MANAGEMENT OF DRUG-RESISTANT TUBERCULOSIS

POLICY GUIDELINES

2010
The following policy guidelines are intended for use by health care professionals involved in the complex and difficult task of managing mono resistant, poly resistant, multidrug-resistant (MDR) and extensive drug-resistant (XDR) tuberculosis patients in South Africa. The document focuses on the clinical management, referral mechanisms and models of care; however, psycho-social support to ensure comprehensive management of the patients, strategies for infection prevention and control and occupational health services for health care workers are also covered.

Legal issues around the management of drug-resistant (DR-TB) are complex and have been addressed in separate documents, guided by the evolving health legislation and the Constitution of South Africa.

Management of DR-TB is still an evolving strategy, and needs to be adapted through evidence-based information. These guidelines contain recommendations based on the most recent and available scientific evidence and expert opinion; however, comments and suggestions from those working in the field are essential to ensure a dynamic process, aimed towards optimal control of DR-TB in South Africa. Please forward these to: The Cluster Manager: Tuberculosis Control and Management, National Department of Health, Private Bag X828, Pretoria, 0001. E-mail: NdjekO@health.gov.za

The National Department of Health would like to acknowledge the technical assistance and invaluable inputs made by all people who were involved in the development of these guidelines innumerable to be listed here individually. A special word of gratitude goes to the University Research Corporation for the financial support for the development of these guidelines.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFB</td>
<td>Acid-Fast Bacilli</td>
</tr>
<tr>
<td>ART</td>
<td>Antiretroviral Therapy</td>
</tr>
<tr>
<td>BID</td>
<td>twice a day</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>CPT</td>
<td>Cotrimoxazole preventive therapy</td>
</tr>
<tr>
<td>CT scan</td>
<td>Computerised tomography scan</td>
</tr>
<tr>
<td>DOT</td>
<td>Directly Observed Therapy</td>
</tr>
<tr>
<td>DOTS</td>
<td>Directly Observed Therapy Short course</td>
</tr>
<tr>
<td>DRS</td>
<td>Drug Resistance Surveillance</td>
</tr>
<tr>
<td>DST</td>
<td>Drug Susceptibility Testing</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>FEV1</td>
<td>Forced expiratory volume in 1 second</td>
</tr>
<tr>
<td>FVC</td>
<td>Forced vital capacity</td>
</tr>
<tr>
<td>FIND</td>
<td>Foundation for Innovative New Diagnostics</td>
</tr>
<tr>
<td>HCT</td>
<td>Hematocrit</td>
</tr>
<tr>
<td>HCWs</td>
<td>Health Care Workers</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>HPF</td>
<td>High-Power Field</td>
</tr>
<tr>
<td>LFT</td>
<td>Liver Function Test</td>
</tr>
<tr>
<td>MDR-TB</td>
<td>Multi-Drug Resistant Tuberculosis</td>
</tr>
<tr>
<td>NDOH</td>
<td>National Department of Health</td>
</tr>
<tr>
<td>XDR-TB</td>
<td>Extensively Drug Resistant Tuberculosis</td>
</tr>
<tr>
<td>DR-TB</td>
<td>Drug-Resistant Tuberculosis</td>
</tr>
<tr>
<td>NTM</td>
<td>Non-Tuberculous Mycobacteria</td>
</tr>
<tr>
<td>PPD</td>
<td>Purified Protein Derivative</td>
</tr>
<tr>
<td>PPM</td>
<td>Public-Private Mix</td>
</tr>
<tr>
<td>QD</td>
<td>once a day</td>
</tr>
<tr>
<td>QID</td>
<td>four times a day</td>
</tr>
<tr>
<td>SCC</td>
<td>Short-Course Chemotherapy</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>TID</td>
<td>three times a day</td>
</tr>
<tr>
<td>TSH</td>
<td>Thyroid-Stimulating Hormone</td>
</tr>
<tr>
<td>UVGI</td>
<td>UltraViolet Germicidal Irradiation</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
ANTITUBERCULOSIS DRUG ABBREVIATIONS

Am  Amikacin
Amx/Clv  Amoxicillin/Clavulanate
Cfz  Clofazimine
Clr  Clarithromycin
Cm  Capreomycin
Cs  Cycloserine
E  Ethambutol
Eto  Ethionamide
Gfx  Gatifloxacin
H  Isoniazid
Im  Imipenem
Km  Kanamycin
LfX  Levofloxacin
Lzd  Linezolid
Mfx  Moxifloxacin
Ofx  Ofloxacin
PAS  P-aminosalicylic acid
Pto  Prothionamide
R  Rifampicin
S  Streptomycin
Th  Thioacetazone
Trd  Terizidone
Vi  Viomycin
Z  Pyrazinamide

TABLES

<table>
<thead>
<tr>
<th>Title</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table I</td>
<td>MDR-TB cases in South Africa 2006-2008</td>
<td>12</td>
</tr>
<tr>
<td>Table II</td>
<td>DR-TB cases registered and started on treatment 2007-2009</td>
<td>12</td>
</tr>
<tr>
<td>Table III</td>
<td>MDR-TB staff responsibilities</td>
<td>29</td>
</tr>
<tr>
<td>Table IV</td>
<td>Responsibilities at every level</td>
<td>32</td>
</tr>
<tr>
<td>Table V</td>
<td>Risk factors for MDR-TB</td>
<td>36</td>
</tr>
<tr>
<td>Table VI</td>
<td>Suggested regimens for mono and poly drug resistant TB in patients where further acquired resistance is not a factor</td>
<td>46</td>
</tr>
<tr>
<td>Table VII</td>
<td>Available second-line drugs for treatment of drug-resistant TB</td>
<td>51</td>
</tr>
<tr>
<td>Table VIII</td>
<td>Grouping of MDR-TB drugs</td>
<td>52</td>
</tr>
<tr>
<td>Table IX</td>
<td>Summary of general principles for constructing XDR-TB treatment regimens</td>
<td>59</td>
</tr>
</tbody>
</table>
Table XIII  Safety of second line drugs during pregnancy  79
Table XIV   Formulations and dosages of second line drugs for children  81
Table XV    Adjustment of drugs in renal insufficiency  84
Table XVI   Monitoring and evaluation of patients  99

FIGURES

Figure I: Units for decentralized management of MDR-TB  19
Figure II: Flow of MDR-TB patients  33
Figure III: Management of hearing loss  77
Figure IV: Flow chart of ART in adult patients with DR-TB  91
Figure V: Management of patients who default  103
Figure VI: Post-treatment follow up flow diagram  108
KEY ISSUES IN THE MANAGEMENT OF DRUG-RESISTANT TUBERCULOSIS

1. Multidrug-resistant tuberculosis (MDR-TB) is defined as tuberculosis (TB) disease where there is in vitro resistance to both isoniazid and rifampicin, with or without resistance to other anti-tuberculosis drugs. As isoniazid and rifampicin are the two most important first-line TB drugs, their removal through resistance from the anti-TB drug armamentarium has serious implications.

2. Extensive drug-resistant tuberculosis (XDR-TB) is defined as MDR-TB and in vitro resistance to any of the fluoroquinolones plus one or more of the injectable second-line anti-TB drugs, ie. kanamycin, amikacin or capreomycin. XDR-TB is extremely difficult and expensive to treat and an exceptionally high mortality (exceeding 90%) has been reported in HIV co-infected XDR-TB patients in Tugela Ferry, KwaZulu-Natal.

3. Prevention is the key to effective control of drug-resistant TB (DR-TB). MDR-TB arises as a result of poor management of TB patients and most cases of XDR-TB arise as a result of poor MDR-TB management. There is, therefore no point in using scarce health care resources for the treatment of drug-resistant TB while neglecting proper implementation of the DOTS strategy.

4. Drug-resistant TB is a laboratory diagnosis and therefore quality-assured laboratory services are of paramount importance. All laboratories that perform drug susceptibility testing (DST) must have internal quality assurance measures in place and participate in external proficiency testing programmes.

5. Management of MDR-TB will be conducted in dedicated MDR-TB units, in other health care facilities and in the community by trained health care workers in an environment with appropriate infection control measures to prevent nosocomial transmission of DR-TB.

6. Uninterrupted supply of appropriate drugs, treatment under direct supervision with proper education and counselling of patients are also required.

7. All provinces must have DR-TB Clinical Review Committees, which would be the only body responsible for making adjustments to a patient’s treatment when indicated, and the decisions on termination of treatment.
management of patients in the hospitals and review clinical progress on a regular basis.

9. Infection control officers and committees must ensure that TB risk assessments are conducted on an annual basis, infection control plans developed and monitored on a regular basis to monitor the effectiveness of the interventions implemented.

10. Mono-and poly-drug-resistant TB requires individualised treatment based on the resistance profile to first-line anti-TB drugs. These patients need to be managed as outpatients but treatment must be initiated by a doctor in the MDR-TB hospital’s outpatients department and the patient registered in the drug resistance TB register.

11. A standardised approach to MDR-TB treatment is recommended for all newly diagnosed MDR-TB or XDR-TB patients. The standardised MDR-TB regimen consists of an intensive phase also called injectable phase of at least six months with five drugs followed by a continuation phase of 18 months (or less) with four drugs. Treatment should be given at least six days per week. The drugs used are Kanamycin or amikacin, levofloxacin (high dose), ethionamide, terizidone or cycloserine and pyrazinamide during the injectable phase. Levofloxacin (high dose), ethionamide, terizidone or cycloserine and pyrazinamide are given during the continuation phase. In patients who were previously exposed to second-line anti-TB drugs for a month or more; the standardized regimen will be modified based on the history of drug usage and DST results.

12. The duration of the injectable phase will be determined by adding 4 months to the TB culture conversion date (date of collection of the first sputum that turned TB culture negative); it has to be six months or more.

13. The duration of treatment will be determined by adding 18 months to the date of TB culture conversion.

14. XDR-TB requires an individualised approach based on the previous history of drug use in a patient and the results of drug susceptibility testing (DST). However, DST for second-line anti-TB drugs is technically complex and much less reliable than DST for first-line anti-TB drugs. Therefore, treatment of XDR-TB should always be initiated under guidance of the clinical management team and the review committees. Practitioners need to remember that DST for injectables and fluoroquinolones are the most reliable of all second-line anti-TB drugs.

15. All patients with drug resistant TB must be offered HIV counselling and testing and those who are co-infected started on cotrimoxazole and anti-retroviral treatment (ART) as soon as ARVs adherence counselling is
completed. All co-infected M/XDR-TB/HIV patients qualify to receive anti-retroviral therapy regardless of their CD 4 count.

16. On going adherence, counselling and psycho-social support must be provided to patients and reinforced throughout treatment. Patients must also be educated about TB prevention and cough hygiene

17. Suspected but unconfirmed MDR and XDR-TB patients must be isolated in a well-ventilated side ward in a TB or district hospital if space allows. If at home, they must be educated about cough hygiene and infection control at home. Treatment needs to be initiated as soon as diagnosis is confirmed. Use of line probe assay is recommended for quicker diagnosis.

18. Close contacts of patients diagnosed with drug-resistant TB must be screened and tested for DR-TB. Those found not to have TB must be routinely screened for DR-TB at six-monthly intervals. There is, as yet, no evidence to support TB preventive therapy.

19. Occupational health services for all staff must be provided in all the hospitals. A register of all health workers who develop TB or DR-TB should be kept at the hospital in order to help determine the risk involved and to inform future policy.

20. DR-TB registers should be kept at the MDR-TB hospitals and all centres that will be capacitated to initiate M/XDR-TB treatment including district hospitals, health centres and updated regularly.

21. Cohort analyses of DR-TB case finding, interim outcomes and final outcomes should be provided at regular intervals to enable assessment of performance and facilitate appropriate corrective action.

22. Annual reviews should be compiled for each MDR-TB hospital on the probable causes of MDR- and XDR-TB, the outcome of treatment and the costs involved. An annual report should be forwarded for the attention of the provincial head of the health department.

23. Periodic surveys of DR-TB prevalence must be undertaken in each province.
# TABLE OF CONTENTS

1. **INTRODUCTION** ............................................................................................................. 10

2. **LEGISLATIVE FRAMEWORK AND PUBLIC HEALTH ETHICS** ............................... 15

3. **ORGANISATION OF SERVICES** ................................................................................ 19

4. **CASE FINDING STRATEGIES** .................................................................................. 36

5. **DIAGNOSIS OF DR-TB** ............................................................................................ 39

6. **MANAGEMENT OF PATIENTS WITH MONO AND POLY DR-TB** ....................... 45

7. **MANAGEMENT OF PATIENTS WITH MDR - TB** ............................................... 47

8. **MANAGEMENT OF PATIENTS WITH XDR-TB** .................................................... 58

9. **ROLE OF SURGERY** ............................................................................................... 64

10. **MANAGEMENT OF DRUG ADVERSE EFFECTS** .................................................. 65

11. **RECOMMENDED DRUGS FOR THE TREATMENT OF ADVERSE EFFECTS** .......... 74

12. **TREATMENT IN SPECIAL SITUATIONS** ................................................................. 78

13. **DR-TB AND HIV** .................................................................................................... 88

14. **MONITORING AND EVALUATION OF PATIENTS WITH DR-TB** ...................... 95

15. **MDR AND XDR-TB CONTACTS** ............................................................................. 113

16. **RECORDING AND REPORTING** ............................................................................. 117

17. **HEALTHCARE WORKERS AND MDR-TB** ......................................................... 125

18. **ANNEXURES** ........................................................................................................... 138
1. INTRODUCTION

At no time in recent history has tuberculosis been as great a concern as today. Despite highly effective drugs, disease and deaths due to *Mycobacterium tuberculosis* are increasing in South Africa, fuelled by the widespread HIV epidemic. The most serious aspect of the TB epidemic has been the emergence of drug-resistant tuberculosis (DR-TB) in the country. DR-TB is a man-made problem, largely being the consequence of human error in any or all of the following:

- Management of drug supply
- Patient management
- Prescription of chemotherapy
- Patient adherence

Anti-TB drugs constitute a two-edged sword – while they kill the mycobacteria, they also select for naturally-resistant mycobacteria. In this way strains can become sequentially resistant to several agents and patients may also acquire further drug-resistant strains through re-infection or superinfection.

1.1 Definitions

Drug-resistant TB is a disease (usually pulmonary) caused by *M. tuberculosis* strains resistant to one or more anti-TB drugs.

MDR-TB is defined as resistance to rifampicin and isoniazid, with or without resistance to other first-line anti-TB drugs.

XDR-TB is defined as resistance to rifampicin, isoniazid, any fluoroquinolone and resistance to one or more of the following injectable anti-TB drugs: kanamycin, amikacin, capreomycin.

Drug resistance is further classified according to the history of previous TB treatment:

- **Resistance in new patients (previously called ‘primary resistance’)** is resistance in cultures from patients with no history of previous TB treatment or patients who have received TB treatment for less than one month previously. Resistance in new patients provides a measure of the degree of transmission of *M. tuberculosis* strains.
- **Resistance in previously treated patients (previously called ‘acquired resistance’)** refers to resistance in cultures from patients with one or more previous TB treatment episodes, of more than one month each. Previously treated patients are also often referred to as re-treatment cases.
possible to assess. Patients may be erroneously labeled as having primary resistance if they do not disclose previous treatment for TB, while patients who fail treatment (and are therefore labelled to have acquired resistance) may have been infected with a resistant strain from the beginning or acquired resistance during treatment. MDR-TB is not the same as disease due to non-tuberculous mycobacteria (NTM). NTMs are commonly resistant to both isoniazid and rifampicin but should not be confused with MDR-TB. These Guidelines are relevant for the management of DR-TB only and not for disease caused by NTM.

1.2 Development of drug-resistant TB

*M. tuberculosis* has the ability to undergo spontaneous, slow but constant mutation, resulting in resistant mutant organisms. This natural phenomenon is genetically determined and varies from drug to drug. The probability of spontaneous resistance to individual first-line anti-TB drugs is as follows:

- Isoniazid: 1 in every $10^6$ cell divisions
- Rifampicin: 1 in every $10^9$ cell divisions
- Streptomycin: 1 in every $10^6$ cell divisions
- Ethambutol: 1 in every $10^5$ cell divisions
- Pyrazinamide: 1 in every $10^5$ cell divisions

Usually, the chromosomal location of resistance to different drugs is not linked; therefore, spontaneously occurring multidrug resistance is extremely rare. For example, the probability of mutation resulting in resistance to isoniazid is $10^{-6}$ and for rifampicin it is $10^{-9}$. The likelihood of spontaneous resistance to both isoniazid and rifampicin is the product of the two probabilities, ie. $10^{-15}$. Since the probability of naturally occurring resistant mutants is very low, a large bacterial load (eg. in lung cavities) is needed for MDR-TB strains to emerge.

Drug resistance, therefore, is the result of selection of resistant mutants in the bacterial population, due to killing of susceptible bacilli by anti-TB drugs. The problem is greatly exacerbated by inadequate treatment such as direct or indirect monotherapy, resulting from intake of a single anti-TB drug or from intake of several drugs with suboptimal concentrations. Susceptible bacilli are killed rapidly and resistant mutants are then able to multiply.
including MDR. Erratic treatment with second-line drugs can result in XDR-TB and virtually untreatable disease.

1.3 Situational analysis

South Africa is ranked as the 4\textsuperscript{th} Drug-resistant tuberculosis (TB) high burden country in the world, behind countries with significantly larger populations such as China, India and Russian Federation. Due to inadequate management of TB over the years, high levels of drug resistant TB (DR-TB), both multi-drug resistant tuberculosis (MDR-TB) and extensively drug resistant tuberculosis (XDR-TB) forms of TB have been witnessed, following the outbreak that happened in Tugela Ferry, KwaZulu Natal in 2006. Almost 7,000 MDR and XDR-TB cases were notified in 2008, keeping up with the steady increase in cases since 2006 as Table 1 shows.

Table I: MDR and XDR cases in South Africa – 2006 to 2008

<table>
<thead>
<tr>
<th>Province</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MDR</td>
<td>XDR</td>
<td>MDR</td>
</tr>
<tr>
<td>Eastern Cape</td>
<td>930</td>
<td>66</td>
<td>1128</td>
</tr>
<tr>
<td>Free State</td>
<td>204</td>
<td>4</td>
<td>216</td>
</tr>
<tr>
<td>Gauteng</td>
<td>714</td>
<td>19</td>
<td>1027</td>
</tr>
<tr>
<td>KwaZulu Natal</td>
<td>2,402</td>
<td>322</td>
<td>2239</td>
</tr>
<tr>
<td>Limpopo</td>
<td>76</td>
<td>3</td>
<td>114</td>
</tr>
<tr>
<td>Mpumalanga</td>
<td>144</td>
<td>1</td>
<td>473</td>
</tr>
<tr>
<td>Northern Cape</td>
<td>178</td>
<td>3</td>
<td>194</td>
</tr>
<tr>
<td>North West</td>
<td>213</td>
<td>15</td>
<td>390</td>
</tr>
<tr>
<td>Western Cape</td>
<td>1,204</td>
<td>29</td>
<td>1459</td>
</tr>
<tr>
<td>South Africa</td>
<td>6,065</td>
<td>462</td>
<td>7,240</td>
</tr>
</tbody>
</table>

As shown in the table I, KwaZulu Natal and Western Cape have notified the highest number of cases followed by Eastern Cape and Gauteng.
As shown in table II, there is a wide gap among the number of M/XDR-TB patients diagnosed, registered and started on treatment. In 2008, programme did not start DR-TB treatment in almost 35% of all diagnosed MDR-TB patients and 32% of all diagnosed XDR-TB patients. The number diagnosed and started on treatment depends on the prevalence of Drug-resistance and accessibility & efficiency of diagnostic and treatment services in the provinces.
• Sustained government commitment;
• Accurate, timely diagnosis through quality assured culture and drug susceptibility testing;
• Appropriate treatment utilizing second-line drugs under strict supervision;
• Uninterrupted supply of quality assured second-line drugs;
• Standardized recording and reporting system.

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

1.5 Prevention of Drug-Resistant TB

• *Standardised first-line regimens for new and re-treatment patients*
  Ensuring cure of new smear-positive patients the first time around will prevent significant development and subsequent spread of drug-resistant TB. This is only possible on a national scale by the use of standardised regimens. Every effort should be made to ensure that patients on regimen 2 (re-treatment) complete their treatment, as they are at higher risk of developing drug-resistant TB.

• *Compliance to treatment protocols*
  Compliance with management guidelines as recommended by the National Department of Health ensures that adequate drugs, in the correct combinations and dosages, are prescribed for the correct period of time. Use of fixed combination drugs eliminates the likelihood of selection of drugs and inadequate dosing due to human error.

• *Patient adherence and supervision of therapy*
  Adherence refers to how well patients complete the full course of prescribed medication. This often depends on adequate counselling, ongoing support, and access to the facility and attitudes of health care staff. Directly observed therapy (DOT) during (at the very least) the intensive phase of treatment is the national policy. Excellent adherence during the intensive phase of treatment, during which time the total bacterial load in the patient is being reduced, is crucial to the prevention of drug-resistant TB. This is especially true for sputum smear-positive patients who have a high bacterial load. DOT in the follow-up phase is also important to help prevent relapse.
2. LEGISLATIVE FRAMEWORK AND PUBLIC HEALTH ETHICS

The Department of Health is legally responsible for control of TB, including DR-TB, as a public health issue and is required to operate within the context of the Bill of Rights enshrined in the Constitution of the Republic of South Africa, 1996. The Bill of Rights affords individual rights to every person and also balances competing rights and communal interests.

2.1 Rights protected by the Constitution:
- Freedom and security of the person: violations of this right arise from enforced isolation or treatment.
- Life: The right to receive treatment and the right of those not infected to be protected from infection.
- Health care: The right to health care services and emergency medical treatment.
- Just administrative action: the right to be heard before a decision is made which adversely affecting individual rights.
- Human dignity: the effects of detention and treatment on an individual’s dignity
- Privacy: disclosure of a patient’s health status to others
- Equality: discriminating between those who will receive treatment or be detained and those who will not
- Freedom of movement and residence: the effect of enforced detention and conditions of release
- Freedom of trade, occupation and profession: the effect of enforced detention and conditions of release.
- Social security: the right to social security, including, if they are unable to support themselves and their dependents, appropriate social assistance

2.2 Other relevant legislation
The following legislation provides a legal framework for the management of MDR-TB:
- The National Health Act 61 of 2003
  Chapter 2 of the Act gives emphasis to the rights to emergency medical treatment; to have full knowledge of one's condition, to exercise one's informed consent, to participate in decisions regarding one's health, to be informed when one is participating in research, to confidentiality and access to health records, of users to lay complaints about the service; and the rights of health workers to be treated with respect.
- The Promotion of Administrative Justice Act 3 of 2000
Provides for the health and safety of persons at work and the protection of employees against hazards through provision of a safe working environment by the employer.

- **The Compensation for Occupational Injuries Diseases Act 130 of 1993 and its Hazardous Biological Agent Regulations (21 December 2001);**
  Provides for the compensation for disability caused by injuries sustained and diseases acquired in the workplace by employees during their employment. This excludes the mines, which are provided for in a separate Act.

- **The Employment Equity Act 55 of 1998**
  Promotes equal opportunity and fair treatment in employment through the elimination of unfair discrimination.

- **Social Assistance Act 13 of 2004 and its regulations**
  Gives effect to the section 27 (1)(c) of the Constitution by providing for the rendering of social assistance to persons and mechanisms for the rendering of such assistance.

- **The Labour Relations Act 66 of 1995**
  Aims to promote economic development, social justice, labour peace and democracy in the workplace. It incorporates the code of good practice, which deals with some of the key aspects of dismissals for reasons related to conduct and capacity.

- **Basic Conditions of Employment Act 75 of 1997.**
  Provides for the minimum conditions of employment that employers must comply with in their workplace.

- **Promotion of Equality and Prevention of Unfair Discrimination Act, 2000**
  Promotes the principles of equality, fairness, social progress, justice, human dignity and freedom. It also prohibits unfair discrimination and unfair denial of access to healthcare services.

- **Promotion of Access to Information Act, 2000**
  Guarantees access to any information held by another person that is required for the exercise or protection of any rights. It also promotes the Constitutional right of access to any information held by the State and therefore impacts access to medical records and history.

- **Unemployment Insurance Act No 63 of 2001**
  Sections 14, 20, 36 provide for claims by the worker if unable to work because of illness

### 2.3 Public health ethics

as a ground for limiting certain rights in order to allow a state to take measures dealing
with a serious threat to the health of the population or individual members of the
population. These measures must be specifically aimed at preventing disease or injury
or providing care for the sick and injured and that due regard shall be had to the
international health regulations of the World Health Organization.”

2.3.1 International Health Regulations

The purpose and scope of these regulations is to prevent, protect against, control and
provide a public health response to the international spread of disease in ways that are
commensurate with and restricted to public health risks and which avoid unnecessary
interference with international traffic and trade. Implementation is guided by the
following principles:
- With full respect for dignity, human rights and fundamental freedom of
persons
- Guided by the Charter of the United Nations and the Constitution of the
WHO
- Guided by the goal of their universal application for the protection of all
people of the world from international spread of disease

The management and prevention of drug-resistant TB like other public health
interventions requires cooperation by all affected and balancing of community and
individual interests. Limitation of individual freedom or choice may be necessary to
protect individuals as well as entire communities.

Individual freedom should however be carefully restricted and only when alternative
approaches to preventing spread, are not likely to be effective. The following guiding
principles should be observed in determining the restrictions:
- Must be provided and carried out in accordance with the law
- Adopting the least restrictive practices that will allow the common good to
be protected.
- Ensuring that restrictions are necessary and proportional to the need for
protection.
- All other less restrictive measures must have been explored first before
implementing the more intrusive public health measures.
- Must be based on scientific evidence that failure to implement the measure
is likely to result in harm to the well-being of the public and society as a
whole and not imposed arbitrarily.
- Attempting to ensure that those impacted by restrictions receive support
and assistance (i.e. job security, financial support for individuals who
are isolated and provision of food parcels and other necessities to their
families, and protection against stigmatization or unwarranted disclosure of
private information).
A fair and standard process must be followed when making the decision to isolate people with confirmed MDR- and XDR-TB in order to achieve favourable outcomes. In order to achieve this, the following must be followed:

- Ensure consistency in applying standards across people and not discriminate based on colour, religion and status.
- Engage patients and their families in the decision-making process and they must give consent.
- All patients must be treated with dignity and respect
- Communication must be clear in local language and culturally sensitive
- There must be transparency, accountability and no hidden agendas
- Maintain impartiality and neutrality in the process of decision-making regarding management.

### 2.3.2 Patient management related challenges

A number of factors need to considered and addressed when managing patients with DR-TB. These include:

1) Patient related
   Some patients might refuse treatment and hospitalization; other patients would like to get treatment but would not agree to be hospitalized. Some patients request discharge from MDR-TB units while still highly infectious. Decentralization of MDR-TB care is a solution to this problem.

2) Community related
   Implications of continued employment for infectious patients, discharging patients who failed treatment back to communities and disclosure of patients condition to family, employer and close contacts need to be discussed with all affected parties. This would require that infection control strategies are implemented in the community to ensure protection of vulnerable groups – children, HIV-positive individuals and intensive community mobilisation to increase awareness and address stigma.

3) Labour related

   The fact that working in MDR-TB hospitals which are a high risk environment for infection, may be a cause for concern for health care workers and result in high turn over of staff, refusal of staff to work in high risk area and difficulties in
3. ORGANISATION OF SERVICES

It is clearly evident from experience in the recent past, that prolonged admission of all MDR-TB patients in specialized hospitals is not feasible. There is also growing evidence from within South Africa and outside countries of improving effectiveness of control with decentralization of services. The diagnosis of DR-TB is made in the clinics, community health centers or district/tertiary TB hospitals. On confirmation of DR-TB the patient would then be referred to the provincial or decentralized MDR-TB unit for assessment and initiation of treatment. It is therefore recommended that each province should have a network comprising a specialized MDR/XDR Unit at its apex, linked to decentralized and satellite units as shown in Figure I.

The framework below describes the roles of the different levels of patient management.

3.1 National level
The national department of health plays a critical role of policy formulation, monitoring, evaluation and support to provinces.

3.2 Provincial level
Each province should have a network comprising a specialized MDR/XDR Unit at its apex and decentralized and satellite units (See Figure I).

Figure I: Units for the decentralized management of MDR-TB

![Diagram showing the decentralized management of MDR-TB units](image-url)
A health facility, where health professionals are specially trained in the initiation and management of MDR-TB treatment.

A MDR-TB unit may be a (stand alone) hospital, a MDR-TB ward in a general hospital, a MDR-TB ward in a TB hospital or in a specialized hospital.

Provincial TB Directorate have the responsibility to form management teams and committees in order to oversee the clinical management of MDR-TB patients in the province.

Management teams/ committees at different levels

- **Provincial DR-TB Clinical Review committees (for all MDR-TB units in the province)**

These committees should be formed in each province to address difficult clinical cases, medico-legal and ethical issues such as termination of MDR-TB treatment. This committee must be multi-disciplinary involving medical officer(s) and/ or professional nurse from the MDR-TB hospital, physician, pathologist, paediatrician, cardio-thoracic surgeon, public health specialist, radiologist, civil society representative, social worker, provincial management and a specialist in legal and ethical issues. Other representatives from government departments such as Social Development, Correctional Services, Military Health Services...
3. Management of chronic drug resistant TB regarding termination of treatment and palliative care
5. Patients who are infectious and are not cooperating with the health professionals and who abscond from hospital and refuse to be admitted

- Hospital clinical management teams (for all provincial MDR-TB units and decentralized units)

Hospital clinical management teams must be in place in all hospitals and consist of a respiratory physician or a specially trained medical officer and professional nurse, a social worker, trained counsellor, psychologist, dietician and an occupational therapist. These teams should oversee all aspects of MDR-TB management and should be collectively responsible for decisions about treatment and surgery. The main functions of the clinical management teams are to:

1. Evaluate patient progress
2. Prescribe appropriate treatment
3. Ensure adequate follow up and management of adverse events
4. Ensure access to specialised counselling
5. To provide training of staff
6. Provide technical support to peripheral MDR-TB hospitals and clinics
7. Problem-solving for complicated cases and treatment failures.

- Hospital patient committees (for provincial MDR-TB units and decentralized units)

All hospitals must have patient committees, which will provide a forum for patients to raise their concerns and needs with management of the hospital. This, as part of the Batho Pele principles and upholding patients rights charter. The frequency of these meetings can be determined by the hospitals.

**Types of MDR-TB units:**

3.2.1 **Provincial MDR-TB unit:** Also known as “Provincial Centre of Excellence”. In each province there is at least one hospital which is a specialized unit for MDR-TB. This hospital will hold a support and supervisory role for the MDR-TB outpatient programme in each province.
monitoring the initial response to treatment and the possible adjustment of medication
- In addition, hospitalisation provides time for effective education and counselling to the patient on MDR and HIV,
- registration and social assessment of the household in preparation for discharge.
- Education and counselling of family and other members of the household on MDR-TB and HIV to optimise the chance of family support for the patient in adhering to the treatment and the implementation of household infection control.

Functions:
- Initiation of treatment of all DR-TB cases after appropriate assessment
- Admission of MDR-TB cases when indicated
- Hospitalization of all XDR-TB cases till two successive TB culture negative
- Referral centre for more complicated cases such as XDR-TB, children, severe side effects, and other associated illnesses.
- Monthly follow up of all DR-TB cases attending at clinic
- DOT to all DR-TB patients attending daily
- Recording and reporting to the provincial department of health
- Ongoing training, support and supervision as well as the routine monitoring and evaluation of the MDR-TB treatment programme in the province (Provincial office to do overall management in the province)
- Provide social support, rehabilitation, educational and skills building programmes for patients
- Provide education and counselling to all patients admitted in hospital
- Prepare a discharge plan for all patients and ensure effective down referrals
- Monitor drug resistant TB patients post discharge until completion of treatment and two years post treatment completion
- Monitor rational usage of second line drugs
- Establish and maintain functional Clinical management Teams
- Compile monthly, quarterly, six monthly and annual reports of Drug Resistant TB patients started on treatment, culture conversion and outcomes
- Provide technical assistance and capacity building to peripheral hospitals and feeder clinics on management of drug resistant TB
- Arrange patients evaluations at Provincial Patient Review Committees

Minimum staffing level:
- Doctor: 1 doctor for 40 beds MDR-TB unit. Assuming an occupancy rate of higher than 75% most of the time.
- Professional nurse/Staff nurse or nursing assistant: 1 professional nurse for 3 Enrolled nurses or nursing assistants. A total of 15 nursing personnel is adequate for a 40 beds unit.
- Pharmacist: 1 pharmacist for a unit of 100 to 200 beds.
- Social worker: 1 for a 40 beds unit
- Dietician: 1 for a 40 beds unit
- Clinical psychologist: 1 for a 40 beds unit
- Occupational therapist: 1 for a 40 beds unit
- Audiologist: 1 for a 100 beds unit
- Physiotherapist: 1 for a 40 beds unit
- Data capturer/Administration clerk: 1 for a 200 beds unit
- Driver: 1 for a 40 beds unit

### 3.2.2 Decentralised MDR-TB unit:

In each province, depending on the need, there will be a number of decentralised MDR-TB units. These units will be responsible for the initiation and management of MDR-TB patients in a defined geographical area, initially as inpatients, but then as outpatients. These units may be whole hospitals or wards or sections of existing provincial, district or sub-district level hospitals.

Patients diagnosed with MDR-TB who are smear microscopy positive will ideally be hospitalised at the decentralised hospital for a period of eight weeks or until they become smear negative on two consecutive tests. This is extremely important given that most patients with MDR-TB in South Africa are co-infected with MDR-TB and HIV and will need to commence both MDR-TB and HAART treatment. Once a patient’s sputum smear microscopy is shown to be negative and they meet the criteria for outpatient treatment (see table V), they can receive treatment whilst living at home.

**Functions:**
- Initiation of treatment of all DR-TB cases after appropriate assessment
- Admission of MDR-TB cases when indicated
- Monthly follow up of all DR-TB cases attending at clinic
- DOT to all DR-TB patients attending daily
- Recording and reporting to the provincial department of health
- Provide social support, rehabilitation, educational and skills building programmes for patients
- Provide education and counselling to all patients admitted in hospital
- Prepare a discharge plan for all patients and ensure effective down referrals
- Monitor drug resistant TB patients post discharge until completion of treatment and two years post treatment completion
- Establish and maintain functional Clinical management Teams
- Compile monthly, quarterly, six monthly and annual reports of Drug Resistant TB patients started on treatment, culture conversion and outcomes
• Provide technical assistance and capacity building to Satellite DR-TB units and feeder clinics on management of drug resistant TB
• Monitor treatment side effects
• Ensure referral of patients with XDR-TB, severe adverse events and complicated disease to the central MDR-TB hospital

Minimum staffing level:
• Doctor: 1 doctor for 40 beds MDR-TB unit. Assuming an occupancy rate of higher than 75% most of the time.
• Professional nurse/staff nurse or nursing assistant: 1 professional nurse for 3 Enrolled nurses or nursing assistants. A total of 15 nursing personnel is adequate for a 40 beds units.

Part-time requirement (these officers are employed in the hospital, and will be required to give 10 to 20% of their time to MDR-TB patients):
• Social worker: 1 for 10 to 20 patients
• Pharmacist: 1 for 10 to 20 patients
• Dietician: 1 for 10 to 20 patients
• Clinical psychologist: 1 for 10 to 20 patients
• Occupational therapist: 1 for 10 to 20 patients
• Audiologist: 1 for 20 to 40 patients
• Physiotherapist: 1 for 10 to 20 patients
• Data capturer: 1 for 10 to 20 patients

3.2.3 Satellite MDR-TB unit: After the assessment and initiation of MDR-TB therapy (by a provincial MDR-TB unit or a decentralised MDR-TB unit) patients may be kept at a satellite MDR-TB unit where they will receive treatment and be monitored daily by nurses with the support of a doctor based at the decentralized site or the provincial centre of excellence when necessary.

Once the patient’s medical condition has improved (weight gain, no fever, no cough etc.) they are tolerating all MDR-TB drugs and highly active antiretroviral therapy (HAART) and they are smear negative they can be discharged to the community and continue receiving treatment either from the injection team or their nearest facility. At times MDR-TB treatment will be administered in institutions such as prisons, mining health facilities or psychiatric hospitals. The initial period of hospitalisation should be between four and six weeks. Initially the patient will return monthly to the MDR-TB hospital for ongoing management of their condition. When the programme is established and staff at satellite centres trained, it may be possible for patients in the continuation phase to be monitored monthly at the
Satellite centre. However, once bi-monthly or quarterly they would need to travel to the decentralised site.

Satellite units may be based at district, psychiatric hospitals, Community Health Centres or correctional services facilities. Satellite MDR-TB units will exist for two purposes:

- To make it possible to initiate MDR-TB therapy for all MDR-TB patients as soon as they are diagnosed, in case beds are unavailable at MDR-TB units
- The patient refuses to start treatment unless they can be closer to home

Satellite MDR-TB units may not initiate MDR-TB treatment. They may become a decentralised MDR-TB unit if there have adequate staff and infrastructure in future.

**Functions:**
- Admission of all MDR-TB cases referred from centralized MDR-TB units or decentralized units
- Monthly follow up of all DR-TB cases attending at clinic
- DOT to all DR-TB patients attending daily
- Provide education and counselling to all patients admitted in hospital
- Prepare a discharge plan for all patients and ensure effective down referrals
- Monitor treatment side effects
- Ensure referral of patients with XDR-TB, severe adverse events and complicated disease to the central MDR-TB hospital

**Minimum staffing level:**
- Professional nurse/ Staff nurse or nursing assistant: 1 professional nurse for 20 MDR-TB patients
- Community health care worker: 1 for 10 patients

**Part-time requirement (optional):**
- Doctor
- Social worker
- Data capturer

### 3.3 District or Sub-Districts

Districts and Sub-Districts have administrative and management role in the management of DR-TB services in the area.
Establish an efficient patient retrieval system for patients who default DR-TB treatment

Arrange transport for patient evaluation and follow-up at the MDR-TB hospital

Appoint disease outbreak teams to conduct contact screening programmes for all close contacts of confirmed DR-TB patients six monthly for two years

Monitor and evaluate DR-TB programme performance

Ensure continuum of care for patients post discharge

Ensure ongoing psycho-social support for patients

Increase awareness through education of communities about Drug Resistant TB

### 3.3.1 PHC facility

Primary health care facilities need to play a significant role in providing injectables at the clinics and providing DOT to all DR-TB patients in the area. This need to be integrated with treatment of other TB and HIV patients. The existing TB nurses will be capacitated to handle these activities. It is not necessary to have MDR-TB nurses at PHC level.

Patients who have access to a PHC clinic will go to this health facility for their daily injection and directly observed therapy (DOT). The facility based staff will monitor side effects and adherence, provide education on the disease and monitor household infection control practices. Minor side effects such as nausea, vomiting and diarrhoea will be managed by the nurse at the facility, but the patient will be referred to the decentralised MDR-TB site for management of more serious side-effects. In addition the nurse at the facility will be responsible for contact tracing and serve as the link between the decentralised MDR-TB site and MDR-TB patients treated at the facility.

PHC facilities treating MDR-TB patients will be supported by the nearest MDR-TB decentralised units or the provincial centre of excellence if it is nearer than decentralized sites.

**Functions:**

- Identification of high risk groups
- To screen and test symptomatic high risk groups
- Trace patients with a confirmed diagnosis of DR-TB
- Notify district coordinator
- Provide initial counselling and education of the patient and family
- Prepare patient for hospital admission when indicated
- Coordinate referral to the MDR-TB hospital
- Trace treatment interrupters
- Monitor treatment side-effects
- Ensure referral of patients with XDR-TB, severe adverse events and complicated disease to the central MDR-TB hospital

**Minimum staffing level:** Part-time requirement/ in some cases full-time depending on patients load
- Doctor (if available)
- Professional nurse/ Staff nurse or nursing assistant: 1 for 20 MDR-TB patients
- Community health care worker: 1 for 10 patients
- Social worker (optional)
- Data capturer: 1 for 50 patients

**Contact tracing and monitoring**
Contact monitoring is an important role of the PHC facilities through tracing/injection teams and MDR-TB mobile units, and supported by DOTS-plus supporters.

Measures for contact tracing and monitoring include:
- All contacts will be listed and examined and those with symptoms tested in accordance with existing TB protocols.
- Contacts with symptoms will be retested for TB and drug susceptibility 6 monthly for two years.
- The MDR-TB mobile team or DOTS-plus supporter seeing to the treatment of the MDR-TB patient will continuously ask for signs and symptoms in contacts.
- VCT will be offered to contacts.

### 3.3.2 Mobile injection team
Mobile injection teams are also called mobile MDR-TB centre. These are units based at the PHC facility or a satellite MDR-TB unit. These teams provide injections to patients at their homes, they supervise intake of oral tablets.

Patients who are unable to access a health facility daily will for the entire duration of the injectable phase of treatment, be visited daily (5 times a week) at home by a mobile MDR-TB unit consisting of a driver and nurse. During these visits the mobile team will administer injectable drugs, observe the patient taking their oral drugs, monitor side effects and contact patients continuously for signs and symptoms.

Patients should be visited daily for the entire duration of the injectable phase of treatment.
carry out TB programme activities such as tracing defaulters from the TB programme or giving retreatment patients streptomycin injections.

Existing TB tracer teams may expand their mandate by taking care of MDR-TB patients. Again, these teams need to take care of all TB and HIV patients. Their scope should not be restricted to MDR-TB care.

Functions:
- DOT to all DR-TB patients in the area
- Monitor treatment side-effects and refer to the nearest health care facility when required
- Maintain appropriate records

Minimum staffing level:
- Professional nurse/ Staff nurse or nursing assistant: 1 for 20 MDR-TB patients
- Community health care worker: 1 for 10 MDR-TB patients
- Driver: 1 for 20 MDR-TB patients

3.4 Community level: DOTS plus supporters/Community Health Workers (CHWs)

Depending on the local situation the DOTS-plus supporters may be community health workers, community DOTS volunteers or family members.

Patients and their designated household treatment supporter (CHWs) will be trained in the natural history of MDR-TB and HIV as well as in basic infection control (e.g. cough hygiene and the basic principles of isolation), familiarity with MDR-TB medications, common side effects/toxicities and the role of HIV in TB infection. Family planning during MDR-TB treatment will be encouraged. CHWs to provide ongoing daily support to MDR-TB patients being treated as outpatients.

If the patient is on HAART, the patient and treatment supporter will receive literacy training according to current practice. This will be given by staff trained in MDR-TB and integrated TB and HIV care. To avoid nosocomial transmission training of the MDR-TB patient and treatment supporter in the clinical setting will be completely separate in space and time from the HAART programme. In addition, education for the patient, household supporter and possibly even the treatment supporter, should be given at individual patients’ home by
- DOT to all DR-TB patients in the area
- **Monitor treatment side-effects and refer to the nearest health care facility when required**
- Maintain appropriate records

The table below describes the responsibilities of staff working at various levels of MDR-TB care

**Table III: MDR-TB staff responsibilities**

<table>
<thead>
<tr>
<th>Staff</th>
<th>Responsibilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doctor</td>
<td>• Assessing patient for co-morbidities and requesting baseline tests</td>
</tr>
<tr>
<td></td>
<td>• Initiating DR-TB treatment regimen for the patient (at Provincial and Decentralized MDR-TB units)</td>
</tr>
<tr>
<td></td>
<td>• Review treatment of patient and make any necessary adjustments</td>
</tr>
<tr>
<td></td>
<td>• Clinical monitoring of patients treatment for adverse events and prompt management. Also reporting of adverse events to the MCC.</td>
</tr>
<tr>
<td></td>
<td>• Prompt referral for tertiary care or specialist care when needed</td>
</tr>
<tr>
<td></td>
<td>• Presents difficult or complicated patients to the clinical management committee or provincial review committee</td>
</tr>
<tr>
<td></td>
<td>• Ensure follow up smears and cultures are conducted and results available on time.</td>
</tr>
<tr>
<td></td>
<td>• Attend meetings; keep up-dated on TB and MDR-TB management and surveillance.</td>
</tr>
<tr>
<td></td>
<td>• Provide education for nurses and other members of the MDR-TB team.</td>
</tr>
<tr>
<td>Professional nurse/Staff nurse or nursing assistant</td>
<td>• Coordination of clinical care with other health professionals;</td>
</tr>
<tr>
<td></td>
<td>• Monitoring of inpatients and referral to doctor when necessary</td>
</tr>
<tr>
<td>Role</td>
<td>Responsibilities</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Support of nursing staff in the decentralised site;</td>
<td>• Responsible for monitoring patient management (MDR-TB register) and compiling a 6 monthly report.</td>
</tr>
<tr>
<td></td>
<td>• Maintains a close relationship with the patient.</td>
</tr>
<tr>
<td></td>
<td>• Administers treatment to the patients</td>
</tr>
<tr>
<td></td>
<td>• Provide ongoing nursing care</td>
</tr>
<tr>
<td></td>
<td>• Completes the patient treatment card for treatment dosages given to the patient</td>
</tr>
<tr>
<td></td>
<td>• Provides counselling for HIV testing</td>
</tr>
<tr>
<td></td>
<td>• Conduct HIV testing on patients who give consent</td>
</tr>
<tr>
<td></td>
<td>• Provide educational talks to patients on a one on one basis or group sessions</td>
</tr>
<tr>
<td></td>
<td>• Plan awareness campaigns within the hospital addressing different topics</td>
</tr>
<tr>
<td>Pharmacist</td>
<td>• Ensure availability of both second TB drugs and ancillary drugs</td>
</tr>
<tr>
<td></td>
<td>• Monitoring drug stock levels</td>
</tr>
<tr>
<td></td>
<td>• Ensure correct storage of the drugs</td>
</tr>
<tr>
<td></td>
<td>• Dispatch drugs for patients who have been discharged to the local clinic or hospital</td>
</tr>
<tr>
<td>Admin clerk/ Data capturer</td>
<td>• Maintenance of data and patient records.</td>
</tr>
<tr>
<td></td>
<td>• Capturing patient data on the electronic drug resistant register (EDR)</td>
</tr>
<tr>
<td></td>
<td>• Compiling and reporting 6 monthly cohort report and other reports needed</td>
</tr>
<tr>
<td>Clinical Psychologist</td>
<td>• Clinical Psychologist conducts initial assessment of patients with psychological problems</td>
</tr>
<tr>
<td></td>
<td>• Conducts one on one or group therapy sessions for patients</td>
</tr>
<tr>
<td></td>
<td>• Refer patients who need expert opinion timeously</td>
</tr>
<tr>
<td>Occupational therapist</td>
<td>• Conduct initial assessment of patients psycho-social status</td>
</tr>
<tr>
<td></td>
<td>• Develop patients insight into disease and behaviour through counselling and education</td>
</tr>
<tr>
<td></td>
<td>• Provide life skills development programmes</td>
</tr>
<tr>
<td></td>
<td>• Provide rehabilitation programmes for patients</td>
</tr>
<tr>
<td></td>
<td>• Monitor patient progress</td>
</tr>
<tr>
<td></td>
<td>• Facilitate support, stress management and behaviour modification</td>
</tr>
<tr>
<td>Role</td>
<td>Responsibilities</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Physiotherapist                           | • Conduct initial assessment of patients with co-morbidities and extensive lung disease  
• Develop treatment programmes for the individual patients  
• Monitor patient progress  
• Assist patients with expectoration for monitoring culture conversion |
| Nursing service manager                    | • Supports and supervises staff on mobile MDR-TB units and staff at facilities administering MDR-TB treatment;  
• Support data capturing and management  
• Liaise with other stakeholders in the geographical area;  
• Organisation and documentation of 6 monthly contact screening;  
• Trace newly identified MDR-TB patients and organise admission to decentralised site;  
• Organise regular monthly visits of MDR-TB outpatients to decentralised MDR-TB site for monthly follow up;  
• Links MDR-TB treatment programme with TB programme. |
| Professional nurse/Staff nurse or nursing assistant at Mobile injection team | • Nurse must have a driving license to be able to drive in the absence of driver  
• Administer daily injections to all MDR-TB patients in the intensive phase of treatment, monitors side effects, adherence and household infection control practices;  
• Support and supervision of DOTS-plus workers;  
• Locate newly diagnosed MDR-TB patients;  
• Trace MDR-TB defaulters;  
• Conduct 6 monthly contact tracing on all household contacts;  
• Ongoing education on adherence, side effects and infection control;  
• Record adherence and side effects and where refer complications or problems in patient management to nurse coordinator. |
Community health care workers/ DOTS-plus supporters

- DOT administration of all doses received outside of health establishments;
- Communication of all routine and emergency clinical issues to mobile unit or field team.
- Ongoing education on adherence and infection control.

Family members

- Provide emotional support and nursing care to the patient during treatment
- Report any problems or change in patient condition to the clinic nurse or community health worker
- Assist with early identification and testing of symptomatic contacts

<table>
<thead>
<tr>
<th>Functions</th>
<th>Provincial/Centralized MDR-TB unit</th>
<th>Decentralized MDR-TB unit</th>
<th>Satellite MDR-TB unit</th>
<th>Mobile MDR-TB Clinic/injection team</th>
<th>Community Supporters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiation of treatment of all DR-TB cases</td>
<td>✓</td>
<td>✓</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>Admission of all MDR-TB cases till two successive smear negative/Culture negative</td>
<td>✓</td>
<td>✓</td>
<td>NO, unless no bed available at provincial or decentralized site</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>Admission of all XDR-TB cases till two successive culture negative</td>
<td>✓</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>Monthly follow up of all DR-TB cases attending at clinic</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>NO</td>
</tr>
<tr>
<td>DOT to all DR-TB patients attending daily</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
Figure 2: Flow of MDR-TB patients:

<table>
<thead>
<tr>
<th>Primary Health Care Facilities/ General Hospitals</th>
<th>Laboratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Identification of all high risk groups – non converters, retreatment, contacts of DR-TB patients • Collection of sputum for microscopy, culture and DST or Line Probe Assay</td>
<td>• Diagnosis • Report sent to requesting facility and MDR-TB hospital within 24 hours of confirmation of diagnosis</td>
</tr>
<tr>
<td>On receipt of results confirming DR-TB • Trace patient • Counsel patient and explain the management and when indicated, the need for hospitalization • Conduct contact screening and testing</td>
<td></td>
</tr>
</tbody>
</table>
Patients are either hospitalized or initiated treatment on ambulatory basis. For initiating treatment following must be done:
- Appropriate assessment
- Written consent
- Counselling of the patient and family
- Preparing a plan for the management with patient’s consent
- Preparation of DR-TB treatment card and registration in DR-TB register

<table>
<thead>
<tr>
<th>Criteria for admission</th>
<th>Criteria for initiating treatment on ambulatory basis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Patient with high grade transmission risk (smear positive)</td>
<td>Essential Criteria:</td>
</tr>
<tr>
<td>• Very sick MDR-TB (patients with extensive resistance patterns, pulmonary cavitations, MDR-TB re-treatments)</td>
<td>• Patient is ambulant in fair to good general condition (BMI &gt; 18.5)</td>
</tr>
<tr>
<td>• Patient with severe adverse reactions to the drugs</td>
<td>• Patient is a low grade transmission risk (smear negative)</td>
</tr>
<tr>
<td>• Patient with other associated diseases</td>
<td>• Patient can access MDR-TB decentralised site monthly or a mobile MDR-TB team</td>
</tr>
<tr>
<td>• All XDR-TB patients</td>
<td>Additional Criteria:</td>
</tr>
<tr>
<td>• Patients who may not have access to decentralized or satellites MDR-TB units until they achieve TB culture conversion</td>
<td>• Patient has stable accommodation</td>
</tr>
<tr>
<td></td>
<td>• Presence of a household member for treatment support in the home</td>
</tr>
<tr>
<td></td>
<td>• Patient has a good reason for not wanting to be hospitalized</td>
</tr>
</tbody>
</table>

The first 3 essential criteria are the most important

<table>
<thead>
<tr>
<th>Discharge criteria</th>
<th>Pass-out criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• For all XDR-TB cases and very sick MDR-TB cases, patients will be discharged after 2 successive sputum culture negative and</td>
<td>Patient may be allowed to leave from MDR-TB unit for maximum 3 consecutive days in a month in bereavement, family emergencies and situations where patient's physical</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
of their disease
- Smear negative
- Have a fixed address and a good family support structure
- No history of previous non compliance with conditions of pass out
- No history of alcohol and substance abuse

On the discharge from the Provincial or Decentralized MDR-TB- TB units:
- Ask about most convenient facility for referral
- Inform patient about management plan
- Notify receiving clinic/ hospital of down referral
- Arrange transport for the patient
- Complete patient treatment follow-up card

Patients are referred to following units depend upon the convenience of the patient after the discharge from hospitalization or after initiation of treatment

<table>
<thead>
<tr>
<th>Provincial units</th>
<th>MDR-TB units</th>
<th>Decentralized MDR-TB units</th>
<th>Satellite units</th>
<th>MDR-TB units</th>
<th>Mobile injection team/ Community supporters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients are registered in Provincial and Decentralized MDR-TB units</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All MDR-TB units are responsible for providing treatment under DOT, recording of the consumption of drugs and injections on DR-TB treatment card</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DR-TB Treatment card is placed at all MDR-TB units as well with community supporters</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4. CASE FINDING STRATEGIES

4.1 Risk groups for MDR-TB

Intensified case finding should be conducted among patients at high risk of MDR-TB based on the history. Specific elements of the history that suggest an increased risk for drug resistance are listed in the table below.

Table V: Risk factors for MDR-TB

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure of retreatment regimen (Regimen 2)/chronic TB patients</td>
<td>Chronic TB patients are defined as patients who are sputum positive at the end of the intensive phase and on completion of re-treatment regimen. These patients have the highest MDR-TB rates, often greater than 80%.</td>
</tr>
<tr>
<td>Exposure to a confirmed MDR-TB patient</td>
<td>Most studies have shown that close contacts of MDR-TB patients have very high rates of MDR-TB. This includes children, who should be started on MDR-TB therapy empirically until proven not to have MDR-TB.</td>
</tr>
<tr>
<td>Failure of treatment regimen for new patients (Regimen 1)</td>
<td>Failures of Regimen 1 or Regimen 3 are patients who remain positive at the end of the intensive phase or become sputum smear or culture positive 5 months or later during the course of treatment. <em>Not all patients who fail Regimen 1 have MDR-TB; this depends on a number of factors, such as treatment compliance.</em></td>
</tr>
<tr>
<td>Relapse and default</td>
<td>Erratic drug intake or early relapse may point to possible MDR-TB. Relapses within the first six months post-treatment may have similar MDR-TB rates as failures. Repeated interruption of treatment can also result in selection for resistant mutants.</td>
</tr>
</tbody>
</table>
Use of drugs that compete with or alter the metabolism of TB drugs, resulting in reduced serum levels

Antifungal agents in the azole family interfere with each other; rifamycins will lower azole levels. In addition, ketoconazole can lower rifampicin levels by 40%-50%.

Co-morbid conditions associated with malabsorption or rapid transit diarrhoea

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

HIV

Numerous MDR-TB outbreaks have been documented in HIV+ individuals as a result of the depressed immune system and high susceptibility to infection.


4.2 Intensified case finding for MDR-TB

Routine culture and first-line DST should be done for the following groups of patients:
- New TB patients who remain sputum smear-positive after two months of treatment or who become positive after five moths of treatment
- All newly diagnosed re-treatment TB patients
- Symptomatic close contacts of confirmed MDR-TB patients
- Symptomatic individuals from known high-risk groups, including health care workers, laboratory workers, prisoners, mine workers and HIV-positive individuals in high MDR-TB prevalence areas.

First-line DST should include testing for isoniazid and rifampicin mainly; ethambutol should not be included as this does not change the management of the patient.

Previously treated TB (retreatment) patients may have had DST results in the past that may no longer reflect the resistant pattern of the strain they have at the time of MDR-TB diagnosis. DST should therefore be performed again in all patients who have received TB treatment since the date of their last DST result.
Young children in particular may not be able to produce sputum specimens, therefore more aggressive measures such as gastric aspiration should be considered to obtain a specimen for confirmation of diagnosis. Children with active TB who are close contacts of patients with MDR-TB can be started on MDR-TB treatment.

4.3 Intensified case finding strategies for XDR-TB

All strains identified as MDR-TB should routinely undergo second-line DST in order to diagnose XDR –TB. In specific instances, i.e. when screening contacts of known XDR-TB patients, second-line DST should be requested together with first-line DST. The tests that should be conducted routinely are kanamycin, ofloxacin, capreomycin and ethionamide. Other tests may be conducted on request by the treating clinician.
5. DIAGNOSIS OF DR-TB

5.1 Introduction

In the majority of cases the development of DR-TB is insidious and the disease progresses over weeks and months. As a result, patients often ignore the symptoms or accept them as symptoms related to the daily stresses, lack of sleep and from being overworked, therefore delay seeking health care.

DR-TB may also be associated with other serious disorders, such as HIV infection, alcoholism, renal failure, diabetes mellitus, cancers and drug abuse. The signs and symptoms of these conditions and their complications can easily obscure those of DR-TB and can also result in considerable delays in diagnosis or in misdiagnosis, especially in patients with HIV infection. It is therefore important that health care workers have a high index of suspicion for DR-TB as early diagnosis and initiation of treatment is critical in the prevention of amplification of resistance and extensive lung damage resulting in complicated forms of disease which are more difficult to treat.

5.2 Signs and symptoms of DR-TB

The symptoms of drug-resistant TB are the same as for drug-susceptible TB:
- Cough
- Chest pain
- Dyspnea
- Haemoptysis
- Systemic symptoms (fever, chills, nights sweats, tiredness, anorexia, weigh loss)

In addition to the systemic effects of DR-TB, there may be remote manifestations unrelated to the site of involvement. These include haematologic abnormalities, hyponatraemia and psychological disorders. The most common haematological manifestations include increases in the peripheral blood leukocyte count and anemia. The increase in leukocyte count is usually slight, but leukemoid reactions and leukopenia may occur. An increase in the peripheral blood monocyte and eosinophil counts may also occur. Anemia is common in disseminated DR-TB disease.

Extra-pulmonary DR-TB presents more of a diagnostic challenge, because it involves relatively inaccessible sites, and depending on the organs involved, fewer bacilli can cause more extensive damage.
• A physical examination
• Bacteriological investigations to confirm the diagnosis

5.3.1 Medical history

A proper history of the patient must be recorded which includes the following:

• Medical history – previous TB episodes – previous treatment regimen, time to smear or culture conversion, treatment outcomes for each episode (if multiple) and participation in clinical trials, chronic medical illness such as other medical conditions such as diabetes mellitus, renal disease, malignancies, chronic malabsorption syndrome, prolonged corticosteroid therapy, immunosuppressive therapy and HIV infection, which may affect clinical management, allergies, pregnancy, last menstrual period, method of contraception, prior psychiatric illness, medication that the patient may be taking other than TB treatment
• Surgical history – any surgical procedures the patient underwent and for what condition
• Work history – particularly mining industry, TB hospital, prison and laboratory
• Social history - substance abuse (alcohol, tobacco and other drugs)
• Previous confinement in a hospital, prison and duration,
• Family history of TB, screening of close contacts, confirmation of disease in and treatment of contacts, history of DR-TB exposure.

All patients who do not know their HIV status should be offered counselling and voluntary testing.

History of presenting symptoms – cough and duration of the cough, sputum production, fever, night sweats, loss of appetite, unintentional weight loss (determine extent of weight loss and the time period), dyspnoea, chest pains, haemoptysis, abdominal pain, nausea, vomiting, diarrhoea, constipation, headache, peripheral leg pain, hearing loss, depression, anxiety.

It is important to determine the baseline clinical parameters on initiation of treatment in order to monitor the patient’s progress whilst on treatment and will enable early detection of any other co-morbidities that may require adjustment of the treatment regimen or ancillary treatment.
• Laboratory and other baseline tests such as chest x-ray, urine pregnancy test (where indicated), urea and electrolytes, creatinine, full blood count, HIV test, liver function tests, audiometry and psychiatric evaluation where indicated.

5.3.2 Physical examination

A physical examination is an essential part of the evaluation of any patient therefore all vital signs must obtain. The physical signs cannot be used to confirm or rule out DR-TB, but can provide valuable information about the patient’s overall condition and other factors that may affect patient management. The clinical presentation of patients with DR-TB is similar to those of patients with drug-susceptible TB, and patients often present with cavitatory lung lesions.

5.3.3 Laboratory diagnosis of MDR and XDR -TB

MDR-TB is often suspected clinically when a patient has a persistently positive smear microscopy or culture and when a patient fails to respond to treatment despite documented good adherence. MDR or XDR -TB can also be suspected when a person has had exposure to a confirmed MDR or XDR -TB patient. Demonstrating in vitro resistance in the M. tuberculosis isolate from the patient is the only definitive diagnosis of MDR or XDR-TB.

The quality of DST is of paramount importance and impacts directly on treatment. All laboratories performing TB culture and drug susceptibility testing must be part of a recognised external quality assurance programme. TB microscopy, TB culture and drug susceptibility test (DST) need to be done. The use of line probe assay is recommended when it becomes available. However it must be noted that line probe assay will only be done on TB smear positive patients. Therefore line probe assay does not replace conventional DST. Patients diagnosed on line probe assay will be started on treatment immediately. Conventional DST confirmation is not required.

5.3.3.1 Microscopy

Although direct microscopy is the cornerstone of diagnosis of pulmonary TB, it cannot distinguish between drug-susceptible and drug-resistant M. tuberculosis, or between different species of mycobacterium. The use of microscopy in DR-TB is limited to:
• Evaluating the infectiousness of patients
visualisation, as only a small amount of the sputum is actually viewed. Nevertheless, the infectiousness of DR-TB patients correlates roughly with the number of AFB in the sputum smear as measured by conventional semi-quantitative methods, other factors being equal. Smear microscopy, however, cannot distinguish viable from nonviable bacilli, so its use in monitoring of progress on treatment is limited. For example, even with adequate treatment, DR-TB patients may become culture negative but remain smear positive suggesting that the bacilli are non-viable.

The turnaround time for microscopy results should be less than 48 hours, depending on the work load and the transport time to the laboratory. Results must be reported as ‘positive/negative for acid fast bacilli’ and quantified, as quantification may serve as an indication of disease severity.

5.3.3.2 Culture

Mycobacteria are slow growing organisms with a mean generation time of 12 to 18 hours, so culture results for TB may take several weeks. Mycobacteria also require special culture media and a variety of suitable culture media and differential tests for species identification are available. A commercial automated system using liquid media (BACTEC Mycobacterial Growth Indicator Tube (MGIT) 960; Becton Dickinson) is used as the culture medium of choice in the National Health Laboratory Service (NHLS). This system uses a fluorescence quenching-based oxygen sensor to detect mycobacterial growth.

Timeous transport of specimens to the laboratory is critical, as any delays will result in a decrease in the viability of mycobacteria as well as contamination due to overgrowth of common respiratory bacteria. Specimens should therefore be kept cool during transportation or refrigerated at 4°C if delays are anticipated. Inadequate decontamination process in the laboratory compromises the growth and isolation of mycobacteria and can adversely affect the culture yield.

Culture results are reported as positive or negative in the MGIT automated system, together with an indication of the time to positivity, which may be a reflection of the severity of disease. The results should always be correlated with the patient’s clinical condition, and investigations repeated if necessary.

False negative cultures may result from inadequate specimens, poor laboratory technique, and delayed transport of the specimens to the laboratory. Cross contamination of specimens may lead to false positive results.
isolates appearing phenotypically resistant to anti-TB drugs may not be drug-resistant TB at all, but may be due to infection with NTM. Treatment of NTM is entirely different from DR-TB therefore *M. tuberculosis* should always be confirmed following culture.

### 5.3.3.4 Drug susceptibility testing

Drug susceptibility testing (DST) is required to make a definitive diagnosis of MDR-TB. DST can be done by several methods. The MGIT methodology distinguishes susceptibility from resistance by comparing growth in plain (control) medium to growth in medium to which specified concentrations of drugs have been added.

#### Limitations of DST

1. With conventional methodologies, growth detection, identification of *M. tuberculosis* and DST may take weeks or even months.
2. Different anti-TB drugs have different ‘critical concentrations’ (the breakpoint between calling a strain resistant or susceptible), which also depend on the culture medium used for DST.
3. DST for first-line anti-TB drugs has been thoroughly studied and consensus reached on appropriate methodologies, critical drug concentrations, and reliability and reproducibility of testing. The intrinsic accuracy of DST varies with the drug tested: for first-line drugs DST is most accurate for rifampicin and isoniazid and less so for streptomycin and ethambutol.
4. DST for second-line anti-TB drugs (SLDs) is much more problematic and has not been standardised internationally, due to technical difficulties related to *in vitro* drug instability leading to drug loss. Laboratory technique also influences DST results. In addition, the drug concentration defining resistance (critical concentration) is often very close to the minimal inhibitory concentration (MIC) required to achieve antitubercular activity, increasing the probability for misclassification of susceptibility or resistance and leading to poor reproducibility of second-line DST results.
5. SLDs that are more stable in different test environments and have shown relatively good reproducibility are aminoglycosides, polypeptides, and fluoroquinolones. The reproducibility and reliability of DST for PAS, cycloserine, terizidone and thioamides are much more limited while the correlation of DST results with clinical response to treatment has not yet been established. In addition, there is no useful correlation with culture results.
more probability of being effective than drugs that test resistant. Discrepant results must be interpreted with care.

DIAGNOSTIC PRINCIPLES

- Usually the first indication that a patient may be harbouring drug-resistant organisms is when s/he fails to respond to treatment despite documented good adherence. This is often supported by the positive smear microscopy at two/three months, which should prompt a culture and drug susceptibility test to be done;
- If the smear microscopy is negative at two months, but becomes positive again at five months, culture and drug susceptibility should be requested.
- If the smear microscopy is negative at two months but the patient’s clinical condition has not remarkably improved or deteriorates, culture and drug susceptibility should also be requested;
- If there is a history of close contact with a confirmed drug-resistant TB patient, culture and drug susceptibility testing should be requested;
- Retreatment patients are at higher risk of harbouring drug resistant organisms, culture and drug susceptibility testing should be routinely requested
- Always await laboratory confirmation of drug resistance;
6. MANAGEMENT OF PATIENTS WITH MONO- AND POLYDRUG - RESISTANT TB

6.1 Introduction

Patients with mono- and polydrug-resistant strains of *M. tuberculosis* are not classified as MDR or XDR-TB. Mono-resistance is defined as resistance to a single first-line anti-TB drug, while poly-resistance is resistance to two or more first-line drugs other than rifampicin and isoniazid.

Routine testing for mono- and polydrug- resistant TB in all TB patients is not recommended as the majority of patients with mono- or poly-resistant TB will be cured with standard first-line chemotherapy.

6.2 Treatment of patients with mono- and polydrug-resistant TB

With the exception of streptomycin, definitive randomized or controlled clinical trials have not been conducted to determine the best treatment options for various types of drug resistance. Recommendations are based on evidence from the pre-rifampicin era, observational studies, general principles of microbiology and therapeutics in TB, extrapolation from anecdotal evidence and expert opinion.

The design of regimens for mono- and polydrug-resistant TB requires experience and should be done under supervision of the provincial DR-TB clinical review committees. The treatment history, DST pattern and the possibility of strains of *M. tuberculosis* having acquired additional resistance should be considered before deciding on an appropriate regimen.

Some of the specific issues that need consideration when designing an appropriate regimen include:

a) **Timing of DST results**

Because of the inevitable delay in culture and DST, 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 that the sputum specimen was collected. The treatment regimens for mono- and polydrug-resistant TB assume that the pattern of drug resistance has not changed during this interval and should not be used if further resistance to any of the drugs is suspected.
be considered for inclusion in the regimen in certain circumstances as a considerable proportion of patients could still harbour pyrazinamide susceptible strains.

c) **Development of further resistance**

Further resistance should be suspected if the patient was on the functional equivalent of only one or two drugs for one month or more. For example, pyrazinamide is not regarded as a good companion drug to prevent resistance. If the patient was functionally only receiving rifampicin and pyrazinamide (due to resistance to isoniazid and ethambutol), resistance to rifampicin may develop. Therefore, it is crucial to determine which functional drugs the patient received between the time of specimen collection and the time of initiation of the treatment regimen.

Table VI: Suggested regimens for mono- and polydrug resistance in patients where further acquired resistance is not a factor

<table>
<thead>
<tr>
<th>Drug resistance pattern</th>
<th>Suggested regimen</th>
<th>Minimum duration of treatment (months)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>H (+/-S or +/- Z or +/- E)</td>
<td>Add ofloxacin and continue Regimen I or II intensive phase for full duration of treatment (except for H)</td>
<td>6 - 9</td>
<td>If patient on Regimen II, Streptomycin should be discontinued after 6 months. If resistant to streptomycin, discontinue it immediately.</td>
</tr>
<tr>
<td>R (+/- any other 1st line drug)</td>
<td>Standardized MDR-TB regimen</td>
<td>18</td>
<td>Notion of potential over treatment. Use of terizidone in the MDR regimen.</td>
</tr>
<tr>
<td>HEZ (+/- S)</td>
<td>Rifampicin, ofloxacin, Ethionamide, plus</td>
<td>18</td>
<td>Six months of kanamycin may strengthen the regimen.</td>
</tr>
</tbody>
</table>

rifampicin mono- or polyresistance. Over treatment is justified by the fact that further
acquired resistance is a problem with mono- and polyresistance since patients will be
exposed to suboptimal treatment regimens while waiting for DST results.

7 MANAGEMENT OF PATIENTS WITH MULTI DRUG RESISTANT TB

7.1 Introduction

Treatment of patients with MDR-TB involves second-line drugs. These are much more
expensive, less effective and have more side effects than first-line TB drugs. The design of
treatment regimens for patients with MDR-TB poses several challenges, complicated by a
limited choice of second-line drugs, with greater toxicity and less efficacy. As with drug-
susceptible TB, the use of multiple drugs is imperative to prevent the development of
additional resistance. Consideration of cross-resistance is also important when designing
treatment regimens for MDR-TB.

Before the patient is referred to the MDR-TB hospital the following must be done at the
diagnosing clinic.

- Full knowledge regarding the treatment must be communicated to the patient;
  this will enable the patient to take a more informed decision about whether or
  not to consent to treatment.
- Counselling and education of the patient and family member - this session should
cover the following: What is MDR or XDR-TB, how do you get it, why do you need
to be admitted in hospital, how long is the hospitalisation and the treatment,
what is going to happen in hospital and after discharge.
- Address any concerns the patient might have
- Verification of the patient’s physical and work address
- Enquire about close contacts at home or work
- Arrange for screening of and testing of all contacts
- Provide a check list of things the patient will need to take with to hospital
- Make the necessary transport arrangements for the patient and a family member
  where necessary to the MDR-TB hospital

7.2 Definitions of terms used to describe treatment strategies

- Common treatment strategies include:
whenever possible. This is favored by most countries. In South Africa, we have a standardized regimen. All newly diagnosed MDR-TB patients receive a standardized regimen.

✓ **Standardized treatment regimen followed by Individualized treatment regimen**

Patients on standardized regimen may be switched to an individualized regimen when other DST results become available. Each regimen is individually designed based on the patient’s previous history of antituberculosis treatment and individual DST results.

✓ **Empiric treatment followed by individualized treatment**

Empirical treatment regimen is given to MDR-TB patients diagnosed on clinical grounds. DST of the presumed MDR-TB contacts are considered as well as DRS data from the representative patient population. Commonly, an empirical regimen is adjusted when DST results on the individual patient become available.

### 7.3 Standardised MDR-TB regimen

The limited number of second-line drugs that are available imposes obvious limitations on the design of adequate MDR-TB treatment regimens. The most successful treatment regimens are those that include multiple drugs, which the patient had not previously received. A standardised MDR-TB regimen is recommended and this is based on the country-specific profiles of drug resistance and previous drug use of second-line drugs.

The design of the standardised regimen is based on first-line DST at diagnosis. DST of ethambutol and pyrazinamide do not have high reproducibility and reliability.

**The standardised regimen consists of at least six months intensive phase treatment with five drugs:**

*Kanamycin/ amikacin, levofloxacin(high dose), ethionamide, terizidone and pyrazinamide* taken at least six times per week during the injectable phase; followed by a continuation phase treatment with four drugs (*Levofloxacin (high dose), ethionamide, terizidone and pyrazinamide*) taken at least six times per week.
Ethambutol may be used as an additional item (6th item in the standardized regimen) in areas with confirmed low prevalence to ethambutol resistance or in patients who have not received ethambutol for more than one month before DR-TB treatment.

The standardized treatment regimen described above applies only to MDR-TB patients previously treated with regime 1 or regime 2 of our TB programme, these are patients who have not been previously exposed to second-line anti-tuberculosis agents.

Patients who were previously exposed to second line anti-tuberculosis drugs will require an individualized regimen based on 2 factors: firstly history of anti-TB drugs received and secondly DST results.

a. In principle, any agent not previously received by the patient is likely to be susceptible and any agent used for more than a month before is likely to be resistant.

b. Most MDR-TB patients who were exposed to first and second line anti-TB drugs and patients with resistance to an injectable or a fluoroquinolone will require drugs such as capreomycin, PASER granules, moxifloxacin or levofloxacin, high dose INH and clofazimine among other drugs in their regimens.

7.4 Second line drugs

The following first and second line drugs are available locally for the treatment of drug-resistant TB.

Pyrazinamide and/or ethambutol are used in second-line treatment, given the limited number of second line drugs available. Resistance to pyrazinamide is neither easy to acquire nor easy to prove by DST. As pyrazinamide has a bactericidal effect in an acid medium (bacilli inside macrophages), it should initially be used in combination with an aminoglycoside (active against multiplying bacilli outside macrophages) to obtain maximum effect.
kanamycin and amikacin. Resistance to kanamycin induces almost complete cross-resistance with amikacin and they should therefore be considered as the same drug. Resistance to kanamycin or amikacin does not necessarily mean resistance to streptomycin. Streptomycin may be used in MDR-TB if shown to be susceptible. Amikacin is as active as kanamycin and better tolerated, but much more expensive.

**Polypeptide:** Capreomycin is a cyclic polypeptide that differs structurally from kanamycin and amikacin and exhibits no uniform cross-resistance with the aminoglycosides.

**Thioamides:** Ethionamide and prothionamide are two different presentations of the same active substance, with bacteriostatic activity against *M. tuberculosis* at therapeutic concentration; they are bactericidal at higher concentrations. The pharmacokinetics of the two preparations is very similar, but prothionamide may be better tolerated. They induce complete cross-resistance and should therefore be regarded as the same drug.

**Fluoroquinolones:**
Ofloxacin or levofloxacin are the preferred drugs in the management of MDR-TB. Levofloxacin is better than ofloxacin, as it contains only the active isomer of ofloxacin. That is why levofloxacin high dose is our drug of choice in MDR-TB patients. However, ofloxacin may be used in the absence of levofloxacin. Both these drugs need to be given in the correct dosages (higher range) as resistance develop easily with too low dosing.

Moxifloxacin is recommended in the treatment of XDR-TB patients, as there is some evidence that strains resistant to ofloxacin/levofloxacin may still be susceptible to moxifloxacin (i.e. there is not complete cross-resistance between these fluoroquinolones).

Ciprofloxacin must not be used as anti-tuberculosis agent in management of DR-TB because of its weak efficacy compared with other fluoroquinolones.

**Terizidone and Cycloserine:** Terizidone is a combination of two molecules of cycloserine and they should therefore be regarded as the same drug. Terizidone and cycloserine are bacteriostatic at the usual dosage. Both drugs have a high incidence of side effects, specifically related to central nervous system toxicity, and can precipitate focal or grand mal seizures with high serum concentrations. Psychotic disturbances and suicidal thoughts have been reported even in patients with appropriate serum concentrations. Pyridoxine (150mg) should be given together with terizidone or cycloserine to prevent neurological side effects. Both are valuable companion drugs in the prevention of resistance to other second-line drugs.

**Para-aminosalicylic acid (PAS):** PAS is a bacteriostatic agent, valuable in preventing resistance to other drugs. It is bulky, unpleasant to take and causes gastrointestinal disturbances; however, enteric-coated formulas are better tolerated.
Table VII: Available second-line drugs for treatment of drug-resistant TB

<table>
<thead>
<tr>
<th>Drug</th>
<th>Activity</th>
<th>Dosage (daily)</th>
<th>Acceptability</th>
<th>Tolerance</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Average</td>
<td>Minimum</td>
<td>Maximum</td>
<td></td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Bactericidal</td>
<td>15mg/kg</td>
<td>750mg</td>
<td>1000mg</td>
<td>Injection</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Bactericidal (against actively</td>
<td>15mg/kg</td>
<td>750mg</td>
<td>1000mg</td>
<td>Injection</td>
</tr>
<tr>
<td></td>
<td>multiplying organisms)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kanamycin</td>
<td>Bactericidal</td>
<td>15mg/kg</td>
<td>750mg</td>
<td>1000mg</td>
<td>Injection</td>
</tr>
<tr>
<td>Amikacin</td>
<td>Bactericidal</td>
<td>15mg/kg</td>
<td>750mg</td>
<td>1000mg</td>
<td>Injection</td>
</tr>
<tr>
<td>Polypeptide</td>
<td>Bacteriostatic</td>
<td>15mg/kg</td>
<td>750mg</td>
<td>1000mg</td>
<td>Injection</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>Bacteriostatic</td>
<td>15mg/kg</td>
<td>750mg</td>
<td>1000mg</td>
<td>Injection</td>
</tr>
<tr>
<td>Thioamides</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethionamide</td>
<td>Bacteriostatic</td>
<td>15-20mg/kg</td>
<td>500mg</td>
<td>750mg</td>
<td>Good</td>
</tr>
<tr>
<td>Prothionamide</td>
<td>Bacteriostatic</td>
<td>15-20mg/kg</td>
<td>500mg</td>
<td>750mg</td>
<td>Good</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Bactericidal (in acid/low pH conditions)</td>
<td>20-30mg/kg</td>
<td>1200mg</td>
<td>1600mg</td>
<td>Good</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>Weakly bactericidal</td>
<td>15-20mg/kg</td>
<td>800mg</td>
<td>800mg</td>
<td>Good</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>Weakly bactericidal</td>
<td>7.5-10mg/kg</td>
<td>750mg</td>
<td>1000mg</td>
<td>Good</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>Bacteriostatic</td>
<td>400mg</td>
<td>400mg</td>
<td>400mg</td>
<td>Good</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Bacteriostatic</td>
<td>15-20mg/kg</td>
<td>1000mg</td>
<td>1200mg</td>
<td>Good</td>
</tr>
<tr>
<td>Tolcinone</td>
<td>Bacteriostatic</td>
<td>15-20mg/kg</td>
<td>500mg</td>
<td>750mg</td>
<td>Good</td>
</tr>
</tbody>
</table>
7.5 Other drugs

Oral medications sometimes referred to as “third-line drugs” that have been used for the treatment of MDR-TB include thioacetazone, clofazimine, amoxicillin-clavulanate, macrolides (clarithromycin and azithromycin) and other rifamycins (rifabutin and rifapentine), imipenem and linezolid.

- Thioacetazone has been associated with the development of Stevens Johnson syndrome in HIV-infected patients; in addition, it shows cross-resistance with ethionamide, prothionamide and isoniazid. It is therefore not recommended for use in the country.

- Clofazimine, an antileprosy drug, which has been known to have in vitro activity against *M. tuberculosis* with unproven clinical efficacy. But a recent study from Bangladesh has shown that clofazimine is an important MDR-TB drug. This is the drug of choice among the others in this group.

- Amoxicillin-clavulanate, clarithromycin and azithromycin have high minimal inhibitory concentrations (MIC) for most strains of *M. tuberculosis* relative to achievable serum concentrations, but clinical efficacy has again not been proven.

- Rifabutin exhibits cross-resistance with rifampicin in up to 80% of patients, while rifapenten has complete cross-resistance with rifampicin.

- Imipenem is a carbapenem. Carbapenems are very broad-spectrum antibiotics. Recent study showed activity against *M. tuberculosis* when given in combination with clavulanic acid. It is however an intravenous drug.

- Linezolid is an oxazolidinone antibacterial. It showed good activity against *M. Tuberculosis* in vitro and has been used with success in MDR/XDR-TB patients in several case reports. Linezolid is however expensive and causes several severe adverse effects.

None of these drugs are therefore recommended for routine MDR-TB treatment. They can, however, be used as experimental options or as the last resort in patients failing conventional MDR-TB or in XDR-TB treatment.

7.6 Second line drug groups

Second-line drugs are grouped according to efficacy, experience of use, and drug class, the different groups are described in table below;
| Group 1: First-line oral drugs | Ethambutol (E)  
<table>
<thead>
<tr>
<th></th>
<th>Pyrazinamide (Z)</th>
</tr>
</thead>
</table>
| Group 2: Injectable drugs     | Streptomycin (S)  
|                               | Kanamycin (Km)  
|                               | Amikacin (Am)  
|                               | Capreomycin (Cm)  
|                               | Viomycin (Vm) |
| Group 3: Fluoroquinolones    | Ofloxacin (Ofx)  
|                               | Levofloxacin (Lvx)  
|                               | Moxifloxacin (Mfx)  
|                               | Gatifloxacin (Gfx) |
| Group 4: Oral bacteriostatic | Ethionamide (Eto)  
| second-line drugs             | Prothionamide (Pto)  
|                               | Cycloserine (Cs)  
|                               | Terizidone (Trd)  
|                               | para-aminosalicylic acid (PAS) |
| Group 5: Drugs of unclear    | Clofazimine (Cfz)  
| efficacy (Not recommended     | Amoxicillin/clavulanate (Am/Clv)  
| for routine use in MDR-TB     | Clarithromycin (Clr)  
| patients)                     | Azithromycin (Azr)  
|                               | Linezolid (Lzd)  
|                               | Thioacetazone (Th)  
|                               | Imipenem  
|                               | High-dose INH |
Standard codes are used for MDR-TB treatment regimens. An MDR-TB regimen consists of two phases:
- the first known as the intensive phase during which a combination of injectable and oral drugs are used
- the second known as the continuation phase during which only oral drugs are used.

The number shown at the beginning stands for the phase duration in months, and is the minimum amount of time that phase should last. The number in subscript (i.e. 3) is the number of drug doses per week. If there is no number in subscript, treatment is daily (a minimum of six times a week). An alternative drug(s) is indicated in brackets. The drugs in the higher groups are written first, followed by others in descending order.

*Example of drug standard codes used to describe drug regimens*

**Regimen: 6Z-Km(Am)-Ofx-Eto-Trd/18Z-Ofx-Eto-Trd**

The regimen above 6 months intensive phase treatment with five drugs. The injectable drug is kanamycin, but there is an option for amikacin. The continuation phase is for at least 18 months with oral agents. Treatment is taken daily throughout the treatment period, which is twenty-four months.

### 7.8 Standardized regimen for adult MDR-TB treatment

**Intensive phase: at least 6 months, guided by TB Culture Conversion (treatment taken at least six times per week)**

<table>
<thead>
<tr>
<th>Patient weight</th>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;33kg</td>
<td>Kanamycin</td>
<td>15-20 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Ethionamide</td>
<td>15-20 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
<td>30-40 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Levofloxacin</td>
<td>750 mg (children: 7.5 to 10 mg/kg)</td>
</tr>
<tr>
<td></td>
<td>Terizidone</td>
<td>15-20 mg/kg</td>
</tr>
</tbody>
</table>
### Drug Dosage Table

<table>
<thead>
<tr>
<th>Patient weight</th>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;33kg</td>
<td>Ethionamide</td>
<td>15-20 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
<td>30-40 mg/kg</td>
</tr>
<tr>
<td>33 - 50 kg</td>
<td>Kanamycin, Ethionamide</td>
<td>500 - 750 mg</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide, Levofloxacin, Terizidone</td>
<td>500 mg, 750 mg, 1000 - 1750 mg, 750 mg, 750 mg</td>
</tr>
<tr>
<td>51 - 70 kg</td>
<td>Kanamycin, Ethionamide</td>
<td>1000 mg</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide, Levofloxacin, Terizidone</td>
<td>750 mg, 1750 - 2000 mg, 750 mg, 750 mg</td>
</tr>
<tr>
<td>&gt;70 kg</td>
<td>Kanamycin, Ethionamide</td>
<td>1000 mg</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide, Levofloxacin, Terizidone</td>
<td>750 - 1000 mg, 2000 - 2500 mg, 750 - 1000 mg, 750 - 1000 mg</td>
</tr>
</tbody>
</table>

**Continuation phase:** at least 18 months after TB culture conversion (treatment taken at least six times per week)
<table>
<thead>
<tr>
<th>Weight Range</th>
<th>Drugs</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>33 - 50 kg</td>
<td>Ethionamide, Pyrazinamide, Levofloxacin, Terizidone</td>
<td>500 mg, 1000-1750 mg, 750 mg, 750 mg</td>
</tr>
<tr>
<td>51 - 70 kg</td>
<td>Ethionamide, Pyrazinamide, Levofloxacin, Terizidone</td>
<td>750 mg, 1750-2000 mg, 750 mg, 750 mg</td>
</tr>
<tr>
<td>&gt;70 kg</td>
<td>Ethionamide, Pyrazinamide, Levofloxacin, Terizidone</td>
<td>750 - 1000 mg, 2000-2500 mg, 750 mg, 750 – 1000 mg</td>
</tr>
</tbody>
</table>

*Pyridoxine (Vit B6) 150 mg (maximum 200mg) to be given daily to patients on Terizidone.

### 7.9 Basic principles of treatment

- Use 5 drugs in intensive or injectable phase and 4 drugs in continuation phase as per standard regimen. Drugs are administered at least six days a week.
- Of the 5 drugs used in intensive phase: give at least 4 drugs with either certain, or almost certain effectiveness. Drugs previously used for a month or more may not be included among drugs with certain effectiveness.
- Each dose should be given under strict supervision throughout the treatment period.
- Sputum specimens are taken every month to do a TB smear microscopy and culture.
- The duration of the injectable phase is guided by TB culture conversion.
- TB culture conversion occurs when a patient obtains two consecutive negative TB culture results on sputum taken 30 days apart; the culture conversion date is the collection date of the first specimen that turned TB culture negative.
• Pyrazinamide and fluoroquinolones should preferably be given once a day as the high peaks attained in once daily dosing may be more efficacious. Once daily dosing is also recommended for other second-line drugs; however, ethionamide, cycloserine, terizidone and para-amino salicylic acid are often given in divided doses during the day to facilitate patient tolerance.

• Pyrazinamide may be used for the entire treatment period if the strain is thought to be susceptible to the drug. Many MDR-TB patients have chronically inflamed lungs, which theoretically produce an acidic environment in which pyrazinamide is active.

• If the patient’s TB organism is resistant to ofloxacin but still susceptible to kanamycin or amikacin: add moxifloxacin, clofazimine and PAS

• If patient’s organism is resistant to kanamycin or amikacin but susceptible to ofloxacin: add capreomycin, clofazimine and PAS

• It is further recommended that culture results, chest x-ray findings and the patient’s clinical status be taken into account in deciding whether or not to continue with the injectable drug for a longer period, particularly in patients for whom the susceptibility pattern is unknown, the effectiveness of the drug is questionable and those with extensive or bilateral pulmonary disease.

• Intermittent therapy with the injectable drug - three times a week after an initial period of two to three months of daily therapy can be considered in patients who have been on the injectable for a prolonged period of time – beyond six months and when toxicity becomes a greater risk to the patient.

7.10 Duration of treatment

The recommended duration of treatment is guided by culture conversion and is determined by adding 18 months to the culture conversion date. Extension for up to 24 months may be indicated in chronic cases with extensive pulmonary damage.

7.11 Extrapulmonary MDR-TB treatment

Extrapulmonary MDR-TB is treated using the same strategies and treatment duration as pulmonary MDR-TB. If the patient has symptoms suggestive of central nervous system involvement and is infected with MDR-TB, the drugs used should have adequate penetration into the central nervous system. Pyrazinamide, ethionamide, cycloserine and terizidone have good penetration; kanamycin, amikacin and capreomycin only show penetration in the presence of meningeal inflammation; PAS has poor or no penetration.
There are no young children or persons with known HIV infection in the household who will be placed at risk

All necessary measures would be taken to prevent spread of infection

Access to the patient by other people will be restricted or controlled.

8 MANAGEMENT OF PATIENTS WITH XDR-TB

8.1 Introduction

By definition, two key classes of second-line anti-TB drugs are compromised in XDR-TB. Individualized treatment regimens are therefore essential and must be designed according to DST results and history of previous drug use.

A detailed clinical history can help suggest which drugs are likely to be ineffective; therefore you may need to obtain records from previous health care providers. The probability of acquired drug resistance increases with the duration of drug administration. In particular, evidence of clinical or bacteriological treatment failure during treatment is highly suggestive of drug resistance. If a patient has used a drug for more than a month with persistent positive smears or cultures, that drug should be considered as ‘probably resistant’, even if DST is reported as susceptible.

DST results should complement rather than invalidate other sources of data about the likely effectiveness of a specific drug. For example, if a history of prior anti-tuberculosis drug use suggests that a drug is likely to be ineffective due to resistance, this drug should not be relied on as one of the four core drugs in the regimen, even if the strain is susceptible in the laboratory. Alternatively, 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 of some second-line drugs.

Another important pitfall is that due to the delays in confirming the diagnosis, the patient may have already been started on a standard or empiric treatment by the time DST results become available from the laboratory. The possibility of further acquired resistance during this time must be considered. If there is a high probability of acquired resistance to a drug after the treatment regimen was started, it would not be included in the empiric regimen.
principles as those for MDR-TB. XDR-TB patients must be hospitalized, preferably at the MDR-TB hospitals.

8.2 Basic principles of treatment

There is currently no international consensus on the optimum duration of XDR-TB treatment; therefore, the same principles as for MDR-TB treatment apply, but clinical assessment of individual patients is required to decide on the termination of XDR-TB treatment.

The following principles must be applied when designing XDR-TB regimens:

- At least four drugs expected or known to be effective or patient has not been exposed to should be included.
- All patients should receive an injectable drug if susceptibility is documented or expected.
- Other medications are added based on estimated susceptibility, drug history, efficacy, side-effect profile. Drugs to be considered are: PAS, ethionamide and terizidone.
- The use of thioacetazone is not recommended because of the high risk of skin rashes that are more prevalent in HIV-positive individuals and can result in Stevens-Johnson syndrome and death. In addition, thioacetazone has cross-resistance with the thioamides (ethionamide and prothionamide) and is considered a relatively weak anti-tuberculosis agent. While thioacetazone is included among Group 5 drugs, it is the least used agent for the treatment of DR-TB and is not available in South Africa.
- Newer rifamycins (eg. rifabutin, rifapentine) have almost complete cross-resistance with rifampicin and should not be considered.
- Group 5 drugs are not recommended for routine use in the treatment of XDR-TB because their contribution to the efficacy of treatment regimens is unclear. However, they can be used in cases where adequate regimens are impossible to construct with available drugs from the other groups and you need to strengthen the regimen. Clofazimine is the drug of choice among the group 5 drugs.

Table IX: Summary of general principles for constructing XDR-TB treatment regimens

<table>
<thead>
<tr>
<th>Basic principles</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Use at least four drugs that are expected to be effective</td>
<td>Effectiveness is supported by a number of factors, these are: DST results show susceptibility, no prior history of treatment with the drug, no known close contacts with resistance to the drug, surveillance data show that resistance is rare.</td>
</tr>
<tr>
<td>2. All patients should receive an injectable drug</td>
<td></td>
</tr>
<tr>
<td>3. Other medications are added based on estimated susceptibility, drug history, efficacy, side-effect profile.</td>
<td>Drugs to be considered are: PAS, ethionamide and terizidone.</td>
</tr>
<tr>
<td>4. The use of thioacetazone is not recommended</td>
<td>Because of the high risk of skin rashes that are more prevalent in HIV-positive individuals and can result in Stevens-Johnson syndrome and death. In addition, thioacetazone has cross-resistance with the thioamides (ethionamide and prothionamide) and is considered a relatively weak anti-tuberculosis agent. While thioacetazone is included among Group 5 drugs, it is the least used agent for the treatment of DR-TB and is not available in South Africa.</td>
</tr>
<tr>
<td>5. Newer rifamycins (eg. rifabutin, rifapentine) have almost complete cross-resistance with rifampicin and should not be considered.</td>
<td></td>
</tr>
<tr>
<td>6. Group 5 drugs are not recommended for routine use in the treatment of XDR-TB because their contribution to the efficacy of treatment regimens is unclear. However, they can be used in cases where adequate regimens are impossible to construct with available drugs from the other groups and you need to strengthen the regimen.</td>
<td>Clofazimine is the drug of choice among the group 5 drugs.</td>
</tr>
</tbody>
</table>
The drug is not commonly used in the area if more of these factors apply the more likely that the drug will be effective.

2. Do not use drugs for which cross-resistance exists
   - All rifamycins have cross-resistance (rifampicin, rifabutin, rifapentine).
   - Fluoroquinolones are believed to have high cross-resistance between each other.
   - Not all aminoglycosides show cross-resistance; in general, only kanamycin and amikacin are fully cross-resistant.

4. Eliminate drugs that are not safe for the patient
   - Known severe allergy or unmanageable intolerance; high risk of severe adverse drug effects such as renal failure, deafness, hepatitis, depression and/or psychosis.

5. Include drugs from Groups 1 to 5 in a hierarchical order
   - Use any Group 1 (oral first-line drugs) to which the strain is still sensitive.
   - Use an effective injectable drug in Group 2.
   - Use the remaining Group 4 drugs to make a regimen of at least four effective drugs.
   - Where you remain with less than four effective drugs, add second-line drugs most likely to be effective, making up a total of 5-7 drugs.
   - Use Group 5 drugs as needed.

6. Prevent, monitor and manage side effects for each of the drugs selected.
   - Laboratory services for haematology, biochemistry, serology, audiometry are required.
   - Establish a baseline before starting the drug.
   - Initiate treatment gradually, split daily doses.
   - Ancillary drugs must be in stock to manage side effects.


The rationale for individualised regimens in the treatment of patients with XDR-TB is that they have to receive drugs that the strain is susceptible to and exclude those that they are resistant to. This is simple, but in practice the DST results for second line drugs is too complex and the tests are not as sensitive as we would like them to be. As previously discussed the margin between the minimum inhibitory concentration and the critical concentration is narrow hence it is easy to misinterpret the results. The only accurate second line DST tests are for kanamycin or amikacin and the fluoroquinolones.
### 8.3 Standardised regimen for adult XDR-TB treatment

<table>
<thead>
<tr>
<th>Patient weight</th>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intensive Phase: Treatment taken daily for at least 6 months, guided by TB culture conversion</td>
<td></td>
</tr>
<tr>
<td>&lt;33kg</td>
<td>Capreomycin</td>
<td>15-20 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin</td>
<td>400 mg</td>
</tr>
<tr>
<td></td>
<td>Ethionamide</td>
<td>15-20 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Terizidone</td>
<td>15-20 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
<td>30-40 mg/kg</td>
</tr>
<tr>
<td></td>
<td>PAS</td>
<td>150 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Clofazimine</td>
<td>3-5 mg/kg</td>
</tr>
<tr>
<td>33 - 50 kg</td>
<td>Capreomycin</td>
<td>500-750 mg</td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin</td>
<td>400 mg</td>
</tr>
<tr>
<td></td>
<td>Ethionamide</td>
<td>500 mg</td>
</tr>
<tr>
<td></td>
<td>Terizidone</td>
<td>500 mg</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
<td>1000-1750 mg</td>
</tr>
<tr>
<td></td>
<td>PAS</td>
<td>8000 mg</td>
</tr>
<tr>
<td></td>
<td>Clofazimine</td>
<td>200 mg</td>
</tr>
<tr>
<td>51 - 70 kg</td>
<td>Capreomycin</td>
<td>1000 mg</td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin</td>
<td>400 mg</td>
</tr>
<tr>
<td></td>
<td>Ethionamide</td>
<td>750 mg</td>
</tr>
<tr>
<td></td>
<td>Terizidone</td>
<td>750 mg</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
<td>1750-2000 mg</td>
</tr>
<tr>
<td></td>
<td>PAS</td>
<td>8000 mg</td>
</tr>
<tr>
<td></td>
<td>Clofazimine</td>
<td>300 mg</td>
</tr>
<tr>
<td>&gt;70 kg</td>
<td>Capreomycin</td>
<td>1000 mg</td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin</td>
<td>400 mg</td>
</tr>
<tr>
<td>Patient weight</td>
<td>Drug</td>
<td>Dosage</td>
</tr>
<tr>
<td>----------------</td>
<td>-----------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td></td>
<td>Continuation Phase: Treatment taken daily for at least 18 months after TB culture conversion</td>
<td></td>
</tr>
<tr>
<td>&lt;33kg</td>
<td>Mofloxacin Ethionamide Terizidone Pyrazinamide PAS Clofazimine</td>
<td>400 mg 15-20 mg/kg 15-20 mg/kg 30-40 mg/kg 150 mg/kg 3-5 mg/kg</td>
</tr>
<tr>
<td>33 - 50 kg</td>
<td>Mofloxacin Ethionamide Terizidone Pyrazinamide PAS Clofazimine</td>
<td>400 mg 500 mg 500 mg 1000-1750 mg 8000 mg 200 mg</td>
</tr>
</tbody>
</table>
The other reinforcing agents or agents with unclear efficacy (Group 5) may only be considered if the patient has a considerable resistance pattern which makes it difficult to construct an effective regimen using the first and second-line drugs.
ROLE OF SURGERY

The treatment of MDR- and XDR-TB is first and foremost chemotherapy. There are, however, limited indications for surgery and these presume that the disease is mainly localised, unilateral and that there is adequate cardiopulmonary reserve. For patients with localised disease, surgery can significantly improve outcomes, provided skilled thoracic surgery and excellent post-operative care are available.

Major indications

- Persistence of positive sputum cultures and lack of radiographic and clinical improvement after six months of adequate therapy and patient adherence.

- Relapse in the same site after a previous adequate course of chemotherapy in a patient who has been adherent.

Minor indications

- In a patient who has undergone sputum conversion but the profile of drug resistance is so great (e.g. resistance to more than four drugs) that if relapse did occur it may be difficult to re-establish sputum culture conversion.

- In a patient who has undergone sputum conversion but there is residual cavitation or gross lobe or lung destruction and hence the potential for relapse.

At least six months of treatment should be given before surgery is considered. In a patient who has not undergone sputum conversion, surgery should only be performed when there is no further possibility of an adequate chemotherapeutic regimen. The decision to perform surgery and the extent of surgery (lobectomy or pneumonectomy) should preferably be made after anatomical localisation of disease by CT scan. Often the apex of a lower lobe is involved together with a corresponding upper lobe and the former should also be removed. Perfusion scans are useful in establishing how much functioning lung is likely to be removed. Basic spirometry (FEV1 and FVC) is adequate in assessing lung function in the majority of patients. Eligible patients should have a FEV1 > 0.8. If the FEV1 is acceptable, analysis of blood for HCT, ABG, urea and electrolytes, creatinine should be performed pre-operatively. ECG is useful for excluding pulmonary hypertension which would contraindicate surgery. A pre-operative ECG should be routinely performed on patients older than 50 years and on patients with diabetes.
10. MANAGEMENT OF DRUG ADVERSE EFFECTS

10.1 Introduction

Almost all patients on MDR and XDR-TB treatment will report adverse effects to the second-line drugs. Close monitoring of patients is necessary to ensure that adverse effects are recognized and addressed quickly. The majority of adverse effects are easy to recognize and patients will often volunteer this information. However, it is important to have a systematic approach to patient interviewing since some patients may be timid about reporting even severe adverse effects. Other patients may be distracted by one side effect and forget to inform the health care provider about others. The timely and aggressive management of adverse effects of the second-line drugs greatly facilitates patient adherence.

10.2 Most common drug adverse effects

Drug adverse effects can be classified under the following categories:
- Minor side effects
- Toxic reactions
- Hypersensitivity reactions
- Idiosyncratic reactions
- Other reactions

Since DR-TB patients receive combination chemotherapy, it is often difficult to determine which drug is the source of the undesired effect as drug-drug interactions may also produce adverse effects. Some adverse effects present soon after treatment is initiated while others tend to manifest later.

The most common adverse effects to second-line anti-TB drugs include:
1. Skin reactions
   Skin reactions ranging from pruritus to rashes and most severely to toxic epidermal necrolysis, sometimes accompanied by fever, may be caused by several agents. These are frequent among patients with HIV infection. In most cases desensitization is successful, and the full range of medications can be re-introduced within one or two weeks.
2. Gastrointestinal symptoms (nausea, vomiting, diarrhoea)
   Symptoms such as nausea, pain and vomiting are common, but may be prodromal symptoms of hepatitis and should be investigated. Monitoring of the response is important; if the symptoms do not subside, liver toxicity must be suspected and investigated.
Impaired hearing or impaired balance is virtually always due to the injectable agents. It is often, but not always, dose-dependent. Audiometry should therefore be performed prior to initiation of treatment and repeated monthly or when indicated, throughout the intensive phase. Patients with pre-existing vestibulo-cochlear impairment should be counselled on the potential risks and informed consent obtained before these drugs are used. Patients complaining of hearing loss or impaired balance should be checked to establish that the dosage given is appropriate for weight and age, as toxicity increases with both.

4. Peripheral neuropathy
Peripheral neuropathy, presenting as paresthesia such as tingling and numbness, starting at the feet with proximal spread is the usual manifestation. Myalgias, weakness and ataxia may accompany these symptoms. Peripheral neuropathy is usually due to cycloserine and terizidone and occurs more commonly in malnourished or alcohol-dependent patients. Pyridoxine or amitriptyline is effective in treating peripheral neuropathy.

5. Electrolyte wasting
Electrolyte wasting is a known complication of the injectable drugs, most frequently with capreomycin. It is generally a late effect that manifests after months of treatment, and is reversible once the injectable is suspended. Electrolyte wasting is often asymptomatic in the early stages but patients complain of muscle cramping and palpitations.

6. Psychiatric symptoms
Infrequently, toxic psychosis, depression, suicidal ideation, anxiety and epileptic convulsions may occur with cycloserine and terizidone. Pyridoxine is usually effective for treating these cases.

7. Nephrotoxicity
This is a well documented adverse effect of all injectable drugs, both the aminoglycosides and capreomycin. This adverse effect is occult (not obviously noted by taking the history of the patient or by physical examination) in onset and can be fatal.

8. Impaired vision
This is most frequently caused by ethambutol. Optic toxicity is not detectable fundoscopically. Patients with impaired vision other than due to myopia, hyperopia or presbyopia should not be given ethambutol.

9. Osteo-articular pain
Arthralgia is a frequent adverse drug event resulting from the accumulation of uric acid caused by pyrazinamide. Acetaminophen or naproxen can alleviate the pain.
10.3 Monitoring of drug adverse effects

Laboratory screening is invaluable for detecting adverse effects that are more occult. During the intensive phase of treatment, patients must be interviewed weekly about adverse effects to the drugs and these recorded utilising the Drug Adverse Effect Monitoring Form (Annexure I). This section will need more detail, especially in dealing with patients who are being managed under ambulatory care.

In the continuation phase the incidence of adverse effects must be monitored monthly utilising the same Form. Line listings of these effects must be provided quarterly to the Provincial TB Coordinator. Serious adverse events which necessitate discontinuation of drugs must be noted in the Serious Adverse Drug Effect Report and a report forwarded within five calendar days to the Provincial TB Coordinator for notification to the Medicines Control Council.

Drug intolerance and patient sensitisation should be managed according to the recommendations contained in these guidelines. Treatment supervisors should enquire about drug adverse effects during every encounter with the patient.

Table 9 provides a guide on the number and frequency of laboratory tests that should be conducted to monitor the development of adverse drug effects.

**Table X: Laboratory monitoring of drug adverse effects**

<table>
<thead>
<tr>
<th>Drug adverse effect</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine</td>
<td>Baseline</td>
</tr>
<tr>
<td></td>
<td>At least monthly while receiving an injectable drug</td>
</tr>
<tr>
<td>Serum potassium</td>
<td>At least monthly while receiving an injectable agent particularly those receiving capreomycin.</td>
</tr>
</tbody>
</table>
Liver serum enzymes | Consider periodic monitoring in patients receiving pyrazinamide for extended periods of time or for patients at risk of hepatitis


10.4 Management of drug adverse effects

Of equal importance to the treatment regimen used is the proper management of drug adverse effects. Second-line anti-tuberculosis drugs have many more adverse effects than first-line anti-tuberculosis drugs.

Proper management of adverse effects begins with pre-treatment patient education, when the patient should be informed in detail about the potential adverse effects that could be caused by the drugs they are taking, and when to notify the health care provider.

Timely and aggressive management of adverse effects is essential. Without it, mortality and permanent disability can be the result, in addition to patient non-adherence. Even if the adverse effects are not particularly dangerous, prompt intervention is important. Patients may have significant anxiety about an adverse effect if they do not understand what is happening. This may in turn augment the severity of the adverse effect, i.e. nausea and vomiting.

The following sequential steps for the management of drug adverse effects are recommended:

1) Management of adverse effects with standardised algorithms
   Most adverse effects can be managed with over-the-counter and common prescription drugs. If they are mild and not dangerous, continuing the treatment regimen, with the help of ancillary drugs where necessary is the best option. Many adverse effects disappear or diminish with time and patients should be encouraged to tolerate the effects until they subside. Psychosocial support is an important component of management of adverse effects.

2) Reduced dosage of suspected drug(s)
   The adverse effects of a number of second-line anti-tuberculosis drugs are highly dose dependent. If a patient cannot tolerate the regimen, the dosage of the
reduce the dosages of multiple drugs simultaneously. However, due to the narrow therapeutic margins of second-line drugs, lowering the dose may affect the efficacy as well, so every effort should be made to maintain an adequate dose of the drug according to body weight.

3) Removal of drug(s) from the regimen
If reduced dosage does not alleviate the adverse effects(s) it may be necessary to remove a drug from the regimen, or to replace the drug with another drug. This final option should be chosen only as a last resort, as it will affect the potency of a regimen.

Monitoring and management of drug adverse effects may have to be more aggressive in patients with concomitant conditions such as:
- Pregnancy and lactation
- Diabetes mellitus;
- Renal insufficiency;
- Acute or chronic liver disease;
- Thyroid disease;
- Mental illness;
- Drug or alcohol abuse;
- HIV infection;

Table XI: Summarises the most common adverse effects, the offending drugs and their management strategies:

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Responsible Agent</th>
<th>Management</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizures</td>
<td>Cs, Trd, FQs</td>
<td>1. Rule out other likely causes 2. Treat any suspected causes 3. Initiate anticonvulsant treatment phenytoin 3-5 mg/kg/day valproic acid 750-1250 g/kg/day carbamazepine 600-1200 mg/day phenobarbitol 60-120 mg/kg/day</td>
<td>• Clinical evaluation is generally sufficient unless there is high suspicion of infectious, malignant, vascular or metabolic cause • Anticonvulsant must be continued until MDR-TB treatment completed or suspected agent discontinued</td>
</tr>
</tbody>
</table>
the offending TB drugs if
the patient’s seizures are
well-controlled and/or the
patient is receiving
anticonvulsant treatment

- Patients with history of
prior seizures may be at
increased risk for
development of seizures
during MDR-TB treatment
- Seizures are not a
permanent sequelae of
MDR-TB treatment

Peripheral
neuropathy

<table>
<thead>
<tr>
<th></th>
<th>Cs</th>
<th>Trd</th>
<th>S</th>
<th>Km</th>
<th>Amk</th>
<th>Cm</th>
<th>Eto/ Pto</th>
<th>FQs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Increase pyridoxine to 200 mg
daily
2. Begin exercise regimen, focusing
on affected regions
3. Initiate therapy with tricyclic
antidepressant drugs
4. Lower dose of suspected drug
5. Discontinue suspected drug
6. Initiate therapy with gabapentin
300mg qid initially, and increase
by 600mg every 3-7 days; max
dose 1200mg tds

- Patients with co-morbid
disease (eg. diabetes, HIV,
alcoholism) more likely to
develop peripheral
neuropathy, but these
conditions are not
contraindications to the
use of the offending TB
drugs.
- Neuropathy is generally
not reversible, but only a
minority (approximately
10%) of patients require
continued intervention to
keep symptoms controlled
once MDR-TB treatment is
completed

Hypothyroidism

<table>
<thead>
<tr>
<th></th>
<th>PAS</th>
<th>Eto/ Pto</th>
</tr>
</thead>
</table>

1. Initiate thyroxine

- Completely reversible upon
discontinuation of
offending drug
### Km Amk Cm

1. Compare with baseline
2. Consider reducing the frequency of the drug administration to 5 times or even 3 times per week
3. Lower the dose of suspected drug if this will not compromise the regimen
4. Discontinue suspected drug if this will not compromise the regimen

---

### Psychosis

<table>
<thead>
<tr>
<th>Cs Tdr FQs Eto/ Pto</th>
</tr>
</thead>
</table>

1. Refer to a psychiatrist for assessment
2. Hold suspected agent for short period of time (1-4 weeks) while psychotic symptoms brought under control
3. Initiate anti-psychotic drugs (eg. risperidone 0.5-2 mg po bd; Haloperidol 1-5mg po or IV or IM repeated every hour as needed)
4. Lower dose of suspected agent if this will not compromise the regimen
5. Discontinue suspected agent if this will not compromise the regimen

- Some patients will need to continue anti-psychotic treatment throughout MDR-TB treatment
- Prior history of psychiatric disease is not a contraindication to the use of the offending TB drugs, but may increase the likelihood of development of psychotic symptoms
- Psychotic symptoms are generally reversible upon MDR-TB treatment completion or discontinuation of the offending agent

### Exposure to Aminoglycosides

- Hearing loss is generally not reversible
- The risk of further hearing loss should be weighed against the risk of stopping the drug in the regimen

### Baseline Hearing Loss

- Hearing loss is generally not reversible
- The risk of further hearing loss should be weighed against the risk of stopping the drug in the regimen

---

### Depression

1. Rule out side effects of concomitant medications, eg. amoxicillin-clavulanate, penicillin, benzodiazepines
2. Refer to psychologist/psychiatrist for assessment

- Importance of personal socio-economic conditions and confinement to hospital should not be underestimated as contributing factor to
3. Initiate group or individual psychological therapy
4. Initiate anti-depressant drugs (eg. amitriptyline, nortriptyline, fluoxetine, sertraline), but use with caution when there is a history of convulsions
5. Increase pyridoxine to 200 mg daily
6. Lower dose of the offending drug if this will not compromise the regimen
7. Discontinue the offending drug if this will not compromise the regimen

- Depression and depressive symptoms may fluctuate during treatment
- History of prior depression is not a contraindication to the use of the offending TB drugs, however, these patients may be at increased risk for developing depression during MDR-TB treatment

Nausea and vomiting

<table>
<thead>
<tr>
<th>Eto/ Pto</th>
<th>PAS</th>
<th>Cm</th>
<th>E</th>
<th>Z</th>
</tr>
</thead>
</table>
| 1. Assess for dehydration and rehydrate if indicated
2. Initiate anti-emetics 30 min prior to administering MDR-TB drugs
3. Administer ethionamide in 3 separate doses
4. Administer ethionamide at night with short-acting benzodiazepine
5. Lower dose of offending drug agent
6. Discontinue use of offending drug |

- Nausea and vomiting is common in the early weeks of treatment and usually abates with time on treatment or supportive therapy
- Electrolytes should be monitored and replenished if vomiting is severe
- Reversible upon discontinuation of suspected agent

Gastritis

<table>
<thead>
<tr>
<th>PAS</th>
<th>Eto/ Pto</th>
<th>E</th>
<th>Z</th>
</tr>
</thead>
</table>
| 1. Administer MDR-TB drugs with a small amount of food
2. Caffeine, cigarettes should be avoided
3. Consider use of
   - Antacids (eg. calcium carbonate, aluminium
   - H2-blockers (eg. cimetidine, ranitidine), proton pump inhibitors (eg. omeprazole) |

- Severe gastritis or gastric ulcers as manifested by hematemesis, melena or hematechezia is rare
- Dosing of antacids should be carefully timed so as not to interfere with the
<table>
<thead>
<tr>
<th>Condition</th>
<th>Meds/Drugs</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis</td>
<td>Z FQs Eto/Pto PAS E</td>
<td>4. Withhold offending drug(s) for short periods of time (eg. 1-7 days)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Lower dose of offending drug</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6. Discontinue the offending drug discontinue of offending drug(s)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• History of prior hepatitis should be carefully analyzed to determine the most likely causative drug(s); these should be avoided in future regimens</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Generally reversible upon discontinuation of offending drug</td>
</tr>
<tr>
<td>Renal failure and nephrotoxicity</td>
<td>S Km Amk Cm</td>
<td>1. Stop treatment pending resolution of the hepatitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Rule out other potential causes of hepatitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Consider suspending the causative drug permanently</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Re-introduce drugs individually while monitoring liver function, with the most likely drug introduced first</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Monitor liver function every 1-2 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• History of diabetes or renal disease is not a contraindication to the use of the offending TB drugs, although patients with co-morbidities may be at increased risk for developing renal failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Renal impairment may be permanent</td>
</tr>
<tr>
<td>Optic neuritis</td>
<td>E</td>
<td>1. Stop agent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Refer patient to an ophthalmologist</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Usually reverses with cessation of the drug</td>
</tr>
<tr>
<td>Arthralgia/arthritis</td>
<td>Z FQs</td>
<td>1. Initiate therapy with non-steroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Initiate exercise regimen/physiotherapy where necessary</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Lower dose of offending drug, if this will not compromise the regimen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Symptoms of arthralgia/arthritis generally diminish over time, even without intervention</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Uric acid levels may be elevated in some patients</td>
</tr>
</tbody>
</table>
Electrolyte disturbances (hypokalemia, hypomagnesemia)

<table>
<thead>
<tr>
<th>Cm</th>
<th>Km</th>
<th>Am</th>
<th>S</th>
</tr>
</thead>
</table>

1. Replenish potassium po or IV
2. Treat associated vomiting or diarrhoea
3. Check magnesium levels if potassium levels do not improve
4. Discontinue arrhythmogenic drugs (eg. digoxin, amyltriptyline, cisapride, haloperidol) if patient is taking them
5. Discontinue aminoglycosides if condition is severe

- Hypokalemia can occur within clinical signs and symptoms and may be life-threatening
- Amiloride 5-10mg qid or spironolactone 25mg qid may decrease the potassium and magnesium wasting and is useful in refractory cases.


* Bold indicates the most likely offending drug

11. RECOMMENDED DRUGS FOR THE TREATMENT OF ADVERSE EFFECTS

A number of ancillary medications and adjuvant therapies are used to manage the adverse effects, reduce morbidity and mortality and improve overall treatment outcomes in DR-TB patients.

The most commonly used drugs and supplements are:

1) Analgesics
   Headaches are a common adverse effect of DR-TB treatment. It is important to rule out other causes such as meningitis, migraine and cluster headaches. Codeine with acetaminophen gives relief to moderate pain and also helps control cough. Stronger analgesics should be used as appropriate.

2) Corticosteroids
   The adjuvant use of corticosteroids in patients on DR-TB treatment has been shown not to increase mortality and can help alleviate symptoms associated with severe respiratory insufficiency, central nervous system involvement and laryngeal TB. The adjuvant use can be tapered gradually over two to three weeks. Prednisone is commonly used, starting at approximately 1 mg/kg and gradually decreasing the dose by 10mg per week. Stopping the prednisone abruptly can be dangerous in patients dependent on corticosteroids. Corticosteroids may also alleviate symptoms in patients with exacerbation of obstructive pulmonary disease. In these cases, prednisone may be given over one to two weeks, starting at approximately 1 mg/kg.
then tapering of the dose by 5-10 mg per day. Patients already using corticosteroids for other conditions should continue their use.

3) Pyridoxine
Pyridoxine is given as adjuvant therapy with cycloserine and terizidone to prevent neurological toxicity and should be provided at a dose of 150 mg/day. The dose may be increased to 300 mg/day when adverse effects related to cycloserine or terizidone use are experienced.

4) Vitamin and mineral supplements
Vitamins (especially vitamin A) and mineral supplements may be given when patients have deficiencies. If minerals are given they should be administered at least one hour before or after the fluoroquinolones, as zinc, iron and calcium can interfere with fluoroquinolone absorption.

5) Respiratory insufficiency
Oxygen can be used to alleviate shortness of breath. Generally, it is indicated in patients with a pO$_2$ < 55mmHg or O$_2$ Saturation < 89%, and should be titrated to raise the O$_2$ Saturation to more than 90%. Oxygen is usually started at 2-4L/min via nasal cannula. If more than 5 L/min is needed, the oxygen should be delivered through a mask. Retention of CO$_2$ can occur in some patients and should be checked when starting oxygen or increasing oxygen delivery. Corticosteroids and morphine also provide significant relief from respiratory insufficiency.

6) Bronchodilators
Bronchodilators alleviate shortness of breath and may suppress cough. Due to the high prevalence of residual lung disease in DR-TB patients, bronchodilators should continued after completion of treatment.

7) Nutritional support
In addition to causing malnutrition, DR-TB can be exacerbated by poor nutritional status. The second-line anti-tuberculosis drugs can also further decrease the appetite, making adequate nutrition a greater challenge. Nutritional support can take the form of providing foods parcels, and whenever possible should include a source of protein.

Table XII: Commonly used ancillary drugs and their indications

<table>
<thead>
<tr>
<th>Indication</th>
<th>Ancillary medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea, vomiting</td>
<td>Metoclopramide, cyclizine, promethazine, bismuth subsalicylate</td>
</tr>
<tr>
<td>Gastritis, peptic ulcers</td>
<td>H$_2$- blockers (ranitidine, cimetidine, famotidine, etc.), proton pump inhibitors (omeprazole, lansoprazole, etc.)</td>
</tr>
<tr>
<td></td>
<td>Avoid antacids because they can decrease absorption of fluoroquinolone</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral candidiasis</td>
<td>Fluconazole, cotrimazole lozenges, Nystatin oral solution</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Loperamide</td>
</tr>
<tr>
<td>Depression</td>
<td>Selective serotonin reuptake inhibitors (fluoxetine), tricyclic antidepressants (amitriptyline)</td>
</tr>
<tr>
<td>Severe anxiety</td>
<td>Lorazepam, diazepam, clonazepam</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Dimenhydrinate</td>
</tr>
<tr>
<td>Psychosis</td>
<td>Haloperidol, thorazine, risperidone (consider benzotropine or biperiden to prevent extrapyramidal side effects)</td>
</tr>
<tr>
<td>Seizures</td>
<td>Phenytoin, carbamazepine, valproic acid, phenobarbital</td>
</tr>
<tr>
<td>Prophylaxis of neurological</td>
<td>Pyridoxine (vitamin B6)</td>
</tr>
<tr>
<td>complications of cycloserine or</td>
<td>terizidone</td>
</tr>
<tr>
<td>terizidone</td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Amitriptyline</td>
</tr>
<tr>
<td>Vestibular symptoms</td>
<td>Meclizine, dimenhydrinate, prochlorperazine, promethazine</td>
</tr>
<tr>
<td>Musculoskeletal pain, arthritis</td>
<td>Ibuprofen, paracetamol, codeine</td>
</tr>
<tr>
<td>Cutaneous reactions, itching</td>
<td>Hydrocortisone cream, calamine, caladryl lotions</td>
</tr>
<tr>
<td>Systemic hypersensitivity reactions</td>
<td>Antihistamines (diphenhydramine, chlorpheniramine, dimenhydrinate), corticosteroids (prednisone, dexamethasone)</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>Inhaled beta-agonists (albuterol, etc.), inhaled corticosteroids (beclomethasone, etc.), oral steroids (prednisone), injectable steroids (dexamethasone, methylprednisolone)</td>
</tr>
</tbody>
</table>
Figure III: Management of hearing loss

- Consider administration 3 x week
- Consider using lower dose
- Continue/discontinue drug after informed decision by patient

Previous exposure to aminoglycoside (e.g., streptomycin)

- Yes
  - Baseline audiometry
    - Assess
    - Discuss implications with patient

- No
  - Hearing loss reported

- Hearing loss confirmed

- Yes
12. TREATMENT IN SPECIAL SITUATIONS

12.1 Introduction

Co-existing or co-morbid conditions often render MDR-TB treatment even more problematic. The following situations require special attention in MDR-TB patients considered for treatment:

1) Oral contraception use
   Birth control is strongly recommended for all women receiving DR-TB treatment because of the potential negative consequences in both mother and foetus of frequent and/or severe adverse drug effects.
   There is no contraindication to taking oral contraceptives with second line drugs; however, since oral contraceptives may have decreased efficacy due to potential drug interactions, other methods such as the use of medroxy-progesterone or barrier methods (e.g. diaphragm or condom) should be considered for use throughout the period of treatment.
   Should the patient opt for oral contraception, they should be made aware of the fact vomiting results in decreased absorption of the pill, and therefore decreased efficacy. They should be advised not to take the pill at the same time with anti-tuberculosis treatment and that if vomiting occurs within the first two hours of taking the pill, she should use a barrier method of contraception.

2) Pregnancy
   Female patients of childbearing age should be tested for pregnancy upon initial evaluation. Second line drugs are not contra indicated in pregnancy but some of the drugs have teratogenic effects and the risk of not treating DR-TB may have serious consequences to both mother and foetus.

   Pregnant patients should be carefully evaluated, taking into consideration the gestational age and the severity of the disease. The risks and benefits of treatment should be carefully considered. The following principles apply:
   
a. Delay DR-TB treatment until the second trimester
      Since the majority of teratogenic effects occur in the first trimester, therapy should be delayed until the second trimester unless life-threatening symptoms occur. The decision to postpone treatment should be agreed upon by both patient and physician. This decision should be based on the clinical judgement resulting from an analysis of life-threatening signs/symptoms, the severity or aggressiveness of the disease (usually reflected in extent of weight loss and radiographic picture during the previous weeks). A discussion of risks and benefits must address any concerns a patient may have in delaying the start of therapy or in using medicines while pregnant.
If the decision is to start therapy, use three or four oral drugs with demonstrated efficacy and then reinforce the regimen with an injectable agent and possibly other drugs immediately postpartum.

b. Avoid injectable agents
Aminoglycosides should not be used in the treatment of pregnant patients as they can be particularly toxic to the developing foetal ear. Capreomycin may carry the same risk of ototoxicity, but it is a drug of choice if an injectable agent cannot be avoided.

c. 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, avoid ethionamide in pregnant patients. The table below shows the safety profile of the second line drugs in pregnancy.

Table XIII: Safety of second line drugs during pregnancy

<table>
<thead>
<tr>
<th>Medication</th>
<th>Safety class*</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethambutol</td>
<td>B</td>
<td>Experience in gravid patients suggests safety</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>C</td>
<td>Use with caution. Most references suggest it is safe to use.</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>D</td>
<td>Avoid use. Documented toxicity to developing foetal ear. Risks and benefits must be carefully considered. Avoid use where possible.</td>
</tr>
<tr>
<td>Kanamycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capreomycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>C</td>
<td>Use with caution. No teratogenic effects seen in humans or in animals for short periods of time (2-4 weeks). Associated with permanent damage to cartilage in weight-bearing joints of immature animals. Experience with long-term use in gravid patients is limited, but given bactericidal activity, benefits may outweigh risks.</td>
</tr>
</tbody>
</table>
## Breastfeeding

### a) Lactating mothers

A woman who is breastfeeding and has active DR-TB should receive a full course of treatment, as timely and properly applied chemotherapy is the best way to prevent transmission of DR-TB to the baby.

### b) Nursing infants

In lactating mothers on treatment, most anti-tuberculosis drugs are found in the breast milk in minute concentrations compared to the therapeutic doses used in treating infants. However, the effects on infants of such exposure during the full course of treatment have not been established. Therefore, the use of infant formula is the only reasonable way to avoid any unknown adverse effects. However, the use of infant formula will depend on multiple factors, including the patient’s resources, safety of water supply, and bacteriological status of the mother. If the setting is not appropriate for infant formula, then breast-feeding may be considered. The mother and baby should not be forced to stay apart. If the mother is smear-positive, she should consider using a mask when in close contact with the infant or leaving the care of the infant to family members until she is negative.
In culture-negative children who have clinical evidence of active TB and close contact with a person who has confirmed MDR or XDR-TB, the child’s treatment should be guided by the DST results and history of TB drug exposure of the contact. There is limited reported experience on the use of the second-line medications for extended periods in children. Careful consideration of the risks and benefits of each drug should be made. Education and counselling of the patient and family is critical at the initiation of treatment. Given that MDR and XDR-TB are life-threatening diseases, no drugs are absolutely contraindicated in children.

It should be noted that while fluoroquinolones have been shown to retard cartilage development in beagle puppies, experience in the treatment of children with cystic fibrosis has failed to demonstrate similar effects in humans. It is now considered that the benefit of fluoroquinolones in treating MDR-TB in children outweighs the risks. Additionally, ethionamide, PAS, cycloserine and terizidone have been used effectively in children and are well tolerated.

In general, drugs dosages should be based on the weight of the child. Monitoring monthly weight is therefore important in children with adjustment of the dosages as the child gains weight. All drugs, including the fluoroquinolones, should be dosed at the higher end of recommended ranges whenever possible, with the exception of ethambutol. Since it is difficult to monitor optic neuritis in children, the maximum dose for ethambutol in children should be 15 mg/kg.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Daily dose mg/kg/day</th>
<th>Frequency</th>
<th>Maximum daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptomycin</td>
<td>Vials: 500 mg, 1 g</td>
<td>20-40</td>
<td>Once Daily</td>
<td>1g</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>Vials: 500 mg, 1g</td>
<td>15–30</td>
<td>Once Daily</td>
<td>1g</td>
</tr>
<tr>
<td>Amikacin</td>
<td>Vials:</td>
<td>15 – 22.5</td>
<td>Once Daily</td>
<td>1g</td>
</tr>
</tbody>
</table>
In children who are not culture-positive at the start of treatment, failure is difficult to assess. As is the case in adults, children should get monthly cultures of either gastric aspirates or (induced) sputum until they become culture-negative. Thereafter two-monthly specimens for culture should be obtained until completion of treatment if they had severe lung disease (same as in adults). Persistent abnormalities on chest radiograph do not necessarily signify a lack of improvement. Failure to gain weight or weight loss (less common) is of particular concern, and often one of the first (or only) signs of treatment failure. Monitoring weight gain would therefore assist in the early detection of treatment failure.

Anecdotal evidence suggests that adolescents are at high risk for poor adherence and poor treatment outcomes, perhaps due to biologic reasons (more advance disease due to late diagnosis) and social factors (more problems with adherence due to peer pressure).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Dosage (mg)</th>
<th>Administration</th>
<th>Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ofloxacin</td>
<td>Tablets: 200, 400 mg</td>
<td>15 – 20</td>
<td>Once daily</td>
<td>800 mg</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>Tablets: 250, 500, 750 mg</td>
<td>7.5 – 10</td>
<td>Once Daily</td>
<td>750 mg</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>Tablets: 400 mg</td>
<td>7.5 – 10</td>
<td>Once Daily</td>
<td>400 mg</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>Tablets: 400 mg</td>
<td>7.5 – 10</td>
<td>Once Daily</td>
<td>400 mg</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>Tablets: 250 mg</td>
<td>15 – 20</td>
<td>Twice daily initially but aim for once daily</td>
<td>1g</td>
</tr>
<tr>
<td>Prothionamide</td>
<td>Tablets: 250 mg</td>
<td>15 – 20</td>
<td>Twice daily</td>
<td>1g</td>
</tr>
<tr>
<td>Terizidone</td>
<td>Capsules: 250 mg</td>
<td>10 – 20</td>
<td>Once daily</td>
<td>1g</td>
</tr>
<tr>
<td>PAS</td>
<td>PASER® 4 g packets</td>
<td>150</td>
<td>Twice daily</td>
<td>12 g</td>
</tr>
</tbody>
</table>

The prognosis of treatment in a diabetic with uncontrolled glucose levels is poor. The responsibility therefore falls on the physician and the patient to ensure proper diabetic care. In addition, diabetes may potentiate adverse effects, especially renal failure and peripheral neuropathy. Oral hypoglycemic drugs can be safely given with second line drugs but ethionamide and prothionamide may make it more difficult to control insulin dependent diabetes.

In the management of the diabetic patient with DR-TB, the following is recommended:

- **Medical follow-up:** Diabetes must be managed closely throughout treatment.
- **Patient education:** The basics on the diet, treatment compliance, weight control, exercise, and foot care should be communicated to the patients, together with the symptoms of hypo and hyper-glycemia and what to do when they occur.
- **Glucose monitoring**
  - Goals for capillary blood testing: 80-120 mg/dl before meals; 100-140 mg/dl before bedtime; the range should be higher if patient has a history of hypoglycemia;
  - Patients may need a period of intensive glucose monitoring until these targets are attained;
  - Once a patient is on a stable dose of insulin, blood sugar may be monitored four times weekly to ensure that targets are being maintained;
  - If a patient is on oral anti-diabetic agents, sugar may be monitored twice weekly.
- **Regular monitoring**
  - Creatinine and potassium should be monitored weekly for the first month and then at least monthly thereafter;
  - If the creatinine rises, creatinine clearance should be checked and the second line drugs should be adjusted accordingly. Once the dose is adjusted, the creatinine should be checked weekly until it has stabilized;
  - HbA1C every three months if treatment changes or patient is not meeting target; every six months if stable. Target: HbA1C<7;
  - Retinal examination annually.
- **Screening and treatment for hypertension**
  - Blood pressure measurements should be conducted monthly
  - Hypertensive patients with diabetes should be started on an ACE-inhibitor.
- **Prevention of diabetic nephropathy**
Renal insufficiency due to longstanding tuberculosis infection itself or previous use of aminoglycosides is not uncommon. Great care should be taken in the administration of second-line drugs in the patient with renal insufficiency, and the dose and/or the interval between dosing should be adjusted based on creatinine clearance.

Table XV: Adjustment of drugs in renal insufficiency

<table>
<thead>
<tr>
<th>Drug</th>
<th>Change in frequency</th>
<th>Recommended dose† and frequency for patients with creatinine clearance &lt; 30 ml/min or for patients receiving haemodialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>No change</td>
<td>300 mg once daily, or 900 mg three times per week</td>
</tr>
<tr>
<td>Rifampin</td>
<td>No change</td>
<td>600 mg once daily, or 600 mg three times per week</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Yes</td>
<td>25–35 mg/kg/dose three times per week (not daily)</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Yes</td>
<td>15–25 mg/kg/dose three times per week (not daily)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Yes</td>
<td>1000-1500 mg per dose three times per week (not daily)</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>Yes</td>
<td>600-800 mg per dose three times per week (not daily)</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>Yes</td>
<td>750–1000 mg per dose three times per week (not daily)</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>No change</td>
<td>400 mg once daily</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>Yes</td>
<td>400 mg per dose three times per week (not daily)</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>Yes</td>
<td>250 mg once daily, or 500 mg/dose three times per week (not daily)</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>No change</td>
<td>250–500 mg/dose daily</td>
</tr>
<tr>
<td>p-Aminosalicylic acid**</td>
<td>No change</td>
<td>4 g/dose, twice daily</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Yes</td>
<td>12–15 mg/kg/dose two or three times per week (not daily)</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>Yes</td>
<td>12–15 mg/kg/dose two or three times per week (not daily)</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>Yes</td>
<td>12–15 mg/kg/dose two or three times per week (not daily)</td>
</tr>
<tr>
<td>Amikacin</td>
<td>Yes</td>
<td>12–15 mg/kg/dose two or three times per week (not daily)</td>
</tr>
</tbody>
</table>

(Adapted from: Partners in Health. The PIH Guide to Medical Management of Multidrug-Resistant Tuberculosis.)
concentrations and adjust accordingly).

** Sodium salt formulations of PAS may result in an excessive sodium load; these should be avoided. Formulations of PAS that do not use the sodium salt (e.g., Jacobus PASER®) can be used without the hazard of sodium retention.

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

The formula to calculate the creatinine clearance (CrCI) or the glomerular filtration rate (GFR) is as follows:

Estimated Glomerular Filtration Rate (GFR):

Men: \[ \frac{(140 - \text{age}) \times (\text{ideal body weight in kg})}{72 \times (\text{serum creatinine, mg/dl})} \]

Women: \[ \frac{(140 - \text{age}) \times (\text{ideal body weight in kg})}{72 \times (\text{serum creatinine, mg/dl})} \times 0.85 \]

Normal values for creatinine clearance are:

Men: 97 to 137 ml/min
Women: 88 to 128 ml/min

An example of adjusting the dose of a medication in renal insufficiency:
A male patient has a serum creatinine = 2.4, age = 59, ideal body weight = 53 kg. What should the dose of Kanamycin be?

Step 1: Calculate the Glomerular Filtration Rate (GFR)

\[
\begin{align*}
\text{GFR} &= \frac{(140 - \text{age}) \times (\text{ideal body weight in kg})}{72 \times (\text{serum creatinine, mg/dl})} \\
&= \frac{(140 - 59) \times (53)}{72 \times 2.4} \\
&= 24.8 \text{ ml/min}
\end{align*}
\]

Step 2: Refer to Table 3 above and make the appropriate dose adjustment.
In this case the 24.8 ml/min falls below 30 ml/min. The dose of kanamycin given in Table 3 is 12-15 mg/kg. The dose to prescribe would be between 12 \times 53 = 636 mg and 15 \times 53 = 795 mg. It is reasonable to choose a dose between these two that is relatively easy to draw up from the vial. In this case, 750 mg three times a week is the logical choice.

Note:
7) Liver disorders

Pyrazinamide is the most hepatotoxic of the first-line anti-tuberculosis drugs. Of the second-line drugs, ethionamide, prothionamide and PAS can also be hepatotoxic, although less so than any of the first-line drugs. Hepatitis is quite rare with the fluoroquinolones, but can occur. In general, patients with chronic liver disease should not receive pyrazinamide. All second line drugs can be used, however close monitoring of liver enzymes is advised, and if significant worsening of liver inflammation is seen, responsible drugs may need to be stopped.

Patients who are hepatitis virus carriers and those with a past history of acute hepatitis or excessive alcohol consumption can be started on second line drugs provided there is no clinical evidence of chronic liver disease; however, hepatotoxic reactions may be more common in these patients and should be anticipated.

Uncommonly, a patient may have DR-TB and unrelated concurrent acute hepatitis. Clinical judgment is necessary in this instance - in some cases it will be possible to defer treatment until the acute hepatitis has resolved; in other cases, it will be necessary to start the treatment during the acute hepatitis phase in which case a combination of four non-hepatotoxic drugs will be the safest option.

8) Seizure disorders

Some patients requiring DR-TB treatment will have a past or present medical history of seizures. The first step is to determine whether the seizures are under control and if the patient is on any treatment. If the seizures are not under control, initiation or adjustment of treatment that the patient is taking will be needed prior to the start of DR-TB treatment. In addition, if other underlying conditions or causes of the seizures exist, they should be corrected.

Cycloserine and terizidone should be avoided in patients with uncontrolled seizures. However, in cases where there is no option, cycloserine/terizidone may be given and the treatment for seizures adjusted as needed to control them. The risk and benefits of using cycloserine/terizidone should be considered and discussed with the patient. When seizures
should be strongly encouraged, treatment is not contraindicated in people who abuse alcohol or drugs. If the treatment is repeatedly interrupted due to the patient’s addiction, then it should be suspended until successful rehabilitation or other measures to ensure adherence are established.

Cycloserine and terizidone will have a higher incidence of adverse effects in the alcohol or drug-dependent patients, including seizures. However, if any of these drugs is considered important to the regimen, it should be used and the patient closely monitored for side effects, and adequately treated when necessary.

10) **Psychiatric disorders**

It is prudent to have a psychiatrist to conduct a psychiatric evaluation on all patients before the start of MDR-TB treatment, or at least all patients with a history of psychiatric illness. The initial evaluation will document any pre-existing psychiatric condition and establish a baseline for comparison if new psychiatric symptoms develop while the patient is on treatment. Any identified psychiatric illness at the start or during treatment should be managed appropriately. There is a high baseline incidence of depression and anxiety in patients with DR-TB, often related to the chronicity of the disease, confinement in hospital and other socioeconomic stressors. If a psychiatrist is not available, the treating physician should document any psychiatric conditions the patient may have at the initial evaluation.

Treatment of the psychiatric condition with the appropriate drugs, individual counselling, and/or group therapy may be necessary to manage the patients. Group therapy has been very successful in providing a supportive environment for DR-TB patients and may be helpful for patients with or without psychiatric conditions. The use of cycloserine or terizidone is not absolutely contraindicated for the psychiatric patient. Adverse effects from these drugs may be more prevalent in the psychiatric patient, but the benefits often outweigh the potential higher risk of adverse effects. Close monitoring is recommended if cycloserine or terizidone is used in patients with psychiatric disorders.

The hospital should have an organized system for management of psychiatric emergencies which include psychosis, suicidal ideation, and any situation involving the patient being a danger to him/ herself or others. Referral mechanisms to deal with psychiatric emergencies (often to psychiatric hospitals with isolation facilities for infectious diseases) should be available twenty-four hours a day.
13. DRUG RESISTANT TB AND HIV

13.1 Introduction

HIV co-infection is a significant challenge for the prevention, diagnosis, and treatment of MDR and XDR-TB. Provider initiated HIV counselling and testing should be routinely offered to all TB patients.

HIV is a powerful risk factor for development of all forms of TB including DR-TB. DR-TB is often associated with higher mortality rates in HIV infected compared with the non-infected.

Diagnosis of DR-TB in HIV positive persons is difficult and all high risk HIV patients with TB should be screened for drug-resistance with DST.

Use of ART in addition to treatment of DR-TB has been reported to improve outcomes of DR-TB in HIV-infected.

The National guidelines on the use of antiretroviral therapy need to be considered in conjunction with the content of this chapter.

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

As with drug sensitive TB, the clinical presentation is influenced by the degree of underlying immunodeficiency. In the earlier stages of HIV infection, the pathology of drug-resistant TB is similar to that seen in HIV negative people with smear positive pulmonary TB being the most commonly seen. As immunodeficiency progresses, extra-pulmonary TB disease becomes more common. Clinical presentation may furthermore be masked by the existence of other opportunistic infections.

The diagnosis of drug-resistant TB in HIV-positive persons is more difficult and may be confused with other pulmonary or systemic infections. Increasingly, the clinical presentation in advanced HIV is extra-pulmonary. This can result in misdiagnosis or delayed diagnosis of DR-TB, which may lead to advanced or complicated drug resistant TB disease and death.

Protocols for diagnosis of drug resistant TB in HIV follow the same principles as for HIV.
13.3 Management of co-infected patients

DR-TB treatment is the same for HIV-positive and HIV-negative patients. However, MDR-TB and XDR-TB treatment is much more difficult and adverse events are much more common in HIV-positive patients. Mortality is high during treatment particularly in the advanced stages of immunodeficiency mainly due to advanced MDR- or XDR-TB disease and other HIV-related opportunistic infections. Patients already on antiretroviral treatment when MDR- or XDR-TB is diagnosed should immediately be started on appropriate treatment.

The current scope of knowledge has not yet provided enough evidence to respond to all concerns related to treatment of patients co-infected with MDR and XDR-TB and HIV. The main questions involve:

− Timing of initiation of antiretroviral treatment (ART) in MDR and XDR-TB patients, the appropriate time to initiate ART in MDR-TB patients is not known and depends on a careful calculation of risks and benefits.
− Drug-drug interactions;
− Overlapping toxicities;
− Adherence to complicated treatment regimens;
− Clinical management of co-infected patients.

The primary goal of antiretroviral therapy is to decrease HIV-related morbidity and mortality:

− The patient should experience fewer HIV-related illnesses;
− The patient’s CD4 count should rise and remain above the baseline count;
− The patient’s viral load should become undetectable (< 50 copies/ml) and remain undetectable on ART.

13.3.1 Timing of initiation of ART in adult DR-TB patients

As per the National ART Guidelines 2010, all HIV co-infected TB patients should be initiated on ART when CD4 cell count is $\leq 350$ cells/ mm$^3$.

All HIV positive, MDR and XDR-TB patients are eligible to start ART irrespective of CD4 cell count. Moreover, these patients must be fast-tracked (ART initiation within 2 weeks of being eligible) for the initiation of ART.
Issues to consider when initiating ART

1. Overlapping adverse effects from ART and second line drugs;
2. Complex drug-drug interactions;
3. Occurrence of immune reconstitution syndrome;
4. Treatment non compliance associated with high pill burden

The simultaneous initiation of ART and second line drugs is associated with adverse effects that may lead to the interruption of both DR-TB and/ or ART. Deferred initiation of ART may help the clinician to identify the potential cause of drug adverse events without neglecting the possibility of concurrent illness.

Two scenarios exist with regard to DR-TB and ART, depending on which condition manifests first:

1. Patient develops DR-TB while on ART

   - Start DR-TB treatment immediately.
   - Antiretroviral therapy should be continued throughout DR-TB treatment.
   - Monitor patient for adverse events, drug-drug interactions and combined toxicities

Development of DR-TB is not indicative of ART failure. It is not a reason to stop either DR-TB or ART or to change any of the regimens.
2. **Patient presents with DR-TB before commencing ART**
   - All patients must be started on ART irrespective of CD4 cell count.
   Moreover the initiation of ART must be fast tracked as soon the DR-TB treatment is tolerated.

Figure IV: Flow chart for ART in adult patients with DR-TB.

**HIV positive patient with diagnosed with DR-TB**

- **Patient on ART at time of diagnosis**
  - Start DR-TB treatment immediately
  - Continue ART throughout DR-TB treatment
  **First-line therapy:**
   1. Tenofovir 300 mg daily
   2. Lamivudine 150mg every 12 hours
   3. Efavirenz 600mg at night
   or
   Nevirapine 200mg every 12 hours

- **Patient not on ART at time of diagnosis**
  - Start ART irrespective of CD4 cell count once DR-TB treatment is tolerated preferably within first month of treatment.
  **First-line therapy:**
   1. Tenofovir 300 mg daily
   and
   2. Lamivudine 150mg every 12 hours
   and
   3. Efavirenz 600mg at night
   or
   Nevirapine 200 mg every 12 hours

**Remember:**
Patients on MDR-TB or XDR-TB treatment and ART are taking a large number of tablets. Do pre-emptive counselling to improve adherence.
In children abacavir is given instead of tenofovir and lopinavir/ritonavir should be given to children below 3 years of age instead of efavirenz. Dosages are available in the national HIV guidelines.

13.4 Prophylaxis for opportunistic infections

Cotrimoxazole is highly effective in preventing:
- *Pneumocystis jirovecii* pneumonia
- Toxoplasmosis
- Pneumococcus
- Salmonella
- Nocardia
- Malaria

The provision of cotrimoxazole to HIV-infected individuals has resulted in a decrease in hospital admissions as well as mortality in TB patients. Current WHO policies require that all HIV-infected symptomatic (stage 2, 3 & 4) adults and children be given cotrimoxazole prophylaxis as part of a minimum package of care. HIV-infected DR-TB patients are usually in WHO stage 3 or 4 and therefore qualify for cotrimoxazole prophylaxis. Ideally cotrimoxazole should be initiated prior to ART on first adherence visit.

Given the higher likelihood of sulfa-related adverse reactions in HIV-positive patients (6-8 times greater than in the general population) sulfa-based prophylaxis should be started at least two weeks apart from MDR or XDR-TB treatment and/or ART. This will allow differentiation between side effects from second line drugs and cotrimoxazole.

**Recommended dosages of cotrimoxazole**

In adults:
Cotrimoxazole 960 mg (two tablets single strength) daily

or

Trimethoprim 5mg/kg plus sulphamethoxazole 25mg/kg daily.
Patients on cotrimoxazole prophylaxis as well as antiretroviral drugs should continue the cotrimoxazole until their CD4 count increases to 350 or above and remains at this level for 3-6 months and then stop. Patients with known hypersensitivity to cotrimoxazole could be given dapsone instead.

### 13.5 Immune reconstitution syndrome

The immune reconstitution syndrome occurs when the improving immune function unmasks a previously occult opportunistic infection (an infection that was present in the patient’s body, but was not clinically evident). Reactions usually occur within a median of 15 days after initiation of ART. They do not appear to be related to any particular regimen but are usually found in patients with advanced HIV. TB is a common immune reconstitution illness and MDR-TB or XDR-TB patients should be pre-emptively counselled about immune reconstitution syndrome.

Patients with advanced HIV, particularly those with a CD4 count < 50 cells/mm³ may become ill with an immune reconstitution illness during the first few weeks of ART, with symptoms of persistent fever, sweats, loss of weight, cough, shortness of breath, worsening pulmonary infiltrates, and decreasing visual acuity (to name but a few).

An immune reconstitution illness is not indicative of drug failure or drug side effects. It is not a reason to stop either DR-TB treatment or antiretroviral therapy, or to change any of the regimens.

Opportunistic infections may present in atypical ways during the phase of immune reconstitution. Management includes high doses of corticosteroids to contain symptoms: prednisolone or methylprednisolone 1 mg/kg for one to two weeks gradually reduced thereafter. It is not unusual to prolong the use of steroids or to restart if symptoms re-occur. Clinicians need to be cautious and attentive to the development of complications due to prolonged use of steroids (e.g. Cytomegalovirus infections). Non-steroidal agents tend to not be helpful.
13.6 Patient monitoring

The co-infected DR-TB patient poses a great challenge and requires intensive monitoring of drug interactions and additive toxicities. The complexity of ART and second line drugs each with its own toxicity profiles (which may be potentiated during dual therapy) demands even more rigorous monitoring in co-infected patients. In addition, other opportunistic infections have to be prevented, monitored and treated.

Patients with DR-TB and HIV may require special socio-economic support. The treatment regimens together are particularly hard to take, the stigma of both diseases can result in serious discrimination, and the risk of mortality is very high.

The monitoring with chest x-rays, smear microscopy and cultures of patients is the same as for HIV-negative DR-TB patients. In patients receiving ART, CD4 counts should be measured at the time of diagnosis and every six months thereafter. A significant decrease in CD4 count is a decrease from baseline of 30% or more.

Viral load should be measured at baseline and at six-monthly intervals, provided that patients have reached virological goal (defined as a one-log/10-fold decrease). If this has not been achieved, an appropriate evaluation of virological failure should be done (assessment of adherence, potency, absorption, and viral resistance). A significant change in plasma viral load is a three-fold or 0.5 log increase or decrease.

ART also requires additional monitoring of tests not usually done in DR-TB treatment. For example, hematocrit and white blood cell count testing in patients on zidovudine, periodic monitoring of liver serum enzymes in patients on nevirapine, and testing of pancreatic enzymes in patients with abdominal pain taking stavudine or didanosine, are required.

13.7 Management of drug adverse effects

In general, HIV positive 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. Many of the medications used to treat DR-TB and HIV have overlapping, or in some cases additive, toxicities. Identifying the source of adverse drug reactions in patients taking treatment for both DR-TB and HIV is difficult. When possible, avoid the use of agents with shared adverse effect profile. However, benefit of a drug may outweigh the risk of adverse effect. If the adverse effect is caused by a shared toxic effect, and no alternative treatment is available, the risk must be assessed and alternatives considered.
- Gastro-intestinal intolerance
- Hepatotoxicity
- Skin rash
- Renal toxicity
- Electrolyte disturbances
- Hypothyroidism etc.

13.7.1 **Hepatotoxicity**
This is a common and potentially serious adverse event. It is defined as:
- An AST and ALT serum level of more than three times the upper limit with accompanying symptoms, or
- An AST and ALT serum level of greater than five times the upper limit without accompanying symptoms.

If hepatitis develops, all potentially hepatotoxic drugs must be stopped, including pyrazinamide, antiretrovirals and cotrimoxazole. Serological tests for hepatitis A, B and C should be performed and the patient should be asked about exposure to alcohol and other hepatotoxins. While the hepatitis is resolving it would be advisable to provide non-hepatotoxic drugs to continue the MDR-TB treatment, such as ethambutol and streptomycin. Treatment may be restarted when the AST, ALT and bilirubin levels have dropped below two times the upper limit of normal levels with significant improvement of symptoms.

13.7.2 Peripheral neuropathy
Neuropathy may be caused by nucleoside analogues (ddI, d4T) and additive toxicity of ethionamide, cycloserine, terizidone and pyrazinamide when given with stavudine and/or didanosine has also been demonstrated. Pyridoxine 150 mg daily should be used in all HIV-infected patients receiving cycloserine/terizidone.

14 **MONITORING AND EVALUATION OF PATIENTS WITH DR-TB**

14.1 **Introduction**

MDR- or XDR-TB disease can be an emotionally devastating experience for patients and their families, while stigma attached to the disease may interfere with adherence to treatment. In addition, the long duration of DR-TB treatment, combined with drug adverse effects, may
sputum conversion may be the first sign of treatment failure. Laboratory evidence of improvement is therefore required, together with regular clinical assessment of the patient.

14.2 Monitoring progress of treatment

Patients on MDR-TB or XDR-TB treatment need to be monitored closely for side-effects and signs of treatment failure. There are essentially three components to treatment monitoring: clinical, laboratory and other investigations.

14.2.1 Clinical evaluation
The patient must be evaluated by the doctor weekly during the injectable phase and monthly during the continuation phase. Different scenarios need to be considered here. During admission, regular medical ward rounds must be conducted. This may be every second day, twice a week or weekly for stable patients, nursing care must be provided daily and the patient record card updated. Patients who are very sick or critical need to be seen on a daily basis by the doctor.
A focused assessment of the patient should be conducted looking at any respiratory distress, gastro-intestinal disturbances, drug intolerance or adverse effects, progression of hearing loss or tinnitus, and neuro-psychiatric effects. A physical exam should be conducted and routine laboratory tests or any other tests that may be indicated at the time.

Weight, height and body mass index (BMI) are also important parameters to monitor. Weight needs to be measured every week during injectable phase, then monthly during continuation phase. Height is to be measured at baseline while BMI need to be looked weekly during admission especially for patients with BMI<18.5.

14.2.2 Bacteriological investigations
Culture and smear conversion are the most important indicators of patient improvement. Smear microscopy and bacteriological culture are therefore used to monitor patient progress throughout treatment and should be performed monthly. Microscopy is useful as a robust indicator of patient progress; however, it cannot distinguish viable organisms from those that are nonviable. Culture is therefore necessary to monitor treatment progress. One sputum specimen should be sent monthly to the NHLS for smear microscopy and culture (not DST).

Definition of conversion
Two types of conversion are considered for DR-TB patients i.e. smear conversion and culture conversion, both require that the smear or culture be positive at the beginning of treatment.

- **Smear conversion** is defined as two consecutive negative smears, taken at least 30 days apart. Time to conversion is calculated as the interval between the date of...
treatment initiation and the date of the first of the two negative consecutive smears (the date of sputum specimen collection should be used).

- **Culture conversion** is defined as two consecutive negative cultures, taken at least 30 days apart. Time to conversion is calculated as the interval between the date of treatment initiation and the date of the first of the two negative consecutive cultures (the date sputum specimen collection should be used).

Patients that are culture and smear negative at the start of treatment for whatever reason do not get counted in the cohort reporting of culture or smear conversion.

Sputum conversion is slower when using second-line anti-tuberculosis drugs. Culture results showing a few colonies should not be automatically regarded as negative in DR-TB patients, nor should a single positive culture preceded by multiple negative cultures be regarded as treatment failure.

Culture conversion is not equivalent to cure. A significant proportion of patients may initially convert and later revert to being culture positive, depending on the initial burden of disease and the level of resistance. For these reasons, cultures should be done regularly throughout treatment.

14.2.3 Other laboratory tests
These are liver function tests, serum creatinine, serum potassium, thyroid stimulating hormone. These tests are used mainly to monitor the development and the management of drug-adverse effects.

All patients with DR-TB must be offered HIV tests if they do not know their HIV status.

A pregnancy test in females patients of child bearing age is also important on admission and when necessary. Patients spend long periods on treatment after admission, hence it is important to consider pregnancy tests in females who are not on contraception.

14.2.4 Chest x-rays
Chest x-rays should be taken whenever the patient’s clinical condition worsens, or whenever surgical intervention is being considered. The chest x-ray results may remain unchanged or show only slight improvement, this does not mean the patient is not improving on treatment therefore; no changes in treatment should be made on the basis of a chest x-ray alone.
• every six months
• and at treatment completion

The chest x-ray is divided into six zones by the mediastinum and horizontal lines through the 2\textsuperscript{nd} and 4\textsuperscript{th} anterior rib shadows. Each zone is described according to disease and cavitation, as follows:

Figure 4: Scoring system for the evaluation of chest x-rays

<table>
<thead>
<tr>
<th>Disease (a)</th>
<th>Score</th>
<th>Cavitation (b)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>No disease</td>
<td>Leave blank</td>
<td>No cavitation</td>
<td>Leave blank</td>
</tr>
<tr>
<td>&lt; 50% of area affected</td>
<td>&lt;</td>
<td>Single cavity, &lt;2cm diameter</td>
<td>1a</td>
</tr>
<tr>
<td>≥ 50% of area affected</td>
<td>&gt;</td>
<td>Single cavity, 2-4cm diameter</td>
<td>1b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Single cavity, &gt;4cm diameter</td>
<td>1c</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multiple cavities, largest &lt;2cm diameter</td>
<td>2a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multiple cavities, largest 2-4cm diameter</td>
<td>2b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multiple cavities, largest &gt;4cm</td>
<td>2c</td>
</tr>
</tbody>
</table>

A composite score is calculated by adding the disease and cavitation scores for each zone, as follows:
The following table presents a summary of parameters to be considered for DR-TB patient monitoring.

Table XVI: Monitoring and evaluation of patients during hospitalization and during ambulatory care

<table>
<thead>
<tr>
<th>Monitoring and Evaluation</th>
<th>Recommended frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluation by doctor</td>
<td>At baseline Twice – three times per week for stable patients and daily for very sick</td>
</tr>
<tr>
<td></td>
<td>patients until conversion Every month or bi-monthly for outpatients on continuation</td>
</tr>
<tr>
<td></td>
<td>phase</td>
</tr>
<tr>
<td>Evaluation by nurse</td>
<td>Daily</td>
</tr>
<tr>
<td>Sputum smear and cultures</td>
<td>At baseline Monthly</td>
</tr>
<tr>
<td>Weight</td>
<td>At baseline and weekly during intensive phase Monthly during continuation phase</td>
</tr>
<tr>
<td>Height</td>
<td>At baseline in adults and children</td>
</tr>
<tr>
<td>Body mass index</td>
<td>At baseline and then monthly</td>
</tr>
<tr>
<td>Drug Susceptibility Testing (DST)</td>
<td>At baseline For patients who remain culture-positive at six months</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>At baseline Every six months (For children every 2 to 3 months in intensive phase)</td>
</tr>
<tr>
<td></td>
<td>At treatment completion When requested by clinician</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>At baseline, then monthly during injectable phase</td>
</tr>
<tr>
<td>Serum potassium</td>
<td>Monthly during injectable phase</td>
</tr>
<tr>
<td>Thyroid stimulating hormone</td>
<td>Every six months if receiving ethionamide and/or PAS Monitor monthly for signs of</td>
</tr>
<tr>
<td></td>
<td>hypothyroidism In children every 2 months</td>
</tr>
<tr>
<td>Liver serum enzymes</td>
<td>Periodic monitoring (every 1-3 months) in patients receiving pyrazinamide for extended</td>
</tr>
<tr>
<td></td>
<td>periods or for patients at risk of hepatitis</td>
</tr>
</tbody>
</table>
14.3 Patient education and counseling

Education, counselling and emotional support are particularly important, much as in any other chronic life-threatening illness. Ongoing intensive counselling will also help to ensure good adherence to the treatment regimen and increase the likelihood of a successful outcome.

Patients and their families should also be educated on an ongoing basis about MDR or XDR-TB, its spread, prevention, treatment, potential drug adverse events, the need for treatment compliance and early testing for MDR/ XDR-TB for other family members should they develop symptoms. Education can be provided by physicians, nurses, community health workers and other health care providers at every encounter with the patient. Information and educational materials should be appropriate to the literacy levels of the population and should also be culturally sensitive.

14.4 Treatment compliance

Patients with DR-TB may be more likely to have had problems with treatment non-compliance in the past. In addition, treatment compliance is made more difficult by prolonged multidrug treatment regimens with drugs that have serious adverse events. Monitoring of patient compliance and support measures to facilitate adherence are therefore particularly important.

MDR-TB treatment and, to a lesser extent XDR-TB treatment, can be successful with high overall rates of treatment compliance when adequate support measures are implemented. Patient support groups and family support for the patients may help improve this.
burdens to patients and their families. Long distances and difficulties accessing services may all contribute to treatment interruption.

The first choice for providing community care to DR-TB patients is to use health care workers where possible. When human or financial resources do not permit the use of health care workers, trained community members can serve as effective treatment supporters. However, community members need intensive training, ongoing supervision and support by health professionals.

Irregular or noncompliant patients continue to pose a challenge to nurses and community health workers particularly following discharge from hospital, therefore any non compliance should be addressed as soon as it is detected. The patient must be counselled again and any issues that may be contributing to the non compliance addressed. If the current arrangement for DOT does not suit the patient the patient anymore, a more suitable arrangement must be agreed upon. The patient must also be assessed for:

- Any psychiatric symptoms, and referred to a psychologist/ psychiatrist for further assessment if necessary
- Alcohol and drug abuse and referred for rehabilitation programmes

Socio-economic factors that could contribute to non compliance such as lack of money for transport, lack of food which may exacerbate some of the gastro-intestinal effects on taking medication must also be investigated. Where these apply the social worker must be contacted.

When all measures have been taken and the patient remains erratic in taking medication a decision will have to be taken to discontinue treatment.

14.5 Maintaining confidentiality

The health care worker and community health worker must maintain strict confidentiality at all times to ensure the patient – provider relationship, as treatment is for long period. In some cases this may entail working out a system where the patient can receive medication without the knowledge of others.

14.6 Social support

The provision of social support to patients may improve chances of adhering with therapy. The social worker should work with the patient and their families to ensure that the patient can access the necessary support during their treatment.
tends to be poor in this group of patients, organisations such as SANCA can assist with the provision of these programmes. Patients who qualify for social grants or disability grants should be assisted to access these. Those who are breadwinners, lost income as a result of admission in hospital and their families in distress should be assisted to access other benefits – social relief of distress grant, an extension beyond the stipulated six months may need consideration for those patient who need longer hospitalisation i.e. non-converters/ treatment failures.

The social worker should also negotiate with the employers to encourage them to offer the patient “paid” sick leave as far as reasonably possible or lodge an application for access to unemployment insurance fund on behalf of the patient whilst hospitalised. An application may be lodged on behalf of the patient who is a breadwinner to access free municipal services through the use of the indigent policy. This is an avenue designed for non-affording people to benefit on basic services like water, electricity and waste removal amongst others. In terms of chapter nine of the Municipal Systems Act, a municipality in relation to the levying of rates and other taxes and the charging of fees for municipal services, it must within make provision for indigent debtors that is consistent with its rates, tariff policies, financial and administrative capacity.

Some of the patients may develop hearing loss due to prolonged use of aminoglycoside or capreomycin resulting in permanent disability and may require disability grants; applications should therefore be processed as soon as confirmation of deafness is confirmed.

**14.7 Management of treatment interruption and default**

When a patient refuses to continue treatment every effort should be made to convince the patient to continue treatment. This should include explaining the implications of discontinuing the treatment, importance of completing the treatment and addressing the reasons for wanting to stop the treatment and other patient concerns. In most cases this is due to the side effects and addressing these more aggressively by providing ancillary treatment and rescheduling the doses might help. An evaluation of the patient should be conducted and this must include an assessment of the patient for any psychiatric illness and/or substance abuse and the patient must be referred accordingly when these exist. Where socio-economic factors are contributing to this, they should be addressed. When all these measures fail, and the patient insists on stopping treatment, the patient should sign a refusal of hospital treatment (RHT) form (Annexure III).
treatment is resumed promptly and effectively. The situation should be addressed in a sympathetic, friendly, and non-judgmental manner. Every effort should be made to address the patients concerns or reasons for interruption to prevent it from happening again.

In patients where treatment has to be restarted following defaulting or interruption, the following should be considered

- Commitment of patient to treatment completion
- Clinical condition of the patient
- Duration of treatment interruption or default

A full physical examination must be conducted and sputum specimen obtained for microscopy, culture and DST, a chest x-ray must be done and compared with previous ones for extent of disease. Counselling of the patient must be conducted and patient must sign the patient consent form before treatment initiation.

The treatment will depend on the stage at which the patient interrupted treatment and the clinical condition of the patient on return for treatment. Patients who have interrupted treatment for more than six months must be clinically evaluated for active disease and if found to have active disease must be started on a new treatment regimen based on their resistance pattern. If found not to have active TB disease, the decision on treatment must be made by the clinical review committee, if not started on treatment, the patient must be followed regularly for signs of relapse.

Figure V: Management of patients who default treatment
Patient on MDR-TB treatment for at least one month

Interruption of two or more months

Return smear positive

Patient was on treatment for less than 3 months
- Restart new treatment using their previous resistance profile.

Patient was on treatment for 3 - 6 months
- Conduct culture and DST
- Restart previous treatment regimen
- Adjust regimen when DST

Patient on treatment for more than 6 months
- Conduct culture and DST
- Start a completely new treatment regimen.

Return smear negative

Patient was on treatment for less than 3 months
- Restart new treatment using their previous resistance profile.

Patient was on treatment for 3 - 6 months
- Restart the patient with the injectable until two consecutive negative cultures
- Treatment should be given for a minimum of 24 months after initial conversion.

Patient on treatment for more than 6 months
- If the patient was off the injectable at the time of interruption and has no evidence of clinical deterioration,
  restart oral medication only (continuation phase)
14.8 End of intensive phase of treatment
The decision to stop the injectable drug should be made following the review of the clinical picture, smear and culture results, chest x-rays. The injectable drug can be stopped when:
- the patient has completed a minimum of six months of intensive phase treatment
- there are two consecutive negative culture results.
- there are at least four drugs to which the strain is still sensitive to that can be used
In patients with high grade resistance, extensive lung disease and in whom the regimen contains only four drugs including the injectable, the injectable may be used for a minimum of 12 months of culture conversion or throughout the treatment period.

14.9 If there is no improvement at 4 months of treatment
If a patient shows minimal or no improvement at the end of the injectable phase, the patient must be re-evaluated as follows:
- Evaluate treatment compliance
- Repeat chest x-ray
- Repeat sputum smear microscopy, culture
  - If culture is still positive repeat first and/or second line drug susceptibility testing – resistance amplification or treatment failure must be considered.

<table>
<thead>
<tr>
<th>Problem</th>
<th>Possible causes</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very slow clinical improvement</td>
<td>- Inadequate therapy, suboptimal dosing</td>
<td>- Treatment is too week-strengthen the treatment regimen, never add single drug</td>
</tr>
<tr>
<td></td>
<td>- No direct observation of treatment, or erratic pill taking by patient</td>
<td>- Replace injectables if patient is susceptibility to the others</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Add two new drugs that</td>
</tr>
<tr>
<td>Failure to respond to an effective treatment regimen</td>
<td>Problems with bacteriology tests (specimen collection error, laboratory error, or contamination)</td>
<td>the strain is sensitive to</td>
</tr>
<tr>
<td>-----------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>- Increase drug doses</td>
<td>- Consider surgery if disease is localized</td>
<td>- If culture conversion is achieved in the following 2-3 month continue the same treatment</td>
</tr>
<tr>
<td>- Smear positive due dead bacilli</td>
<td>- Repeat DST</td>
<td>- When new DST results is available adjust treatment regimen</td>
</tr>
</tbody>
</table>

### 14.10 Recurrence of positive cultures after culture conversion

Re-appearance of single or multiple positive smears or cultures should be considered as possible evidence of treatment failure. Patients must therefore, be re-evaluated to determine the course of action. The DST should be repeated to determine whether this is a different strain from the initial one or there has been amplification of resistance. During this period two or more drugs should be added to the regimen whilst awaiting DST results.

- **If the strain and resistance profile is similar to the initial one**
  This could be treatment failure in which case the treatment may need to be modified based of resistance profile or extended until the patient has had 18 consecutive months of negative cultures.

- **If the strain and resistance profile is completely different from the initial one**
  This could be due to contamination or a new infection, the latter being the least likely. The cultures should be repeated twice and documented as negative before concluding that this is due to a contaminant.

### 14.11 Treatment completion

The patient is considered to have completed treatment when they have completed at least 18 months of treatment after culture conversion and 24 months for those who had...
14.12 Follow-up after treatment completion.
Patients who complete a full course of MDR- or XDR-TB treatment should be followed up for at least two years after cure. The follow up visits must be conducted every six months and should mainly focus on:

- Assessing the patient for symptoms and signs of relapse.
- Conducting smear and culture every six months
- Radiographic evaluation as needed for development of respiratory symptoms.
- In patients who had residual lung disease, response to ancillary medicines must be monitored

Patients should be advised to report to the nearest clinic when they experience symptoms of TB at any stage. Patients failing to come for appointments must be traced; therefore knowledge about each patient during the follow-up phase must be obtained.
Figure VI: Post treatment follow-up flow diagram

Follow-Up Appointment (Every 6 Months)

Update Patient Weight
Update Patient Personal Details
Screen for TB Signs & Symptoms

Symptoms Absent

Symptoms present

No abnormalities detected on physical examination

Collect Sputum for Microscopy Culture and DST (H.R)

Microscopy/ culture positive
MDR confirmed

Microscopy/ culture positive:
MDR not confirmed

Appointment Dates (ddmmmyy)
14.13 MDR-TB and XDR-TB treatment failures
When no response to treatment is seen at six months of treatment, i.e. if bacteriological conversion is not seen or if clinically deterioration is evident. Re-assessment of the regimen and treatment plan, and formulation of a new plan of action is necessary. Avoid just adding one or two drugs to an apparently failing regimen, instead try to redesign the regimen with four effective drugs.

14.13.1 Patients with suspected MDR-TB treatment failure
Patients that show clinical, radiographical, or bacteriological evidence of persistent active disease or re-appearance of disease after six months of treatment should be evaluated for possible failure. In addition, patients who show rapid clinical deterioration before month 6 should also be evaluated.

The following steps should be taken for patients with suspected treatment failure:

- The treatment card should be reviewed to confirm that the patient has been adherent. The health-care worker should investigate whether the patient has taken all the medicines. A non-confrontational interview should be undertaken without the presence of the treatment supervisor.

- A non-confrontational interview with the treatment supervisor should be done without the presence of the patient. Questions should be asked to rule out possible manipulation of the treatment supervisor by the patient. If this is suspected, the treatment supervisor should be switched to another patient and the patient should be assigned a new treatment supervisor.

- The treatment regimen should be reviewed in relation to medical history, contacts, and all available treatment reports. If the regimen is deemed inadequate a new regimen should be designed.

- The bacteriological data should be reviewed. Often the smear and culture data provides the strongest evidence that a patient is not responding to therapy. A single positive culture in the presence of otherwise good clinical response is not necessarily indicative of treatment failure, especially if follow-up cultures are negative or the number of colonies is decreasing. Positive smears with corresponding negative cultures may reflect dead bacilli, thereby not indicating
14.13.2 Patients with apparent MDR-TB treatment failure

There is no single indicator that determines whether treatment is failing; however, a point is reached when it is clear that the patient is not going to improve. Signs indicating failure include:

- Persistent positive smears or cultures after 12 months of treatment;
- Extensive and bilateral lung disease with no option for surgery;
- High-grade resistance with no option to add additional agents;
- Deteriorating clinical condition that usually includes weight loss and respiratory insufficiency.

All of these signs need not necessarily be present to declare failure of the treatment regimen; nevertheless, cure is highly unlikely when they all exist. Of note is that the epidemiological definition of treatment failure for recording outcomes is often different from the process of suspending treatment in a patient when it is failing. The epidemiological definition is an outcome to account for the patient in treatment cohort analysis; the clinical decision to suspend treatment is one made after all other options have been explored, and cure of the patient has been determined to be highly unlikely.

14.14 Suspending treatment

MDR-TB or XDR-TB treatment can be terminated provided that appropriate counseling has been offered to the patient, and the patient has been heard before a final decision is made. Termination of treatment should be considered in the following circumstances:

- Where the patient no longer consents to receiving treatment
- Where there is a negligible chance of success, even where the patient wishes the treatment to continue. This would apply to those who are chronic defaulters in whom the treatment may not be effective, may result in amplification of resistance, treatment failure or patients with advanced terminal disease.

Suspending treatment should only be considered after all other options for treatment have been explored as this is a delicate situation and difficult for family members and caretakers, but it is especially difficult for the patient as treatment is often viewed as his/her only hope. Psychosocial support must be rendered to the patient and family.

If the DR-TB clinical management team is confident that all medications have been taken and that there is no possibility of adding other drugs or surgery, the treatment should be considered a failure and suspension of therapy recommended or provision of palliative care.
The patient’s quality of life - the medications used in DR-TB treatment have considerable side effects, and continuing them while the treatment is failing may cause additional suffering;

Continuing treatment that is failing can amplify resistance in the patient’s strain, resulting in resistance to all available anti-tuberculosis drugs. This ‘super-resistant strain’ can be transmitted to others.

A consultative process with the patient and family should be embarked upon and both parties should understand and accept the decision for suspension of treatment and alternative care offered. Depending on the patient’s condition this can be provided at home, hospital or hospice. Usually this process takes a number of visits and occurs over several weeks. Home visits during the process offer an excellent opportunity to talk with family members and the patient in a familiar environment. Treatment should not be suspended before the patient understands and accepts the reasons to do so, and agrees with the supportive care offered. The household should be assessed for risk of infection and family educated on measures to be taken to minimise risk of transmission of infection and patients should be advised to avoid contact with the general public and especially with susceptible persons, such as young children or HIV-infected individuals.

14.15 Palliative/ supportive care
A number of palliative measures can be implemented once DR-TB treatment is suspended. Supportive measures are summarized in the table below.
• **Pain control.** Paracetamol, or codeine with paracetamol gives relief to moderate pain. Codeine also helps control cough; other cough suppressants can be added. If possible, stronger analgesics, including morphine, should be used when indicated.

• **Relief of respiratory insufficiency.** Oxygen can be used to alleviate shortness of breath. Morphine also provides significant relief from respiratory insufficiency and should be offered if available.

• **Nutritional support.** Often small and frequent meals are best for a terminally ill person. Intake will decrease as the patient’s condition deteriorates. Treat nausea and vomiting or any other conditions that interfere with nutritional support.

• **Regular medical visits.** When treatment is stopped ongoing medical and psychological support to the patient must be provided, through regular visits by the medical team. Depression and anxiety, if present, should be addressed.

• **Continuation of ancillary medicines.** All necessary ancillary drugs should be continued as needed.

• **Hospitalisation, hospice care or nursing home care.** Looking after a terminally ill family member at home can be quite difficult. Hospice care should be offered to families who want to keep the patient at home. Inpatient care should be available for those patients where home care is not possible.

• **Preventive measures.** Oral care, prevention of bedsores, bathing and prevention of muscle contractures should be ensured for all patients as part of care. Regular scheduled movement of the bedridden patient is very important.

• **Infection control measures.** The patient who is taken off of DR-TB treatment because of failure often remains infectious for long periods of time. Infection control measures should be continued.
15 MDR-TB AND XDR-TB CONTACTS

15.1 Introduction

The opportunity to halt the spread of MDR- and XDR-TB in the communities and to diagnose and treat the disease early is often lost because close contacts of MDR- and XDR-TB patients are not investigated.

Close contacts are defined as persons living in the same household, or spend many hours a day together with the patient in the same indoor space. While data is limited, studies have shown that close contacts of MDR- and XDR-TB patients often have MDR- and XDR-TB disease respectively and should therefore be appropriately managed.

15.2 Evaluating the risk of MDR-TB in contacts

Factors that should be considered when investigating contacts of patients include:

- The likelihood of infection in contacts thought to be newly infected.
- The likelihood that the contact, if infected, will develop active disease.

“Contacts before the initiation of treatment” that have had exposure to a patient with active disease and are likely to be newly infected should be evaluated to assess the likelihood of the actual infection being an MDR- or XDR-TB strain of M. tuberculosis. Factors that should be considered include:

1) Infectiousness of the index patient
   MDR-TB or XDR-TB patients, who cough and are sputum smear-positive, are substantially more infectious than those who do not cough or are sputum smear-negative sputum.

2) Closeness and intensity of the exposure
   Persons who share air space with a patient with active disease for a prolonged time (e.g. a household member, hospital room mate) are at higher risk for infection than those who have a brief exposure. Exposure in a small, enclosed, poorly ventilated space is more likely to result in transmission of infection than exposure in a large, well-ventilated space. Exposure during cough-inducing procedures (e.g. sputum induction, bronchoscopy) may greatly increase the risk of transmission of infection.

3) Likelihood of exposure to persons with drug-susceptible TB.
The most potent factor that increases the probability of developing active disease following infection is impaired immunity, such as that seen in HIV infection. It should be remembered, however, that there are many other medical causes of impaired immunity:

- Malnutrition
- Congenital syndromes
- Certain haematological diseases
- Endocrine diseases
- Renal disease
- Diabetes mellitus
- Patients who are receiving immunosuppressive drugs (steroids, anti-cancer chemotherapy) or radiation therapy.

15.3 Management of asymptomatic contacts of MDR-TB/ XDR-TB patients

The use of second-line drugs for preventive therapy in MDR-TB or XDR-TB contacts is not recommended. To date, no controlled clinical trials have been conducted to assess the efficacy of treatment for latent MDR/ XDR-TB infection. Close monitoring of asymptomatic patients for development of symptoms is therefore more appropriate, particularly in high TB burden settings where many different tubercle strains (most often drug-susceptible) are circulating. Given the real possibility that contacts may have been infected by drug-susceptible strains, it is acceptable practice to manage asymptomatic contacts of DR-TB patients in the same way as contacts of drug-susceptible TB patients.

Asymptomatic contacts of smear-negative MDR/ XDR-TB patients should be managed according to the standard recommendations for contacts of drug-susceptible TB patients.

Asymptomatic contacts of smear-positive MDR/ XDR-TB cases should be rapidly identified and screened. Child contacts aged five years and younger should be considered for isoniazid preventive therapy irrespective of state of health and tuberculin response.

Asymptomatic child contacts aged five years and younger and HIV-infected children irrespective of age should be considered for isoniazid preventive therapy. All of these children should receive a clinical examination, Mantoux tuberculin skin test and a chest radiograph. If any evidence of disease, specimens (from any appropriate source) should be obtained for culture and DST before commencing anti-TB treatment according to the DST of the likely adult source case (that is MDR or XDR-TB treatment if adult source case has MDR or XDR-TB). If the children are well and chest radiograph is normal, all exposed and infected children (therefore irrespective of TST result) should receive preventive therapy (isoniazid at 10-15mg/kg/day for 6 months). HOWEVER, isoniazid preventive therapy often fails in these children, therefore regular two-monthly follow-up for symptoms (and CXR if indicated) should be done for first 6 months and 3-monthly thereafter for a minimum of two years.
In children older than five years and HIV negative adults, a strongly reactive tuberculin test indicates infection but not necessarily disease. The decision to start these persons on preventive (drug-susceptible) treatment depends on clinical history, examination and investigation.

Contacts of MDR/ XDR-TB patients should report the first symptoms of possible TB and a careful risk assessment should be made. Sputum should be sent for smear, culture and DST. A chest X-ray should also be done.

Contacts who are HIV-positive should be followed up every six months for a period of two years and encouraged to report symptoms of TB as soon as they become evident.

15.4 Management of symptomatic contacts of MDR/ XDR-TB patients

15.4.1 Adult contacts

All symptomatic close contacts of MDR/ XDR-TB cases should be examined immediately. If the contact appears to have active tuberculosis disease, culture and DST should be performed. While awaiting DST results, an empiric regimen based on either the resistance pattern of the index case or the most common resistance pattern in the community may be started.

If the work-up of a symptomatic adult is negative for TB, a trial of a broad-spectrum antibiotic that is not active against tuberculosis such as trimethoprim/sulfamethoxazole can be used. If the patient continues to be symptomatic, chest computed tomography, and/or directed bronchoscopy for smear and culture should be considered. If these diagnostic tools are not available or the results are not conclusive a diagnosis should be made with the clinical information at hand. If the initial work up is not suggestive of active tuberculosis, but the contact remains symptomatic, physical examinations should be repeated, together with monthly smears and cultures and repeat chest X-rays as needed.

15.4.2 Child contacts

MDR/ XDR-TB should be suspected in the following situations:

- Children who are contacts of a patient with confirmed MDR/ XDR-TB.
- Children who are contacts of patients who died of tuberculosis while on treatment and there are reasons to suspect it was MDR/ XDR-TB.
- Children with bacteriologically proven TB that are not responding to first-line drugs despite treatment compliance.
fevers. Bacteriologic confirmation may be difficult to obtain due to the inability of children to produce sputum, the paucibacillary nature of paediatric TB, and the increased likelihood of extra-pulmonary TB in children. While every effort should be made to establish a bacteriologic diagnosis by DST in a child with suspected MDR/ XDR-TB, it is not always possible.

Symptomatic child contacts of MDR/ XDR-TB patients should receive:
- A medical evaluation, including history and physical examination;
- Skin testing with tuberculin purified protein derivative (PPD);
- A chest X-ray (computerized tomography is helpful, especially in documenting hilar adenopathy);
- Culture and DST: If the child is very young or cannot expectorate sputum, sputum induction with chest percussion or gastric aspiration should be performed.

If the tuberculin skin test is >5 mm, the chest x-ray is negative and the gastric aspirate or sputum culture negative, the child can be treated with a broad spectrum antibiotic that is not active against tuberculosis, such as trimethoprim/ sulfamethoxazole. The child should be followed up closely, with monthly evaluations that include sputum or gastric aspirate culture and chest x-rays, until three months of negative cultures or resolution of the symptoms occurs. If the patient’s clinical condition is highly suggestive of tuberculosis or progressively worsens, empiric treatment designed according to the DST pattern of the strain from the index case based may be started.
16 RECORDING AND REPORTING

16.1 Introduction

The information system for DR-TB is an extension of the TB information system and defines the minimum tools necessary to monitor the management of DR-TB patients effectively. This information system allows the managers at the different levels to monitor programme performance by following the distribution and trends in MDR-TB notification and the treatment outcomes of patients started on Regimen IV. It does not include the detailed information that health care workers may need to manage individual patients, this is however is contained in the patient clinical records and other forms used in the hospitals and clinics.

Particular attention must be paid to full documentation of patient particulars and every effort must be made to ensure that all patients are seen by the management team regularly during the treatment period to ensure a comprehensive management plan. The patient, facility records must be completed daily and updated monthly on the paper based and electronic DR-TB register. Each hospital must have a person responsible for data management and compile case finding, case holding and treatment outcome reports.

16.2 Case definitions for MDR-TB and XDR-TB

Case definitions for MDR-TB and XDR-TB are used for the following reasons:

1. To allow proper patient registration and epidemiological notification;
2. To facilitate case allocation to appropriate treatment categories;
3. To facilitate case evaluation according to site, bacteriology and treatment history;
4. To evaluate programme performance through cohort analyses.

A case of MDR-TB is defined as a patient with bacteriologically proven TB whose disease is due to bacilli showing in vitro resistance to rifampicin and isoniazid, with or without resistance to other first-line anti-TB drugs.

MDR-TB diagnosed through DST is also called “Confirmed MDR-TB”.

Not confirmed MDR-TB cases are patients that have commenced MDR-TB treatment after a recommendation by a provincial DR-TB review committee on the basis of clinical data.
A case of XDR-TB is defined as a patient with bacteriologically proven TB whose disease is due to bacilli showing \textit{in vitro} MDR together with resistance to any fluoroquinolone plus resistance to one or more of the following injectable anti-TB drugs: kanamycin, amikacin, capreomycin.

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

<table>
<thead>
<tr>
<th>Category I: NEW</th>
<th>A patient who has received no anti-tuberculosis treatment for TB, MDR-TB or XDR-TB or received less than one month of anti-tuberculosis drugs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category II: Previously treated with first-line drugs only</td>
<td>Patient who has been treated for one month or more for TB with only first-line drugs</td>
</tr>
<tr>
<td>Category III: Previously treated with second-line drugs</td>
<td>Patient who has been treated for one month or more for TB or DR-TB with one or more second-line drugs, with or without first-line drugs.</td>
</tr>
</tbody>
</table>

Site of disease is classified according to pulmonary or extra-pulmonary involvement:
- Pulmonary MDR/ XDR-TB refer to disease involving the lung parenchyma only.
- Extra-pulmonary MDR/ XDR-TB refer to organs other than the lungs.
- A patient with both pulmonary and extra-pulmonary MDR/ XDR-TB constitutes a case of pulmonary MDR/ XDR-TB.
- The case definition for extra-pulmonary MDR/ XDR-TB in several sites depends on the site with the most severe form of disease.

Severity of disease is classified according to bacteriological status (smear or culture, positive or negative) at diagnosis.

16.3 Data collection tools and flow of information

The DR-TB data collection tools are similar to the TB data tools; others are the same such as suspect register and the referral forms. This section describes the core set of tools that are used for patient management and surveillance.
| DR-TB Patient Identity card (green and red) | Nurse/ doctor/ community health worker | Patient |
| DR-TB Patient Consent Form | TB sister and TB clinician | MDR-TB Hospital |
| DR-TB Treatment Follow-Up card (pink) | Nurse/ Doctor | Clinic or district hospital where patient is down referred for continuation of treatment |
| TB Sputum Request Form | Nurse/ doctor | Health facilities |
| TB Patient Referral Form | Nurse/ doctor | Health facilities |
| DR-TB Register (Paper based, Electronic) | Data capturer Information officer or Person responsible for data | MDRT-TB Hospital |

16.3.1 DR-TB treatment card

Health care workers administrating drugs daily to the patient must use this card to complete all the necessary demographic and management information about the patient. This card should be completed when a patient is started on DR-TB treatment and updated daily. It should remain in the MDR-TB hospital and a patient follow up card issued when the patient is discharged from the hospital, but must be updated monthly when the patient comes for follow up at the hospital.

The card contains the following sections:

- **Basic demographic information**: Name, gender, age, at least two physical addresses (patient, next of kin or friend, work) as well contact details.
- **DR-TB register number and date of registration**
- **Previous tuberculosis treatment episodes**: All TB episodes that the patient has had should be recorded here for both sensitive and resistant TB.
- **Previous medical history**: History of any other medical condition for which the patient might be taking medication or previously took medication for as well as substance abuse or the need to be referred for treatment or rehabilitation.
- **Site of disease:** The affected organ must be specified in cases with extra-pulmonary TB disease. The International Classification of Diseases (ICD 10) Codes should be used.
- **Drug resistance history:** The number refers to whether it was a new, primary or re-treatment (after default/ failure/ relapse)
- **Regimen and doses:** The initial treatment regimen is recorded on the treatment card, as well as any changes and adjustments in treatment.
- **Sputum results for microscopy and culture:** Monthly monitoring of smear and culture is required. The date and results of any DST conducted are recorded on the treatment card
- **Drug susceptibility results:** The date and results of any DST conducted are recorded on the treatment card
- **Record of daily administration of drugs:** Each end every dose of oral or injectable drugs administered to the patient is recorded in this section.
- **Adverse effects:** Any adverse effects that the patient experiences are graded and recorded. Any drug adjustments, adjuvant therapy or additional drugs for the management of side effects must be recorded.
- **Clinical progress notes:** Weight, laboratory test results and chest x-ray findings monitoring these items can be recorded on the treatment card in the monthly drug administration section in the last column.
- **Outcome of treatment:** At the end of treatment the outcome should be recorded on the treatment card according to the outcome definitions.

16.3.2 **DR-TB treatment follow-up card**
This card collects the same information as the treatment card but when the patient is discharged from the hospital or referred to another hospital, they take this card with them to the receiving facility. The health care worker at the clinic updates the card daily during follow up care and the information on this card is used to update the hospital treatment card on a monthly basis. The receiving clinic should notify the hospital when patient arrives at the clinic by completing the referral acknowledgement slip and sending it back to the hospital or by facsimile or telephonic confirmation where possible.

16.3.3 **DR-TB register**
This register records all patients who receive treatment for drug resistant TB including mono and poly resistance. It is used to monitor progress of patients whilst on treatment and allows for evaluation of the programme through quarterly, six-monthly and annual analysis of case finding, culture conversion and treatment outcomes.
16.3.4 Patient identity card

Once a patient is diagnosed with DR-TB, a patient identity card should be completed at the same time that the treatment card is completed, and should be kept by the patient. The card contains the following:

- Demographic details (name, age, sex, address)
- DR-TB register number
- Registration group
- Essential treatment information (start date, regimen, adverse effects, clinical progress)
- Health centre where the patient will receive treatment
- Dates of appointments
16.4 Treatment outcome definitions

The outcome definitions are based on bacteriological culture as a monitoring tool:

**Cure:** A patient who has completed treatment and has been consistently culture-negative for five consecutive months in the final twelve months of treatment. If 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 thirty days apart.

**Treatment completed:** A patient who has completed treatment but does not meet the definition for cure due to lack of bacteriologic results (i.e. less than five cultures were performed in the final twelve months of treatment).

**Death:** A patient who dies from any cause whilst on DR-TB treatment.

**Treatment default:** A patient who interrupts DR-TB treatment for two or more consecutive months for any reason.

**Treatment failure:** A patient who has had two or more of the five consecutive cultures taken in the final twelve months are positive, or if any one of the final three cultures are positive.

**Transfer out:** A patient who has been transferred to a reporting unit in another province and for whom the treatment outcome is unknown.

**Treatment stopped due to adverse drug reactions:** A patient who develops adverse drug reactions whilst on DR-TB and could not continue treatment in spite of the management of the adverse drug reactions as per protocols and the decision has been taken to stop treatment.

**Treatment stopped due to other reasons:** A patient who could not continue on DR-TB treatment for any other medical reason than adverse drug reactions, and a decision to stop treatment was made.

**Still on treatment:** A patient who for any reason is still on treatment at the time of submission of treatment outcome report.
An MDR/ XDR-TB cohort is defined as a group of patients registered with MDR/ XDR-TB during a specified time period (i.e. one year). The date of the diagnostic DST result and the treatment start date should also be entered in the register but it is the date on which the patient is registered that determines to which cohort the patient belongs. All diagnosed MDR/ XDR-TB patients should be offered treatment. If any patients are left untreated, the reasons for exclusion should be explicitly delineated. Some examples of reasons for exclusion from treatment include:

- Died before treatment was initiated
- Patient unwilling/ refuses treatment
- Drug supply shortage
- Limited health facility access
- Clinical reasons
- Social reasons

Cohort analysis of treatment outcomes should be performed on all patients started on treatment DR-TB treatment, regardless of treatment duration. They should be stratified by the case registration groups; further sub-analysis of cohorts according to HIV status, history of previous second-line drug use, DST pattern, and regimen utilized is also useful.

The analysis of MDR/ XDR-TB treatment outcomes should be performed 36 months after the last patient enrolment date in the cohort. All patients should be assigned the first outcome they experience for recording and reporting purposes. However, it is recommended that any subsequent outcomes also be recorded, e.g. death after default or cure after default.

Patients still on treatment at the end of a designated cohort treatment period must also be explicitly identified as such, and whether they were culture-positive or negative at the time of the cohort analysis.

16.6 Quarterly report of DR-TB case finding

The quarterly report is divided into five blocks. The blocks report the following information:

- **Blocks 1: DR-TB patients confirmed and started on Regimen IV treatment.** These blocks are filled in from the laboratory and DR-TB register.
- **Blocks 2: Confirmed MDR-TB and XDR-TB cases registered during the quarter.** These blocks are easily filled in from the information collected in the DR-TB Register.
Each defined cohort should have an interim or preliminary outcome report. This report should be developed by the central TB unit and should be based on the DR-TB treatment register. Since reporting at the end of treatment is very late (after two or even three years), interim results are desirable for all cohorts.

**Annual report of treatment outcome of DR-TB cases**
This report shows the final results of treatment by year of treatment started, for all cases together as well as for cases stratified by smear and culture results and patient registration category.

Since treatment is of long duration, the results will reflect the management of treatment during a prolonged period in the past. In order to assess quicker changes in default, failure, deaths etc., optional forms for preliminary outcomes are also available. An electronic system will generate these reports much easier.
17. HEALTH CARE WORKERS AND DRUG-RESISTANT TB

17.1 Introduction

TB is an occupational disease and health care workers have the legal right to a safe working environment where adequate protection is provided against infection. The onus rests on employer to provide a safe work environment or alternative employment for health care workers with HIV infection, or other medical conditions leading to compromise immunity, which are therefore at greater risk.

Section 14 of the Occupational Health and Safety Act, outlines the general duties of employees, these include:

- The employees must take reasonable care when carrying out work and to co-operate with the employer in creating a safe and health-working environment.
- The employees must comply with the procedures of the organisation in the interests of safety and health.
- The employees must report unsafe conditions and incidents or injuries to own self or other employer in the same shift.
- The employee may not interfere or misuse any equipment that may be provided by the employer to reduce a risk.

Section 8 of the OHSA outlines the General duties of employers, these include:

- Providing and maintaining a safe and healthy working environment with equipment that is not hazardous to the employees or any other person.
- Removing hazards where possible.
- Reduce risk where possible.
- Control the risks at a tolerable level when the risk is inherent to the business.
- Monitor the controls to ensure efficacy.
- Medical surveillance is recommended where certain hazardous exposures occur, notably noise above 85 decibels (dB), chemical and biological agent exposure.
- Informing employees of the nature and severity of the risks to which they are exposed and the necessary safe working procedures, which include the use of, appropriate personal protective equipment (PPE).
- Training of employees in safe working procedures and the correct use of PPE.
- Enforcing compliance with the OHSAct.

Hazardous Biological Agents (HBA) Regulations.
<table>
<thead>
<tr>
<th>Group 1</th>
<th>Unlikely to cause human disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 2</td>
<td>May cause human disease</td>
</tr>
<tr>
<td></td>
<td>Hazard to exposed persons</td>
</tr>
<tr>
<td></td>
<td>Unlikely to spread to community</td>
</tr>
<tr>
<td></td>
<td>Effective prophylaxis &amp; treatment</td>
</tr>
<tr>
<td>Group 3</td>
<td>May cause severe human disease</td>
</tr>
<tr>
<td></td>
<td>Serious hazard to exposed persons</td>
</tr>
<tr>
<td></td>
<td>Risk of spread to community</td>
</tr>
<tr>
<td></td>
<td>Effective prophylaxis / treatment</td>
</tr>
<tr>
<td>Group 4</td>
<td>Causes severe human disease</td>
</tr>
<tr>
<td></td>
<td>Serious hazard to exposed persons</td>
</tr>
<tr>
<td></td>
<td>Risk of spread to community</td>
</tr>
<tr>
<td></td>
<td>No effective prophylaxis / treatment</td>
</tr>
</tbody>
</table>

The employer has a duty to classify any HBA not listed in the schedules in the most appropriate grouping.

Section 4 deals with dissemination of information and training and what this must cover ranging from understanding the risk of infection to personal protection and engineering controls, the necessity for personal air sampling, medical surveillance, good housekeeping, personal hygiene and safe working procedures.

Section 5 deals with the duties of persons exposed to a HBA focusing mainly on the prevention of uncontrolled release of an agent (in this case *M. tuberculosis*), adherence to instructions regarding environmental and health practices and the disposal of materials containing the agent (*M. tuberculosis*) including the decontamination and disinfection requirements.

Sections 6, 7, and 8 places the onus on the employer to ensure that risk assessments are conducted, exposure is monitored on a regular basis and that medical surveillance of the employees is provided. The medical records of employees and risk assessment must be safely kept for a period of 40 years (Section 9).

Sections 10 and 11 address the control measures for prevention of exposure and the use of personal protective equipment.
The COIDA provides for compensation of health care workers contracting DR-TB, where the employee has contracted the disease and that such a disease has arisen out of and in the course of his or her employment involving the handling of or exposure to patients with DR-TB.

Employees are entitled to compensation if they are injured while working or contract any work-related disease. The types of compensation paid to workers for injuries or diseases are:
- Medical aid,
- Temporary disablement,
- Permanent disablement
- Fatalities

An employee or someone on his behalf has the responsibility to report a disease, in writing, to the employer as soon as possible after a doctor’s diagnosis. If they fail to do this within 12 months of diagnosis, he/ she will lose any rights to benefits (Section 43).

Employers must complete and submit the Employer’s Report of an Occupational Disease (W.Cl.1) to the Compensation Commissioner within 7 days after an injury and within 14 days of being notified of the diagnosis of a disease. Subsequently, the following reports must be submitted;
- First Medical Report for an Occupational Disease (W.Cl.22);
- Claim for Compensation for an Occupational Disease (W.Cl.14);
- Progress Medical Reports (W.Cl.22) until the worker’s illness is stable;
- Final Medical Report of an Occupational Disease (W.Cl.26) once the worker is stable

The Commissioner has the responsibility to acknowledge the receipt of the documentation, register the claims and make the decision to accept liability or not and employer and employee informed accordingly. The Commissioner may refuse to award the whole or a portion of compensation and may hold the employer responsible for medical costs in cases where wilful misconduct or neglect of either the HCW or the employer could be proven.

The COIDA, Schedule 3 lists TB as compensable only in the following work situations:
- Crystalline silica (alpha quartz) as in the mines
- M. tuberculosis or NTMs (Non-tuberculous Mycobacteria ) transmitted to an employee during the performance of health care work from a patient suffering from active open tuberculosis.
respiratory protective equipment and inadequate sputum collection procedures can result in exposure of HCWs, other patients and visitors to infection.

The priorities of infection control (for in-patients and out-patients)

There are three levels of infection control (IC) measures:

- Administrative (managerial) – which aim to reduce health care worker (HCW) and patient exposure
- Environmental – aiming to reduce the concentration of infectious particles
- Personal respiratory protection - protects HCWs in areas where the concentration of infectious particles cannot be adequately reduced by administrative and environmental controls.

Administrative controls are the most important and together with environmental controls will reduce but not eliminate the risk therefore in some high risk areas personal respiratory protective equipment may be used by people entering the high risk areas.

17.2.1 Administrative controls

The first and most important level of infection control is the use of administrative measures to prevent infectious particles from being generated, thereby reducing the exposure of HCWs to *M. tuberculosis*. Important administrative measures include:

- Developing and implementing an effective infection control plan to ensure rapid identification, isolation, testing and treatment of DR-TB suspects and patients
- Implementing effective work practises
- Educating, training and counselling of HCW about TB
- Screening of HCW for TB disease and infection

17.2.2 Environmental controls

Environmental controls are the second line of defence for the prevention of nosocomial transmission of DR-TB. When employed in conjunction with administrative controls, environmental controls can be effectively used to reduce the concentration of infectious particles to which HCWs or patients are exposed. Environmental controls are therefore most important in areas where there may be exposure to highly concentrated infectious particles, such as wards containing XDR-TB patients, wards containing large numbers of MDR-TB patients, sputum induction areas, bronchoscopy suites, laboratories performing culture and susceptibility testing, and autopsy rooms.

The best way of reducing high concentrations of infectious particles in the work environment is through:

1) Ventilation.
Adequate ventilation may be achieved by:

- **Open windows** that maximise natural ventilation and dilute the air (the simplest and least expensive technique).
- **Overhead fans**, which may be used to further, enhance natural ventilation in settings where windows can remain open.
- **Exhaust fans** which control the direction of air flow to prevent contamination in the areas adjacent to the infectious source and open windows and overhead fans are insufficient.
- **Exhaust ventilation systems** that provide at least six air changes per hour and prevent contaminated air from escaping into ‘clean’ parts of the facility. The most common way, in which such ventilation can be established is through the use of negative pressure ventilation, in which a room is kept at negative pressure relative to the surrounding area and air is drawn into the room from the corridor and exhausted directly outside.

2) **Air sanitization through air filtration or ultraviolet germicidal irradiation (UVGI)**

Use of UVGI to kill infectious organisms or air filtration methods to remove infectious particles may be an option in some facilities where additional measures need to be implemented to further minimise risk. However, there is little evidence if any to prove the effectiveness of these methods.

Laboratory studies show that *M. tuberculosis* is killed if the organisms are exposed to UV light sufficiently. For UVGI to be effective, however, contaminated air must come into contact with the light rays, which may be a major problem in areas where air circulation is poor, and its effectiveness may be limited in areas where the humidity is high and in dusty areas. A final major limitation to the use of UVGI is the inability to assess its effectiveness in the field, especially given the various types of available products, positions in rooms, and variability of room air mixing in various settings.

If UVGI is installed, a regular program of maintenance is essential. Responsibility should be assigned to ensure that the lamps are dusted periodically and changed at regular intervals. It is also important to periodically assess airflow to ensure that airflow patterns maximise the killing of the mycobacteria by UVGI. The quality of UVGI lamps is very important. Usually a good lamp will last 5 000 to 10 000 hours (7 - 14 months), after that, the irradiance drops off rapidly. Irradiance should be
Because neither administrative nor engineering controls can provide complete protection, the third line of defence against nosocomial DR-TB transmission is the use of personal protection. This can prevent the wearer from spreading or acquiring the infection, depending on the type of equipment. The only types available for DR-TB are masks and respirators.

1) Surgical masks
Surgical masks are meant to prevent the spread of micro-organisms from the person wearing the mask to others by capturing the large wet particles near the source, which in this case is the mouth. They do not provide adequate protection to the wearer from inhaling infectious droplet nuclei in the air. Masks usually have limited filtration capacity and are loosely fitted over the mouth and nose, allowing free entrance of aerosolised mycobacteria.

Although not the highest priority intervention, disposable masks can be used to reduce aerosols generated from potentially infectious DR-TB patients. They should therefore be considered for use by suspected and confirmed DR-TB patients.

2) Respirators
Respirators are a type of mask that covers the mouth and nose; they contain special filter material and are designed to fit tightly to the face to prevent leakage between the face and the edge of the mask. Respirators are designed to filter very small particles, including airborne mycobacterium. An industrial mask with a 1μm particle size and a filter efficiency of more than 95% is recommended. Disposable particulate respirators are the simplest and recommended devices to be used.

For a respirator to be effective there must be a tight seal between the mask and the wearer’s face. If the respirator does not fit correctly, infectious particles will likely follow the path of least resistance and any leak between the face and the mask is a potential entry point for infectious droplet nuclei. Each individual should therefore be “fit tested” to ensure that an appropriate model is used for each worker and minimise the risk of leakages.

Disposable respirators are relatively costly, but may be reused if well maintained – proper handling when wearing and removing them, good storage. They should be discarded when they become soiled, wet, or appear to lose their structural integrity, and the machine to be replaced. Respirators should be stored in a location of adequate air circulation.
In all facilities training on the correct use of the respirators including putting them on and removing them, there must be procedures for:

- selecting respirators for use in the facility
- storing and re-use of the respirators
- evaluating the effectiveness of the use of respirators
- Fit testing to ensure correct fit of respirator

### 17.3 Specific measures for prevention of nosocomial infection

1. Assigning infection control officers in the health facilities who will be responsible for developing infection control plans implement plans, monitoring and evaluation of the effectiveness of the measures implemented

2. Establish an multidisciplinary infection control committee comprising of infection control officer, microbiologist, medical practitioner/physician, pharmacist, housekeeping supervisor/manager food service manager, laundry service manager, maintenance manager and hospital manager

3. Conducting risk assessments to evaluate the risk for transmission in each area and occupational group within the facility, these must be repeated annually to evaluate the effectiveness of the IC interventions

   - Classification of risk for a facility, specific area, occupational group should be based on the profile of TB in the community, the number of infectious TB patients admitted or seen the area or ward, the estimated number of infectious TB patients an occupational category is exposed to, results of PPD test conversions among HCW and possible person-to-person transmission of *M. tuberculosis*

4. Develop an infection control plan based on the risk assessment

   - Developing and implementing policies or protocols for early identification, diagnosis and treatment of patients who may infectious TB

5. Providing prompt triage for and appropriate management of patients who may have infectious TB in the outpatient department

   - Vigorous efforts to identify patients with active TB disease
   - Symptomatic screening of symptomatic patients
   - Symptomatic screening tool
   - Separate waiting area for TB suspects
   - Provide tissues for use to cover the mouth when coughing and sneezing
• Isolation practises to be implemented in the facility
• Monitoring of isolation practises
• Management of patients who do not adhere to isolation practises
• Criteria for discontinuing isolation

7) Effectively planning arrangements for discharge
• Discharge planning in the hospital should include a confirmed outpatient appointment with the provider who will ensure continuum of care until the patient is cured, placement into case management (DOT) or outreach programmes, ensure systems to supply drugs.

8) Planning, installing and evaluating ventilation and other engineering controls to reduce the risk of exposure to *M. tuberculosis*

9) Planning, implementing, maintaining and evaluating a respiratory protection programme

10) Education, training of HCW about TB, effective methods for preventing transmission of infection and the benefits of medical surveillance programmes

11) Developing and implementing a programme for periodic counselling and screening of HCW for latent infection and active disease

12) All HCW should be importance of compliance to infection control interventions to minimize risk of exposure to infectious agents

13) HCW who have a health condition that compromises cell mediated immunity and are placed in high risk areas should be offered alternative employment

14) Information provided by the HCW’s regarding their HIV status should be treated confidentially

15) Prompt evaluation of nosocomial transmission, including PPD test conversions or active TB in HCW, epidemiological association of cases among HCW, patients, contacts of patients or HCW who have TB but were not promptly identified and isolated. The aim of epidemiological investigation is to:
• determine the likelihood that the transmission of and infection with M TB has occurred in the facility
• determine the extent to which *M. tuberculosis* has been transmitted
• identify people who have been exposed and infected enabling them to start treatment early
• identify factors that could have contributed to the transmission and infection and to implement appropriate interventions
• Evaluate the effectiveness of any interventions that are implemented and to ensure that exposure to and transmission of *M. tuberculosis* has been
The risk of infection with TB depends on the severity of disease in the source case and on prolonged, intensive exposure to this case. It follows, therefore, that all HCWs are not at equal risk of acquiring infection, and that for many cadres of HCWs the risk is almost equal to that of the general community. The following categories of risk may be surmised:

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk</td>
<td>HCWs in prolonged close contact with infectious (smear-positive) MDR tuberculosis cases, e.g. nursing staff and other medical staff in MDR tuberculosis hospitals and wards</td>
</tr>
<tr>
<td></td>
<td>HCWs involved in aerosol-producing procedures, e.g. pulmonary physicians, respiratory technicians and other medical staff performing bronchoscopy, sputum induction, tracheal intubation, aerosolised pentamidine therapy and autopsy procedures;</td>
</tr>
<tr>
<td></td>
<td>HCWs who are immuno-compromised and who are involved in regular MDR tuberculosis patient management.</td>
</tr>
<tr>
<td>Medium risk</td>
<td>HCWs in primary health care centres who are involved in sputum collection procedures from tuberculosis suspects;</td>
</tr>
<tr>
<td></td>
<td>HCWs in prolonged close contact with retreatment tuberculosis patients, especially if such patients have a history of more than one previous treatment episodes and a record of poor adherence.</td>
</tr>
<tr>
<td>Low risk</td>
<td>HCWs in primary health care centres involved in management of tuberculosis patients on therapy;</td>
</tr>
<tr>
<td></td>
<td>Health care facility support staff, such as porters, cleaners and administrative staff;</td>
</tr>
<tr>
<td></td>
<td>HCWs in general hospitals and community health centres</td>
</tr>
</tbody>
</table>

17.5 Infection control plans

The development of the infection control plan is based on the results of the risk assessment. The plan should be specific for each area and occupational group in the facility. A facility may have a combination of low, intermediate, and high-risk areas or occupational groups at the same time.

Irrespective of the level of risk, the following principles must apply:

- Ongoing education and training on the transmission and pathogenesis of tuberculosis, the consequences of DR tuberculosis, the infection control measures implemented in the facilities and importance of compliance to these.
- The importance of a continuous awareness of risk situations and their avoidance should be stressed.
- Sputum collection should be done in an open area or cough booths where these are available.
- Inpatients who are coughing should be in a single ward with good outside ventilation, the door must remain shut and the windows open as far as possible if the ward is not under negative pressure.

17.5.1 Cough hygiene

The prevention of DR-TB focuses on both the infectious patient (and infected material) and on the HCW at risk of getting infected.

All patients should be instructed to cover their mouths and noses with handkerchief, surgical mask or a tissue during coughing and other forms of forced expiration. After use, these materials should be disposed of in small plastic or paper refuse bags, which should be regularly changed and discarded into larger refuse bags for incineration. Alternatively, 5% concentrations of an iodine-containing solution or a hypochlorite solution containing 10 000 ppm active chlorine should be used for disinfection and disposal.

HCW’s should wear particulate respirators which are impermeable to droplet nuclei when nursing patients or collecting sputum.

17.5.2 Sputum collection

Collection of sputum specimens should take place in the open air on the sunny side of the ward. A special veranda should be built for this purpose in the case of bad weather. The correct procedure for sputum collection must be implemented and patients must be observed during the collection. The HCW should:
- Stand directly behind the patient so as to minimize droplet infection exposure
- The patient should hold the container as close to the mouth as possible
- The patient must close the container immediately after expectoration
- All sputum jars should be labelled prior to collection taking place to minimize handling of specimens
- Gloves are to be worn when handling specimens
- Hands should be washed with appropriate disinfectant if hands have contacted sputum without gloves
- The lids of sputum containers should be properly closed to avoid spillage
- If breakage or spillage occurs, gloves should be worn, spillage covered with paper towel and wiped up and area cleaned with warm water and detergent.
During cough inducing procedures, disposable apron, gloves and particulate filter respirators need to be worn.
Hand washing procedures must be followed before and after each patient contact procedure
All instruments must be washed in the ward to remove respiratory secretions before being sent to CSSD
All resuscitation equipment must be in order and no mouth-to-mouth resuscitation should take place
Each patient must be supplied with a disposable sputum mug with a lid and sputum mugs must be replaced three times per day

17.5.3 Isolation practises

Isolation wards for the following categories of patients must be available in the MDR-TB hospitals to prevent cross infection with different or new strains of M. tuberculosis:

- New patients admitted into a ward must be isolated from those who have been on treatment for more than two weeks.
- MDR-TB patients must be isolated from XDR-TB
- Children from adults
- Very sick from stable patients

In hospital settings, isolation may be stopped after a patient has three negative sputum smear microscopy results taken on three separate occasions, and shows maintained clinical improvement, including resolution of cough. If sputum smears in MDR-TB and XDR-TB patients remain consistently positive but repeated sputum cultures are negative, consideration can also be given to removing them from isolation if they have also shown clinical improvement. Positive smear and negative culture may be due to dead bacilli visualized during microscopy.

17.5.4 Medical surveillance programme

Medical surveillance programme for all employees. The objectives surveillance programmes are:

- To establish the baseline of TB infection status of the workers
- To identify those with latent TB infection and offer them preventive therapy to decrease their risk of developing active TB
The elements of the medical surveillance programme include the following:

- Pre-placement
- Ongoing surveillance
- Exit
- Post-employment

1) **Baseline health assessment of employees**
   This includes medical history of the employee relating to past tuberculosis disease, BCG vaccination status, underlying medical conditions which may increase susceptibility of the employee to tuberculosis and previous contact with people/patients with confirmed tuberculosis.
   Sputum microscopy and culture must be done for all symptomatic employees
   Baseline tests to be conducted:
   - Chest x-ray
   - Mantoux tuberculin skin test (TST)
   - Lung function tests
   - Glucose blood and urine levels
   - Hepatitis B

2) **Provider-Initiated Counselling and Testing (PICT)**
   Health care workers should be counselled about the risks of working with DR-TB patients, the necessary precautions that must be taken, and the substantially increased risks if they are, or become, HIV positive. Voluntary HIV counselling and testing should be offered on the basis that alternative working environments will be sought for those who are HIV positive and who wish to minimise their risk of infection with DR-TB. Any disclosure of HIV status should be voluntary, made to a designated health care provider, and held in the strictest confidence.

3) **Ongoing surveillance**
   The table below indicates the recommended frequency of ongoing medical surveillance based on the facility, and activity risks

<table>
<thead>
<tr>
<th>Activity risk</th>
<th>Health care facility risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>High</td>
<td>Six-monthly</td>
</tr>
<tr>
<td>Low</td>
<td>Annually</td>
</tr>
</tbody>
</table>
HCWs should declare information on their health status in the form of answers to specific questions relating to the early signs and symptoms of tuberculosis. These include cough for longer than three weeks, weight loss (unexplained loss of 10% or more of body weight), anorexia, night sweats and the frequent occurrence of colds or other respiratory infection episodes in recent weeks. When these are present the individual must be investigated for TB.

The following tests should be conducted routinely:

- **Full size chest x-ray examinations** must be conducted for evidence of recent tuberculosis disease. Individuals exhibiting changes on serial examination should be evaluated for tuberculosis, both clinically and microbiologically.
- **Tuberculin skin test** to detect converters. Individuals with TST reactions of <10 mm should be re-tested. Strongly positive reactors with skin test diameters of >15 mm and recent skin converters should be evaluated clinically and microbiologically.

4) **Post-exposure monitoring**
If any HCW has been exposed to an infectious DR-TB patient for more than two hours or to aerosolised infected material (e.g. in autopsy rooms), their monitoring files should be consulted and their chest x-ray and TST records reviewed. The HCW should also be carefully monitored clinically. Eight weeks after the exposure episode, a chest x-ray examination should be performed, together with a TST in cases where the previous reaction diameter was <10 mm.

5) **Record keeping**
Each worker should have a confidential disease-monitoring file in which screening procedures for tuberculosis, the minimum physical examination and tests to be conducted, as well as other health-related data, including records of results of tests conducted and updates of any changes in the health status of the worker are recorded. Other essential information that should be recorded includes:

- Name, job title, position, placement in facility, shift and hours worked
- Date of employment in the health facility
- Results of baseline assessment
- Results of regular ongoing assessment
- Record of reported TB exposure
- Management plans for treatment and follow-up of workers with confirmed disease
- Management and follow-up of workers on preventive therapy
- Counseling provided to the worker
As a general rule, health care workers who contract DR-TB through work should not be dismissed on the basis of incapacity at the expiry of their paid sick leave. A fair procedure should be followed, including an investigation into the nature and extent of the incapacity, the effects of treatment, and alternatives to dismissal. This would usually result in extended sick leave being granted. The provision of extended sick leave to an employee, at least on an unpaid basis or at less than full pay, in order to undergo treatment for MDR-TB would be regarded as fair. Fairness can only be tested in the circumstances of each particular case, and factors such as disability insurance and ill-health retirement benefits as alternatives would be relevant.

**ANNEXURE 1: DRUG ADVERSE EFFECT FORM**

**ADVERSE DRUG REACTION AND PRODUCT QUALITY PROBLEM REPORT FORM**

(Identities of reporter and patient will remain strictly confidential)

**NATIONAL ADVERSE DRUG EVENT MONITORING CENTRE**  
Medicines Control Council,  
Tel: (021) 447-1618  
The Registrar of Medicines,  
Fax: (021) 448-6181  
Department of Health  
In collaboration with the WHO International Drug Monitoring Programme

**PATIENT INFORMATION**

Name (or initials): ............................................................  
Age:.................................  
Weight (kg):..............................  
Sex: ..................................  
DOB :...... / ......./ .........  
Height (cm) :..............................

**ADVERSE REACTION/PRODUCT QUALITY PROBLEM**

Adverse reaction\(^1\)  
and/or Product Quality problem\(^2\)  
Date of onset of reaction: :....../........./......  
Time of onset of reaction: ......h........min

Description of reaction or problem (Include relevant tests/lab data, including dates):

**1. MEDICINES/VACCINES/DEVICES (include all concomitant medicines)**

<table>
<thead>
<tr>
<th>Trade Name &amp; Batch No.</th>
<th>Daily Dosage</th>
<th>Route</th>
<th>Date Started</th>
<th>Date Stopped</th>
<th>Reasons for use</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Asterisk Suspected Product)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ADVERSE REACTION OUTCOME (Check all that apply)

- death
- disability
- life-threatening hospitalisation
- congenital anomaly
- required intervention to prevent permanent impairment/damage
- event reappeared on rechallenge: Y N
- Rechallenge not done
- Treatment (of reaction)...

Recovered: Y N
Sequelae: Y N
Describe Sequelae:...

COMMENTS: (e.g. Relevant history, Allergies, Previous exposure, Baseline test results/lab data)

2. PRODUCT QUALITY PROBLEM:

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Batch No</th>
<th>Registration No</th>
<th>Dosage form &amp; strength</th>
<th>Expiry Date</th>
<th>Size/Type of container</th>
</tr>
</thead>
</table>

Product available for evaluation: Y N

REPORTING DOCTOR/PHARMACIST Etc:

NAME: .................................................................
QUALIFICATIONS: ....................................................
ADDRESS: ............................................................
.................................................................
.................................................................
.................................................................

Signature Date

TEL: (........).........................

This report does not constitute an admission that medical personnel or the product caused or contributed to the event.

ADVICE ABOUT VOLUNTARY REPORTING
Report adverse experiences with:
- medications (drugs, vaccines and biologicals)
- medical devices (including in-vitro diagnostics)
- traditional and herbal remedies
- For Adverse Events Following Immunisation (AEFI), please follow the reporting procedure recommended by the Expanded Programme in Immunisation (EPI)

Please report:
- adverse drug reactions to recently marketed products
- serious reactions and interactions with all products
- adverse drug reactions which are not clearly reflected in the package insert.

Report even if:
- you’re not certain the product caused the event
- you don't have all the details

Report Product Quality Problems such as:
- suspected contamination
- questionable stability
- defective components
- poor packaging or labelling
- therapeutic failures

Important numbers:

Investigational Products and Product Quality Problems:
- (012) 326-4344 to fax a report
- (012) 312-0000 to report by phone

Registered Medicines and Traditional and Herbal remedies:
- (021) 448-6181 to fax a report
- (021) 447-1618 to report by phone

Adverse Events Following Immunisation:
- (012) 312 0110 to phone for information
- (012) 321 9882 to fax a report
Confidentiality: Identities of the reporter and patient will remain strictly confidential.

Your support of the Medicine Control Council’s adverse drug reaction monitoring programme is much appreciated. Information supplied by you will contribute to the improvement of drug safety and therapy in South Africa.
GUIDELINES FOR ADVERSE DRUG REACTION REPORTING

National Pharmacovigilance Programme
The Medicines Control Council (MCC) has a responsibility to ensure the safety, efficacy and quality of all medicines used by the South African public. The National Pharmacovigilance Programme is coordinated by the MCC and has two dedicated Units responsible for the monitoring of the safety of medicines. The National Adverse Drug Event Monitoring Centre (NADEMC) in Cape Town monitors the safety of all registered medicines in South Africa. In addition, a focused surveillance unit at MEDUNSA is responsible for monitoring the safety of anti-retroviral (ARV) medicines and complementary medicines. The unit at MEDUNSA is also responsible for monitoring the safety of unregistered medicines used during clinical trials.

What is Pharmacovigilance?
Pharmacovigilance is defined as the science and activities concerned with the detection, assessment, understanding and prevention of adverse reactions to medicines (i.e. adverse drug reactions or ADRs). The ultimate goal of this activity is to improve the safe and rational use of medicines, thereby improving patient care and public health.

What is an Adverse Drug Reaction (ADR)?
The Medicines Control Council (MCC) defines an Adverse Drug Reaction (ADR) or adverse reaction as a response to a medicine which is noxious and unintended, including lack of efficacy, and which occurs at any dosage and can also result from overdose, misuse or abuse of a medicine.

Who should report Adverse Drug Reactions?
All health care workers, including doctors, dentists, pharmacists, nurses and other health professionals are encouraged to report all suspected adverse reactions to medicines (including vaccines, X-ray contrast media, traditional and herbal remedies), especially when the reaction is not in the package insert, potentially serious or clinically significant.
• Educational initiatives to improve the safe use of the medicine
• Appropriate package insert changes to include the potential for the reaction
• Changes in the scheduling or manufacture of the medicine to make it safer

The purpose of ADR reporting is to reduce the risks associated with the use of medicines and to ultimately improve patient care.

**Will reporting have any negative consequences on the health worker or the patient?**
An adverse drug reaction report does not constitute an admission of liability or that the health professional contributed to the event in any way. The outcome of a report, together with any important or relevant information relating to the reaction, will be sent back to the reporter as appropriate. The details of a report are stored in a confidential database. The names of the reporter or any other health professionals named on a report and the patient will be removed before any details about a specific adverse drug reaction are used or communicated to others. The information is only meant to improve the understanding of the medicines used in the country.

**Is the event possibly an ADR?**
The following factors should be considered when an adverse drug reaction is suspected:

1. **What exactly is the nature of the reaction?** *(describe the reaction as clearly as possible and where possible provide an accurate diagnosis)*

2. **Did the reaction occur within a reasonable time relationship to starting treatment with the suspected medicine?** *(some reactions occur immediately after administration of a medicine while others take time to develop)*

3. **Is the reaction known to occur with the particular medicine as stated in the package insert or other reference?** *(If the reaction is not documented in the package insert, it does not mean that the reaction cannot occur with that particular medicine)*

4. **Did the patient recover when the suspected medicine was stopped?** *(some reactions can cause permanent damage, but most reactions are reversible if the medication is stopped)*

5. **Did the patient take the medicine again after the reaction abated (i.e. rechallenge). If so, did the same reaction occur again?** *(In most situations it is not possible or ethical to rechallenge the patient with the same medicine. If such information is available or if such a rechallenge is necessary, recurrence of the event is a strong indicator that the medicine is may be responsible*
The following adverse drug reactions should be reported:

- All ADRs to newly marketed drugs or new drugs added to the EDL
- All serious reactions and interactions
- ADRs that are not clearly stated in the package insert.
- All adverse reactions or poisonings to traditional or herbal remedies

Report even if you are not certain the medicine caused the event.

What Product Quality Problems should be reported?
The following product quality problems should be reported:

- Suspected contamination
- Questionable stability
- Defective components
- Poor packaging or labelling
- Therapeutic failures

How can ADRs be prevented from occurring?
Some ADRs are unavoidable and cannot be prevented. However, most ADRs can be prevented by following the basic principles of rational use of medicines.

How are adverse drug reactions reported?
An Adverse Drug Reaction/Product Quality Report Form is enclosed in this book and should be completed in as much detail as possible before returning it by fax or post to any of the addresses provided below. Additional forms can be obtained by contacting the MCC at these addresses. Report forms may also be accessed via the following website:

http://www.mccza.com

1. The Registrar of Medicines
   Medicines Control Council, Department of Health, Private Bag X828
   Pretoria, 0001
   Tel: (021) 312 0295; Fax: (021) 3123106

2. The National Adverse Drug Event Monitoring Centre (NADEMC)
   C/o Division of Pharmacology, University of Cape Town,
   Observatory, 7925
   Tel: (021) 447 1618; Fax: (021) 448 6181

3. MEDUNSA Pharmacovigilance Unit
   Fax (012) 521 4335
ANNEXURE 2: CONSENT FORM

CONSENT FORM FOR DR-TB PATIENTS

Undertaking by patient

I, ..................................................................................................................(name patient) of (residential physical address) ...........................................................................................................

Understand the nature of my disease and treatment as explained by the doctor/nurse, hereby give an undertaking that

1. I will follow the prescribed and agreed treatment regimen and to conscientiously comply with the instructions given to improve my health and protect that of others
2. I agree to spend to be hospitalized for the duration to be determined by my doctor/nurse in order to facilitate administration of the treatment and clinical monitoring during this period
3. I will inform the doctor/nurse of any difficulties or problems in following treatment, or if any part of the treatment is not clearly understood
4. I will provide the sputum specimen required for testing to monitor clinical progress
5. I will provide the blood specimen required for monitoring adverse events caused by the drugs
6. I will undergo audiometric tests required to monitor adverse events
7. I will adhere to cough hygiene practices at all times to prevent spreading the infection to others
8. I will show consideration and respect for the rights of other patients and health-care providers during my stay in the hospital

I understand that if I wilfully interrupt my treatment the following measures could apply:

1. My treatment could be stopped.
2. Any form of social support I may be getting will be stopped

Name .............................................................................................. Signature Patient: ...........................................

Date: ..................................................................................................
I, ...................................................................................................................... (name)

Undertake to:

1. Explain fully to you the nature of your disease and explain the treatment plan to you (including any side effects you might experience).
2. Provide you with regular clinical progress reports whilst on treatment
3. Ensure confidentiality of your medical condition at all times
4. Address your complaints or concerns to the best of my ability
5. Address any socio-economic problems you may encounter whilst in hospital as far as reasonably possible

Name: ........................................................................ Signature: ........................................

Date: ........................................

Witness ........................................................................ Date: ........................................

Witness ........................................................................ Date: ........................................

ANNEXURE 3: Guidelines for referral of DR-TB patients for review by the Provincial DR-TB Review Committee (PRC)

Any patient diagnosed with DR-TB, must follow a process of documentation, education/awareness and evaluation of conditions for good treatment adherence, before starting on a suitable treatment regimen. This involves the patient and possibly their families, provided that the patient is adequately informed of the process and is in agreement with it. Only when the above-mentioned requirements/criteria are fulfilled should the patient be started on DR treatment.

All patients who are, chronic defaulters, non-converters, have more extensive resistance, treatment failures must be referred to the PRC for a decision to continue or stop treatment.

The committee will consider each case and make recommendations to the hospital on the management and records of all decisions taken by the committee must be kept safely for medico-legal purposes as well as monitoring compliance with those recommendations.

The province must coordinate the meetings based on cases submitted for review.
b) The MDR form

c) The contract signed by patient and relevant health care workers on initiation

of treatment.

The MDR Co-ordinator of the MDR Centre will check submission and accept for review only if paperwork is complete and the basic requirements for the review have been met.

The referring institution will be notified of meeting date and patient will be requested to attend the review meeting, wherever this is possible.

The Review Board will peruse the submission, interview the patient where possible, discuss the case, and make recommendations.

The referring facility will be informed of the Review Board’s decision and within 10 working days.

ANNEXURE 4: STANDARD REFUSAL OF HOSPITAL TREATMENT FORM
1. the undersigned, leave the Hospital on my own responsibility and against the advice of the attending doctor.

Witnesses: 1. 

Signature of patient: 

2. Date: Time: 

1. the undersigned, take the patient Hospital on my own responsibility and against the advice of the attending doctor.
ANNEXURE 5: PASS-OUT CONSENT FORM FOR DR-TB PATIENTS

I, .........................................................................................................................................................(Name patient) of (residential physical address)
................................................................................................................................................................
................................................................................................................................................................
Understand the conditions of the pass out as explained to me by the doctor/ nurse and hereby give an undertaking to abide by these conditions. During this period, I will be resident at the following address
................................................................................................................................................................
................................................................................................................................................................
................................................................................................................................................................
I will take precautions to prevent spreading the infection to people I come into close contact with, and will continue to take my medication as explained.
I will report back at the hospital on the .................. day of the ............... month ............... , as agreed upon and understand that during this time the hospital cannot take responsibility for my well being. If I experience any problems during this period I will inform my local clinic or the hospital as soon as possible.

Name of Patient ................................. Signature: .................................
Date: .................................
ANNEXURE 6: THE PROVINCIAL DRUG RESISTANT TB REVIEW COMMITTEE TERMS OF REFERENCE

Composition:

Medical officer(s) and/or professional nurse from the MDR-TB hospital, physician, pathologist, paediatrician, cardio-thoracic surgeon, public health specialist, radiologist, civil society representative, social worker, provincial management and a specialist in legal and ethical issues.
Other representatives from government departments such as Social Development, Correctional Services, Military Health Services, SASSA and mining industry may be included in this committee.

Aim:

To contain the MDR and XDR-TB epidemic by reducing the period of infectivity and/or decreasing exposure to contacts through standardised therapeutic and public health interventions.

Objectives

- To advice and recommend appropriate clinical management of individual DR-TB patients within available resources.
- To address the dilemma posed to the individual clinician by offering
To review chronic cases those are failing treatment and advise on treatment withdrawal and palliative care.

- To recommend approval or to decline use of salvage regimens in individual patients.
- To recommend confinement where applicable.
- To make policy recommendations in relation to chronic patients

Case reviews

- To undertake systematic reviews of individual chronic patients and decide on future management including treatment withdrawal, regimen-change, palliation and confinement.
- To document these decisions and issue written recommendations on each patient, in the manner required legally defending and/or ensuring compliance with those recommendations.

Referral criteria

For clinical decision on re treatments / salvage regimens/ withdrawal of treatment:

- MDR/ XDR-TB patients who revert back to culture positive after having had 2 negative cultures.
- MDR-TB/ XDR-TB patients who remain culture positive for longer then 6 months after treatment is initiated. These would include true failures, patients who default / interrupt treatment and patients with limited treatment options due to side-effects.
- MDR patients who are eligible for review include those who re-present after 2 previous interruptions of MDR regimens where there is reasonable expectation that the patient will interrupt again.
- XDR patients failing on standard regimens.
- Patients with sensitive strains, but phenotypical MDR/XDR
- Disruptive patients who cannot be kept in care.
- Refusal of patients to take treatment, be admitted to hospital or be confined.
- Overall deteriorating clinical condition that usually includes weight loss and respiratory insufficiency
- Patients with concomitant disease e.g. cancer

For decision on confinement / isolation

- Any of the cases above where applicable.
MDR clinical records are often extensive and it is usually not possible to extract essential information from the folder at the board meeting.

The information must be presented in user-friendly summary format; the folders may be perused if required.

The referring clinician must forward the referral form to the designated administrative assistant/secretariat.

The secretariat must check all the submissions for completeness, follow up with referring hospital for missing documents and prepare the documents for meetings.

The referring clinician is informed of the date of review or advised if the referral is incomplete.

**Documentation required**

<table>
<thead>
<tr>
<th>INFORMATION</th>
<th>DOCUMENT</th>
<th>WHOM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Counseling</td>
<td>Patient education and counselling form sheet</td>
<td>MDR counsellor / social worker, patient</td>
</tr>
<tr>
<td></td>
<td>Social worker assessment report</td>
<td></td>
</tr>
<tr>
<td>Contract</td>
<td>Patient Consent Form</td>
<td>MDR counsellor / social worker, patient</td>
</tr>
<tr>
<td>Socio-economic, environment report</td>
<td>Patient’s family social assessment report</td>
<td>Social worker / clinic staff</td>
</tr>
<tr>
<td></td>
<td>results. Summary of treatment and adherence.</td>
<td></td>
</tr>
<tr>
<td>Interview with patient and family</td>
<td></td>
<td>Social worker/ Doctor, Counsellor</td>
</tr>
<tr>
<td>Clinical records and results of investigations conducted</td>
<td>Patient treatment folder including CXR’s, CT scans etc</td>
<td>Hospital staff</td>
</tr>
<tr>
<td>Original patient adherence record</td>
<td>Patient treatment folder</td>
<td>Hospital staff</td>
</tr>
</tbody>
</table>

**Proceedings**

The quorum must constitute 50% of committee members should the key specialist consultant not be available on the day of the meeting. They must be consulted on an ad hoc basis prior to meeting for their written recommendations on the patients to be presented.

Meeting proceedings will include:

− Presentation by the treating medical officer...
- Structured discussion by committee, with minute taking
- Decision or recommendations [or deferment of decision if further input/information is needed]
- A report is compiled by the Secretariat and signed off by the chairperson of the committee, and submitted to the provincial Head of Health.
- The referring institution and clinician must be informed of the decision against which they can appeal, if there are sufficient grounds for this
- Copies of referrals and committee decisions must be kept by the Secretariat

(Adapted from the Western Cape DOH Review Committee Terms of Reference)