both bacteriological techniques (smear and culture) should be used to

monitor patients throughout therapy. The date of the first set of negative cultures and smears is used as the date of conversion (and the date to determine the length of the intensive phase and treatment).

2.4 Category IV patient registration group based on history of previous antituberculosis treatment

Category IV patients should be assigned a registration group based on their treatment history, which is useful in assessing the risk for MDR-TB. The registration groups will describe the history of previous treatment and do not purport to explain the reason(s) for drug resistance. Classification is determined by treatment history at the time of collection of the sputum sample that was used to confirm MDR-TB. The groups are as follows:

- **New.** (Same definition as in classification according to previous drug use). A patient who has received no or less than one month of antituberculosis treatment.
- **Relapse.** A patient whose most recent treatment outcome was “cured” or “treatment completed”, and who is subsequently diagnosed with bacteriologically positive TB by sputum smear microscopy or culture.
- **Treatment after default.** A patient who returns to treatment, bacteriologically positive by sputum smear microscopy or culture, following interruption of treatment for two or more consecutive months.
- **Treatment after failure of Category I.** A patient who has received Category I treatment for TB and in whom treatment has failed. Failure is defined as sputum smear positive at five months or later during treatment.
- **Treatment after failure of Category II.** A patient who has received Category II treatment for TB and in whom treatment has failed. Failure is defined as sputum smear positive at five months or later during treatment.
- **Transfer in.** A patient who has transferred in from another register for treatment of DR-TB to continue Category IV treatment.
- **Other.** There are several types of patients who may not fit into any of the above categories. The NTCP will classify these patients into groups that are meaningful according to the local epidemiology of disease. Examples include the following: sputum smear positive patients with unknown previous treatment outcome; sputum smear positive patients who received treatment other than Category I or II (possibly in the private sector); previously treated patients with extrapulmonary TB; patients who have received several unsuccessful treatments, were considered incurable by health staff and who have lived with active TB disease with no or inadequate treatment for a period of time until Category IV treatment became available (so-called “chronic” patients)

All patients should have their HIV status recorded at the start of treatment. Rapid HIV testing should be performed according to national protocol if there is any doubt about the patient's HIV status, or if the patient has not been tested recently.

2.5 Treatment outcome definitions for Category IV treatment

The following are mutually exclusive Category IV outcome definitions that rely on the use of laboratory smear and culture as a monitoring tool. They have been constructed to parallel the six DOTS outcomes for drug-susceptible TB. All patients should be assigned the first outcome they experience for the treatment being evaluated for recording and reporting purposes.

- **Cured.** A Category IV patient who has completed treatment according to NTCP programme protocol and has at least five consecutive negative cultures from samples collected at least 30

days apart in the final 12 months of treatment. If only one positive culture is reported during that time, and there is no concomitant clinical evidence of deterioration, a patient may still be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative cultures taken at least 30 days apart.

- **Treatment completed.** A Category IV patient who has completed treatment according to programme protocol but does not meet the definition for cure because of lack of bacteriological results (i.e. fewer than five cultures were performed in the final 12 months of treatment).
- **Died.** A Category IV patient who dies for any reason during the course of MDR-TB treatment.
- **Failed.** Treatment will be considered to have failed if two or more of the five cultures recorded in the final 12 months of therapy are positive, or if any one of the final three cultures is positive. (Treatment will also be considered to have failed if a clinical decision has been made to terminate treatment early because of poor clinical or radiological response or adverse events. These latter failures can be indicated separately in order to do sub-analysis).
- **Defaulted.** A Category IV patient whose treatment was interrupted for two or more consecutive months for any reason.
- **Transferred out.** A Category IV patient who has been transferred to another reporting and recording unit and for whom the treatment outcome is unknown.

Patients who have **transferred in** should have their outcome reported back to the treatment centre from which they originally were registered. The responsibility of reporting their final outcomes belongs to the original treatment centre.

2.6 Cohort analysis

All patients should be analysed in two different cohorts (groups of patients) depending on the purpose:

The treatment cohort includes only patients who start Category IV treatment. It is defined by the date of start of Category IV treatment. The purpose is mainly to assess result of treatment and trends over time.

The diagnostic cohort includes patients diagnosed with MDR-TB (identified in the DST register by date of DST result) during a specific period of time. The purpose is mainly to assess the number of patients with DR-TB, in subgroups and over time. This allows the programme to evaluate delay in treatment start and proportion of patients who started treatment.

The recommended timeframe for Category IV treatment cohort analysis reflects the long duration of Category IV regimens. Cohort analyses will be carried out at 24 months and, if needed, repeated at 36 months after the last patient starts treatment. For each treatment cohort, an interim status will be assessed at 6 months after the start of treatment to monitor programme progress.

3 Case-finding strategies

3.1 Targeting risk groups for DST

Routine DST at the start of treatment may be indicated for all TB patients or only in specific groups of patients at increased risk for drug resistance.

TABLE 3.1: Target groups for DST *

RISK FACTORS FOR DR-TB	COMMENTS
Failure of re-treatment regimens and chronic TB cases	Chronic TB cases are defined as patients who are still sputum smear-positive at the end of a re-treatment regimen. These patients have perhaps the highest MDR-TB rates of any group, often exceeding 80%
Exposure to a known DR-TB case	Most studies have shown close contacts of MDR-TB patients to have very high rates of MDR-TB. Management of DR-TB contacts.
Failure of Category I	Failures of Category I are patients who while on treatment are sputum smear-positive at month 5 or later during the course of treatment. Not all patients in whom a regimen fails have DR-TB, and the percentage may depend on a number of factors, including whether rifampicin was used in the continuation phase and whether DOT was used throughout treatment. More information on regimen implications for Category I failures is given below.
Failure of antituberculosis treatment in the private sector	Antituberculosis regimens from the private sector can vary greatly. A detailed history of drugs used is essential. If both isoniazid and rifampicin were used, the chances of MDR-TB may be high. Sometimes second-line antituberculosis drugs may have been used, and this is important information for designing the re-treatment regimen.
Patients who remain sputum smear-positive at month 2 or 3 of SCC	Many programmes may choose to do culture and DST on patients who remain sputum smear-positive at months 2 and 3. This group of patients is at risk of DR-TB, but rates can vary considerably.
Relapse and return after default without recent treatment failure	Evidence suggests that most relapse and return after default cases do not have DR-TB. However, certain histories may point more strongly to possible DR-TB; for example, erratic drug use or early relapses.
Exposure in institutions that have DR-TB outbreaks or a high DR-TB prevalence	Patients who frequently stay in homeless shelters, prisoners in many countries and health-care workers in clinics, laboratories and hospitals can have high rates of DR-TB.
Residence in areas with high DR-TB prevalence	DR-TB rates in many areas of the world can be high enough to justify routine DST in all new cases.
History of using antituberculosis drugs of poor or unknown quality	The percentage of DR-TB caused by use of poor-quality drugs is unknown but considered significant. It is known that poor-quality drugs are prevalent in all countries. All drugs should comply with quality-assured WHO standards.

*Adopted from the WHO programmatic management of DR-TB guidelines

3.2 DST specimen collection

DST is a case-finding strategy and it is recommended that two sputum specimens be obtained for culture and that DST be performed with the specimen that produces the best culture. DST does not routinely need to be carried out in duplicate.

3.3 Case-finding in paediatric patients

Paediatric cases require adjustments in diagnostic criteria and indications for treatment. Younger children in particular may not be able to produce sputum specimens on demand. Children should not be excluded from treatment solely because sputum specimens are not available; smear- and culture-negative children with active TB who are close contacts of patients with DR-TB can be started on Category IV regimens.

3.4 Case-finding of patients with mono- and poly-drug resistance

Mono- and poly-drug resistant strains are strains that are resistant to antituberculosis drugs but not to both isoniazid and rifampicin. Most diagnostic strategies used by DR-TB control programmes will also identify cases of mono- and poly-drug resistance, in addition to MDR-TB cases. Patients with mono- or poly-drug resistance may require modifications to their SCC regimens or to be moved to Category IV regimens.

3.5 Use of rapid molecular testing

Case-finding strategies can be greatly enhanced with rapid drug-resistance testing, which significantly improves the ability to identify earlier cases of DR-TB that can be isolated and started on treatment.

Rifampicin is the most potent antituberculosis drug of the first-line regimen, and rifampicin resistance most commonly occurs with concomitant isoniazid resistance. A positive rapid test for rifampicin resistance is a strong indicator that a patient may have MDR-TB while a negative test makes a final diagnosis of MDR-TB highly unlikely.

Table 3.1 is a suggested the use of rapid drug-sensitivity testing for identification and initial management of patients suspected of TB who is at increased risk of DR-TB. Administrative infection control measures including isolation should start as soon as a patient is identified as a TB suspect. Rapid testing can identify DR-TB quickly and allows patients to be taken off general TB wards where they may infect others with resistant strains.

3.6 Use of second-line DST in case-finding and diagnosing XDR-TB

Swaziland DR-TB control programmes does not have the capacity to perform DST of second-line drugs and tests for the second-line injectable agents (kanamycin, amikacin and capreomycin) and a fluoroquinolone are done at the supra national reference laboratory. This will enables ability to perform case-finding for XDR-TB and to assure proper treatment.

The two strongest risk factors for XDR-TB are:

- **Failure of an anti-TB regimen that contains second-line drugs including an injectable agent and a fluoroquinolone.**
- **Close contact with an individual with documented XDR-TB or with an individual for whom treatment with a regimen including second-line drugs is failing or has failed.**

4 Treatment strategies for MDR-TB and XDR-TB

4.1 Essential assessments before designing a treatment strategy

In Swaziland the treatment strategies were developed after analysis of the Rapid Drug Resistance TB Survey on MDR/XDR-TB and consideration was also given to the availability and use of antituberculosis drugs in the country. 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) is to be determined by the National Representative Drug Resistant TB Survey that is to be conducted in the year 2009. Most second-line antituberculosis drugs have been used rarely (with the exception of ciprofloxacin use in the syndromic management of STIs) and are likely to be effective in DR-TB regimens. However a study will be carried out to determine the frequency of use of second-line antituberculosis drugs in the country.

Patients confirmed with MDR TB by DST for first line drugs should be put on Standardized Treatment Regimen followed by Individualized Treatment Regimen. It is strongly recommended that MDR-TB be confirmed in all patients enrolled on a standardized Category IV regimen. Otherwise, misclassification of patients will either deny isoniazid and rifampicin to patients who would benefit from these drugs, or unnecessarily expose patients to potentially toxic first- or second-line drugs that they do not need. The regimen for each patient will be adjusted to an Individualized Treatment Regimen when DST results to SLDs become available.

4.2 Classes of antituberculosis drugs

The classes of antituberculosis drugs have traditionally been divided into first- and second-line drugs, with isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin being the primary first-line drugs. These guidelines often refer to this classification but also use a group system based on efficacy, experience of use and drug class. These groups are referred to in the following sections and are very useful for the design of treatment regimens. The different groups are shown in Table 4.1. Not all drugs in the same group have the same efficacy or safety.

Table 4.1: Method of grouping antituberculosis drugs

Grouping	Drugs
Group 1 First-line oral agents	isoniazid (H); rifampicin (R); ethambutol (E); pyrazinamide (Z); rifabutin (Rfb) ^a
Group 2 Injectable agents	kanamycin (Km); amikacin (Am); capreomycin (Cm); streptomycin (S)
Group 3 Fluoroquinolones	moxifloxacin (Mfx); levofloxacin (Lfx); ofloxacin (Ofx)
Group 4 Oral bacteriostatic second-line agents	ethionamide (Eto); protionamide (Pto); cycloserine (Cs); terizidone (Trd); <i>p</i> -aminosalicylic acid (PAS)
Group 5 Agents with unclear role in DR-TB treatment (not recommended by WHO for routine use in DR-TB patients)	clofazimine (Cfz); linezolid (Lzd); amoxicillin/clavulanate (Amx/Clv); thioacetazone (Thz); imipenem/cilastatin (Ipm/Cln); high-dose isoniazid (high-dose H); ^b clarithromycin (Clr)

^a Rifabutin is not on the WHO List of Essential Medicines. It has been added 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.

Group 1. Group 1 drugs, the most potent and best tolerated, should be used if there is good laboratory evidence and clinical history to suggest 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.

Group 2. All patients should receive a Group 2 injectable agent if susceptibility is documented or suspected. These guidelines suggest the use of kanamycin or amikacin as the first choice of an injectable agent, given the high rates of streptomycin resistance in DR-TB patients. In addition, both these agents are low cost, have less ototoxicity than streptomycin and have been used extensively for the treatment of DR-TB throughout the world. Amikacin and kanamycin are considered to be very similar and have a high frequency of cross-resistance. If an isolate is resistant to both streptomycin and kanamycin, or if DRS data show high rates of resistance to amikacin and kanamycin, then capreomycin should be used.

Group 3. All patients should receive a Group 3 medication if the strain is susceptible or if the agent is thought to have efficacy. Ciprofloxacin is no longer recommended to treat drug-susceptible or drug-resistant TB. Currently, the most potent available fluoroquinolones in descending order based on in vitro activity and animal studies are: moxifloxacin = gatifloxacin > levofloxacin > ofloxacin. While ofloxacin is commonly used because of relatively lower cost, the later-generation fluoroquinolones, moxifloxacin and levofloxacin, are more effective and have similar adverse effect profiles. Gatifloxacin should only be used when there is no other option of a later-generation fluoroquinolone and where close follow up can be assured. A later-generation fluoroquinolone is recommended for treatment of XDR-TB.

Group 4. Group 4 medications are added based on estimated susceptibility, drug history, efficacy, side-effect profile and cost. Ethionamide or prothiomamide is often added because of low cost; however, these drugs do have some cross-resistance with isoniazid. If cost is not a constraint, PAS may be added first, given that the enteric-coated formulas are relatively well tolerated and it shares no cross-resistance to other agents. When two agents are needed, cycloserine is used often in conjunction with ethionamide or protionamide or PAS. Since the combination of ethionamide or protionamide and PAS often causes a high incidence of gastrointestinal adverse effects and hypothyroidism, these agents are usually used together only when three Group 4 agents are needed: ethionamide or protionamide, cycloserine and PAS. Terizidone contains two molecules of cycloserine. It can be used instead of cycloserine and is assumed to be as efficacious, but there are no direct studies comparing the two. The approach of slowly escalating drug dosage is referred to as “drug ramping”. The drugs in Group 4 may be started at a low dose and escalated over two weeks.

Group 5. Group 5 drugs are not recommended by WHO for routine use in DR-TB treatment because their contribution to the efficacy of multidrug regimens is unclear. However, they can be used in cases 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 DR-TB. If a situation requires the use of Group 5 drugs, these guidelines recommend using at least two drugs from the group, given the limited knowledge of efficacy.

4.3 Designing a treatment regimen

The following are the basic principles involved in any regimen design:

- **Regimens should be based on the history of drugs taken by the patient.**
- **Drugs commonly used in the country and prevalence of resistance to first-line and second-line drugs should be taken into consideration when designing a regimen.**
- **Regimens should consist of at least four drugs with either certain, or almost certain, effectiveness. If the evidence about the effectiveness of a certain drug is unclear, the drug can be part of the regimen but it should not be depended upon for success. Often, more than**

four drugs may be started if the susceptibility pattern is unknown, effectiveness is questionable for an agent(s) or if extensive, bilateral pulmonary disease is present.

- Starting with a strong standardized regimen is recommended and then later adjusted to individualized regimen because patients for whom regimens with second-line drugs fail are very difficult to cure.
- Drugs are administered seven days a week.
- When possible, pyrazinamide, ethambutol and fluoroquinolones should be given once per day as the high peaks attained in once-a-day dosing may be more efficacious. Once-a-day dosing is permitted for other second-line drugs depending on patient tolerance; however ethionamide/prothionamide, Terizidone/cycloserine and PAS have traditionally been given in split doses during the day to reduce adverse effects.
- The drug dosage should be determined by body weight. A suggested weight-based dosing scheme is shown in table 4.3.

Treatment of adverse drug effects should be immediate and adequate in order to minimize the risk of treatment interruptions and prevent increased morbidity and mortality due to serious adverse effects. Where side effects occur, preference should be given to treating the side effects and avoid stopping the drugs.

- An injectable agent (an aminoglycoside or capreomycin) is used for a minimum of six months and at least four months past culture conversion (see table 4.4 on duration of injectable use).
- The minimum length of treatment is 18 months after culture conversion (see table 4.4 on duration of treatment).
- Each dose is given as directly observed therapy (DOT) throughout the treatment. A treatment supporter card is marked for each observed dose.
- DST of drugs with high reproducibility and reliability (and from a dependable laboratory) should be used to guide therapy. It should be noted that the reliability and clinical value of DST of some first-line and most of the second-line antituberculosis drugs have not been determined. DST does not predict with 100% certainty the effectiveness or ineffectiveness of a drug. A DST of drugs such as ethambutol, streptomycin and Group 4 and 5 drug does not have high reproducibility and reliability; these guidelines strongly caution against basing individual regimens on DST of these drugs.
- Pyrazinamide can be used for the entire treatment if it is judged to be effective. Many DR-TB patients have chronically inflamed lungs, which theoretically produce the acidic environment in which pyrazinamide is active. Alternatively, in patients doing well, pyrazinamide can be stopped with the injectable phase if the patient can continue with at least three certain, and effective drugs especially where pyrazinamide side effects are unbearable.
- There is well-known cross-resistance between some of the antibiotics used in treating TB. All rifamycins have high levels of cross-resistance. Fluoroquinolones are believed to have variable cross-resistance between each other, with in vitro data showing that some later-generation fluoroquinolones remain susceptible when earlier-generation fluoroquinolones are resistant. In these cases, it is unknown if the later-generation fluoroquinolones remain effective clinically.
- Amikacin and kanamycin have very high cross-resistance. Capreomycin and viomycin have high cross-resistance. Other aminoglycosides and polypeptides have low cross-resistance. Prothionamide and ethionamide have 100% cross-resistance. Ethionamide can have cross-resistance to isoniazid if the inhA mutation is present. Thioacetazone cross-resistance to

- **isoniazid, ethionamide and PAS has been reported but is generally considered to be low**
- **In revising regimens add at least 3 new sensitive drugs.**
- **Early DR-TB detection and prompt initiation of treatment are important factors in determining successful outcomes.**

4.4 Role of drug susceptibility testing

In Swaziland where reliable DST is available, standardized regimens may be chosen as a strategy over individualized regimens for the following reasons:

- Interpretation of DST to some of the first- and second-line drugs is difficult and could mislead regimen design. Standardized regimens can give guidance to clinicians and prevent basing decisions on DST that is not reliable. These guidelines do not recommend using DST of ethambutol, pyrazinamide and the drugs in Groups 4 and 5 to base individual regimen design.
- Where turnaround time for culture-based DST methods is long, patients at increased risk for DR-TB and with deteriorating clinical condition should be placed on an empirical or standardized Category IV regimen until DST results are available.
- The laboratory may not perform DST of certain drugs, or may perform them at different times. Results from rapid methods (molecular) may be available within days, but only for certain first-line drugs such as isoniazid and rifampicin. Second-line DST will only be performed on specimens after resistance to first-line drugs is confirmed or where special request is made by the clinician.

It is important to note that delays in treatment while awaiting DST can result in increased morbidity and mortality, as well as longer periods of infectiousness.

4.5 Standardized treatment

All patients in a defined group or category receive the same regimen. Suspected MDR-TB should be confirmed by DST whenever possible. For a standardized regimen that will treat the vast majority of patients with four effective drugs, it is often necessary to use five or six drugs to cover all possible patterns of resistance. In most cases, an injectable agent and a fluoroquinolone form the core of the regimen. The principle is to use one established standardized regimen with most powerful drugs for all patients with highest probability to be sensitive.

In some circumstances it may be convenient to wait for DST results if the laboratory uses a rapid method with a turnaround time of 1 to 2 weeks. In addition, in a patient with chronic disease treated several times with second-line drugs, waiting for DST results may be prudent even if the turnaround time is several months, as long as the patient is clinically stable and appropriate infection control measures are in place.

The recommended Category IV Standardized Treatment is: **Km-Lfx-Eto-CS (TRD)-PAS-Z**

4.6 Individualized treatment

Each regimen is designed on the basis of previous history of antituberculosis treatment and individual DST results of patients. If DST results are not known for all the first-line drugs, the choice can be guided by knowledge of prevalence of resistance based on sample surveys. The design of an individualized regimen differs from that of standardized treatment regimens in that it uses the resistance pattern of the infecting strain of the individual patient as another source of data, in addition to the patient's treatment history and the prevailing resistance patterns in the community.

Every effort should be made to supplement the patient's memory with objective records from previous

health-care providers. A detailed clinical history can help to indicate which drugs are likely to be ineffective. The probability of acquired resistance to a drug increases with the length of time it has been administered. In particular, evidence of clinical or bacteriological treatment failure (positive smears or cultures) during a period of regular drug administration is highly suggestive of drug resistance. If a patient used a drug for longer than one month with persistent positive smears or cultures, the strain should be considered as “probably resistant” to that drug, even if by DST it is reported as susceptible. Resistance can develop in some cases in less than one month.

The results of DST should complement rather than invalidate other sources of data about the likely effectiveness of a specific drug. If a history of previous antituberculosis drug use suggests that a drug is likely to be ineffective as a result of resistance, this drug should not be relied upon as one of the four core drugs in the regimen even if the strain is susceptible in the laboratory. However, if the strain is resistant to a drug in the laboratory, but the patient has never taken it and resistance to it is extremely uncommon in the community, this may be a case of a laboratory error or a result of the limited specificity of DST for some second-line drugs. Commonly, an empirical treatment is adjusted in each patient when his or her DST results become available.

Combinations of these treatment strategies are often used as illustrated as in the following table.

Table 4.2 Steps in defining the recommended strategies for Swaziland

Patient group	Recommended strategy^a	
New patient with active TB	Start Category I treatment Perform DST of at least H and R in patients not responsive to Category I (for non converters at 2/3 months or treatment failures at 5 months). Rapid DST techniques are preferable	
Patient in whom Category I failed	Perform DST of isoniazid and rifampicin at a minimum in all patients before treatment starts Start Standardized Category IV treatment	
Patient in whom Category II failed	Perform DST of H and R at a minimum in all patients before treatment starts. Perform DST of Km, Cm, Ofx, Mfx, Eto if initial DST returns DR-TB. Start Category IV Standardized treatment while awaiting DST Adjust regimen to individualized treatment when DST results become available.	
Patient with history of relapse or patient returning after default	Perform DST of H and R at a minimum in all patients before treatment starts Start Category II treatment while awaiting DST Adjust regimen to a Category IV standardized regimen if DST returns DR-TB	
Contact of MDR-TB patient now with active TB (Contact resistance pattern known)	<i>Close contact with high risk of having the same strain</i>	Perform rapid diagnosis and DST of H and R at a minimum in all patients before treatment starts Start Category IV individualized treatment based on DST of index strain Adjust to individualized regimen according to DST results
	<i>Close contact with high risk of having the same strain</i>	Perform rapid diagnosis and DST of H and R at a minimum in all patients before treatment starts Start Category IV Standardized treatment while awaiting DST Adjust to individualized regimen according to DST results

Patient with documented MDR-TB	Documented, or almost certain, susceptibility to a FQ and IA	Start Category IV Standardized treatment .
	Documented, or almost certain, susceptibility to FQ Documented, or almost certain, resistance to an IA	Start Category IV Standardized treatment . Use an IA with documented susceptibility. If the strain is resistant to all IAs, use one for which resistance is relatively rare eg Capreomycin.
	Documented, or almost certain, resistance to a FQ Documented, or almost certain, susceptibility to IA	Start Category IV Standardized treatment . Use a higher generation FQ
Patient in whom Category IV failed or Patient with documented MDR-TB and history of extensive second-line drug use	Perform DST of (Km, Cm, Ofx, Mfx, Eto)IA and FQ (and H and R if not already done) before treatment starts Start Category IV Standardized treatment for XDR-TB while awaiting DST Adjust regimen according to DST results	
Patient with documented or almost certain XDR-TB	Start Category IV Standardized treatment for XDR-TB Z-CM-MFX-ETO-CS(TRD)-PAS-AMX/CLV-CFZ	

^a Whenever possible, perform DST of injectable agents (IA), fluoroquinolone (FQ) and Ethionamide (Eto) if MDR-TB is documented.

Table 4.3: Dosing of anti-tuberculosis drugs is based on the weight of the patient.

Drug	Average daily dosage	33-50 KG	51–70 KG	>70 KG (max dose)
Isoniazid (H) (100, 300 mg)	4–6 mg/kg daily	200-300 mg	300 mg	300 mg
Rifampicin (R) (150, 300 mg)	10–20 mg/kg daily	450-600 mg	600 mg	600 mg
Ethambutol (E) (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 mg	2000-2500 mg
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
Capreomycin (Cm) (1 g vial)	15–20 mg/kg daily	500-750 mg	1000 mg	1000 mg

Ofloxacin (Ofx) (200 mg)	Usual adult dose is 800 mg	800 mg	800 mg	800-1000 mg
Levofloxacin (Lfx) (250 mg, 500 mg)	Usual adult dose is 1000 mg	750 mg	750-1000 mg	750-1000mg
Moxifloxacin (Mfx) (400 mg)	Usual adult dose is 400 mg	400 mg	400 mg	400 mg
Ethionamide (Eto) (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
Terizidone (Trd) (250 mg)	15–20 mg/kg daily	500 mg	750 mg	750–1000 mg
PASER (4 g sachets)	150 mg/kg daily	8 g	8 g	8 -12 g

All patients receiving cycloserine or terizidone should receive pyridoxine. The recommended daily dose is 50 mg for every 250 mg of cycloserine/terizidone.

Once daily dosing for all drugs is preferred. However, most patients cannot tolerate once-daily dosing of ethionamide, cycloserine and PAS, and these drugs may be given in divided doses twice-daily.

4.7 Completion of the injectable agent (intensive phase)

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

The use of an individualized approach that reviews the cultures, smears, X-rays (improvement/worsening picture: i.e duration can be at least 6 months after conversion when there is extensive lung damage) and the patient's clinical status may also help in deciding whether to continue an injectable agent longer than the above recommendation, particularly in the case of patients for whom the susceptibility pattern is unknown, effectiveness is questionable for an agent(s), or extensive or bilateral pulmonary disease is present. In extreme circumstances, in patients infected with highly resistant strains, the clinician may opt to continue the injectable during the entire course of treatment. In these cases, the clinician may decrease the frequency to 3 times/week or 6 days a week after conversion.

Table 4.4: Treatment phases

	Duration	Characteristics
Initial Phase	At least 6 months and at least four months after the patient first become and remain smear-or culture-negative.	Close monitoring for side effects At least 5-6 drugs Includes injectable drugs daily. DOT for every dose taken
Continuation Phase	At least 18 months from time of culture conversion.	Less side effects Usually all oral drugs preferably given once daily. DOT for every dose taken

4.8 Duration of treatment

The recommended duration of treatment is guided by culture conversion. Despite emerging evidence that shorter regimens may be efficacious, these guidelines recommend continuing therapy for a minimum of 18 months after culture conversion until there is conclusive evidence to support a shorter duration of treatment. Extension of therapy to 24 months may be indicated in chronic cases with extensive pulmonary damage.

4.9 Extrapulmonary DR-TB

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

4.10 Surgery in Category IV treatment

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

Resection surgery should be timed to offer the patient the best possible chances of cure with the least morbidity. Thus, the timing of surgery may be earlier in the course of the disease when the patient's risk of morbidity and mortality is lower, for example, when the disease is still localized to one lung or one lung lobe. In other words, surgery should not be considered as a last resort. Generally, at least two months of therapy should be given before resection surgery in order to decrease the bacterial infection in the surrounding lung tissue. Even with successful resection, an additional 12–24 months of chemotherapy should be given.

Specialized surgical facilities should include stringent infection control measures, since infectious substances and aerosols are generated in large quantities during surgery and during mechanical ventilation and postoperative pulmonary hygiene manoeuvres.

General indications for resection surgery include patients who remain smear-positive, with resistance to a large number of drugs; and localized pulmonary disease. Computerized tomography if available, pulmonary function testing and quantitative lung perfusion/ventilation are recommended as part of the preoperative work-up. Major Surgery if indicated should be in the hands of a thoracic surgeon.

4.11 Adjuvant therapies in DR-TB treatment

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

4.11.1 Nutritional support

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

Nutritional support to be given;

- **Provision of free staple foods, and whenever possible should include a source of protein.**
- **Vitamin B6 (pyridoxine) should also be given to all patients receiving cycloserine or terizidone to prevent adverse neurological effects.**
- **Vitamins (especially vitamin A)**
- **Mineral supplements can be given in areas where a high proportion of the patients have deficiencies. If minerals (zinc, iron, calcium,etc.) are given, they should be administered at a different time from the fluoroquinolones, as they can interfere with the absorption of these drugs.**

4.11.2 Corticosteroids

The adjuvant use of corticosteroids in DR-TB patients has been shown not to increase mortality and can be beneficial in conditions such as severe respiratory insufficiency, and central nervous system or pericardial involvement. Prednisone is commonly used, starting at approximately 1 mg/kg and gradually decreasing the dose to 10 mg per week when a long course is indicated. Corticosteroids may also alleviate symptoms in patients with an exacerbation of obstructive pulmonary disease. In these cases, prednisone may be given in a short taper over 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.

4.11.3 Treatment of XDR-TB

The standardized treatment for XDR-TB suspects and confirmed cases is: **Z-CM-MFX-ETO-CS (TRD)-PAS-AMX/CLV-CFZ**, while awaiting DST, adjust regimen according to second line DST results. All confirmed XDR-TB cases will be managed at the TB hospital.

4.12 Organization of DR-TB treatment.

4.12.1 The National tuberculosis Hospital

The national tuberculosis hospital is responsible for specialized management of tuberculosis that includes drug resistant tuberculosis. It is equipped with highly skilled professionals and will be responsible for implementing the clinical components of the drug resistant tuberculosis guidelines. The admission criteria to the TB hospital are as follows:

All confirmed MDR cases will be admitted for a minimum of 3 weeks but maybe prolonged for up to even more than 6 months. During the three weeks, patients will be initiated on MDR-TB intensive treatment, evaluated for HIV and ART eligibility, community treatment support, drug adverse effects and drug interactions etc. After 3 weeks in some exceptional cases (see criteria below), MDR patients and with agreement of the case management committees may be discharged for ambulatory care. ART will be initiated at the MDR-TB Hospital for all HIV/TB co-infected patients who are eligible (those who opt in). After discharge patients on ART will be followed up at TB Clinics until MDR treatment is over.

The purposes for admission include:

1. Initiation of treatment
2. Adherence issues
3. patient very sick

4. Severe adverse effects
5. Immobility
6. Vulnerable patients eg orphan, mentally , socially or physically handicapped
7. patient request for re-admission after initial discharge

All confirmed XDR-TB patients will be admitted until sputum culture conversion or for a minimum of 6 months.

The discharge criteria are:

1. Adequate infection control measures in the home are ensured
2. Adequate treatment support for DOT during the intensive phase is assured
3. Adequate nutritional and social patient support
4. Measures to ensure transport to the MDR-TB hospital for regular follow up is taken care of
5. At the end of intensive MDR-TB treatment when the patient has two consecutive sputum culture negative

The referring health facility should inform the outpatient department of the TB hospital before transporting the patients for admission. Transport for clients referred to the TB hospital shall be arranged by the referring facility or the national TB referral hospital.

The composition of the CMC includes: The Senior Medical officer, a medical officer, Two MDR-TB nurses, two social workers, Physiotherapist, psychologist and the MDR-TB focal person of the hospital.

4.12.2 Ambulatory Care

Patients may receive ambulatory care when

- **Adequate infection control measures in the home are ensured - minimizing further risk to family and friends**
- **Adequate treatment support is assured**
- **Adequate nutritional and social patient support are organized**
- **Measures to ensure transport to the MDR-TB hospital for regular follow up is in place**

Patients will be reviewed twice daily by DOTS worker (clinic staff if receiving injections and DOT worker otherwise). Ambulatory patients will be reviewed monthly (from OPD) after discharge. In every quarter, 2 consecutive reviews will be at the diagnostic facility, while the third will be a major review at the MDR-TB hospital or more frequently if clinically indicated.

Infection control is also very important for ambulatory care in the intensive phase. Adequate patient education and measures surrounding infection control include:

- **cough hygiene**
- **education - including not to go to school/work until conversion**
- **isolation - separate sleeping area must be arranged including away from spouse and children**
- **adequate ventilation in home**
- **masks**
- **community and family education**

In addition special attention must be given to congregate settings: prisons, army, school, churches, workplace and education on ventilation, education, isolation (not going/appropriate situation). All MDR suspects and MDR patients should be given long term sick leave until culture conversion

Upon discharge;

- **A transfer letter written to the TB unit in triplicate (1 copy remains at TB hospital in patient's file, 1 copy sent with the patient to take to TB unit, 1 copy sent from the TB hospital to the TB unit).**
- **Transport to patient's home to be provided on discharge.**
- **Patient discharged with DOT supporter card and MDR TB adherence supporter informed by the discharging staff, MDR-TB adherence supervisor at the TB hospital**
- **Follow up after discharge;**
- **During intensive phase—monthly at the TB hospital.**
- **During continuation phase—every 3rd month at the TB hospital, and monthly in between the 3 months at TB unit nearest to patient's home.**
- **Termination of treatment – at the TB hospital.**
- **The following M&E tools will be used by DR-TB programme**
 - DR TB Suspects Register.
 - Duplicate treatment card.
 - DOT Supporter cards for DR TB.
- **Items to be brought by the patient on review:**
 - Patient to come with Patient card and DOT supporter card for monitoring of adherence.
 - Patient to bring 2 sputum specimens for smear and culture. The patient will come with an early morning sputum and Spot examination to be done on one of the specimens for smear results.

5 Mono- and poly-resistant strains (drug-resistant tuberculosis other than MDR-TB)

5.1 General considerations

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

5.2 Consequences for reporting

Patients whose regimens require minor adjustments should be recorded in the traditional BMU Tuberculosis Register. These regimens are considered “modifications” of Category I or Category II treatment. They are not classified as Category IV treatments, which are regimens designed to treat MDR-TB. The adjustment should be noted in the comments section of the Register and the adjusted treatment continued for the indicated length of time.

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

Patients with mono- and poly-resistant will start standardized category 4 treatment plus the sensitive first line drugs. When a decision has been made to modify standardized SCC, the most effective regimen should be chosen from the start to maximize the likelihood of cure; effective drugs should not be withheld for later use. An expert should be consulted.

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

DST results. The DST result that prompts a change in treatment may not accurately reflect the bacterial population at the time it is reported since it reflects the bacterial population at the time the sputum was collected.

If DST of pyrazinamide is not available, pyrazinamide cannot be depended upon as being an effective drug in the regimen. Some clinicians would add pyrazinamide to those regimens because a significant percentage of patients could benefit from the drug; however, it would not be counted upon as a core drug in the regimen.

The design of regimens for mono- and poly-resistant cases of TB requires experience; it is recommended for programmes with good infrastructure that are capable of treating MDR-TB. **A Case management committee meets periodically to determine individually designed treatments for mono- and poly-resistance. The CMC will review the treatment history, DST patterns and the possibility of strains of *M. tuberculosis* having acquired new resistance, and then determines the regimen.**

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

6.1 Pregnancy

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

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

Start treatment of drug resistance in second trimester or sooner if condition of patient is severe.

Since the majority of teratogenic effects occur in the first trimester, therapy may be delayed until the second trimester. The decision to postpone the start of treatment should be agreed by both patient and doctor after analysis of the risks and benefits. It is based primarily on the clinical judgment resulting from the analysis of life-threatening signs/symptoms and severity/aggressiveness of the disease (usually reflected in extent of weight loss and lung affection during the previous weeks). When therapy is started, three or four oral drugs with demonstrated efficacy against the infecting strain should be used and then reinforced with an injectable agent and possibly other drugs immediately postpartum.

Avoid injectable agents. For the most part, aminoglycosides should not be used in the regimens of pregnant patients and can be particularly toxic to the developing fetal ear. Capreomycin may 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 teratogenic effects have been observed in animal studies. If possible, ethionamide should be avoided in pregnant patients.

6.2 Breastfeeding

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

In lactating mothers on treatment, most antituberculosis drugs will be found in the breast milk in concentrations that would equal only a small fraction of the therapeutic dose used in an infant. However, any effects on infants of such exposure during the full course of DR-TB treatment have not been established. Therefore, when resources and training are available, it is recommended to provide infant formula options as an alternative to breastfeeding when infant formula is provided, fuel for boiling water and the necessary apparatus (stove, heating pans and bottles) must also be provided, as well as training on how to prepare and use the infant formula. All this should be free of charge to poor patients. The mother and her baby should not be completely separated. However, if the mother is sputum smear-positive, the care of the infant should be left to family members until she becomes sputum smear-negative, if this is feasible. When the mother and infant are together, this common time should be spent in well-ventilated areas or outdoors. In some settings, the mother may be offered the option of using a surgical mask or an N-95 respirator until she becomes sputum smear-negative.

6.3 Contraception

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

For patients with mono- and poly-resistant TB that is susceptible to rifampicin, the use of rifampicin interacts with the contraceptive drugs resulting in decreased efficacy of protection against pregnancy. A woman on oral contraception while receiving rifampicin treatment may choose between two options: following consultation with a physician, use of an oral contraceptive pill containing a higher dose of estrogen (50 µg); or use of another form of contraception.

6.4 Children

Children with DR-TB generally have primary resistance transmitted from an index case with DR-TB. Evaluation of children who are contacts of DR-TB patients is discussed in Chapter 10. When DST is available, it should be used to guide therapy, although children with paucibacillary TB are often culture-negative. Nevertheless, every effort should be made to confirm DR-TB bacteriologically by the use of DST and to avoid exposing children unnecessarily to toxic drugs.

The treatment of culture-negative children with clinical evidence of active TB disease and contact with a documented case of DR-TB should be guided by the results of DST and the history of the contact's exposure to antituberculosis drugs.

There is only limited reported experience with the use of second-line drugs for extended periods in children. The risks and benefits of each drug should be carefully considered in designing a regimen. Frank discussion with family members is critical, especially at the outset of therapy. DR-TB is life-threatening, and no antituberculosis drugs are absolutely contraindicated in children. Children who have received treatment for DR-TB have generally tolerated the second-line drugs well.

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

In general, antituberculosis drugs should be dosed according to body weight (see Table 6.1). Monthly monitoring of body weight is therefore especially important in paediatric cases, with adjustment of doses as children gain weight.

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

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

Table 6.1: Paediatric dosing of second-line antituberculosis drugs

Drug	Daily dose (mg/kg)	Frequency	Maximum daily dose
streptomycin	20–40	Once daily	1 g
kanamycin	15–30	Once daily	1 g
amikacin	15–22.5	Once daily	1 g
capreomycin	15–30	Once daily	1 g
ofloxacin	15–20	Twice daily	800 mg
levofloxacin	7.5–10	Once daily	750 mg
moxifloxacin	7.5–10	Once daily	400 mg
ethionamide	15–20	Twice daily	1 g
protionamide	15–20	Twice daily	1 g
cycloserine	10–20	Once or twice daily	1 g
<i>p</i> -aminosalicylic acid	150	Twice or thrice daily	12 g

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

6.5 Diabetes mellitus

Diabetic patients with MDR-TB are at risk for poor outcomes. In addition, the presence of diabetes mellitus may potentiate the adverse effects of antituberculosis drugs, especially renal dysfunction and peripheral neuropathy. Diabetes must be managed closely throughout the treatment of DR-TB. The health-care provider should be in close communication with the physician who manages the patient's diabetes. Oral hypoglycaemic agents are not contraindicated during the treatment of DR-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.

6.6 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 7.2.

Table 6.2 Adjustment of antituberculosis medication in renal insufficiency^{a, b}

Drug	Change in frequency?	Recommended dose ^c 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 ^d
terizidone	–	Recommendations not available

protionamide	No change	250–500 mg per dose daily
ethionamide	No change	250–500 mg per dose daily
<i>p</i> -aminosalicylic acid ^c	No change	4 g/dose, twice daily
streptomycin	Yes	12–15 mg/kg per dose two or three times per week (not daily) ^f
capreomycin	Yes	12–15 mg/kg per dose two or three times per week (not daily) ^f
kanamycin	Yes	12–15 mg/kg per dose two or three times per week (not daily) ^f
amikacin	Yes	12–15 mg/kg per dose two or three times per week (not daily) ^f

^a Adapted from Treatment of tuberculosis

^b For Group 5 drugs see manufacturers' recommendations on adjustment in renal insufficiency.

^c To take advantage of the concentration-dependent bactericidal effect of many antituberculosis drugs, standard doses are given unless there is intolerance.

^d 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).

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

^f Caution should be used with the injectable agents in patients with renal function impairment because of the increased risk of both ototoxicity and nephrotoxicity.

6.7 Liver disorders

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

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

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

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

6.8 Seizure disorders

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

addition, any other underlying conditions or causes of seizures should be corrected.

Cycloserine should be avoided in patients with active seizure disorders that are not well controlled with medication. However, in cases where cycloserine is a crucial component of the treatment regimen, it can be given and the anti-seizure medication adjusted as needed to control the seizure disorder. The risks and benefits of using cycloserine should be discussed with the patient and the decision on whether to use cycloserine made together with the patient.

In mono- and poly-resistant cases, the use of isoniazid and rifampicin may interfere with many of the anti-seizure medications. Drug interactions should be checked before their use (see table 7.1 for drug interactions).

Seizures that present for the first time during antituberculosis therapy are likely to be the result of an adverse effect of one of the antituberculosis drugs. More information on the specific strategies and protocols to address adverse effects is provided in Chapter 8.

6.9 Psychiatric disorders

It is advisable for psychiatric patients to be evaluated by a health-care worker with psychiatric training before the start of treatment for DR-TB. The initial evaluation documents any existing psychiatric condition and establishes a baseline for comparison if new psychiatric symptoms develop while the patient is on treatment. Any psychiatric illness identified at the start of or during treatment should be fully addressed. There is a high baseline incidence of depression and anxiety in patients with MDR-TB, often connected with the chronicity and socioeconomic stress factors related to the disease.

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

The use of cycloserine is not absolutely contraindicated for the psychiatric patient. Adverse effects from cycloserine may be more prevalent in the psychiatric patient, but the benefits of using this drug may outweigh the potentially higher risk of adverse effects. Close monitoring is recommended if cycloserine is used in patients with psychiatric disorders.

All health-care workers treating DR-TB should work closely with a mental health specialist and have an organized system for psychiatric emergencies. Psychiatric emergencies include psychosis, suicidal ideation and any situation involving the patient's being a danger to him or herself or others. Additional information on psychiatric adverse effects is provided in Chapter 8.

6.10 Substance dependence

Patients with substance dependence disorders should be offered treatment for their addiction. Complete abstinence from alcohol or other substances should be strongly encouraged, although active consumption is not a contraindication for antituberculosis treatment. If the treatment is repeatedly interrupted because of the patient's dependence, therapy should be suspended until successful treatment or measures to ensure adherence have been established. Good DOT gives the patient contact with and support from health-care providers, which often allows complete treatment even in patients with substance dependence.

Cycloserine will have a higher incidence of adverse effects (as in the psychiatric patient) in patients dependent on alcohol or other substances, including a higher incidence of seizures. However, if cycloserine is considered important to the regimen, it should be used and the patient closely observed for

adverse effects, which are then adequately treated.

6.11 HIV-infected patients

Given the important interaction between HIV infection and drug-susceptible and DR-TB, a full chapter (Chapter 7) is devoted to this subject.

7 Drug-resistant tuberculosis and HIV

7.1 General considerations

HIV coinfection is a significant challenge for the prevention, diagnosis and treatment of DR-TB, especially in the case of MDR-TB and XDR-TB. Reports have shown high mortality rates among HIV-infected patients with DR-TB, and alarming mortality rates in patients coinfecting with XDR-TB and HIV. Early diagnosis of DR-TB and HIV, prompt treatment with adequate regimens, sound patient support and strong infection control measures are all essential components in the management of DR-TB in HIV-infected people.

Recent global drug resistance surveillance suggests an association between HIV and MDR-TB in some parts of the world, although specific factors involved in this association have not been determined. HIV is a powerful risk factor for all forms of TB, and DR-TB outbreaks, including XDR-TB outbreaks in HIV-infected patients, appear to be common. DR-TB is often associated with higher mortality rates in the HIV-infected compared with the non-infected; however, the use of ART in addition to treatment of DR-TB has been reported to improve outcomes of DR-TB in the HIV-infected.

7.2 Concomitant treatment of DR-TB and HIV

The treatment of DR-TB in patients with HIV is very similar to that in patients without HIV and is described in Chapter 7, with the following exceptions:

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

7.2.1 Initiating ART treatment in patients with DR-TB

The use of ART in HIV-infected patients with TB improves survival for both drug-resistant and susceptible disease. As stated above, cohorts of patients treated for DR-TB without the benefit of ART have experienced mortality rates often exceeding 90%. The likelihood of adverse effects could compromise the treatment of either HIV or DR-TB if both treatments are started simultaneously. On the other hand, undue delay in the start of ART could result in significant risk of HIV-related death among patients with advanced disease. For this reason, all HIV co-infected patients being treated for MDR-TB should start ART, irrespective of CD4 count. The preferably regimen is: **AZT+3TC+EFZ**, however AZT should be changed to D4T in case of anaemia, if the patient is diagnosed with severe peripheral neuropathy d4t can be substituted by abacvir.

The optimal timing for the introduction of ART in patients receiving MDR-TB treatment is unknown. However, since HIV immunocompromised patients are at high risk for death, it is reasonable to start ART should be started as soon as second-line TB drugs are tolerated. This may be as soon as one week in asymptomatic patients. There are no known interactions between second-line TB drugs and ARV's.

7.2.2 DR-TB in patients already receiving ART

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

The second issue is whether the presentation of active DR-TB in a patient on ART constitutes ART failure. The principles of determining failure in such cases are described in other WHO documents. If ART failure has been diagnosed, it is not recommended to begin a new second-line ART regimen at the same time as initiation of a DR-TB regimen. Instead, continue the present ART regimen and switch to the second-line ART regimen 2–8 weeks after the start of DR-TB treatment.

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

Currently, little is known about drug–drug interactions between second-line antituberculosis agents and antiretroviral therapy. There are several known interactions between drugs used to treat HIV and TB, which are summarized below.

- **Rifamycin derivatives.** While rifamycin derivatives are not routinely used in DR-TB treatment, they are used in the treatment of rifampicin-sensitive poly- and mono-resistant TB.
- **Quinolones and didanosine.** Buffered didanosine contains an aluminium/magnesium-based antacid and, if given jointly with fluoroquinolones, may result in decreased fluoroquinolone absorption; it should be avoided, but if it is necessary it should be given six hours before or two hours after fluoroquinolone administration. The enteric coated (EC) formulation of didanosine can be used concomitantly without this precaution.
- **Ethionamide/prothionamide.** Based on limited existing information of the metabolism of the thiamides (ethionamide and prothionamide), this drug class may have interactions with antiretroviral drugs. Ethionamide/prothionamide is thought to be metabolized by the CYP450 system, although it is not known which of the CYP enzymes are responsible. Whether doses of ethionamide/prothionamide and/or certain antiretroviral drugs should be modified during the concomitant treatment of DR-TB and HIV is completely unknown.
- **Clarithromycin.** Clarithromycin is a substrate and inhibitor of CYP3A and has multiple drug interactions with protease inhibitors and NNRTIs. If possible, the use of clarithromycin should be avoided in patients coinfecting with DR-TB and HIV because of both its weak efficacy against DR-TB and multiple drug interactions.

7.2.4 Potential drug toxicity in the treatment of HIV and DR-TB

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

Adverse effects that are common to both antiretroviral and antituberculosis drugs are listed in Table 7.1. It should be noted that relatively very little is known about the rates of adverse effects in the concomitant treatment of DR-TB and HIV. Table 7.1 is meant to alert the clinician to potentially overlapping and additive toxicities, and as of the writing of these guidelines is based on preliminary, non-published data

and expert opinion.

When possible, avoid the use of agents with shared adverse effect profiles. Often, however, the benefit of using drugs that have overlying toxicities outweighs the risk. Therefore, if two drugs with overlapping toxicities are determined to be essential in a patient's regimen, these guidelines recommend increased monitoring of adverse effects rather than disallowing a certain combination.

Table 7.1: Potential overlapping and additive toxicities of ART and antituberculosis therapy (Drugs that are more strongly associated with adverse effects appear in bold)

Toxicity	Antiretroviral agent	Antituberculosis agent	Comments
Peripheral neuropathy	D4T, ddI, ddC	Lzd, Cs, H, Aminoglycosides, Eto/Pto, E	Avoid use of D4T, ddI and ddC in combination with Cs or Lzd because of theoretically increased peripheral neuropathy. If these agents must be used and peripheral neuropathy develops, replace the ARV agent with a less neurotoxic agent.
Central nervous system (CNS) toxicity	EFV	Cs, H, Eto/Pto, Fluoroquinolones	Efavirenz has a high rate of CNS adverse effects (confusion, impaired concentration, depersonalization, abnormal dreams, insomnia and dizziness) in the first 2–3 weeks, which typically resolve on their own. If these effects do not resolve on their own, consider substitution of the agent. At present, there are limited data on the use of EFV with Cs; concurrent use is accepted practice with frequent monitoring for CNS toxicity. Frank psychosis is rare with EFV alone.
Depression	EFV	Cs, Fluoroquinolones, H, Eto/Pto	Severe depression can be seen in 2.4% of patients receiving EFV. Consider substituting for EFV if severe depression develops. The severe socioeconomic circumstances of many patients with chronic disease can also contribute to depression.
Headache	AZT, EFV	Cs	Rule out more serious causes of headache such as bacterial meningitis, cryptococcal meningitis, CNS toxoplasmosis, etc. Use of analgesics (ibuprofen, paracetamol) and good hydration may help. Headache secondary to AZT, EFV and Cs is usually self-limited.
Nausea and vomiting	RTV, D4T, NVP, and most others	Eto/Pto, PAS, H, E, Z and others	Nausea and vomiting are common adverse effects and can be managed. Persistent vomiting and abdominal pain may be a result of developing lactic acidosis and/or hepatitis secondary to medications.
Abdominal pain	All ART treatment has been associated with abdominal pain	Eto/Pto, PAS	Abdominal pain is a common adverse effect and often benign; however, abdominal pain may be an early symptom of severe adverse effects such as pancreatitis, hepatitis or lactic acidosis.

Pancreatitis	D4T, ddI, ddC	Lzd	<p>Avoid use of these agents together. If an agent causes pancreatitis suspend it permanently and do not use any of the pancreatitis producing anti-HIV medications (D4T, ddI, or ddC) in the future.</p> <p>Also consider gallstones or alcohol as a potential cause of pancreatitis.</p>
Diarrhea	All protease inhibitors, ddI (buffered formula)	Eto/Pto, PAS, Fluoroquinolones	<p>Diarrhoea is a common adverse effect. Also consider opportunistic infections as a cause of diarrhoea, or clostridium difficile (a cause of pseudomembranous colitis).</p>
Hepatotoxicity	NVP, EFV, all protease inhibitors (RTV > other protease inhibitors), all NRTIs	H, R, E, Z, PAS, Eto/ Pto, Fluoroquinolones	<p>Follow hepatotoxicity treatment recommendations in Chapter 11.</p> <p>Also consider TMP/SMX as a cause of hepatotoxicity if the patient is receiving this medication.</p> <p>Also rule out viral etiologies as cause of hepatitis (Hepatitis A, B, C, and CMV).</p>
Skin rash	ABC, NVP, EFV, D4T and others	H,R, Z, PAS, Fluoroquinolones, and others	<p>Do not re-challenge with ABC (can result in life-threatening anaphylaxis). Do not re-challenge with an agent that caused Stevens-Johnson syndrome.</p> <p>Also consider TMP/SMX as a cause of skin rash if the patient is receiving this medication.</p> <p>Thioacetazone is contraindicated in HIV because of life-threatening rash.</p>
Lactic acidosis	D4T, ddI, AZT, 3TC	Lzd	<p>If an agent causes lactic acidosis, replace it with an agent less likely to cause lactic acidosis.</p>
Renal toxicity	TDF (rare)	Aminoglycosides, Cm	<p>TDF may cause renal injury with the characteristic features of Fanconi syndrome, hypophosphataemia, hypouricaemia, proteinuria, normoglycaemic glycosuria and, in some cases, acute renal failure. There are no data on the concurrent use of TDF with aminoglycosides or Cm. Use TDF with caution in patients receiving aminoglycosides or Cm.</p> <p>Even without the concurrent use of TDF, HIV-infected patients have an increased risk of renal toxicity secondary to aminoglycosides and Cm. Frequent creatinine and electrolyte monitoring every 1 to 3 weeks is recommended.</p> <p>Many ARV and antituberculosis medications need to be dose adjusted for renal insufficiency.</p>

Nephrolithiasis	IDV	None	No overlapping toxicities regarding nephrolithiasis have been documented between ART and antituberculosis medications. Adequate hydration prevents nephrolithiasis in patients taking IDV. If nephrolithiasis develops while on IDV, substitute with another protease inhibitor if possible.
Electrolyte disturbances	TDF (rare)	Cm, Aminoglycosides	Diarrhoea and/or vomiting can contribute to electrolyte disturbances. Even without the concurrent use of TDF, HIV-infected patients have an increased risk of both renal toxicity and electrolyte disturbances secondary to aminoglycosides and Cm.
Bone marrow suppression	AZT	Lzd, R, Rfb, H	Monitor blood counts regularly. Replace AZT if bone marrow suppression develops. Consider suspension of Lzd. Also consider TMP/SMX as a cause if the patient is receiving this medication. Consider adding folinic acid supplements, especially if receiving TMP/SMX.
Optic neuritis	ddI	E, Eto/Pto (rare)	Suspend agent responsible for optic neuritis permanently and replace with an agent that does not cause optic neuritis.
Hyperlipidemia	Protease inhibitors, EFV	None	No overlapping toxicities regarding hyperlipidemia have been documented between ART and antituberculosis medications.
Lipodystrophy	NRTIs (especially D4T and ddI)	None	No overlapping toxicities regarding lipodystrophy have been documented between ART and antituberculosis medications.
Dysglycemia (disturbed blood sugar regulation)	Protease inhibitors	Gfx, Eto/Pto	Protease inhibitors tend to cause insulin resistance and hyperglycaemia. Eto/Pto tend to make insulin control in diabetics more difficult, and can result in hypoglycaemia and poor glucose regulation. Gatifloxacin is no longer recommended by the GLC for use in treatment of TB because of this side-effect.
Hypothyroidism	D4T	Eto/Pto, PAS	There is potential for overlying toxicity, but evidence is mixed. Several studies show subclinical hypothyroidism associated with HAART, particularly stavudine. PAS and Eto/Pto, especially in combination, can commonly cause hypothyroidism.

7.2.5 Monitoring of DR-TB and HIV therapy in coinfecting patients

HIV treatment must be taken daily without exception to prevent the evolution of drug resistance. Since DOT is an important component of DR-TB therapy, programmes would be advised to explore the provision of TB medications and ARVs through concomitant DOT or other methods of adherence support. This is particularly important in the setting of second-line antituberculosis therapy, since it can result in a large pill burden and numerous adverse effects that make taking ARVs more difficult.

The complexity of antiretroviral regimens and second-line antituberculosis treatment, each with its own

toxicity profiles and some of which may be potentiated by concomitant therapy, demands rigorous clinical monitoring. Chapter 8, Table 8.1 describes the monitoring requirements while on DR-TB therapy and indicates where any extra monitoring is required for patients coinfecting with HIV and/or on ART.

If the patient shows signs of antituberculosis treatment failure, the same evaluation described in Chapter 8 is warranted. In addition, the ART regimen should be evaluated for possible treatment failure, as described in other WHO guidelines.

Patients with HIV-associated DR-TB may require special socioeconomic, nutritional and psychosocial support in order to successfully complete treatment.

7.2.6 Immune reconstitution inflammatory syndrome

This syndrome can present as a paradoxical worsening of the patient's clinical status, often due a previously subclinical and unrecognized opportunistic infection. These reactions may present as fever, enlarging lymph nodes, worsening pulmonary infiltrates, respiratory distress or exacerbation of inflammatory changes at other sites. It generally presents within three months of the initiation of ART and is more common with a low CD4 cell count (<50 cells/mm³).

It is important to note that IRIS is a diagnosis of exclusion. Patients with advanced AIDS may show clinical deterioration for a number of other reasons. New opportunistic infections or previously subclinical infections may be unmasked following immune reconstitution and cause clinical worsening. IRIS can also be confused with TB treatment failure, and coinfecting patients may be demonstrating progression of TB disease due to drug resistance.

The management of IRIS is complex and depends on the clinical status of the patient and the site and extent of involvement. Non-steroidal anti-inflammatory drugs in mild disease and corticosteroids in moderate-severe disease are recommended. Most patients can be treated without interruption of ART.

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

8.1 Pretreatment screening and evaluation

Pre treatment assessment is done in order to identify those patients at greater risk of adverse effects, poor outcomes and also to establish a baseline. This must include

- **a thorough medical history and physical examination**
- **initial laboratory evaluations**
-

Identification of certain pre-existing conditions will require more intensive follow up (Chapter 9). These include

- **HIV infection**
- **diabetes mellitus**
- **renal insufficiency**
- **acute or chronic liver disease**
- **thyroid disease**
- **mental illness**
- **drug or alcohol dependence**
- **Pregnancy and breast feeding**
-

Contraception during treatment for women of childbearing age should be discussed.

All patients starting MDR-TB treatment should have the following tests:

1. Tests to be done on site:
 - Hematology: FBC, malaria, peripheral blood film comments
 - Chemistry: Most chemistry parameters including, Glucose, RFT (K, Urea, Creatinine), LFT
 - Serology: HIV rapid testing
 - Flow-cytometry: CD4 and CD8 counts and CD4% in children
 - ZN or Fluorescent microscopy of sputum smears

Tests to be referred to the NRL:

- TB cultures and DST

8.2 Monitoring progress of treatment

Patients should be monitored closely for signs of both treatment failure and side-effects. As objective laboratory tests often lag behind clinical response the most important way to monitor response to treatment is through *regular history-taking and physical examination*.

The classic symptoms of TB—cough, sputum production, fever and weight loss—generally improve within the first few months of treatment and should be monitored frequently by health-care providers.

The recurrence of TB symptoms after sputum conversion, for example, may be the first sign of treatment failure.

For **children**, height and weight should be measured regularly to ensure that they are growing normally.

A normal growth rate should resume after a few months of successful treatment.

The **chest radiograph** may be unchanged or show only slight improvement, especially in re-treatment patients with chronic pulmonary lesions.

Chest radiographs/x-ray (CXR) should be taken:

- **at least every six months**
- **when a surgical intervention is being considered,**
- **or whenever the patient's clinical situation has worsened.**

NB: there will be a mobile team from the TB hospital on a monthly basis to review patients at the TB diagnostic level

8.3 Sputum

The most important objective evidence of improvement is conversion of the sputum smear and culture to negative. While sputum smear is still useful clinically because of its much shorter turnaround time, sputum culture is much more sensitive and is necessary to monitor the progress of treatment. Sputum examinations are also dependent on the quality of the sputum produced, so care should be taken to obtain adequate specimens.

Persistently positive sputums and cultures for AFB should be assessed for NTM, as overgrowth with NTM in lung damage secondary to TB is not uncommon. In such cases, although DR-TB may be adequately treated, treatment may need to be directed towards the NTM as well.

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

Sputum smears and cultures should be monitored monthly until the end of the intensive phase. After the end of the intensive phase, the minimum period recommended for bacteriological monitoring is monthly for smears and two monthly for cultures (Table 8.1) but more often if clinically indicated.

For patients who remain smear- and culture-positive during treatment or who are suspects for treatment failure, DST can be repeated after 3 months of treatment.

Protocol for collection of sputum samples in the follow up of Drug Resistant TB patients:

- 2 samples for all patients for follow up, entered the patient in the DR register and allocate the same surveillance number as in the diagnosis.
- Fill in the Laboratory Request Form A and the History Form B will be appropriately.
- For adults, the patient will be given instructions to collect 2 sputum samples: On the day for review the patient will collect the first morning sample, Sample A at home. On the same day at the Clinic, the patient will be issued with a sputum container to collect a spot sample B. Both samples should then be sent to the Laboratory following the SOPs.
- In the local Laboratory, smear microscopy will be done on sample A, and results reported to the requesting HCW. Both samples should be stored to await transportation to the NRL for culture only or culture and DST.
- Follow up samples for culture only and culture and First Line DST will be done at the NRL.

- For follow up samples for culture and second line DST, culture will be done at the NRL and if there is growth, the isolate will be sent to SA MRC laboratory.

Exchange of *M. tuberculosis* cultures between countries (e.g. for diagnostic DST, retesting or proficiency testing) is always subject to international regulations, including national import and export regulations specific to individual countries.

Given the risks associated with transport of specimens and/or cultures from patients suspected of having DR-TB, guidelines are provided in the laboratory manual for safe packaging and transportation of the samples. In transporting sputum samples or isolates for second line DST to MRC, regulations recommended by the Universal Postal Union, the International Civil Aviation Organization and the International Air Transport Association will be adhered to. Health Care Workers and drivers will be trained on the guidelines for safe handling of infectious substances.

Sputum samples will be picked from Diagnostic sites twice a week and dropped at the NRL. Samples for second line DST will be picked from the NRL once a week and sent to MRC. For efficiency, commercial courier will be contracted. The cold chain system will be followed during sample transportation and storage to reduce on bacterial contamination during cultures.

8.4 Monitoring for adverse effects during treatment

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

The majority of adverse effects are easy to recognize. Commonly, if enabled, patients will volunteer that they are experiencing adverse effects. However, it is important to have a systematic method of patient interviewing since some patients may be 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.

All DOT workers, hospital; clinic or community health worker should be trained to screen patients regularly for symptoms of common adverse effects, what simple management they can advise and when to refer:

- **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 is invaluable for detecting certain adverse effects that are more occult. The recommendations in Table 8.1 are an estimate of the minimal frequency of essential laboratory screening. More frequent screening is advisable, particularly for high-risk patients.

Nephrotoxicity is a known complication of the injectable drugs, both of the aminoglycosides and of capreomycin. This adverse effect is occult (not obviously noted by taking the history of the patient or by physical examination) in onset but can be fatal. The optimal timing for checking serum creatinine is unknown, but we advise checking serum creatinine at least monthly. In addition, patients with a history of renal disease (including co-morbidities such as HIV and diabetes), advanced age or any renal symptoms

should be monitored more closely, particularly at the start of treatment. An estimate of the glomerular filtration rate may help to further stratify the risk of nephrotoxicity in these patients.

Electrolyte wasting is a known complication of the antituberculosis injectable drugs, especially capreomycin. It is generally a late effect occurring after months of treatment, and is reversible once the injectable drug is suspended. Since electrolyte wasting is often occult in the early stages and can be easily managed with electrolyte replacement, serum potassium should be checked at least monthly in high-risk patients, and in all those taking capreomycin.

Hypothyroidism is a late effect provoked by PAS and ethionamide. It is suspected by clinical assessment and confirmed by testing the serum level of thyroid stimulating hormone (TSH). The use of these agents together can produce hypothyroidism in up to 10% of patients. Since the symptoms can be subtle, it is recommended that patients are screened for hypothyroidism with a serum TSH at baseline, 6 months, and then tested again every 6 months or sooner if symptoms arise. The dosing of thyroid replacement therapy should be guided using serum levels of TSH.

Table 8.1: Laboratory Monitoring

Base Line	Follow up
Sputum smear microscopy	Monthly
Sputum Culture	Monthly until the end of the intensive phase then 2 monthly
Drug susceptibility	If remain smear /culture-positive repeat DST after 3 months of treatment. Repeat DST at 6 monthly and there after . there is a positive culture after initial conversion
Renal Function Tests (Serum creatinine & K+)	Every two weeks for the first two months when initiating an injectable drug, then monthly while receiving injectable. Patients with baseline renal insufficiency should receive more frequently.
Thyroid Stimulating Hormone (TSH)	Every 6 months if receiving PAS and ETO and PTO:TSH is sufficient for screening for hypothyroidism; it is not necessary to measure hormone thyroid levels
Liver serum enzymes	Monthly in patients <ul style="list-style-type: none"> ▪ receiving pyrazinamide ▪ HIV infected ▪ patients at risk or with symptoms of hepatitis
HIV screening,CD4	Repeat as clinically indicated (every 3-6 months)
Pregnancy tests (women of child bearing age)	Repeat as clinically indicated. All women of child bearing age should be provided with family planning.
Full Blood Count	Monthly or as clinically required For HIV-infected patients on ART, monitor monthly initially and then as needed based on symptoms

8.5 Management of adverse effects

Second-line drugs have many more adverse effects than the first-line antituberculosis drugs.

Proper management of adverse effects begins with patient education. Before starting treatment, the patient should be instructed in detail about the potential adverse effects that could be produced by the prescribed drug regimen, and if and when to notify a health-care provider.

Prompt evaluation, diagnosis and treatment of adverse effects are extremely important, even if the adverse effect is not particularly dangerous as this may influence adherence. Patients may have significant fear and anxiety about an adverse effect if they do not understand why it is happening. These emotions in turn may augment the severity of the adverse effect, as in the case of nausea and vomiting. Long periods of time without medical evaluation also promote feelings of isolation and abandonment by the health-care

system.

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. With cycloserine and ethionamide, for example, a patient may be completely intolerant at one dose and completely tolerant at a slightly lower dose. Unfortunately, given the narrow therapeutic margins of these drugs, lowering the dose may also affect efficacy, so every effort should be made to maintain an adequate dose of the drug according to body weight. Lowering the dose by more than one weight class should be avoided.

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 (or terizidone) prescribed.

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

Table 8.2: Common adverse effects and the suggested management strategies.

Adverse effect	Suspected agent(s)	Suggested management strategies	Comments
Seizures	Cs, H, fluoro-quinolones	<ol style="list-style-type: none"> 1. Suspend suspected agent pending resolution of seizures. 2. Initiate anticonvulsant therapy (e.g. phenytoin, valproic acid). 3. Increase pyridoxine to maximum daily dose (200 mg per day). 4. Restart suspected agent or reinitiate suspected agent at lower dose, if essential to the regimen. 5. Discontinue suspected agent if this can be done without compromising regimen. 	<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. 3. Patients with history of previous seizures may be at increased risk for development of seizures during MDR-TB therapy.

Peripheral neuropathy	Cs, Lzd, H, S, Km, Am, Cm, Vi, Eto/Pto, fluoroquinolones	<ol style="list-style-type: none"> 1. Increase pyridoxine to maximum daily dose (200 mg per day). 2. Change injectable to capreomycin if patient has documented susceptibility to capreomycin. 3. Initiate therapy with tricyclic antidepressants e.g. amitriptyline. Non-steroidal anti-inflammatory drugs or acetaminophen may help alleviate symptoms. 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. 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; however, some patients may experience improvement when offending agents are suspended.
Hearing loss and vestibular disturbances	S, Km, Am, Cm, Clr	<ol style="list-style-type: none"> 1. Document hearing loss and compare with baseline audiometry if available. 2. Change parenteral treatment to capreomycin if patient has documented susceptibility to capreomycin. 3. Decrease frequency and/or lower dose of suspected agent if this can be done without compromising the regimen (consider administration three times per week). 4. Discontinue suspected agent if this can be done without compromising the regimen. 	<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 is generally not reversible. 3. The risk of further hearing loss must be weighed against the risks of stopping the injectable in the treatment regimen. 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.
Psychotic symptoms	Cs, H, fluoroquinolones, Eto/Pto	<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. 2. Initiate antipsychotic therapy. 3. Lower dose of suspected agent if this can be done without compromising regimen. 4. Discontinue suspected agent if this can be done without compromising regimen. 	<ol style="list-style-type: none"> 1. Some patients will need to continue antipsychotic treatment throughout MDR-TB therapy. 2. Previous history of psychiatric disease is not a contra-indication to the use of agents listed here but may increase the likelihood of psychotic symptoms developing during treatment. 3. Psychotic symptoms are generally reversible upon completion of MDR-TB treatment or cessation of the offending agent.

<p>Depression</p>	<p>Socio-economic circumstances, chronic disease, Cs, fluoroquinolones H, Eto/Pto</p>	<ol style="list-style-type: none"> 1. Improve socioeconomic conditions. 2. Offer group or individual counselling. 3. Initiate antidepressant therapy. 4. Lower dose of suspected agent if this can be done without compromising the regimen. 5. Discontinue suspected agent if this can be done without compromising regimen. 	<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.
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TABLE 8.2 Common adverse effects, suspected agent(s) and management strategies (continued)

ADVERSE EFFECT	SUSPECTED AGENT(S) ^a	SUGGESTED MANAGEMENT STRATEGIES	COMMENTS
Gastritis	PAS, Eto/Pto	<ol style="list-style-type: none"> 1. H2-blockers, proton-pump inhibitors, or antacids. 2. Stop suspected agent(s) for short periods of time (e.g, one to seven days). 3. Lower dose of suspected agent, if this can be done without compromising regimen. 4. Discontinue suspected agent if this can be done without compromising regimen. 	<ol style="list-style-type: none"> 1. Severe gastritis, as manifested by haematemesis, melaena or haematechezia, is rare. 2. Dosing of antacids should be carefully timed so as to not interfere with the absorption of antituberculosis drugs (take 2 hours before or 3 hours after antituberculosis medications). 3. Reversible upon discontinuation of suspected agent(s).
Hepatitis	Z, H, R, Eto/Pto, PAS, E, fluoro-quinolones	<ol style="list-style-type: none"> 1. Stop all therapy pending resolution of hepatitis. 2. Eliminate other potential causes of hepatitis. 3. Consider suspending most likely agent permanently. Reintroduce remaining drugs, one at a time with the most hepatotoxic agents first, while monitoring liver function. 	<ol style="list-style-type: none"> 1. History of previous hepatitis should be carefully analysed to determine most likely causative agent(s); these should be avoided in future regimens. 2. Generally reversible upon discontinuation of suspected agent.
Renal toxicity	S, Km, Am, Cm, Vm	<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 dosing 2–3 times a week if drug is essential to the regimen and patient can tolerate (close monitoring of creatinine). 4 Adjust all antituberculosis medications according to the creatinine clearance. 	<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. Renal impairment may be permanent.
Electrolyte disturbances (hypokalaemia and hypomagnesaemia)	Cm, Vm, Km, Am, S	<ol style="list-style-type: none"> 1. Check potassium. 2. If potassium is low, also check magnesium (and calcium if hypocalcaemia is suspected). 3. Replace electrolytes as needed. 	<ol style="list-style-type: none"> 1. If severe hypokalaemia is present consider hospitalization. 2. Amiloride 5–10 mg QD or spironolactone 25 mg QD may decrease potassium and magnesium wasting and is useful in refractory cases. 3. Oral potassium replacements can cause significant nausea and vomiting. Oral magnesium may cause diarrhoea.
Optic neuritis	E, Eto/Pto	<ol style="list-style-type: none"> 1. Stop E. 2. Refer patient to an ophthalmologist. 	<ol style="list-style-type: none"> 1. Usually reverses with cessation of E. 2. Rare case reports of optic neuritis have been attributed to streptomycin.
Arthralgias	Z, fluoro-quinolones	<ol style="list-style-type: none"> 1. Initiate therapy with non-steroidal anti-inflammatory drugs. 2. Lower dose of suspected agent if this can be done without compromising regimen. 3. Discontinue suspected agent if this can be done without compromising regimen. 	<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. Allopurinol appears not to correct the uric acid levels in such cases.

^a See list of drug abbreviations, page vi.

Note: Drugs in bold type are more strongly associated with the adverse effect than

Table 8.3 Commonly used ancillary medications (bolded drugs are provided free by the NTCP)

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 fluoroquinolones
Oral candidiasis (non-AIDS patient)	Fluconazole , clotrimazole lozenges
Diarrhoea	Loperamide
Depression	Selective serotonin reuptake inhibitors (fluoxetine , sertraline), tricyclic antidepressants (amitriptyline)
Severe anxiety	Lorazepam, diazepam , clonazepam
Insomnia	Dimenhydrinate
Psychosis	Haloperidol , thiorazine, risperidone (consider benzotropine or biperiden to prevent extrapyramidal effects)
Seizures	Phenytoin, carbamazepine , valproic acid, phenobarbital
Prophylaxis of neurological complications of cycloserine	Pyridoxine (vitamin B ₆)
Peripheral neuropathy	Amitriptyline
Vestibular symptoms	Meclizine, dimenhydrinate, prochlorperazine, promethazine
Musculoskeletal pain, arthralgia, headaches	Ibuprofen, paracetamol, paracodeine
Cutaneous reactions, itching	Hydrocortisone cream, calamine, caladryl lotions
Systemic hypersensitivity reactions	Antihistamines (diphenhydramine, chlorpheniramine, dimenhydrinate), corticosteroids (prednisone, dexamethasone)
Bronchospasm	Salbutamol, Inhaled beta-agonists (salbutamol, albuterol, etc.), inhaled corticosteroids (beclomethasone, etc.), oral steroids (prednisone), injectable steroids (dexamethasone, methylprednisolone)
Hypothyroidism	Levothyroxine

9 Treatment delivery and adherence

9.1 Community-based care and support

Community-based care and support is any action or help provided *by, with or from* the community, including situations in which patients are receiving ambulatory treatment. This support contributes to, and may even be necessary to, patient recovery.

9.1.1 The relationship of community-based support and hospitalization for DR-TB.

CHWs and community-based support can facilitate timely access to the hospital. During hospitalization, the community-based network can continue to accompany patients and provide additional support as needed. With an efficient network for community-based care, the patient will be able to return to ambulatory treatment sooner, resulting in less nosocomial transmission, reduced hospitalization costs and more hospital beds available for other patients. Understanding and compassion are often lacking in hospitals that cater to general diseases because of health workers' fear of contracting DR-TB, as well as lack of experience in dealing with DR-TB.

9.1.2 Costs and sustainability.

When care is rooted in the community, ownership by the community supporters will make the support more sustainable. The CHW in the form of the Rural Health Motivators are often the backbone of a community-based support network. The trained CHWs for MDR will be certified as part of the Swaziland NTCP and will receive a regular stipend reflecting the amount of time that they spend each day participating in community-based care and supporting and travel and communication costs. The added cost of a strong CHW network is cost effective because it contributes to lower rates of failure and prevention of further drug resistance.

9.1.3 Adherence to therapy

Some patients will have developed DR-TB due to poor adherence in the past. Adherence to MDR-TB therapy is particularly difficult because of its prolonged treatment regimens with larger numbers of drugs that have more serious adverse effect profiles. Thus, MDR-TB patients are at increased risk of non-adherence to treatment. Adherence is an essential element to prevent the generation of pan-resistant strains with the potential for community-wide spread and virtually no possibility of cure for the patient.

MDR-TB treatment can be successful, with high overall rates of adherence, when adequate support measures are provided. These measures include enablers and incentives for delivery of DOT to ensure adherence to treatment.

9.1.4 Education of patients

All patients and their families should receive education about MDR-TB, its treatment, potential adverse drug effects and the need for adherence to therapy. Educational interventions should commence at the start of therapy and continue throughout the course of treatment. Education can be provided by physicians, nurses, lay and community health workers and other health-care providers. Written materials for literate patients should be available through all these settings.

9.1.5 Directly observed therapy (DOT)

All MDR-TB patients must receive DOT throughout treatment in hospital, community or at health centres for every dose of treatment. DOT should be provided in a way that does not place undue burdens on patients and their families e.g. transportation times and distances should be limited. In Swaziland this will include an OD regime.

There will be a pool of MDR TB community treatment supporters who have been identified through a range of sources but have all received intensive core training on MDR, DOTS, infection control and adverse effects management. They will receive a small incentive to cover communication and travel costs. They will be drawn from different aspects of the community including

When the community treatment supporter is adequately trained, understands infection control and adverse effects and is acceptable to the NTCP they will appear on the national list of recognized MDR treatment supporters and will be able to support up to 5 patients with DR TB. With appropriate training and support

they can visit patients in their homes or work places.

Receiving DOT from a community member is often a convenient alternative to the health centre and can result in excellent treatment adherence. However, community members need more intensive training, ongoing supervision by the motorcycle adherence officers. It is recommended that the patient's DOT worker should not be a family member. Family relationships are often complicated for the MDR-TB patient, and a family observer could be subject to subtle manipulation by the patient, relatives, employers, etc.

The DOT worker should explore the need to maintain strict confidentiality regarding the patient's disease. In some cases, this may entail working out a system whereby the patient can receive medication without the knowledge of others.

9.1.6 Socioeconomic interventions

Socioeconomic problems, including hunger, inadequate housing and unemployment are all common in Swaziland should be addressed to enable patients and their families to adhere to MDR-TB treatment. These problems have been successfully tackled through the provision of "incentives" and "enablers". These include:

- **nutritional supplementation - all patients are currently entitled to fortified corn soya but where possible and if assessed as appropriate they should be supplied with additional for packs of beans, nuts etc**
- **transportation fees and transport to facility for monthly appointments**
- **temporary accommodation in the form of Hope House, community huts or occasionally a tent free health care education of patients, family and peers on MDR-TB treatment**
- **and early and effective management of adverse effects, advice and assistance in administrative matters relating to the treatment;**

9.1.7 Social and emotional support

Having MDR-TB can be an emotionally devastating experience for patients and their families. Considerable stigma is attached to the disease and this may interfere with adherence to therapy. In addition, the long nature of MDR-TB therapy combined with the adverse effects of the drugs may contribute to depression, anxiety and further difficulty with treatment adherence. The provision of emotional support to patients may increase the likelihood of adherence to therapy. This support may be organized in the form of support groups including current HIV expert patients support groups. Also one-to-one support by physicians, nurses, DOT workers and family members is very important. Motorcycle adherence officers can offer additional support in some cases.

9.1.8 Follow-up of the non-adherent patient

When a patient fails to attend a DOT appointment the DOT worker should make every effort to visit the patients home the same day and identify why the patient has not attended. Addressing the situation in a sympathetic, supportive manner every effort should be made to listen the patients reasons and to work with the patient and family to ensure this doesn't happen again. Referrals should be made to the appropriate person who may be the motorcycle adherence officer, a nurse, a social worker, or doctor. Transportation problems, nutritional problems and adverse reactions should be addressed.

9.1.9 Early and effective management of adverse drug effects

Although rarely life-threatening, the adverse effects of second-line drugs can be debilitating for patients. Patients experiencing high rates of adverse effects may be at increased risk of non-adherence. Therefore,

early and effective management of adverse effects should be part of adherence-promotion strategies in the management of MDR-TB. Management of adverse effects is addressed in more detail in Chapter 8.

10 Management of contacts of MDR-TB patients

10.1 General considerations

Opportunities to halt the transmission of resistant mycobacteria in communities and to treat MDR-TB in a timely fashion are often squandered. The main reasons are lack of investigation of contacts of MDR-TB patients, and failure to ask patients presenting with active TB disease about any history of exposure to MDR-TB.

While all contacts of TB require investigation, DR-TB requires the most vigilance. Because of the severe risk of morbidity and mortality of XDR-TB, contact tracing of cases of XDR-TB should be given the highest level of alertness and priority. **The Swaziland National TB Control Programme considers contact investigation of XDR-TB as an emergency situation.**

10.2 Definitions

Close contacts of MDR-TB patients are defined as **people living in the same household, or spending many hours a day together with the patient in the same indoor living space since the patient became symptomatic with cough (or within the last 3 months if this is not known).**

This will include:

- **People spending nights in the same room as patient**
- **People spending time in common living areas (kitchen etc)**
- **Very close associates such as girlfriend/boyfriend**
- **People who have spent a total of more than 8 hours in close proximity of the patient in an enclosed space, since the patient became ill. This can be over more than one occasion. (including colleagues next to them on a production line, sit next to at school etc)**
-

It is important that a thorough exploration of the patients life is undertaken as this will not only include **household** contacts but possibly work, school and church etc. Close contacts of MDR-TB patients who develop active TB most commonly have drug-resistant disease.

Casual contacts would include most work, school and social contacts. These will not usually be screened unless they are thought to be susceptible (< 5 years old, immuno-compromised) or unless the index case (patient) seems to have been highly infectious (> 10 % of close contacts are found to be infected). Screening of casual contacts has been found to be far less productive. In a country of high prevalence like Swaziland further cases of TB may likely to be identified but these may be from other sources and not necessarily a drug resistant strain.

DR-TB requires careful and thorough contact tracing. Because of the severe risk of morbidity and mortality of XDR-TB, contact tracing of cases of XDR-TB should be given the highest level of alertness and priority.

10.3 Contact tracing procedure

Initial contact tracing should be done at the time of diagnosis. Contact tracing may be done by doctors, nurses or motorcycle adherence officers who have knowledge and experience in contact tracing.

Initially the patient should be informed of who may be at risk by explaining the risk factors (as above). He/She should then be given time to compile a list of contacts. The contact tracing form should be filled for each patient including any known risk factors, reason considered to be at risk, any known

symptoms.

All of these close contacts should be traced. Initially a home visit should be carried out. This will usually be by a Motorcycle adherence officer who has knowledge and experience of contact tracing and infection control.

The rest of the contact tracing form will be completed following a symptomatic question screen, and identifying further close contacts at the home. It is not infrequent that patients may not consider a spouse to be at risk, or a child who is staying with them but not one of the direct families.

This visit will fulfil several goals including

1. Identifying contacts
2. Symptomatic screening of contacts
3. Health education of family including how TB is spread, infection control, effective isolation of the patient when receives ambulant care, nutrition, adherence and TB/ HIV issues.
4. Education of family and contacts of symptoms of TB and encouragement to present to hospital as soon as they develop symptoms and to explain that they are a close contact for the next 2 years
5. Encouragement to have HIV tests if they do not currently know their status

Any symptomatic patient should be provided with bottles for smear, culture and DST and referred to a clinician for assessment.

If it is decided that contact tracing of people other than in the household then this should be done sensitively and appropriately. If there is just one or two people to contact the initial contact should be attempted by telephone and appointment made to assess them in a clinical setting. If this cannot be achieved then a home, school, or workplace visit may be necessary. In all cases every attempt should be made to maintain patient confidentiality but informing line managers, head teacher etc may be necessary to perform inspection of the facility and interview staff can be discreetly. The patient should be kept fully informed and should be clear that every attempt will be made to maintain confidentiality and any information imparted will be kept minimal. It often helps to discuss with the patient the extent to which they are happy for information to be shared with colleagues.

10.4 Management of symptomatic adult contacts of a patient with MDR-TB

All close contacts of MDR-TB cases should be identified through contact tracing and evaluated for active TB by a health-care provider. If the contact appears to have active TB disease, culture and DST should be performed. If DST is not available, or while DST results are awaited, an empirical regimen based either on the resistance pattern of the index case or on the most common resistance pattern in the community may be started. Delay in the diagnosis of MDR-TB and start of appropriate treatment can lead to increased morbidity and mortality as well as unchecked amplification and transmission of drug-resistant strains of TB.

When investigation of a symptomatic adult contact yields no evidence of TB, a trial of a broad-spectrum antibiotic, particularly one that is not active against TB, such as trimethoprim/sulfamethoxazole, can be used. If the patient continues to have symptoms, chest computed tomography and/or directed bronchoscopy for smear and culture should be considered if available. Where these diagnostic tools are

not available or the results are not conclusive, a diagnosis should be based on the clinical information at hand. If the initial investigation is not suggestive of active TB but the contact remains symptomatic, repeat physical examinations, smears and cultures should be performed monthly with repeat chest X-ray as needed.

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

MDR-TB should be suspected in children with active TB in the following situations:

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

The diagnosis of TB is more difficult in children than in adults. Symptoms of TB in young children can be nonspecific, e.g. chronic cough or wheeze, failure to thrive and recurrent fevers. Bacteriological confirmation may be difficult to obtain because of the inability of children to generate a sputum sample, as well as the paucibacillary nature of paediatric TB and the increased likelihood of extrapulmonary TB in children. While every effort should be made to establish a bacteriological diagnosis (and obtain DST) in a child with suspected MDR-TB, in practice paediatric cases are often not confirmed bacteriologically. Use of scoring systems that have been produced to aid screening and diagnosis of active TB is strongly recommended (see *Tuberculosis treatment Guidelines for National tuberculosis control programme on the management of tuberculosis in children*).

Symptomatic paediatric household contacts should receive:

- **An evaluation by a physician, including history and physical examination.**
- **Tuberculin skin testing with purified protein derivative (PPD).**
- **A chest X-ray examination (computerized tomography if available is helpful especially in documenting hilar adenopathy).**
- **Sputum smear, culture and DST: every effort should be made to establish a bacteriological diagnosis (and obtain DST) in a child with suspected DR-TB. Bacteriological confirmation may include more aggressive measures such as induced sputum, gastric aspirate, lymph node aspirate or other relevant sample, plus culture and DST. (Note: gastric aspiration should only be undertaken where culture facilities are available due to the low yield from microscopy and the distress involved for the child. Culture specimens need to be processed within the hour because the acidic juices will kill the bacteria relatively quickly).**
- **HIV counselling and testing (if parent(s) known, or suspected to be, HIV-infected) or routinely for all cases.**

When the tuberculin (PPD) skin test result is >5 mm but the chest radiograph and gastric aspirate or sputum smear are negative, the symptomatic child can be treated with a broad-spectrum antibiotic that is not active against TB, such as trimethoprim/sulfamethoxazole. The child should be followed closely, with evaluations including smear test and culture on samples from induced sputum or gastric aspirates, or sputum samples whenever possible, as well as chest X-rays. The optimal frequency of these evaluations has not yet been determined. It is not clear whether the frequency of evaluation recommended for adults can be applied to children. If a child's clinical condition is highly suggestive of TB, or progressively deteriorates, empirical therapy designed according to the DST pattern of the strain from the index case

can be started.

Children with MDR-TB who are incorrectly entered in SCC may suffer significant and protracted morbidity as a result of ongoing active disease, with the possibility of lifelong disability or even death. Because children with TB may never become sputum smear-positive, it is reasonable to initiate empirical MDR-TB therapy based on the DST pattern of the contact. If DST of the contact is not available, therapy can be based on the common DST patterns of resistance in the community.

10.6 Chemoprophylaxis of contacts of MDR-TB index cases

The only chemoprophylaxis regimens to have been studied are based on isoniazid and, to a lesser extent, rifampicin. Since by definition MDR-TB is resistant to both of these drugs, it is unlikely that use of these drugs to treat latent infection caused by an MDR-TB strain will prevent the development of active TB disease.¹

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

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

¹ Tuberculin skin tests become positive in most patients infected with TB irrespective of whether the strain is susceptible or resistant.

11 Drug resistance and infection control

11.1 The priorities of infection control

DR-TB is transmitted in the same manner as drug-susceptible TB. Well-documented outbreaks of highly drug-resistant strains of TB constitute convincing evidence that DR-TB is transmissible, especially among highly vulnerable populations and in institutional settings. Moreover, because DR-TB patients may respond to treatment slowly and remain sputum smear-positive longer than other TB patients, they may infect more contacts.

11.1.1 Administrative controls

The risk of transmission to patients and health-care workers decreases when community-based ambulatory treatment is established and hospital stays are reduced. Although most transmission is likely to have occurred before the diagnosis and start of treatment, ambulatory patients should be advised to avoid contact with the general public and with particularly susceptible people, such as young children or individuals with HIV infection and isolation of sleeping areas if possible at home. Health-care workers visiting TB patients at home before treatment is well established should wear properly fitted personal respirator masks. All staff to work at the DR-TB hospital should undergo a full medical examination which should include HIV testing. Administrative controls include policies and procedures intended to promptly identify infectious cases so that additional precautions can be taken. They necessitate the appointment of infection control's focal person for the institution, and an infection control committee representing key departments of the facility. The initial task of the committee is the formulation of a comprehensive infection control plan for the institution, including a programme for the education of all staff on infection control policies and procedures.

An important aspect of administrative control measures is the **physical separation** of patients known or suspected to have TB or DR-TB (especially smear-positive cases) from other patients, especially those who are immunocompromised. In many resource-limited settings, however, isolation rooms are not available and patients are mixed together in open wards. A second, less satisfactory but practical, solution is to separate rather than isolate patients. In this approach, patients with TB are grouped together and apart from those with suspected DR-TB, who are grouped together. This separation may be difficult as wards are usually separated by sex, which increases the number of different areas required. The presence of a substantial number of HIV-infected patients further complicates separation as they are not only potentially infectious but also highly vulnerable to intercurrent infection and reinfection from others. Placing HIV-infected patients on wards with known or suspected TB together with other TB or MDR-TB patients should always be avoided.

Infectious patients with XDR-TB, whether infected with HIV or not, should not be placed on general wards. Given the high mortality associated with XDR-TB, **isolation until the patient is no longer infectious** is recommended. Another administrative issue is the length of time patients spend in the hospital.

Attention should also be paid to **outpatient clinical settings**. Because of the risk of severe morbidity and mortality in HIV-infected persons from DR-TB, persons with known DR-TB should receive routine care outside of normal HIV care settings.

11.1.2 Environmental controls

Environmental (or engineering) controls assume that unsuspected, untreated TB patients will enter

hospitals despite all efforts to identify them. Engineering controls attempt to reduce the concentration of infectious droplet nuclei in the air. They include natural and/or mechanical ventilation, ultraviolet germicidal irradiation (UVGI) and high-efficiency particulate air filtration. Environmental methods should never replace administrative controls; in fact, they work together.

In addition, there are certain high-risk settings, such as sputum induction rooms, bronchoscopy rooms and rooms for the evaluation of newly admitted patients who may have untreated TB or DR-TB, where engineering interventions are necessary to reduce risk. **Personal respiratory protection** (special masks)

Because administrative and engineering controls cannot provide complete protection, the third line of defence against nosocomial TB transmission is the use of personal respirators.

Personal respirators are fundamentally different from, and more expensive than, the more familiar surgical masks which they resemble. Surgical masks are designed to protect the operating field from relatively large respiratory droplets generated by surgeons and surgical nurses. They are relatively loose-fitting and made of paper or cloth; they are not adequate for prevention of TB infection.

Masks that prevent TB transmission are known as “particulate respirators” or simply “respirators”. They are designed to protect the wearer from tiny (1–5 µm) airborne infectious droplets. The filtration media through which air passes must capture these minute particles; most importantly, the respirator must fit tightly on the face, especially around the bridge of the nose. Ideally, respirators should be “fit tested” for individual wearers. In addition to choosing the proper model for each worker, this process serves to educate workers on how to put on their respirators correctly to minimize face-seal leakage. Men with beards cannot be properly fitted with personal respirators. Institutions purchasing respirators are advised to look for models that are specifically designed to protect against TB and that meet international standards of quality.

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

11.2 High Risk areas

Special precaution will be required in the following high risk areas: laboratory, medical wards, X-ray department, out patients departments, TB units, ART units, pharmacy and other congregated areas with the health care facilities.

Baseline health status of the health care workers will be required at the time of enrolment and at regular intervals, pregnant and HIV positive staff to be relocated to less risk sections within the department, ensure use of personal protective equipment especially respirators and gowns, close monitoring of mechanical ventilation for functionality. On medical wards, patient cohorting should be done based level of infectivity, type of resistance and patents who have converted separated from those who have not converted. Cough hygiene should strictly be enforced. Protective clothing will be required while caring for isolated patients. Patients who are DR-TB accessing x-ray services should be encouraged to wear masks while accessing the service. In OPD in the DR-TB hospital , triaging on should be done based on whether the patients have XDR-TB or DR-TB and likewise those who are of known HIV status separated/ attended to as priority to prevent them from contracting more deadly strains while in the OPD

11.3 Measures to reduce infection transmission in community settings where there is congregation

Patient education should emphasize minimizing opportunities for transmission of DR-TB to the community in situations of congregation by observing cough hygiene and where possible avoiding places such as church, public transport, markets, and funerals before culture conversion. Screening for TB is encouraged for persons staying in congregate institutions for example school children joining boarding schools and on prisoners on entry and at regular 6 monthly intervals. The patient should sleep in a separate room if possible, avoid contact with children until smear and culture conversion. Family members should be advised to keep doors and windows open as long as possible to improve natural ventilation.

12 Category IV recording and reporting system

12.1 Aims of the information system and performance indicators

The aims of the information system are twofold:

- **To allow NTCP at national and local level to monitor overall programme performance (such as patients started on treatment and treatment results), to follow trends in the number of cases notified, to plan drug supply, and to provide the basis for programme and policy developments.**
- **To aid clinical providers in management of individual patients.**

The performance indicators include:

- **The number of patients in whom MDR-TB is detected in the laboratory**
- **The number of MDR-TB patients started on treatment**
- **Interim treatment outcome at 6-months of MDR-TB cases**
- **Final outcome of MDR-TB treatment.**

12.2 Scope of the information system

The information system for treatment of DR-TB is based upon, and is an extension of, the basic DOTS information system. The forms have therefore been designed to be as similar as possible to the standard forms used in DOTS programmes. The core information system should be consistent across settings to permit comparison. The core system does not include all of the detailed information that treatment units may need to manage individual patients; that information is contained in clinical records and other special forms used in the wards or clinics, and depends on local requirements and practices.

12.3 Main forms/registers and flow of information

The forms and registers include the following:

- **Category IV Treatment Card (Form 01);**
- **Category IV Register (Form 02);**
- **Request for sputum examination (Form 03);**
- **Laboratory Register for culture and DST (Form 04).**
- **DR-TB Suspects register**
- **Treatment support card**
- **Patient identity card**

Reports include:

- **Quarterly report on MDR-TB detection and Category IV treatment start (Form 05);**
- **Six-month interim outcome assessment of confirmed MDR-TB cases (Form 06);**
- **Annual report of treatment result of confirmed MDR-TB patients starting Category IV treatment (Form 07).**

12.3.1 Category IV Treatment Card (Form 01)

The Category IV Treatment Card contains the following sections:

Page 1

- **Basic demographic and clinical information. Records name, address, sex, age, weight and**

site of disease.

- **Category IV registration number.** This is a new unique identification number assigned when the patient is entered in the Category IV Register.
- **Date of Category IV registration.** Provides registration date in the Category IV Register.
- **Previous BMU TB registration number and date of registration.**
- **Registration group according to result of previous antituberculosis treatment.** See Chapter 2, section 2.4 for definitions.
- **Previous TB treatment episodes.** Lists and describes any previous antituberculosis treatment and outcomes. Start with the earliest treatment and label it number 1. Use the drug abbreviations given on the front of the treatment card. Also note here the outcome of any previous treatment.
- **Previous use of second-line antituberculosis drugs.** Documents use of any of the second-line drugs listed at the front of the chart for antituberculosis treatment for more than one month.
- **Meetings review panel (Case management committee).** These guidelines promote periodic meetings with the group of caregivers involved with Category IV patients. This section provides a space to record major decisions by the panel.

Page 2

- **HIV testing information.** This section is filled in for all patients. If tested for HIV, include date of testing and results. If HIV-infected, indicate whether patient is on ART and/or CPT.
- **HIV flow sheet.** This section is only filled in for HIV-infected patients.
- **Monitoring of weight.** Weight should be recorded at least monthly.
- **Monitoring of laboratory data including creatinine, potassium, liver function tests, and thyroid tests.** Recommendations regarding the interval for monitoring these indicators can be found in Chapter 8.

Page 3

- **Medical diagnoses other than TB.** All other important medical diagnoses are recorded here, including diabetes, hypertension, cardiomyopathy, HIV, opportunistic infections, etc.
- **Monitoring and recording adverse effects.** Record date, adverse effects and suspected drug(s).

Page 4

- **DST results.** Record the date of sputum collection and results of all DST performed.
- **Monitoring of chest X-ray.**
- **Monitoring of smear and culture.** Record date of sputum collection, sample number in the laboratory register and result of smear and culture. “Prior” refers to the sample used to indicate Category IV registration; include the date and result of that sample. Month “0” is the time of specimen collection at the start of the Category IV regimen. Requirements for monitoring of smear and culture are described in Chapter 8.

Pages 5 and 6

- **Regimen.** Record the initial Category IV regimen and later changes. Use one line for each date on which a drug(s) is changed. If drug dosage is progressively increased (e.g. starting 250 mg of ethionamide daily and increasing by 250 mg over 2–3 days until the full dose is reached), record this in the patient’s medical record (not on the treatment card).
- **Record of daily observed administration of drugs.** This is constructed with one line per month to facilitate assessment of adherence. Mark one box for each day the entire treatment is administered. Additionally, if dosing is twice daily, one slash mark could be

made for the A.M. dose and a second, intersecting mark could be made for the P.M. dose; if both are received, the box would contain an “x”. An alternative is a more detailed system containing one box for each drug prescribed daily, since there may be some inconsistency in administration among drugs.

- **Outcome of treatment.** Chapter 2, Section 2.5 provides definitions. Record the outcome of treatment when the final bacteriology results become available.

12.3.2 Category IV Register (Form 02)

The NTP should have two TB registers: a BMU Tuberculosis Register and a Category IV Register. The Category IV Register is the record of all patients who start Category IV treatment (see Chapter 2 for a general definition of Category IV patients). This register allows quick assessment of the implementation of Category IV, facilitating quarterly reporting and analysis of treatment start and outcomes. However, only the TB hospital will register all MDR-TB patients in the country

The BMU Tuberculosis Register is the traditional register used by Diagnostic TB centres in which all TB patients are first registered. In order to integrate the treatment of Categories I, II, III and IV, this register should be modified in three ways:

1. If culture is being done in addition to smear examination in a substantial number of cases, dates of collection and results should be added to both the initial testing and the follow-up areas.
2. Capability to record DST should be added, including the date of collection of the sample and the drugs that are being tested.
3. Any patient who is switched to a Category IV regimen because of resistance (without meeting the formal criteria of failure) should have the outcome category “Change to Category IV” entered in the BMU Tuberculosis Register.

When a patient is starting Category IV treatment, the health staff in the diagnostic treatment unit should enter the patient in the Category IV Register and indicate in the BMU Tuberculosis Register that the patient has entered Category IV. The date of registration should be the day when the health staff enters the patient in the Category IV Register. The Category IV Register should be updated regularly from the Category IV Treatment Card and from the laboratory registers. Patients should be recorded consecutively by their date of registration. There should be a clear separation (extra line) when a new quarter is started. Patients infected with more complicated mono- and poly-resistance strains (involving R or HEZ resistance) or any mono- and poly-resistant strains that may have developed into MDR-TB should be entered into the Category IV Register.

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

Any patient with mono- or poly resistance whom it has been determined should stay in the DR-TB programme should not be crossed out of the Category IV Register. Whether the patient continues on the

same Category IV regimen (often done in programmes using standardized regimens) or gets an individualized regimen based on DST can be documented on the treatment card and the final outcome reported in the Category IV Register. *These patients do not need to appear in Forms 05, 06 and 07 of the DR-TB reporting forms as they do not have MDR-TB.*

The following information is recorded in the Category IV Register:

- **Category IV registration number.**
- **Date of Category IV registration.**
- **Name, sex, date of birth, address (from treatment card, p. 1).**
- **BMU TB registration number.** All patients should have been entered in a BMU Tuberculosis Register. A patient who for any reason has never been registered in the BMU Tuberculosis Register should be registered there and the number transferred to the Category IV Register.
- **Site of disease (from treatment card, p. 1).** Pulmonary, extrapulmonary or both. Patients with both pulmonary and extrapulmonary TB should be classified as a case of pulmonary TB.
- **Registration group (from treatment card, p. 1).** Described in Chapter 2, section 2.4.
- **Second-line drugs received for more than one month prior to registration (from treatment card, p. 1).**
- **DST (from treatment card, p. 4).** Date sample taken, date of DST result and the results. Enter the DST that resulted in the patient being registered as a Category IV patient. Follow-up DSTs are not recorded in the register. If the patient has more than one DST, results are recorded on the treatment card. If DST is performed in a staged fashion (e.g. of rifampicin and isoniazid first, followed by other first-line drugs, and then of second-line drugs) all results from the same sample should be recorded in the register.
- **Category IV regimen (from treatment card, p. 5).** Record the initial Category IV regimen using the drug abbreviations. Include milligram doses and number of tablets.
- **Date of start of Category IV treatment (from treatment card, p.5).**
- **Smear and culture monitoring results (from treatment card, p.4).** Record all smear and culture results, even if done more often than the recommended frequency.
- **Final outcome (from treatment card, p.6).** See Chapter 2, section 2.5 for definitions.
- **HIV status (from treatment card, p.2)** Testing results, CPT and ART treatment information.
- **Comments.**

12.3.3 Request for sputum examination (Form 03)

The upper portion is for requesting smear microscopy, the middle portion for culture and the lower portion for DST; the last section is used for reporting the results. When DST is requested, the registration group should be added. Results should be sent stepwise as they become available.

12.3.4 Laboratory Register for culture and DST (Form 04)

Laboratories will have separate registers for sputum smear microscopy and culture, while reference laboratories carrying out DST should have additional space in the culture register for DST results (see Form 04). The Laboratory Register should be compared regularly with the Category IV Register to ensure that all confirmed MDR-TB cases are entered in the Category IV Register.

12.3.5 Quarterly report on MDR-TB detection and Category IV treatment start (Form 05)

This report is used to assess the number of MDR-TB cases detected (distribution and trends) and the number of MDR-TB cases who start treatment. The report should be made quarterly in line with the routines of the NTCP. The report should be made by the unit managing MDR-TB. The quarterly report

includes:

- **The number of patients, with date of result showing MDR-TB during the relevant quarter taken from the Laboratory Register. Optionally, the patients could be split by registration group.**
- **The number of MDR-TB patients started on Category IV treatment during the quarter, taken from the Category IV Register.**
- **If relevant, the number of XDR-TB cases registered (after cross-checking DST results with type of resistance) and the number of XDR-TB cases started on XDR-TB treatment should be added. Since there may be a considerable delay between Category IV registration and the start of Category IV treatment, patients who start treatment during the quarter may not be the same as those detected with DR-TB. The information provides an approximation of treatment coverage. The NTCP will calculate the average delay between detection of DR-TB and treatment start.**

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

Since treatment takes on average two years before final results are known, the NTCP needs updated information on treatment outcome. Form 06 can be used to report bacteriological status (negative, positive or no information) of those still on treatment at 6 months, and for those who have already defaulted, died or transferred out, this can be recorded as the final outcome. Bacteriological results are based on the smear and culture data during months 5 and 6 of treatment. Consider the 6-month outcome assessment unknown for a particular patient if a culture or smear result is unknown for either month 5 or 6.

All cases from the Category IV Register should be included in this report. The form should be completed 9 months after the closing day of the cohort. This allows culture information at month 6 of treatment to be included for all patients in the cohort. For instance, TB patients who started treatment during the first quarter of a year (1 January to 31 March), should have the form filled in from 1 January of the following year.

12.3.7 Annual report of treatment result of confirmed MDR-TB patients starting Category IV treatment

This report is made by the central unit and shows the final result of treatment by year of treatment start. All the patients are classified by previous use of antituberculosis drugs (none, only first-line drugs, also second-line drugs). If relevant, results for patients with XDR-TB could be added. All data can be extracted from treatment cards and Category IV Register. Form 07 is first completed at 24 months after the last patient in the cohort started treatment. Most of the patients will have finished treatment by 24 months, allowing preliminary assessment of cure rates. Since a few patients may be on treatment for longer than 24 months, the form may be completed again at 36 months, which will then be considered the final result.