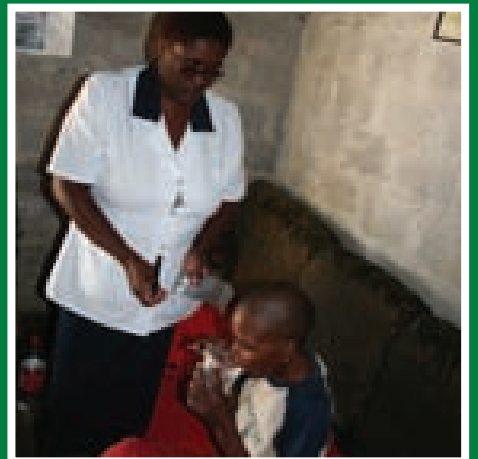


# MANAGEMENT OF DRUG-RESISTANT TUBERCULOSIS

## POLICY GUIDELINES



health

Department:  
Health  
REPUBLIC OF SOUTH AFRICA

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**August 2011**



**health**

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Department:  
Health  
**REPUBLIC OF SOUTH AFRICA**

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## FOREWORD

South Africa is the third highest tuberculosis (TB) burden country in the world, lagging behind two countries, China and India, significantly larger populations than ours. The increasing emergence of drug-resistant strains of TB is due to treatment defaulters and other challenges ranging from delays in initiating treatment, inadequate bed capacity, poor infection control in health facilities, and new infections.

The following policy guidelines are intended for use by health care professionals involved in the complex and difficult task of managing mono- and poly-resistant TB, MDR- and XDR-TB patients in South Africa. The guidelines focus on the clinical management, referral mechanisms and models of care. However, psychosocial support to ensure comprehensive management of the patients, strategies for infection prevention and control, and occupational health services for health care workers (HCWs) are covered.

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

Management of DR-TB is 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 opinions. Comments and suggestions from those working in the field are essential to ensure a dynamic process, aimed at optimal control of DR-TB in South Africa.



A handwritten signature in blue ink, appearing to read 'A. Motsoaledi', with a stylized flourish at the end.

**Minister of Health**  
**Dr. Aaron Motsoaledi**

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**Director-General for Health**  
**Ms. M.P. Matsoso**

## ABBREVIATIONS

<b>ADR</b>	Adverse Drug Reaction
<b>AFB</b>	Acid-Fast Bacilli
<b>ALT</b>	Alanine Aminotransferase
<b>ART</b>	Antiretroviral Therapy
<b>ARV</b>	Antiretroviral
<b>AST</b>	Aspartate Aminotransferase
<b>BD</b>	Twice a Day
<b>BID</b>	Twice a Day
<b>CDC</b>	Centers for Disease Control and Prevention
<b>CPT</b>	Cotrimoxazole Preventive Therapy
<b>CT scan</b>	Computerised Tomography Scan
<b>d4t</b>	Stavudine
<b>ddI</b>	Didanosine
<b>DOT</b>	Directly Observed Therapy
<b>DOTS</b>	Directly Observed Therapy Short course
<b>DR-TB</b>	Drug-Resistant Tuberculosis
<b>DRS</b>	Drug Resistance Surveillance
<b>DST</b>	Drug Susceptibility Testing
<b>ECG</b>	Electrocardiogram
<b>FEV1</b>	Forced Expiratory Volume in 1 second
<b>FVC</b>	Forced Vital Capacity
<b>FIND</b>	Foundation for Innovative New Diagnostics
<b>GXP</b>	GeneXpert
<b>HCT</b>	Hematocrit
<b>HCW</b>	Health Care Worker
<b>HIV</b>	Human Immunodeficiency Virus
<b>HPF</b>	High-Power Field
<b>LFT</b>	Liver Function Test
<b>MDR-TB</b>	Multi-Drug Resistant Tuberculosis
<b>MGIT</b>	Mycobacterial Growth Indicator Tube
<b>NDOH</b>	National Department of Health
<b>NTM</b>	Non-Tuberculous Mycobacteria
<b>PHC</b>	Primary Health Care
<b>PPD</b>	Purified Protein Derivative
<b>PPM</b>	Public-Private Mix
<b>QD</b>	Once a Day
<b>QID</b>	Four Times a Day
<b>SANCA</b>	South African National Cancer Association

<b>SCC</b>	Short-Course Chemotherapy
<b>TB</b>	Tuberculosis
<b>TDS</b>	Three times a Day
<b>TID</b>	Three times a Day
<b>TSH</b>	Thyroid-Stimulating Hormone
<b>UIF</b>	Unemployment Insurance Fund
<b>UVGI</b>	UltraViolet Germicidal Irradiation
<b>XDR-TB</b>	Extensively Drug-Resistant Tuberculosis
<b>WHO</b>	World Health Organisation

## ANTI-TUBERCULOSIS DRUG ABBREVIATIONS

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

# EXECUTIVE SUMMARY

## 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-TB 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. Extensively drug-resistant tuberculosis (XDR-TB) is defined as MDR-TB and in vitro resistance to any of the fluoroquinolones and any injectable (i.e., 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 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.
4. DR-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. All smear negative, TB culture positive patients should be started on MDR-TB community treatment. TB microscopy positive patients who refuse to be admitted may not be denied MDR-TB treatment. All GeneXpert positive patients with resistance to rifampicin should be started on MDR-TB treatment. MDR-TB diagnosis should be confirmed after initiating on treatment.
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 are responsible for making recommendations on difficult patients, and make decisions on termination of treatment.
8. All MDR-TB hospitals must have multidisciplinary clinical management teams. These teams will take collective decisions on the comprehensive 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 require 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 resistant TB register. Mono-drug resistance to INH should be treated with the following fixed combination drugs: rifampicin + isoniazid + pyrazinamide + ethambutol (RHZE).
11. A standardised approach to MDR-TB treatment is recommended for all newly diagnosed MDR- 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, moxifloxacin, ethionamide, terizidone or cycloserine and pyrazinamide during the injectable phase. Moxifloxacin, 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 standardised 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 four 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 DR-TB must be offered HIV counselling and testing, and those who are co-infected must be started on cotrimoxazole and antiretroviral treatment (ART) as soon as ARV adherence counselling is completed. All co-infected MDR/XDR-TB/HIV patients qualify to receive antiretroviral therapy (ART) regardless of their CD4 count.
16. On-going adherence, counselling and psychosocial 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 and GeneXpert are recommended for quicker diagnosis.
18. Close contacts of patients diagnosed with DR-TB must be screened and tested for DR-TB. Those who do not have TB must be routinely screened for DR-TB at six-monthly intervals. Currently, there is, 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 initiating MDR- and 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. In order to increase access to care for MDR-TB patients in South Africa, nurse-initiated treatment is an option that has proven successful in HIV management throughout the world. Nurse-initiated MDR-TB treatment will be part of decentralised MDR-TB services.

# 1. INTRODUCTION

# 1. INTRODUCTION

At no time in recent history has tuberculosis become of great concern as today. Despite highly effective drugs, disease and deaths due to *Mycobacterium tuberculosis* are increasing in South Africa, fuelled by the HIV epidemic. The most serious aspect of the TB epidemic has been the emergence of DR-TB in the country. DR-TB is a man-made problem, largely due to 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 super-infection.

## 1.1. Definitions

DR-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, and 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 the 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.
- **Resistance levels in re-treatment** are always higher than in new patients, and provide an indication of the extent to which patients were appropriately treated.

The terms ‘primary’ and ‘acquired’ have been discontinued as epidemiological terminology, as the exact causative nature of drug resistance in a patient is not always possible to assess. Patients may be erroneously labelled 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 differs from non-tuberculosis mycobacteria (NTM). NTMs are commonly resistant to both isoniazid and rifampicin but should not be confused with MDR-TB. These Policy 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 (i.e.,  $10^{-15}$ ). Since the probability of naturally occurring resistant mutants is very low, a large bacterial load (e.g., in lung cavities) is needed for MDR-TB strains to emerge.

Drug resistance 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.

Erratic TB treatment with first-line drugs, either through clinical error (i.e., prescription of inadequate drugs, adding one drug to a failing regimen or programme failure with high treatment non-compliance and default) can result in the emergence of resistance, including MDR-TB. Erratic treatment with second-line drugs can result in XDR-TB a virtually untreatable disease.

## 1.3. Situational Analysis

South Africa is the world's third highest burden TB country, only lagging behind countries with significantly larger populations, such as China and India. South Africa is also ranked the fifth highest DR-TB high burden country. In addition, the numbers of MDR-TB and XDR-TB patients have increased due to the concurrent HIV epidemic and inadequate management of TB. There has been a steady increase in cases since 2006, possibly due to increased case detection (Tables I and II). In 2010, the NHLS diagnosed 7 386 MDR-TB and 741 XDR-TB cases. The reason for the decrease in the number of cases between 2009 and 2010 is not clear.

**Table I Number of MDR-TB Patients, 2004-2010 (Laboratory Diagnosis from NHLS)**

PROVINCE	2004	2005	2006	2007	2008	2009	2010	TOTAL
Eastern Cape	379	545	836	1092	1501	1858	1782	<b>7993</b>
Free State	116	151	198	179	381	253	267	<b>1545</b>
Gauteng	537	676	732	986	1028	1307	934	<b>6200</b>
KwaZulu-Natal	583	1024	2200	2208	1573	1773	2032	<b>11393</b>
Limpopo	59	40	77	91	185	204	126	<b>782</b>
Mpumalanga	162	134	139	506	657	446	312	<b>2356</b>
Northern Cape	168	155	188	199	290	631	353	<b>1984</b>
North West	130	203	225	397	363	520	158	<b>1996</b>
Western Cape	1085	1192	1179	1771	2220	2078	1422	<b>10947</b>
<b>SOUTH AFRICA</b>	<b>3219</b>	<b>4120</b>	<b>5774</b>	<b>7429</b>	<b>8198</b>	<b>9070</b>	<b>7386</b>	<b>45196</b>

**Table II Number of XDR-TB Patients, 2004-2010 (Laboratory Diagnosis from NHLS)**

PROVINCE	2004	2005	2006	2007	2008	2009	2010	TOTAL
Eastern Cape	3	18	61	108	175	123	320	808
Free State	1	6	3	4	3	3	7	27
Gauteng	5	14	19	38	30	65	37	208
KwaZulu-Natal	59	227	336	241	181	254	201	1499
Limpopo	-	2	5	2	2	6	6	23
Mpumalanga	-	-	-	12	14	18	5	49
Northern Cape	4	10	3	7	19	40	39	122
North West	1	5	9	4	4	13	14	50
Western Cape	12	16	28	42	60	72	112	342
<b>SOUTH AFRICA</b>	<b>85</b>	<b>298</b>	<b>464</b>	<b>458</b>	<b>488</b>	<b>594</b>	<b>741</b>	<b>3128</b>

As shown in Tables I and II, KwaZulu-Natal and Western Cape notified the highest number of cases followed by Eastern Cape and Gauteng.

As shown in Table III, there is a wide gap between the number of MDR- and XDR-TB patients diagnosed, registered and started on treatment. In 2009, the programme did not start DR-TB treatment in approximately 50% of all diagnosed MDR-TB patients. The numbers diagnosed and started on treatment depend on the prevalence of drug-resistance and accessibility and efficiency of diagnostic and treatment services in the provinces.

**Table III Number of MDR- and XDR-TB Patients Started on Treatment, 2007-2010**

PROVINCE	2007		2008		2009		2010	
	MDR	XDR	MDR	XDR	MDR	XDR	MDR	XDR
Eastern Cape	932	171	772	135	847	135	927	224
Free State	158	7	233	7	148	6	167	5
Gauteng	497	45	414	40	512	25	607	30
KwaZulu-Natal	788	170	1039	163	927	177	1788	235
Limpopo	71	2	104	0	88	3	119	3
Mpumalanga	148	0	272	3	198	5	298	6
Northern Cape	145	11	148	8	253	13	230	37
North West	156	4	159	1	175	9	143	14
Western Cape	439	64	890	34	995	58	1034	61
<b>SOUTH AFRICA</b>	<b>3334</b>	<b>474</b>	<b>4031</b>	<b>391</b>	<b>4143</b>	<b>431</b>	<b>5313</b>	<b>615</b>

## 1.4. Framework for Managing Drug-Resistant TB

Management of DR-TB is organised around five components like the DOTS strategy, because the underlying principles are the same, namely:

- Sustained government commitment;
- Accurate, timely diagnosis through quality assured culture and drug susceptibility testing;
- Appropriate treatment utilising second-line drugs under strict supervision;
- Uninterrupted supply of quality assured second-line drugs; and
- Standardised recording and reporting system.

## 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 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 a 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.

### Drug Supply

The uninterrupted supply of anti-TB drugs to treatment points is crucial in preventing drug resistance.

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

## 2. LEGISLATIVE FRAMEWORK AND PUBLIC HEALTH ETHICS

The Department of Health is legally responsible for the 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 the uninfected 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 affects 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 emphasises 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**

Gives effect to the right to administrative action that is lawful, reasonable and procedurally fair and to the right to written reasons for administrative action as contemplated in section 33 of the Constitution of the Republic of South Africa, 1996.

#### **The Occupational Health and Safety Act 85 of 1993**

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 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**

The Siracusa Principles on the Limitation and Derogation of Provisions in the International Covenant on Civil and Political Rights<sup>1</sup> state, “Public health may be invoked as grounds 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 WHO.
- Guided by the goal of their universal application for the protection of all people of the world from international spread of disease.

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<sup>1</sup> The United Nations, Economic and Social Council, U.N. Sub-Commission on Prevention of Discrimination and Protection of Minorities, Siracusa Principles on the Limitation and Derogation of Provisions in the International Covenant on Civil and Political Rights, Annex, UN Doc E/CN.4/1984/4 (1984)

The management and prevention of DR-TB requires cooperation by all affected and balancing of community and individual interests. Limitation of individual freedom of 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:

- Provide and manage treatment in accordance with the law.
- Adopt the least restrictive practices that will allow the common good to be protected.
- Ensure that restrictions are necessary and proportional to the need for protection.
- Explore all less restrictive measures before implementing more intrusive public health measures.
- Base intervention 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.
- Attempt to ensure that those impacted by restrictions receive support from the community (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 stigmatisation 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 avoid discrimination based on colour, religion and status.
- Engage patients and their families in the decision-making process and ensure that they give consent.
- Treat all patients with dignity and respect.
- Communicate clearly in local language and culturally sensitive manner.
- Ensure 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 be considered and addressed when managing patients with DR-TB.

#### **Patient**

Some patients might refuse treatment and hospitalisation; other patients may wish to be treated but do not agree to be hospitalised. Some patients request discharge from MDR-TB units while still highly infectious. Decentralisation of MDR-TB care is a solution to this problem.

#### **Community**

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 requires that infection control strategies are implemented in the community to ensure protection of vulnerable groups (e.g., children, HIV-positive people) and intensive community mobilisation to increase awareness and address stigma.

#### **Labour**

Working in MDR-TB hospitals exposes staff to a high risk environment for infection, which is a cause for concern for HCWs often results in high staff turnover, refusal to work in high risk areas, and difficulties in recruiting staff. It is vital to ensure that adequate infection control measures are implemented, all staff is protected and occupational health services and compensation for workers who contract the disease are provided.

# **3. ORGANISATION OF SERVICES**



## 3. ORGANISATION OF SERVICES

The Policy Guidelines has been developed based on previous experience in Peru, current efforts at out-patient MDR-TB treatment in KwaZulu-Natal, and in the Western Cape. The Policy Guidelines describe the roles of the different levels of patient management.

### 3.1. Types and Functions of DR-TB Units

A DR-TB unit is a health facility where health professionals have been trained to initiate and manage the treatment of DR-TB patients. A DR-TB unit may be a (stand-alone) hospital, a DR-TB ward in a general hospital, or a DR-TB ward in a TB hospital or other specialised hospital.

Hospitalisation provides time for:

- Initiating DR-TB and HIV treatment;
- Monitoring the initial response to treatment and possibly adjusting medication;
- Educating and counselling the patient on MDR-TB and HIV;
- Assessing the household in preparation for discharge; and
- Educating and counselling the family and other household members on DR-TB and HIV to optimise family support for the patient in treatment adherence and implementation of household infection control.

#### 3.1.1. Provincial Level

The centralised DR-TB unit is also known as the “Provincial Centre of Excellence”. Each province has at least one hospital that is a specialised DR-TB unit. This hospital will perform a supporting and supervisory role for the MDR-TB outpatient programme in each province, and as the centre of excellence, provide technical advice to the decentralised MDR-TB sites.

#### Functions of the Centralised DR-TB Unit

- Initiating treatment of all DR-TB cases after appropriate assessment;
- Admitting DR-TB cases from the geographic area around the unit;
- Ensuring hospitalisation of all XDR-TB cases until there are two successive negative TB cultures;
- Assessing all DR-TB patients attending the clinic each month;
- Providing DOT to all DR-TB patients attending the unit each day;
- Recording and reporting to the provincial Department of Health;
- Providing on-going training, support and supervision for all the facilities in the province;
- Providing social support, rehabilitation, educational and skills building programmes for patients;
- Providing education and counselling to all patients admitted in hospital;
- Preparing a discharge plan for all patients and ensuring effective down referrals;
- Monitoring DR-TB patients post discharge until completion of treatment and two years post treatment completion;
- Monitoring rational usage of second-line drugs and ancillary drugs for side effects management;
- Establishing and maintaining functional clinical management teams;
- Compiling monthly, quarterly, six-monthly and annual reports of DR-TB patients started on treatment, their culture conversion and outcomes;
- Providing technical assistance and capacity building to decentralised DR-TB units, and feeder clinics on management of DR-TB; and
- Arranging patients’ evaluations at provincial patient review committees.

### 3.1.2. Districts or Sub-Districts

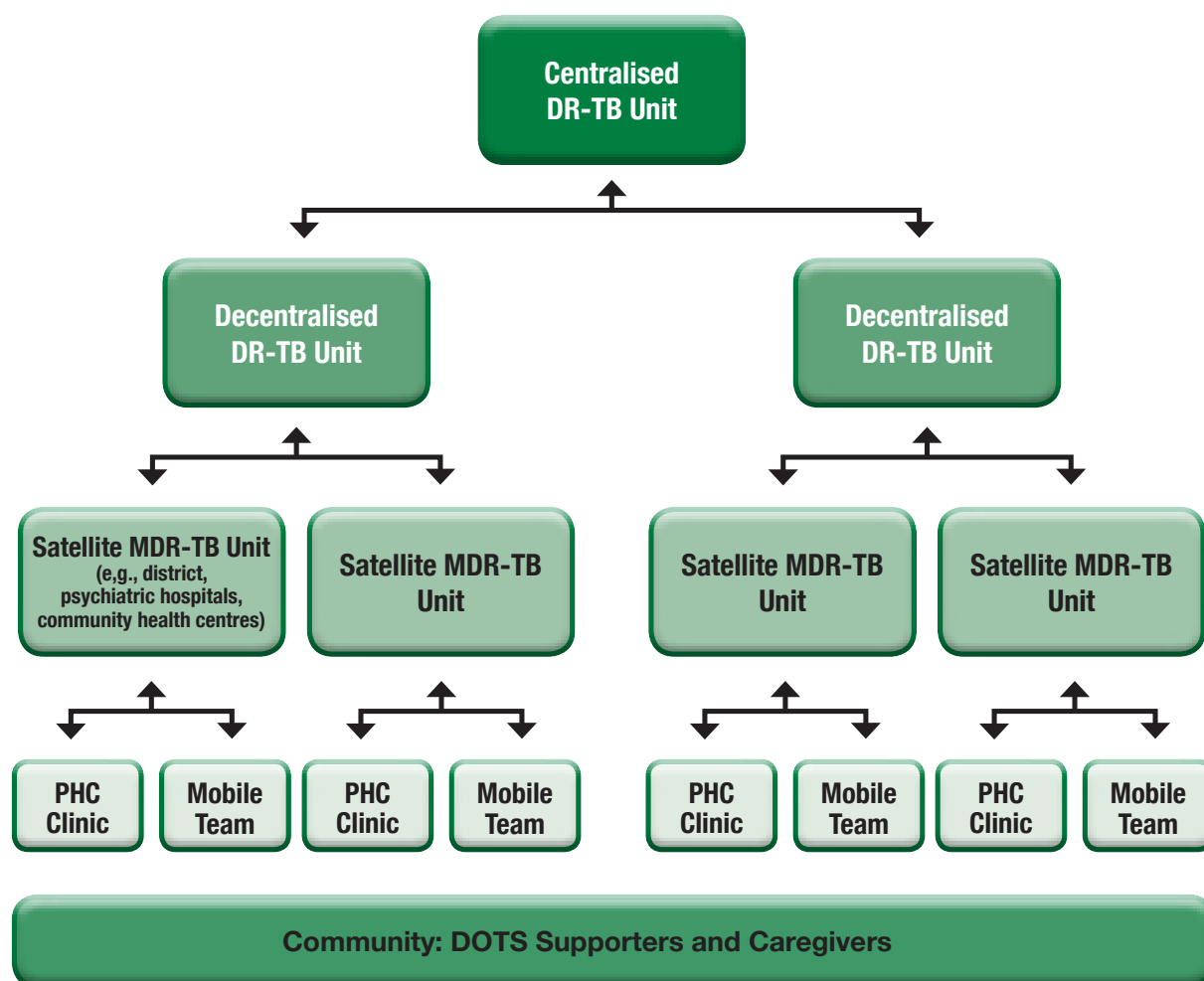
Districts and sub-districts have administrative and management responsibilities in ensuring effective DR-TB services in the area. Their primary functions are to:

- Trace all confirmed DR-TB patients and refer to the DR-TB hospital;
- Ensure availability of drugs for the patient at the clinic or district hospital;
- Establish an efficient patient retrieval system for patients who default DR-TB treatment;
- Arrange transportation for patient evaluation and follow-up at the DR-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;
- Conduct household assessments prior discharging patients from DR-TB units;
- Monitor and evaluate DR-TB programme performance;
- Ensure continuum of care for patients post discharge;
- Ensure on-going psychosocial support for patients; and
- Increase awareness and education about DR-TB among communities.

**Table IV Recommended Staffing Levels for the Centralised DR-TB Unit**

Staff	Recommended Staffing Levels
Doctors	1 doctor for each 40-bed centralised DR-TB unit (assuming a general occupancy rate of more than 75%).
Operational nursing manager	1 for each unit
Nurses	1 professional nurse for 3 enrolled nurses or nursing assistants. 15 nurses are adequate for a 40-bed unit.
Pharmacist	1 pharmacist for a unit of 100 to 200 beds.
Social worker	1 for a 40-bed unit
Dietician	1 for a 40-bed unit
Clinical psychologist	1 for a 40-bed unit
Occupational therapist	1 for a 40-bed unit
Audiologist	1 for a 100-bed unit
Physiotherapist	1 for a 40-bed unit
Data capturer/ administration clerk	1 for a 40-bed unit
Administration clerk	1 for a 40-bed unit
General Assistants	8 for a 40-bed unit
Housekeeper	1 for each unit
Driver	1 for each 40-bed unit

**Figure I Units for the Decentralised Management of DR-TB**



Satellite MDR-TB Units exist to complement bed capacity of decentralised sites. They are essentially transitional and should be capacitated to become decentralised sites. Mobile teams are to be attached to PHC services but operate within the community.

### 3.1.3. Decentralised DR-TB Units

There will be a number of decentralised DR-TB units in each province, depending on the need, but at least one unit per district is required. These units will be responsible for the initiation and management of DR-TB patients in a defined geographical area, initially as inpatients, but then when appropriate, as outpatients. These units may consist of whole hospitals, wards or sections of existing provincial, district or sub-district level hospitals.

**NOTE:** Decentralised DR-TB units with adequate human resources and infrastructure capacity may initiate treatment and follow up on XDR-TB cases according to the national and provincial Department of Health's discretion. At least one decentralised unit is required for each district.

Patients diagnosed with MDR-TB who are smear microscopy positive will be hospitalised at the decentralised DR-TB units for up to eight weeks or until they become smear negative on two consecutive tests. This is important given that most patients in South Africa with MDR-TB are co-infected with HIV and will need to commence treatment for both diseases.

Once a patient's sputum smear microscopy is negative and they meet the criteria for outpatient treatment (see Figure 2), they may receive treatment while living at home. Smear positive patients who refuse admission but are willing to receive medication should still be treated.

### Functions of the Decentralised MDR-TB Units

Districts and sub-districts have administrative and management responsibilities in ensuring effective TB and DR-TB services in their areas. Their primary functions are:

- Initiating treatment of all MDR-TB cases after appropriate assessment;
- Admitting DR-TB cases when indicated;
- Providing transportation for patient evaluation and monthly follow up of all DR-TB cases attending clinic;
- Tracing confirmed DR-TB patients and referring them to the DR-TB hospital;
- Providing DOT to all DR-TB patients attending the unit daily;
- Providing social support, rehabilitation, educational and skills building programmes for patients;
- Providing education and counselling to all patients admitted to hospital;
- Preparing a discharge plan for all patients and ensuring effective down referrals;
- Monitoring DR-TB patients post discharge until completion of treatment and two years post treatment completion;
- Ensuring availability of drugs and monitoring rational usage of second-line drugs;
- Establishing and maintaining functional clinical management teams;
- Recording and reporting to the provincial Department of Health;
- Compiling monthly, quarterly, six monthly and annual reports of DR-TB patients started on treatment, culture conversion and outcomes;
- Monitoring and evaluating DR-TB programme performance;
- Providing technical assistance and capacity building to satellite MDR-TB units and feeder clinics on management of DR-TB;
- Monitoring treatment side effects;
- Ensuring referral of patients with XDR-TB, adverse drug reactions (ADRs) and complicated disease to the centralised DR-TB unit; and
- Tracing all confirmed cases.

**Table V Recommended Staffing Levels of the Decentralised DR-TB Units**

Staff	Recommended Staffing Levels
Doctors	1 doctor for each 40-bed decentralised DR-TB unit (assuming a general occupancy rate of more than 75%).
Nurses	1 professional nurse for 3 enrolled nurses or nursing assistants. 15 nurses are adequate for a 40-bed unit.
<b>Part-time Staff:</b> These officers are usually employed by hospitals, and will be required to give 10% to 20% of their time to DR-TB patients	
Pharmacist	1 for 10-20 patients
Social worker	1 for 10-20 patients
Dietician	1 for 10-20 patients
Clinical psychologist	1 for 10-20 patients
Occupational therapist	1 for 10-20 patients
Audiologist	1 for 10-40 patients
Physiotherapist	1 for 10-20 patients
Data capturer	1 for 10-20 patients

### 3.1.4. Satellite MDR-TB Units

Satellite units may be based at district or psychiatric hospitals, community health centres, or correctional services facilities. These are transitional structures that should have the capacity to become decentralised sites. Satellite MDR-TB units should exist to:

- Admit and follow up MDR-TB patients initiated on treatment at decentralised sites; and
- Serve patients who refuse to start treatment unless they are closer to home.

After the assessment and initiation of MDR-TB therapy (by a centralised or decentralised DR-TB unit), patients may be referred to a satellite MDR-TB unit where they will receive treatment and are monitored daily. Nurses, with the support of a doctor based at the centralised or decentralised DR-TB sites should monitor the health of the patient.

An improvement in the patient's medical condition (e.g., weight gain, no fever, no cough, etc.) indicates that s/he is tolerating all MDR-TB drugs and HAART and is smear negative. Patients can be discharged to the community and continue receiving treatment either from the mobile team or their nearest primary health-care facility. At times MDR-TB treatment may be administered in institutions such as prisons, mining health facilities or psychiatric hospitals. The initial period of hospitalisation should be between two and eight weeks.

Initially the patient should return monthly to the decentralised DR-TB site for on-going management of their condition. When the programme is established and the staff at satellite MDR-TB sites are trained, it may be possible for patients in the continuation phase to be monitored monthly at satellite MDR-TB sites. Until then, the patient should travel once bi-monthly or quarterly to the decentralised DR-TB site.

Satellite MDR-TB units should not initiate MDR-TB treatment. They may eventually be upgraded to a decentralised MDR-TB unit if they have adequate and trained staff and infrastructure.

### Functions of Satellite MDR-TB Units

- Admitting all MDR-TB cases referred from centralised or decentralised DR-TB units;
- Ensuring monthly follow up of all DR-TB patients attending the unit;
- Providing DOT to all DR-TB patients attending daily;
- Educating and counselling all patients admitted to hospital;
- Preparing a discharge plan for all patients and ensuring effective down referrals;
- Monitoring treatment side effects; and
- Ensuring referral of patients with XDR-TB, severe ADRs, and complicated disease to the centralised DR-TB site.

**Table VI Recommended Satellite MDR-TB Unit Staffing Levels**

Staff	Recommended Staffing Levels
Nurses (professional or staff nurse or nursing assistant)	1 professional nurse for 20 patients
Community Caregiver	1 for 10 patients
<b>Part-time Staff</b>	
Doctor	Optional
Social worker	Optional
Data capturer	Optional

### 3.1.5. Primary Health Care Facilities

Primary health care (PHC) facilities play a significant role in providing injectables at clinics and DOT to all DR-TB patients in their areas. This must be integrated with the treatment of other TB and HIV patients. The existing TB nurses will be trained to handle these activities. It is not necessary to have dedicated DR-TB nurses at the primary health care level.

Patients who have access to a PHC clinic should utilise the health facility for their daily injections and 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 should be managed by the nurse at the facility, but the patient should be referred to the decentralised DR-TB unit for management of more serious side effects. In addition, the nurse at the facility should be responsible for contact tracing and serve as the link between the decentralised DR-TB unit and MDR-TB patients treated at the facility.

PHC facilities treating MDR-TB patients will be supported by the nearest decentralised DR-TB unit or the centralised DR-TB unit or provincial centre of excellence if it is closer to the facility.

#### Functions of Primary Health Care Facilities

- Identifying high risk groups;
- Screening and testing symptomatic high-risk groups;
- Tracing patients with a confirmed diagnosis of DR-TB;
- Notifying the district TB coordinator;
- Providing initial counselling and education of the patient and family;
- Preparing patient for hospital admission when indicated;
- Coordinating referrals to the centralised and decentralised DR-TB units;
- Ensuring monthly follow up of all DR-TB cases attending a clinic;
- Providing DOT to all DR-TB patients attending daily;
- Conducting contact screening of close contacts;
- Following up patients initiated to start community-based treatment or patients who are post discharge from hospital;
- Coordinating follow up visits in hospital;
- Tracing treatment interrupters;
- Collecting monthly sputum and other routine tests;
- Monitoring treatment side effects and;
- Ensuring referral of patients with XDR-TB, severe ADRs, and complicated disease to the centralised DR-TB unit.

#### Contact Tracing and Monitoring

Contact tracing and monitoring is an important role of the PHC facilities through the mobile teams and DOTS supporters. Measures for contact tracing and monitoring include:

- Listing and examining all contacts and testing those with symptoms in accordance with existing TB protocols;
- Re-testing contacts with symptoms for TB and drug susceptibility six-monthly for two years;
- Ensuring that the MDR-TB patient is continuously screened for signs and symptoms; and
- Offering HIV counselling and testing to contacts.

**Table VII Recommended Primary Health Care Staffing Levels**

Staff	Recommended Staffing Levels
Doctor	Part-time or full-time depending on patient load.
Nurses (professional or staff nurse or nursing assistant)	Part-time or full-time depending on patient load.
Community caregiver	1 for 10 patients
Social worker	Optional
Data capturer	1 for 50 patients

**3.1.6. Mobile Teams**

Mobile teams are also called mobile MDR-TB units. These are units based at the PHC facility or a satellite MDR-TB unit. They provide injections to patients at their homes, supervise intake of oral tablets, and educate family about infection control.

Patients who are unable to access a health facility daily should, for the duration of the injectable phase of treatment, be visited daily at home (five times a week) by a mobile team, which should consist of a driver and nurse. During these visits, the team will administer injectable drugs, observe the patient taking their oral drugs, 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 should be managed by the nurse on the mobile team, but the patient should be referred to the decentralised DR-TB site for management of more serious side effects. The mobile MDR-TB unit should also be responsible for contact tracing and serve as the link between the decentralised DR-TB site and MDR-TB patients in the community. In some instances the mobile MDR-TB unit will also carry out TB programme activities such as tracing defaulters from the TB programme or giving re-treatment 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 of Mobile Teams**

- Provide DOT to all DR-TB patients in the area;
- Provide patient, family and community education on TB;
- Monitor treatment side effects and referring to the nearest health-care facility when necessary; and
- Maintain appropriate records.

**Table VIII Recommended Mobile Team Staffing Levels**

Staff	Recommended Staffing Levels
Nurses (professional or staff nurse or nursing assistant)	1 for 20 patients
Community caregiver	1 for 10 patients
Driver	1 for 20 patients



### 3.1.7. Community Level: DOTS Supporters/Caregivers

Depending on the local situation, the DOTS supporters may be community caregivers, community DOTS volunteers or family members. It should be noted that training is very important for this cadre of supporters, and compensation should be considered because DOT is the department's core business. Family members should only be used as a last option because they may be coerced by other family members, making them less objective as community caregivers.

Patients and their designated household treatment supporters must be trained on 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), MDR-TB medications, common side effects/toxicity, and the role of HIV in TB infection. Family planning during MDR-TB treatment should be encouraged. Community caregivers should provide on-going daily support to MDR-TB patients who are treated on an outpatient basis.

If the patient is on HAART, the patient and treatment supporter should receive literacy training according to current practice. This must be given by staff trained in MDR-TB and integrated TB and HIV care. Any training that takes place in the clinical setting will be separated in space and time from the HAART programme to avoid nosocomial transmission. In addition, education for the patient, household supporter, and possibly even the treatment supporter should be given at individual patients' home by the mobile MDR-TB unit.

Given the important role of the treatment supporter, s/he should preferably be HIV-negative and have access to a support group and regular TB screening.

### Functions of Community Level Services

- Provide DOT to all DR-TB patients in the area;
- Provide patient, family and community education on TB;
- Monitor treatment side effects and referring to the nearest health-care facility when required; and
- Maintain appropriate records.

Table IX describes the responsibilities of staff working at various levels of MDR-TB care.

**Table IX Staff Responsibilities**

Staff	Responsibilities
Doctor	<ul style="list-style-type: none"> <li>• Assess patient for co-morbidities and requesting baseline tests.</li> <li>• Initiate DR-TB treatment regimen for the patient (at centralised and decentralised DR-TB units).</li> <li>• Review treatment of patient and make any necessary adjustments.</li> <li>• Provide clinical monitoring of patients' treatment for ADRs and prompt management.</li> <li>• Report ADRs to the Medicines Control Council.</li> <li>• Provide prompt referral for tertiary care or specialist care when needed.</li> <li>• Ensure necessary laboratory tests are conducted timeously for adequate monitoring of the patient and his/her response to treatment.</li> <li>• Attend meetings, and keep up-to-date about TB and DR-TB management and surveillance.</li> <li>• Educate nurses and other members of the DR-TB team.</li> </ul>



Staff	Responsibilities
Professional nurse/staff nurse or nursing assistant	<ul style="list-style-type: none"> <li>• Coordinate clinical care with other health professionals.</li> <li>• Monitor inpatients and refer to doctor when appropriate.</li> <li>• Coordinate household assessment, discharge of patient, and linkages to outpatient services.</li> <li>• Manage the weekly MDR-TB outpatient clinic, ensuring that there is a functioning filing system and laboratory results are retrieved and recorded before the patient is attended to by a doctor for the monthly review.</li> <li>• Manage and coordinate MDR-TB outpatients.</li> <li>• Support nursing staff in the decentralised DR-TB site.</li> <li>• Monitor patient management (MDR-TB register) and compile a six-monthly report.</li> <li>• Maintain a close relationship with the patient.</li> <li>• Administer treatment to the patient.</li> <li>• Provide on-going nursing care.</li> <li>• Complete the patient treatment card for treatment dosages given to the patient.</li> <li>• Provide counselling for HIV testing.</li> <li>• Conduct HIV testing on patients who give consent.</li> <li>• Provide educational talks to patients on a one-on-one basis or in group sessions.</li> <li>• Plan awareness campaigns on different topics to be conducted within the hospital.</li> <li>• Ensure MDR-TB register is updated regularly.</li> <li>• Ensure patients who miss appointments or who default are followed up by tracing team.</li> <li>• Liaise with mobile teams with regard to patients.</li> <li>• Support mobile teams and community caregivers.</li> </ul>
Pharmacist	<ul style="list-style-type: none"> <li>• Ensure availability of second-line anti-TB and ancillary drugs.</li> <li>• Monitor drug stock levels.</li> <li>• Ensure correct storage of the drugs.</li> <li>• Dispatch drugs for patients who have been discharged to the local clinic or hospital.</li> </ul>
Admin clerk/Data capturer	<ul style="list-style-type: none"> <li>• Retrieve data related to sputum and other lab results from the laboratory and update patient records.</li> <li>• Capture patient data on the Electronic Drug Resistant TB Register (EDRWeb)</li> <li>• Compile and submit six-monthly cohort and other reports as needed.</li> </ul>
Clinical psychologist (if available)	<ul style="list-style-type: none"> <li>• Conduct initial assessment of patients with psychological problems.</li> <li>• Conduct one on one or group therapy sessions for patients.</li> <li>• Refer patients who need expert opinion timeously.</li> </ul>

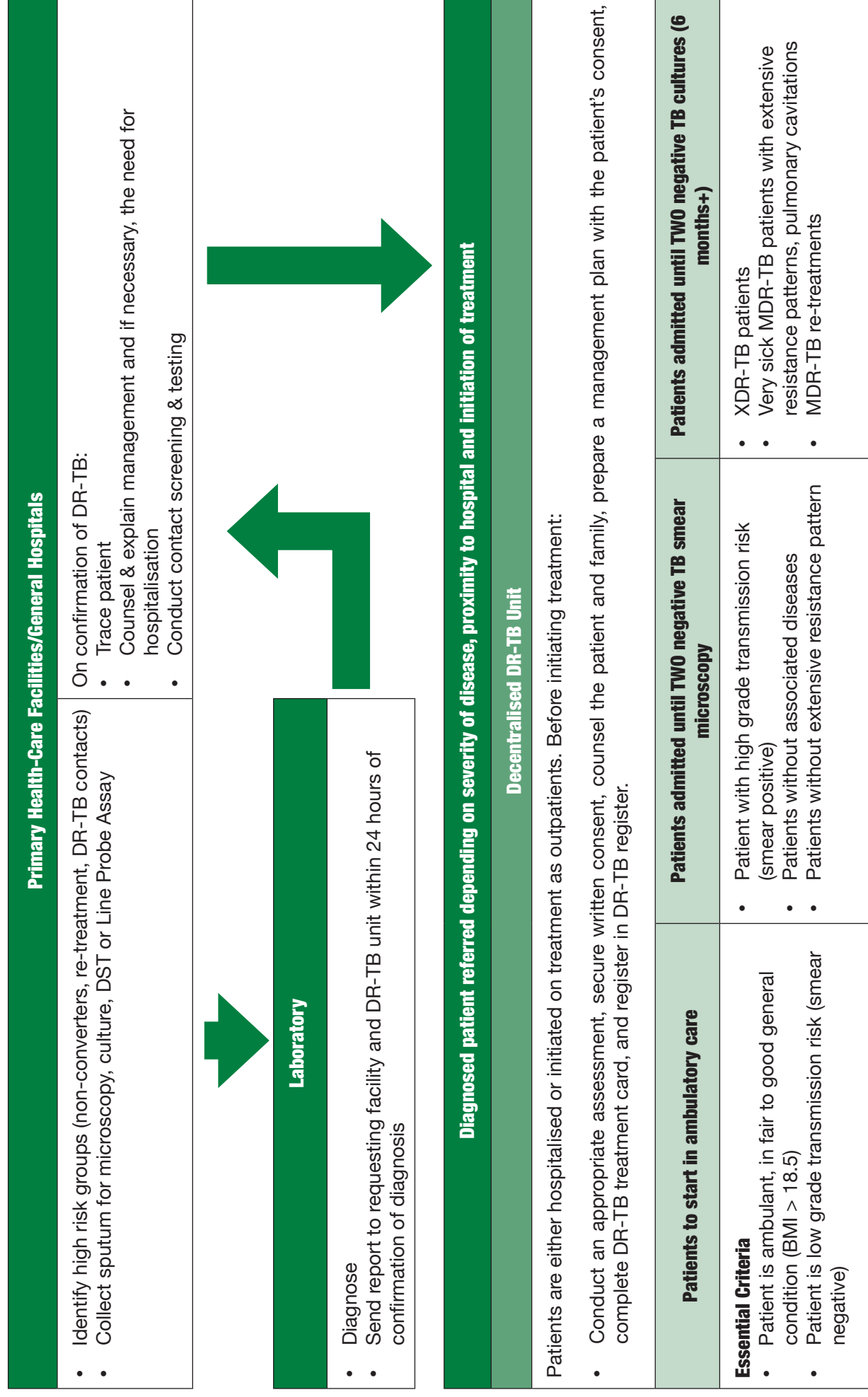
Staff	Responsibilities
<b>Occupational therapist (if available)</b>	<ul style="list-style-type: none"> <li>• Conduct initial assessment of patients' psycho-social status.</li> <li>• Develop patients' insight into disease and behaviour through counselling and education.</li> <li>• Provide life skills development programmes.</li> <li>• Provide rehabilitation programmes for patients.</li> <li>• Monitor patient progress.</li> <li>• Facilitate support, stress management, and behaviour modification groups.</li> <li>• Plan pre-vocational training programmes.</li> </ul>
<b>Audiologist</b>	<ul style="list-style-type: none"> <li>• Conduct baseline assessments for all patients prior to initiation of treatment and inform doctor if hearing impaired.</li> <li>• Monitor patients monthly for hearing impairment during the injectable phase and inform doctor if hearing deteriorates.</li> <li>• Recommend management of patient with hearing impairment.</li> </ul>
<b>Physiotherapist (if available)</b>	<ul style="list-style-type: none"> <li>• Conduct initial assessment of patients with co-morbidities and extensive lung disease.</li> <li>• Develop treatment programmes for the individual patients.</li> <li>• Monitor patient progress.</li> <li>• Assist patients with expectoration for monitoring culture conversion.</li> </ul>
<b>Nursing service manager</b>	<ul style="list-style-type: none"> <li>• Liaise with mobile teams and staff at facilities administering MDR-TB treatment to outpatients.</li> <li>• Ensure recording and reporting procedures are up-to-date.</li> <li>• Liaise with other stakeholders in the geographical area.</li> <li>• Organise and document six-monthly contact screening.</li> <li>• Trace newly identified MDR-TB patients and organise admission to decentralised DR-TB unit.</li> <li>• Organise regular monthly visits for MDR-TB outpatients to decentralised DR-TB units for monthly follow up.</li> <li>• Coordinate activities of the tracing team and monitor their activities.</li> <li>• Participate in district DR-TB team.</li> <li>• Link DR-TB treatment programme with TB programme.</li> </ul>
<b>Professional nurse/staff nurse/nursing assistant at mobile team</b>	<ul style="list-style-type: none"> <li>• Possess a driving license to provide transportation in the absence of driver.</li> <li>• Administer daily injections to all MDR-TB patients in the intensive phase of treatment, monitor side effects, adherence, and household infection control practices.</li> <li>• Support and supervision of DOTS supporters.</li> <li>• Locate newly diagnosed MDR-TB patients.</li> <li>• Trace MDR-TB defaulters.</li> <li>• Conduct six-monthly contact tracing on all household contacts.</li> <li>• Provide on-going education on adherence, side effects, and infection control.</li> <li>• Record adherence and side effects and where refer complications or problems in patient management to nurse coordinator.</li> </ul>

Staff	Responsibilities
Driver	<ul style="list-style-type: none"> <li>• Drive mobile team to administer daily injections to all MDR-TB patients in the intensive phase of treatment.</li> <li>• Transport patients for diagnosis, follow up, and admissions.</li> <li>• Drive mobile MDR-TB unit to trace treatment interrupters and defaulters.</li> </ul>
Caregivers/DOTS supporters	<ul style="list-style-type: none"> <li>• Assist with DOT administration of all doses received outside of health establishments.</li> <li>• Communicate all routine and emergency clinical issues to mobile team.</li> <li>• Provide on-going education on adherence and infection control.</li> <li>• Recognise side effects, record and report to nurses and doctors.</li> </ul>
Family members	<ul style="list-style-type: none"> <li>• Provide emotional support and nursing care to the patient during treatment.</li> <li>• Report any problems or changes in patient condition to the clinic nurse or community caregiver.</li> <li>• Assist with early identification and testing of symptomatic contacts.</li> </ul>

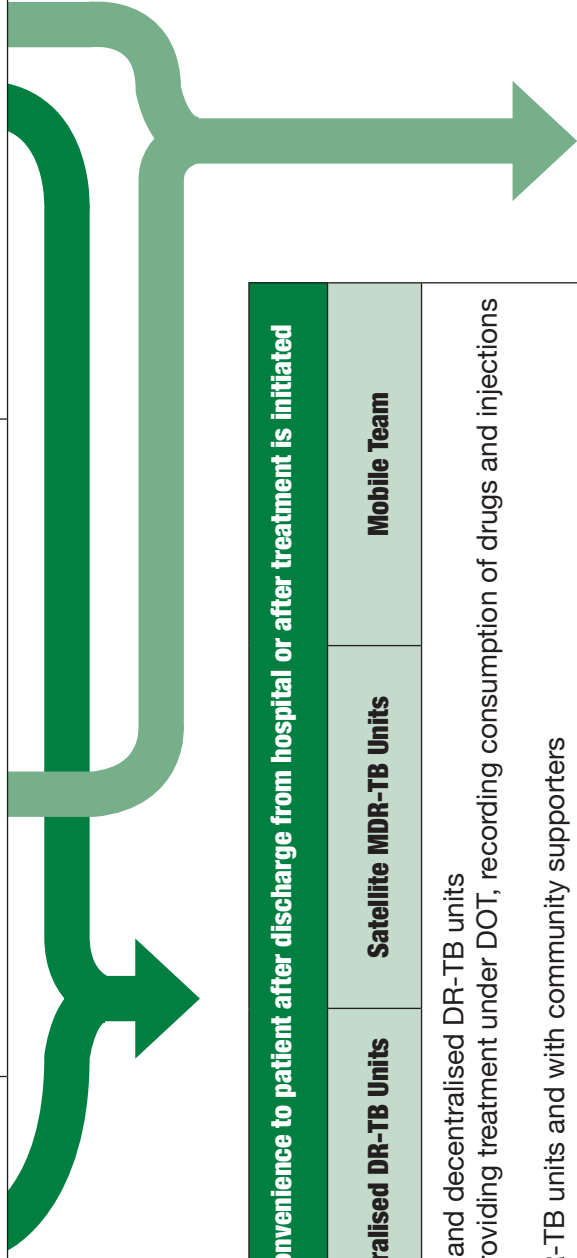
**Table X Responsibilities at Every Level**

Functions	Centralised MDR-TB Unit	Decentralised MDR-TB Unit	Satellite MDR-TB Unit	PHC	Mobile Team	Community Caregivers
Admission of all MDR-TB cases till two successive smear negative/ culture negative	√	√	NO, Unless no bed availability at centralised or decentralised DR-TB units	NO	NO	NO
Admission of all XDR-TB cases until two successive culture negatives are obtained	√	NO Unless there is space and capacity to manage XDR-TB	NO	NO	NO	NO
Monthly follow up of all DR-TB cases attending at clinic	√	√	√	√	√	NO
DOT to all DR-TB patients attending daily	√	√	√	√	√	√
Recording and reporting (DR-TB Register and EDRWeb)	√	√	NO <sup>1</sup>	NO*	NO*	NO*
Monitoring and supervising DR-TB clinical management in the province	√	NO	NO	NO	NO	NO

Figure II Flow of DR-TB Patients



<ul style="list-style-type: none"> <li>Start all GeneXpert positive with resistance to rifampicin on MDR-TB treatment</li> <li>Patient refuses admission or beds are unavailable</li> </ul> <p><b>Additional Criteria</b></p> <ul style="list-style-type: none"> <li>Stable accommodation</li> <li>Household treatment support</li> <li>Good reason for not wanting to be hospitalised</li> </ul>	<ul style="list-style-type: none"> <li>Severe adverse drug reactions</li> <li>Other associated diseases</li> <li>May not have access to decentralised or satellite units – until they achieve TB culture conversion</li> </ul>
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Patients are referred depending on convenience to patient after discharge from hospital or after treatment is initiated			
Centralised DR-TB Units	Decentralised DR-TB Units	Satellite MDR-TB Units	Mobile Team
<ul style="list-style-type: none"> <li>Patients registered in centralised and decentralised DR-TB units</li> <li>All DR-TB units responsible for providing treatment under DOT, recording consumption of drugs and injections on DR-TB treatment card</li> <li>DR-TB treatment card is at all DR-TB units and with community supporters</li> </ul>			

On discharge from centralised/decentralised DR-TB units: <ul style="list-style-type: none"> <li>Ask about most convenient facility for referral</li> <li>Inform patient about management plan</li> </ul>	<ul style="list-style-type: none"> <li>Notify receiving clinic/hospital of down referral</li> <li>Arrange transport for the patient</li> <li>Complete patient treatment follow-up card</li> </ul>
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## 3.2. Management Teams/Committees at Different Levels

The provincial TB directorates are responsible for setting up management teams and committees to oversee the clinical management of DR-TB patients in the province.

### 3.2.1. Provincial DR-TB Review Committee

Each province should establish a management team to support and advice in difficult clinical cases, medico-legal and ethical issues such as termination of MDR-TB treatment in a patient who does not respond to treatment. This committee must be multi-disciplinary and should include medical officers and/or professional nurses from the DR-TB hospital, physicians, pathologists, paediatricians, cardio-thoracic surgeons, public health specialists, radiologists, civil society representatives, social workers, provincial management and a specialist in legal and ethical issues. Other representatives from government departments such as Social Development, Correctional Services, Military Health Services, South African Social Security Agency, and the mining industry may be included in this committee.

This committee advises and recommends on the following:

- Appropriate clinical management of individual MDR- and XDR-TB patients;
- Use of salvage regimens in individual patients with high-grade resistance;
- Management of chronic drug resistant TB regarding termination of treatment and palliative care;
- Management of patients who refuse treatment;
- Management of infectious patients who do not cooperate with the health professionals and those who abscond from hospital or refuse to be admitted; and
- Development of provincial criteria on pass-outs.
- Identification and resolutions to health systems issues contributing to poor service delivery such as delays in culture results or shortages of medication.

### 3.2.2. District and Sub-District Level

At a district and sub-district level co-ordination of DR-TB activities will be done by the district and sub-district TB co-ordinators and the district TB team if there is one. This team will be responsible for:

- Informing (PHC) staff of the latest developments regarding DR-TB;
- Disseminating and training PHC staff on the latest guidelines regarding when sputum cultures should be taken so that patients with DR-TB are diagnosed as soon as possible;
- Referring patients diagnosed with DR-TB to the decentralised unit for initiation of treatment;
- Ensuring that PHC staff feel supported in their treatment of patients with DR-TB;
- Ensuring that there are no interruptions in treatment as the patient moves from being an inpatient to receiving care in the community; and
- Monitoring and referring patients receiving treatment in the community.

Patient support groups should be formed at all levels of care to enhance adherence.

## 3.3. Treatment Follow Up

DR-TB treatment should be monitored closely through daily DOTS and recording of patients taking their drugs and receiving injections. Sputum for smear microscopy and culture should be collected every month for the duration of treatment. Depending on where the patient receives care, daily DOTS and recording of patients taking their drugs and receiving injections should be done by the decentralised DR-TB site, mobile team or the satellite unit administering medication. Sputum collection and the monitoring of smear microscopy, culture and DST results should be conducted at the decentralised DR-TB site.

Adverse drug reactions should be monitored continuously by the facility where the patient receives treatment or the mobile team and DOTS supporters. ADRs should be assessed using a check-list and where necessary reported without delay to supervising unit. ADRs must be treated aggressively as this will enhance treatment adherence.

Details of the patient's HIV status and HAART, including the commencement date and treatment regimen must be recorded in the patients' notes. The clinical and laboratory evaluations that should be conducted monthly are listed in Table XI.

**Table XI Monthly Clinical and Laboratory Evaluations**

Microbiological assessment (microscopy and culture)
Pregnancy test (on women of childbearing age without documented contraception)
Weight and vital signs
Urea and electrolytes during injectable phase of treatment
Audiometry during injectable phase of treatment or as symptoms warrant
Vision
ADRs/side effects daily during injectable phase or monthly during continuation phase
Adherence

### 3.4. Infection Control

#### 3.4.1. Home Infection Control

Mobile teams including DOTS supporters should educate patients and household members. Home infection control will be encouraged and monitored. Home infection control includes the following:

- Ensuring adequate ventilation/open windows;
- Isolating patient (own bedroom where possible);
- Promoting cough hygiene;
- Ensuring that patients use surgical mask during waking hours while at home or when meeting with others;
- Refraining from close contact with children;
- Maximising time in open-air environment (e.g., receiving visitors outside);
- Advising all household members and regular contacts to undergo HIV tests;
- Minimising contact with known HIV positive patients; and
- Ensuring that household members are screened for TB and DR-TB every six months.

#### Infection Control during Home Visits

Mobile teams should decrease the risk of contracting DR-TB by adhering to the following infection control measures:

- Wearing an N95 respirator (health workers and DOTS supporters);
- Keeping home visits or clinical evaluations brief, and whenever possible, conduct these outside or in a well-ventilated room with as much distance as possible from the patient;
- Educating the patient on cough hygiene and avoiding close contact;
- Providing the patient with a surgical mask when close contact is required; and
- Collecting sputum outside, observing prescribed infection control precautions.



### 3.4.2. Infection Control during Patient Transport

When transporting DR-TB patients, the following infection control measures should be observed:

- Use compartmentalised vehicles separating the airspace of the driver from that of the passengers;
- Open vehicle windows;
- Provide surgical mask for patient;
- Provide N95 masks for medical staff and driver; and
- Educate patient.

Health workers who have contact with DR-TB patients should know their HIV status. If they do not, they should be encouraged to be tested for HIV. Health workers who are HIV-positive should commence ART when appropriate and be screened every six months for TB and have a TB culture done at the time of ART initiation and on an annual basis.

### 3.5. Building Treatment Capacity to Meet the Increasing Burden of MDR-TB

It is clear that cases of MDR-TB are on the rise in South Africa. To meet this need, treatment services are being expanded to decentralised treatment facilities and community-based programmes are being developed and expanded. It is imperative that innovative approaches to expand access to MDR-TB treatment are explored.

Nurse-initiated treatment programmes are an important option that has proven successful for HIV management throughout the world. Data on nurse-initiated TB/HIV treatment are beginning to emerge in conference proceedings. South African researchers have documented the successful integration of a nurse-based screening algorithm for pulmonary TB compared with physician diagnosis, and a randomised controlled trial is now underway to evaluate PALSA-Plus nurse-led management strategies throughout primary health-care clinics.

The mounting evidence for nurse management coupled with the continued expansion of community-based MDR-TB programs compels key stakeholders to consider the most appropriate approaches to address the epidemiologic circumstances facing the country.

### 3.6. Conclusion

Issues addressed in this Section, Organisation of Services, are also covered in the Multi-Drug Resistant Tuberculosis: A Policy Framework on Decentralised and Deinstitutionalised Management for South Africa. Our MDR-TB services are still medical practitioner-driven. All MDR-TB patients are being initiated on treatment by medical practitioners. Given the high burden of MDR-TB in the country, we will gradually phase in nurse-initiated MDR-TB component to address this challenge.

## **4. CASE FINDING STRATEGIES**

## 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 XII Risk Factors for MDR-TB**

Risk Factor	Comments
Failure of retreatment regimen (Regimen 2)/ chronic TB patients	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%.
Exposure to a confirmed MDR-TB patient	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.
Failure of treatment regimen for new patients (Regimen 1)	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.  Not all patients who fail Regimen 1 have MDR-TB; this depends on a number of factors, such as treatment compliance.
Relapse and default	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.
History of concomitant use of medications that interfere with TB drug absorption	Antacids containing aluminium or magnesium selectively compete with TB drugs, particularly with isoniazid and fluoroquinolones.
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 positive individuals as a result of the depressed immune system and high susceptibility to infection.

(Adapted from: World Health Organization. Guidelines for the Programmatic Management of drug-resistant Tuberculosis (WHO/HTM/TB/2005.361), World Health Organization: Geneva, Switzerland, 2008).

## 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 months of treatment.
- All newly diagnosed re-treatment TB patients.
- Symptomatic close contacts of confirmed MDR- and XDR-TB patients.
- Symptomatic individuals from known high-risk groups, including HCWs, 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 and streptomycin should not be included routinely as this does not change the management of MDR-TB 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 may not be able to produce sputum specimens, therefore other measures such as gastric aspiration and/or induced sputum should be considered to obtain a specimen for confirmation of diagnosis. Children with TB disease who are close contacts of patients with MDR-TB may be started on MDR-TB treatment until it is confirmed that they do not have MDR-TB.

## 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 or rule out 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, moxifloxacin and ethionamide. Other tests may be conducted on request by the treating clinician.

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

## 5. DIAGNOSIS OF DR-TB

### 5.1. Introduction

In the majority of cases, the development of DR-TB is insidious and 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 HCWs 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 DR-TB are the same as for drug-susceptible TB:

- Cough
- Chest pain
- Dyspnoea
- Haemoptysis
- Systemic symptoms (i.e., fever, chills, night sweats, tiredness, anorexia, weight 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 anaemia. 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. Anaemia 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 much greater damage.

### 5.3. Assessing a Patient for DR-TB

An initial evaluation for DR-TB should include:

- A complete medical history
- A physical examination
- Bacteriological investigations to confirm the diagnosis

#### 5.3.1. Medical History

A proper history of the patient must be recorded. These should include the elements listed below.

- History of presenting symptoms including 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.

- Medical history should include 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 including any surgical procedures the patient has undergone and the reasons.
- Work history should focus on any experience in the mining industry, stay in either TB hospital or prison and laboratory work.
- Social history should include substance abuse (alcohol, tobacco and other drugs).
- Previous confinement in a hospital, prison and duration should be noted.
- Family history of TB, screening of close contacts, confirmation of disease in and treatment of contacts, history of DR-TB exposure should be noted.

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

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-morbid conditions that may require adjustment of the treatment regimen or ancillary treatment.

- The initial physical examination must include the examination of the skin, head, neck, oropharynx, cardiovascular system, pulmonary system, abdominal organs, extremities, and nervous system. The vital signs (i.e., heart rate, blood pressure, respiratory rate, weight and height) must be recorded.
- 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 be obtained. 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 cavitary 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 result, or 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 or suspected 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 including TB microscopy, TB culture and DST. The use of line probe assay is recommended. However, it must be noted that the line probe assay will only be done on TB smear positive patients or culture positive patients. Therefore the 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.
- Triaging specimens for culture and DST.
- Confirming that bacterial growth on culture are acid-fast bacilli and not contaminants.

The sensitivity of smear microscopy is in the region of 30% to 60% when compared to culture, as at least 5 000 to 10 000 organisms per ml of sputum need to be present to allow visualisation, as only a small amount of the sputum is actually viewed. Nevertheless, the infectiousness of DR-TB patients correlates crudely 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. 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 the 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. It can also 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.

### **5.3.3.3. Identification of *M. tuberculosis***

The overwhelming majority of mycobacterial isolates will be *M. tuberculosis* in HIV negative patients. However, the prevalence of non-tuberculous mycobacteria (NTM) can be higher in HIV positive patients. Unless the species is confirmed as *M. tuberculosis*, mycobacterial isolates appearing phenotypically resistant to anti-TB drugs may not be DR-TB, but 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 definite 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

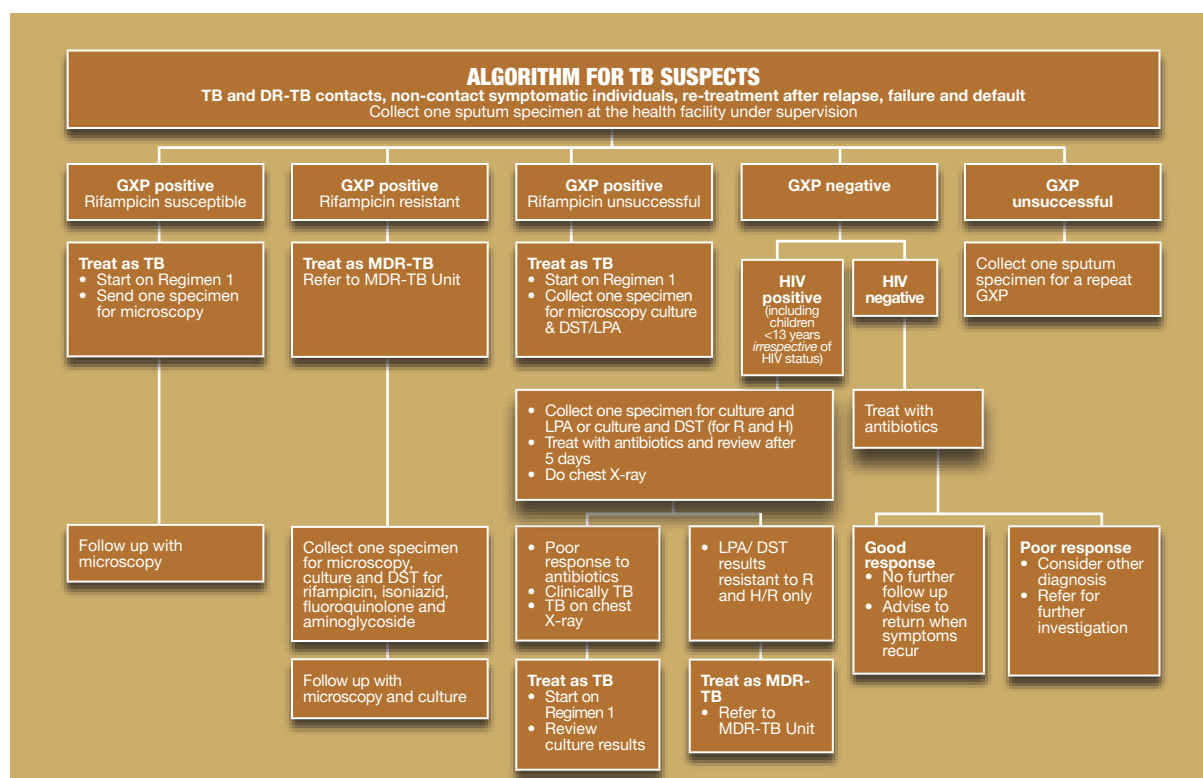
- With conventional methodologies, growth detection, identification of *M. tuberculosis* and DST may take weeks or even months.
- Different anti-TB drugs have different 'critical concentrations' (the breakpoint between calling a strain resistant or susceptible), which also depend on the culture medium used for DST.
- DST for first-line anti-TB drugs has been thoroughly studied and consensus reached on appropriate methodologies, critical drug concentrations, and reliability and reproducibility of testing. The 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.
- 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 anti-mycobacterial activity, increasing the probability for misclassification of susceptibility or resistance and leading to poorer reproducibility of second-line DST results.
- 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, the relevance of in vitro cross-resistance between drugs in the same group is difficult to interpret clinically.

HCWs treating patients with DR-TB must be aware of the limitations of DST and interpret the results with the constraints in mind. TB organisms that test susceptible to specific drugs have a higher probability of responding effectively on treatment with those drug(s) than organisms that test drug-resistant. Discrepant results must be interpreted with care.

### 5.3.3.5. The Use of GeneXpert in the Diagnosis of MDR-TB

GeneXpert MTB/RIF (GXP) is a relatively new diagnostic tool for TB diagnosis in South Africa. This test has an advantage over the existing TB smear microscopy because it has higher sensitivity, specificity and identifies many patients that would not have been diagnosed using TB microscopy. The Xpert MTB/RIF test reports MTB detected or not detected and also provides data on the state of susceptibility or resistance to rifampicin.

The following algorithm will be used with regard to GXP:



All patients with GXP MTB positive results (rifampicin susceptible or inconclusive) will be started on TB treatment at the point of diagnosis.

All patients with GXP MTB positive results with resistance to rifampicin will be referred to MDR-TB facilities to commence MDR-TB treatment. The following steps will be followed at the MDR-TB facility regarding GXP MTB positive patients with resistance to rifampicin:

1. Open patient's file.
2. Examine patient prior to starting treatment.
3. Take a sputum sample for TB culture and DST for MDR-TB confirmation.
4. Start MDR-TB treatment. Isoniazid (INH) may be included.
5. Register these patients under the category MDR-TB 'not confirmed'.
6. Review MDR-TB treatment after receiving laboratory confirmation, meaning that MDR-TB treatment will be continued if diagnosis is confirmed; MDR-TB treatment maybe stopped if MDR-TB is not confirmed. However, as already outlined conventional culture and DST is an imperfect gold standard and therefore results should be interpreted in the clinical context and the possibility of falsely negative phenotypic DST should also be borne in mind. An experienced physician should be consulted if appropriate. A new and updated Xpert cartridge will become available late 2011 and this recommendation may be revised in the light on performance characteristics of the new cartridge.
7. Review patient's category in the register: change from MDR-TB not confirmed to MDR-TB confirmed upon laboratory TB culture and DST or Line Probe Assay (LPA); on the contrary the MDR-TB not confirmed will be de-registered or deleted from DR-TB register and recorded as drug-susceptible TB on ETR.net.

**Note:** When a sample is taken from GXP MTB positive rifampicin-resistant patients, the following will take place:

1. The sample will be subjected to smear microscopy test
2. All smear positive tests will be subjected to Line Probe Assay leading to a quick confirmation
3. All smear negative samples will go through TB culture (MGIT) and later be subjected to LPA if the sample becomes culture positive and TB bacilli identified. This will take longer.
4. If an organism is shown to be resistant to rifampicin and/or isoniazid, DST for second-line drugs (fluoroquinolone and aminoglycoside) will also be performed.

## DIAGNOSTIC PRINCIPLES

- Usually the first indication that a patient may be harbouring drug-resistant organisms is when she/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 DR-TB patient, GXP will be done and follow the algorithm
- Retreatment patients are at higher risk of harbouring drug resistant organisms, GXP will be done and follow the algorithm.
- Line Probe Assay is a confirmatory diagnosis for MDR-TB.
- All patients that are GXP positive for TB with rifampicin resistance will be started on MDR-TB treatment but these patients will require laboratory confirmation using conventional DST tests and/or Line Probe Assay.

## **6. MANAGEMENT OF PATIENTS WITH MONO- AND POLY- DRUG RESISTANT TB**

## 6. MANAGEMENT OF PATIENTS WITH MONO- AND POLY-DRUG RESISTANT TB

### 6.1. Introduction

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

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

### 6.2. Treatment of Patients with Mono- and Poly-Drug Resistant TB

With the exception of streptomycin, definite randomised 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 poly-drug 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 should be considered when designing an appropriate regimen are described below.

#### 6.2.1. 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 as it reflects the bacterial population at the time that the sputum specimen was collected. The treatment regimens for mono- and poly-drug 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.

#### 6.2.2. Use of Pyrazinamide DST Results

DST results for pyrazinamide are unreliable and resistance to pyrazinamide should be assumed depending on the prior treatment history; in this case an alternative regimen should be used. However, pyrazinamide should be considered for inclusion in the regimen in certain circumstances as a considerable proportion of patients could still harbour pyrazinamide susceptible strains.

#### 6.2.3. 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 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 XIII Suggested Regimens for Mono- and Poly-Drug Resistance in Patients where Further Acquired Resistance is not a Factor**

Drug resistance pattern	Suggested regimen	Minimum duration of treatment (months)	Comments
<b>H</b>	Continue Regimen I or II intensive phase for full duration of treatment (except for H).  In practice it is easier fixed drug combinations RHZ + EMB for children < 8 years and RHZE for individuals > 8 years.	6 - 9 months based on symptomatic response to treatment, weight gain and sputum culture combinations.  A minimum of 6 months treatment after culture conversion is adequate.	Monitor the patient with sputum smear microscopy and culture on monthly basis throughout treatment.  Monthly clinical assessment required.  Refer to MDR-TB expert at unit if patient is not responding well to treatment.
<b>R</b> (+/- any other 1 <sup>st</sup> line drug than H)	Standardised MDR-TB regimen plus INH.	18 months after culture conversion	These patients will need confirmation of diagnosis if diagnosed through GXP; however, LPA is a confirmatory diagnosis.
<b>Poly-resistant TB cases</b>			Refer to MDR-TB expert for regimen design based on resistance pattern and history of anti-tuberculosis drugs used.

(Adapted from: World Health Organization. Guidelines for the Programmatic Management of Drug-resistant Tuberculosis (WHO/HTM/TB/2005.361), World Health Organization: Geneva, Switzerland, 2008)

The regimens in Table XIII, which is a simplified table, are an adaptation of regimens suggested in the WHO guidelines.

All mono- and poly-drug resistant patients are to be recorded in the DR-TB register. All provinces that are still keeping them in the drug-susceptible register should put systems in place to address this matter.

Patients that are mono-drug resistant to rifampicin must be recorded as MDR-TB 'not confirmed'.

Mono- and poly-drug resistant TB patients should be followed using:

- TB microscopy and TB culture every month during intensive phase until TB culture conversion.
- TB microscopy and culture monthly during continuation phase
- DST (repeated) if unsatisfactory clinical and biological progress after 3-4 months of treatment.

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

## 7. MANAGEMENT OF PATIENTS WITH MDR-TB

### 7.1. Introduction

Treatment of patients with MDR-TB involves second-line drugs. They 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:

- Ensure that all details regarding the treatment are communicated to the patient; this will enable the patient to take an informed decision on consent to treatment.
- Counsel and educate the patient and family member. This should include information on what MDR- or XDR-TB is, how one is infected, why one needs to be admitted to hospital, length of hospitalisation and the treatment, what is going to happen in hospital and what happens after discharge.
- Address any patient concerns.
- Verify 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 checklist 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:

#### **Standardised Treatment Regimen**

Drug-Resistance Survey (DRS) data from representative patient population are used to base regimen design in the absence of individual DST. All patients in a defined group or category receive the same regimen. Not confirmed MDR-TB patients should be confirmed by DST whenever possible. In South Africa, we have a standardised regimen. All newly diagnosed MDR-TB patients receive a standardised regimen.

#### **Standardised Treatment Regimen followed by Individualised Treatment Regimen**

Patients on standardised regimen may be switched to an individualised regimen when other DST results become available. Each regimen is individually designed based on the patient's previous history of anti-tuberculosis treatment and individual DST results.

#### **Empiric Treatment followed by Individualised Treatment**

Empirical treatment regimen is given to MDR-TB patients diagnosed on clinical grounds. DST of the presumed MDR-TB contact is 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 available second-line drugs 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, moxifloxacin, ethionamide, terizidone and pyrazinamide taken at least six times per week during the injectable phase followed by a continuation phase treatment with four drugs (moxifloxacin, ethionamide, terizidone and pyrazinamide) taken at least six times per week.

Levofloxacin will be used in patients who may not tolerate moxifloxacin.

Administration of the standardised regimen has been simplified across four weight bands to accommodate the formulations available in the country while complying with the international requirements for minimum, maximum and average dose per kg.

**Ethambutol may be used as an additional item (sixth item in the standardised 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 **standardised 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 individualised regimen based on two factors: firstly history of anti-TB drugs received and secondly DST results.

- 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.
- 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, para-amino salicydic acid 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 DR-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. 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.

**Ethambutol** is a valuable agent for preventing the emergence of resistance to other drugs. Ethambutol is no longer part of the standardised regimen due to lack of high reproducibility, reliability and high level resistance to MDR-TB strains.

**Aminoglycosides:** Kanamycin and amikacin are parenteral drugs that are structurally similar. Strains resistant to streptomycin are usually susceptible to kanamycin and amikacin. Resistance to kanamycin induces almost complete cross-resistance with amikacin and they should be considered as the same drug. Amikacin is as active as kanamycin and better tolerated, but much more expensive.

**Polypeptide:** Capreomycin is a cyclic polypeptide that differs structurally from kanamycin, amikacin and does not exhibit 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 concentrations; 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:** Moxifloxacin is a preferred drug in the management of MDR- and XDR-TB. There is limited evidence that shows that strains resistant to ofloxacin may still be susceptible to moxifloxacin (i.e., there is not complete cross-resistance between these fluoroquinolones). Ofloxacin and levofloxacin will be used in patients younger than 8 years and adults who may not tolerate moxifloxacin.

**Ciprofloxacin** must not be used as an anti-tuberculosis agent in the 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 recommended 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 in patients with appropriate serum concentrations. Pyridoxine (150 mg) 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, since they do not have cross-resistance with other active TB 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 XIV Second-Line Drugs for Treating Drug-Resistant TB**

Drug	Activity	Dosage (daily)			Acceptability	Tolerance	Toxicity
		Average	Min	Max			
Aminoglycosides							
Streptomycin	Bactericidal (against actively multiplying organisms)	15mg/ kg	750 mg	1000 mg	Injection	Moderate	Medium
Kanamycin		15mg/ kg	750 mg	1000 mg	Injection (painful)	Poor	Medium
Amikacin		15mg/ kg	750 mg	1000 mg	Injection (painful)	Poor	Medium
Polypeptide							
Capreomycin		15mg/ kg	750 mg	1000 mg	Injection	Moderate	Medium
Thioamides							
Ethionamide	Bacteriostatic	15-20 mg/kg	500 mg	750 mg	Good	Moderate	Medium
Prothionamide		15-20 mg/kg	500 mg	750 mg	Good	Moderate	Medium

Drug	Activity	Dosage (daily)			Acceptability	Tolerance	Toxicity
		Average	Min	Max			
Pyrazinamide	Bactericidal (in acid/ low pH conditions)	20-30 mg/kg	1200 mg	1600 mg	Good	Moderate	Low
Fluoroquinolones							
Levofloxacin	Weakly bactericidal	7.5-10 mg/kg	750 mg	1000 mg	Good	Good	Low
Moxifloxacin		400 mg	400 mg	400 mg	Good	Good	Low
Other drugs							
Ethambutol	Bacteriostatic	15-20 mg/kg	1000 mg	1200 mg	Good	Good	Low
Terizidone	Bacteriostatic	15-20 mg/kg	500 mg	750 mg	Good	Moderate	High
Cycloserine		10-20 mg/kg	500 mg	750 mg	Good	Moderate	High
PAS	Bacteriostatic	150 mg/kg	8 g	12 g	Bad (bulk, taste)	Poor	Low

## 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 is 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 this 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.
- Amoxycillin-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 rifapentine has complete cross-resistance with rifampicin.
- Imipenem is a carbapenem. Carbapenems are very broad-spectrum antibiotics. A 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 should be considered if cost permits.

Therefore, none of these drugs are recommended for routine MDR-TB treatment. They can be used when it is difficult to design treatment regimen with drugs in Groups 1-4. XDR-TB patients will require drugs in Group 5 to be part of their treatment regimen.

## 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:

**Table XV Grouping of MDR-TB Drugs**

Group	Drugs
<b>Group 1:</b> First-line oral drugs	Ethambutol (E) Pyrazinamide (Z)
<b>Group 2:</b> Injectable drugs	Kanamycin (Km) Amikacin (Am) Capreomycin (Cm) Viomycin (Vm)
<b>Group 3:</b> Fluoroquinolones	Levofloxacin (Lvx) Moxifloxacin (Mfx) Gatifloxacin (Gfx)
<b>Group 4:</b> Oral bacteriostatic second-line drugs	Ethionamide (Eto) Prothionamide (Pto) Cycloserine (Cs) Terizidone (Trd) Para-Aminosalicylic Acid (PAS)
<b>Group 5:</b> Drugs of unclear efficacy (Not recommended for routine use in MDR-TB patients)	Clofazimine (Cfz) Amoxicillin/clavulanate (Amx/Clv) Clarithromycin (Clr) Azithromycin (Azr) Linezolid (Lzd) Thioacetazone (Th) Imipenem High-dose INH

(Adapted from: World Health Organization. Guidelines for the Programmatic Management of Drug-resistant Tuberculosis (WHO/HTM/TB/2005.361), World Health Organization: Geneva, Switzerland, 2008).

## 7.7. Standard Codes for Drugs and Regimens

Standard codes are used for MDR-TB treatment regimens. An MDR-TB regimen consists of two phases:

- **Phase 1:** The intensive/injectable phase where a combination of injectable and oral drugs is used.
- **Phase 2:** 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 duration that phase should last. The number in subscript (i.e.,<sub>3</sub>) 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). The 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)-Mfx-Eto-Trd/ 18Z-Mfx-Eto-Trd**

The above regimen is 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 in total.

## 7.8. Standardised Regimen for Adults (including children 8 years and older) MDR-TB Treatment

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

**Table XVI Intensive Phase: Standardised Regimen for Adult and Children 8 Years and Older (MDR-TB Treatment)**

Patient weight	Drug	Dosage
<33kg	Kanamycin	15-20 mg/kg
	Moxifloxacin	400 mg (children: 7.5-10 mg/kg)
	Ethionamide	15-20 mg/kg
	Terizidone	15-20 mg/kg
	Pyrazinamide	30-40 mg/kg
33 - 50 kg	Kanamycin	500-750 mg
	Moxifloxacin	400 mg
	Ethionamide	500 mg
	Terizidone	750 mg
	Pyrazinamide	1000-1750 mg
51 - 70 kg	Kanamycin	1000 mg
	Moxifloxacin	400 mg
	Ethionamide	750 mg
	Terizidone	750 mg
	Pyrazinamide	1750-2000 mg
>70 kg	Kanamycin	1000 mg
	Moxifloxacin	400 mg
	Ethionamide	750-1000 mg
	Terizidone	750-1000 mg
	Pyrazinamide	2000-2500 mg

**Continuation phase: at least 18 months after TB culture conversion (treatment taken at least six times per week)**

**Table XVII Continuation Phase: Standardised Regimen for Adult and Children 8 Years and Older (MDR-TB Treatment)**

Patient weight	Drug	Dosage
<33kg	Moxifloxacin	400 mg
	Ethionamide	15-20 mg/kg
	Terizidone	15-20 mg/kg
	Pyrazinamide	30-40 mg/kg
33 - 50 kg	Moxifloxacin	400 mg
	Ethionamide	500 mg
	Terizidone	750 mg
	Pyrazinamide	1000-1750 mg
51 - 70 kg	Moxifloxacin	400 mg
	Ethionamide	750 mg
	Terizidone	750 mg
	Pyrazinamide	1750-2000 mg
>70 kg	Moxifloxacin	400 mg
	Ethionamide	750-1000 mg
	Terizidone	750-1000 mg
	Pyrazinamide	2000-2500 mg

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

\*\* Adults who may not tolerate moxifloxacin will be given levofloxacin at the following dosage: 750 mg for patients weighing below 51 kg, and 1000 mg for patients with a weight equal or above 51 kg.

**Table XVIII Standardised MDR-TB Treatment Regimen for Children Younger than 8 Years**

Drug	Dosage
Amikacin	15-22.5 mg/kg
Levofloxacin	<5 years: 10mg/kg twice daily (max 1000 mg) >5 years: 10mg/kg once daily (max 1000 mg)
Ethionamide	15-20 mg/kg
Terizidone	15-20 mg/kg
Pyrazinamide	30-40 mg/kg

**NB: Ethambutol may be given at the dosage of 20 – 25 mg/kg.**

## 7.9. Basic Principles of Treatment

- Use five drugs in intensive or injectable phase and four drugs in continuation phase as per standard regimen. Drugs are administered at least six days per week.

- Of the five drugs used in intensive phase: Give at least four 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 for 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.
- The injectable phase is determined by adding four months to the culture conversion date if the total duration is less than six months then the patient should receive a total of six months injection because the injectable phase must be at least six months.
- Capreomycin should be considered for use in patients with renal insufficiency, hearing loss, or peripheral neuropathy.
- 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 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; and PAS has poor or no penetration.

## 7.12. Terminal Illnesses

Terminally ill patients, where circumstances permit, may be discharged for care by family members, with the consent of the family. Conditions, under which the patient may be discharged, include:

- The patient will remain within the confines of his/her home.
- 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. 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. Individualised 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 specimen for culture and DST was collected, this drug should not be counted as one of the four drugs in the core regimen.

XDR-TB patients have a much-reduced chance for cure and a very high risk of premature death; therefore, management of these cases should be prioritised using the same principles as those for MDR-TB. XDR-TB patients must be hospitalised, 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.
- A recent South African study undertaken in four provinces from South Africa, and confirmed in a recent meta-analysis, found that moxifloxacin improved outcomes in the face of ofloxacin resistance. The use of moxifloxacin is therefore recommended.
- 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 thiomides (ethionamide and prothionamide) and is considered a relatively weak anti-TB 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 (e.g. rifabutin, rifapentine) have almost complete cross-resistance with rifampicin.



- Group 5 drugs should be considered where in cases where adequate regimens are impossible to construct with available drugs from the other groups and you need to strengthen the regimen. The total dosage will depend on the degree of uncertainty and regimen will often contain five or more drugs. Clofazimine is the drug of choice among the group 5 drugs.

**Table XIX Summary of General Principles for Constructing XDR-TB Treatment Regimens**

Basic principles	Comments
<b>1. Use at least four drugs that are expected to be effective</b>	Effectiveness is supported by a number of factors, these are: <ul style="list-style-type: none"> <li>• DST results show susceptibility.</li> <li>• No prior history of treatment with the drug.</li> <li>• No known close contacts with resistance to the drug.</li> <li>• Surveillance data show that resistance is rare.</li> <li>• The drug is not commonly used in the area.</li> </ul> If more of these factors apply the more likely that the drug will be effective.
<b>2. Do not use drugs for which cross-resistance exists</b>	<ul style="list-style-type: none"> <li>• All rifamycins have cross-resistance (rifampicin, rifabutin, rifapentine).</li> <li>• Fluoroquinolones are believed to have high cross-resistance between each other.</li> <li>• Not all aminoglycosides show cross-resistance; in general, only kanamycin and amikacin are fully cross-resistant.</li> </ul>
<b>4. Eliminate drugs that are not safe for the patient</b>	<ul style="list-style-type: none"> <li>• Known severe allergy or unmanageable intolerance; high risk of severe ADRs such as renal failure, deafness, hepatitis, depression and/or psychosis.</li> </ul>
<b>5. Include drugs from Groups 1 to 5 in a hierarchical order</b>	<ul style="list-style-type: none"> <li>• Use any Group 1 (oral first-line drugs) to which the strain is still sensitive.</li> <li>• Use an effective injectable drug in Group 2.</li> <li>• Use the remaining Group 4 drugs to make a regimen of at least four effective drugs.</li> <li>• 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.</li> <li>• Use Group 5 drugs as needed.</li> </ul>
<b>6. Prevent, monitor and manage side effects for each of the drugs selected.</b>	<ul style="list-style-type: none"> <li>• Laboratory services for haematology, biochemistry, serology, and audiometry are required.</li> <li>• Establish a baseline before starting the drug.</li> <li>• Initiate treatment gradually, split daily doses.</li> <li>• Ancillary drugs must be in stock to manage side effects.</li> </ul>

(Adapted from: World Health Organization. Guidelines for the Programmatic Management of Drug-resistant Tuberculosis (WHO/HTM/TB/2005.361), World Health Organization: Geneva, Switzerland, 2008).

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.

Based on the above, the recommended standardised regimen for XDR-TB is as follows but may be modified based on DST results:

6 Cm-Mfx-Eto-Trd -Z-PAS-Clofazimine/ 18 Mfx-Eto-Trd or Cs-Z -PAS/Clofazimine

### 8.3. Standardised Regimen for Adult XDR-TB Treatment

Table XX Standardised Regimen for Adult XDR-TB Treatment

Patient weight	Drug	Dosage
Intensive Phase: Treatment taken daily for at least 6 months, guided by TB culture conversion		
<33kg	Capreomycin	15-20 mg/kg
	Moxifloxacin	400 mg
	Ethionamide	15-20 mg/kg
	Terizidone	15-20 mg/kg
	Pyrazinamide	30-40 mg/kg
	PAS	150 mg/kg
	Clofazimine	3-5 mg/kg
33 - 50 kg	Capreomycin	500-750 mg
	Moxifloxacin	400 mg
	Ethionamide	500 mg
	Terizidone	500 mg
	Pyrazinamide	1000-1750 mg
	PAS	8000 mg
	Clofazimine	200 mg
51 - 70 kg	Capreomycin	1000 mg
	Moxifloxacin	400 mg
	Ethionamide	750 mg
	Terizidone	750 mg
	Pyrazinamide	1750-2000 mg
	PAS	8000 mg
	Clofazimine	300 mg
>70 kg	Capreomycin	1000 mg
	Moxifloxacin	400 mg
	Ethionamide	750-1000 mg
	Terizidone	1000 mg
	Pyrazinamide	2000-2500 mg
	PAS	8000-12000 mg
	Clofazimine	300 mg

**Table XXI Continuation Phase: Treatment Taken Daily for at Least 18 months after TB Culture Conversion**

Patient Weight	Drug	Dosage
<33kg	Moxifloxacin	400 mg
	Ethionamide	15-20 mg/kg
	Terizidone	15-20 mg/k
	Pyrazinamide	30-40 mg/kg
	PAS	150 mg/kg
	Clofazimine	3-5 mg/kg
33 - 50 kg	Moxifloxacin	400 mg
	Ethionamide	500 mg
	Terizidone	500 mg
	Pyrazinamide	1000-1750 mg
	PAS	8000 mg
	Clofazimine	200 mg
51 - 70 kg	Moxifloxacin	400 mg
	Ethionamide	750 mg
	Terizidone	750 mg
	Pyrazinamide	1750-2000 mg
	PAS	8000 mg
	Clofazimine	300 mg
>70 kg	Moxifloxacin	400 mg
	Ethionamide	750-1000 mg
	Terizidone	1000 mg
	Pyrazinamide	2000-2500 mg
	PAS	8000-12000 mg
	Clofazimine	300 mg

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.

XDR-TB treatment for children is essentially like adults. Same drugs used in adults are to be administered to children with one exception: levofloxacin should be used in children younger than 8 years.

## **9. ROLE OF SURGERY**

## 9. ROLE OF SURGERY

The treatment of MDR- and XDR-TB is primarily 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 treatment outcomes, provided skilled thoracic surgery and excellent post-operative care are available. A multidisciplinary team approach should be employed when dealing with patients being considered for surgery.

### **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. Minimal contra lateral disease is not a contra-indication to surgery. The role of PET-CT scans in guiding surgery remains unclear. 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.

The resected part of the lung should be sent for histology, culture and drug susceptibility testing. Sputum cultures should be performed immediately post-surgery and then monthly until two consecutive negative cultures have been obtained. If the patient was culture-negative at the time of surgery the treatment should continue for at least 18 months after culture conversion. If the patient was culture positive, treatment should continue for another 24 months.

# **10. MANAGEMENT OF ADVERSE DRUG REACTIONS**

# 10. MANAGEMENT OF ADVERSE DRUG REACTIONS

## 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 drug reactions (ADRs) are recognised and addressed quickly. The majority of ADRs are easy to recognise 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 ADRs. 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 Adverse Drug Reactions

Adverse drug reactions 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-to-drug interactions may also produce adverse effects. Some ADRs present soon after treatment is initiated while others tend to manifest later.

The most common adverse reactions to second-line anti-TB drugs are described below.

### 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 desensitisation is successful, and the full range of medications can be re-introduced within one or two weeks.

### Gastrointestinal Symptoms (nausea, vomiting, diarrhoea)

Symptoms such as nausea, pain and vomiting are common, but may be prodromal symptoms of hepatitis such as jaundice and therefore close clinical observation is mandatory. Gastrointestinal symptoms can usually be dealt with by taking the medication with a non-fatty meal or before going to bed. Monitoring of the response is important, if the symptoms do not subside, liver toxicity must be suspected and investigated.

### Ototoxicity

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.

### Peripheral Neuropathy

Peripheral neuropathy, presenting as paraesthesia such as tingling and numbness, starting at the feet with proximal spread is the usual manifestation. Myalgia, 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.

### **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 cramps and palpitations.

### **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.

### **Nephrotoxicity**

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

### **Impaired Vision**

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

### **Osteo-articular Pain**

Arthralgia is a ADR drug event resulting from the accumulation of uric acid caused by pyrazinamide. Acetyl salicylic acid commonly alleviates the symptoms. Intermittent administration of Pyrazinamide will also reduce the effect of uric acid retention. Allopurinol is ineffective.

### **Hypothyroidism**

Is a late effect provoked by PAS and ethionamide and physical symptoms can be subtle.

## **10.3. Monitoring Adverse Drug Reactions**

Laboratory screening is invaluable for detecting ADRs that are more occult. During the intensive phase of treatment, patients must be interviewed weekly about adverse reactions to the drugs and these recorded utilising the Adverse Drug Reaction 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 ADRs must be monitored monthly utilising the same Form. Line listings of these effects must be provided quarterly to the Provincial TB Coordinator. Serious ADRs which necessitate discontinuation of drugs must be noted in the Serious Adverse Drug Reaction Report and a report sent within five calendar days 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 ADRs during every encounter with the patient.

Table XXII provides a guide on the number and frequency of laboratory tests that should be conducted to monitor the development of ADRs .



**Table XXII Laboratory Monitoring of Adverse Drug Effects**

ADR	Frequency
<b>Serum creatinine</b>	<ul style="list-style-type: none"><li>• Baseline.</li><li>• At least monthly while receiving an injectable drug.</li></ul>
<b>Serum potassium</b>	<ul style="list-style-type: none"><li>• At least monthly while receiving an injectable agent particularly those receiving capreomycin.</li></ul>
<b>Thyroid stimulating hormone</b>	<ul style="list-style-type: none"><li>• Baseline.</li><li>• Ideally, once between months 6 and 9 of treatment, if receiving ethionamide and/or PAS.</li><li>• Monitor for signs/symptoms of hypothyroidism.</li></ul>
<b>Liver serum enzymes</b>	<ul style="list-style-type: none"><li>• Consider periodic monitoring in patients receiving pyrazinamide for extended periods of time or for patients at risk of hepatitis.</li></ul>

(Adapted from: World Health Organization. Guidelines for the Programmatic Management of Drug-resistant Tuberculosis (WHO/HTM/TB/2005.361), World Health Organization: Geneva, Switzerland, 2008).

## 10.4. Management of Adverse Drug Reactions

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

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

Timely and aggressive management of ADRs is essential. Without it, mortality and permanent disability can be the result, in addition to patient non-adherence. Even if the ADRs 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 reaction (i.e., nausea and vomiting).

The following sequential steps for the management of ADRs are recommended:

### 1. Management of ADRs with Standardised Algorithms

Most ADRs can be managed with over-the-counter and common prescription drugs. If they are mild, continuing the treatment regimen, with the help of ancillary drugs where necessary is the best option. Many ADRs 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 ADRs.

### 2. Reduced Dosage of Suspected Drug(s)

The adverse reactions of a number of second-line anti-tuberculosis drugs are highly dose dependent. If a patient cannot tolerate the regimen, the dosage of the suspected drug(s) may be reduced until the adverse reactions subside. If it is not clear which drug is the cause of the adverse effect(s), the dosage of each drug can be reduced sequentially until the culprit drug is identified. In this case, when the dosage of a second drug is reduced, the first drug of which the dosage was reduced should be returned to normal dosage. If reduction of dosage of individual drugs does not result in the disappearance of the ADRs, it may be necessary to 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 ADR 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 ADRs 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; and
- HIV infection.

The following table summarises the most common ADRs, the offending drugs and their management strategies.

**Table XXIII Common Adverse Drug Reactions**

ADR	Responsible Agent	Management	Comments
Seizures	Cs Trd FQs	<ol style="list-style-type: none"><li>1. Rule out other likely causes.</li><li>2. Treat any suspected causes.</li><li>3. Initiate anticonvulsant treatment phenytoin 3-5 mg/kg/day; valproic acid 750-1250 mg/day; carbamazepine 600-1200 mg/day; phenobarbital 60-120 mg/day.</li><li>4. Increase pyridoxine to 200 mg daily.</li><li>5. Lower dose of offending drug.</li><li>6. Discontinue offending drug.</li></ol>	<ul style="list-style-type: none"><li>• Clinical evaluation is generally sufficient unless there is high suspicion of infectious, malignant, vascular or metabolic cause.</li><li>• Anticonvulsant must be continued until MDR-TB treatment completed or suspected agent discontinued</li><li>• History of prior seizure disorder is not a contraindication for the use of the offending TB drugs if the patient's seizures are well-controlled and/or the patient is receiving anticonvulsant treatment.</li><li>• Patients with history of prior seizures may be at increased risk for development of seizures during MDR-TB treatment.</li><li>• Seizures are not permanent sequelae of MDR-TB treatment.</li></ul>

ADR	Responsible Agent	Management	Comments
Peripheral neuropathy	Cs Trd S Km Am Cm Eto/Pto FQs	<ol style="list-style-type: none"> <li>1. Increase pyridoxine to 200 mg daily.</li> <li>2. Begin exercise regimen, focus on affected regions.</li> <li>3. Initiate therapy with tricyclic antidepressant drugs.</li> <li>4. Lower dose of suspected drug.</li> <li>5. Discontinue suspected drug.</li> <li>6. Initiate therapy with gabapentin 300 mg qid initially, and increase by 600 mg every 3-7 days; max dose 1200 mg tds.</li> </ol>	<ul style="list-style-type: none"> <li>• Patients with co-morbid disease (e.g., diabetes, HIV, alcoholism) more likely to develop peripheral neuropathy, but these conditions are not contraindications to the use of the offending TB drugs.</li> <li>• Neuropathy is generally not reversible, but only a minority (approximately 10%) of patients requires continued intervention to keep symptoms controlled once MDR-TB treatment is completed.</li> </ul>
Hypothyroidism	PAS Eto/Pto	<ol style="list-style-type: none"> <li>1. Initiate thyroxine.</li> </ol>	<ul style="list-style-type: none"> <li>• Completely reversible upon discontinuation of offending drug.</li> <li>• The use in combination of PAS and Eto or Pto is more frequently associated with hypothyroidism than their individual use.</li> </ul>
Hearing loss	S Km Am Cm	<ol style="list-style-type: none"> <li>1. Conduct audiometry and compare with baseline.</li> <li>2. Consider reducing the frequency of the drug administration to 5 times or even 3 times per week.</li> <li>3. Lower the dose of suspected drug if this will not compromise the regimen.</li> <li>4. Discontinue suspected drug if this will not compromise the regimen.</li> </ol>	<ul style="list-style-type: none"> <li>• Patients with prior exposure to aminoglycosides may have baseline hearing loss.</li> <li>• Hearing loss is generally not reversible.</li> <li>• The risk of further hearing loss should be weighed against the risk of stopping the drug in the regimen.</li> </ul>

ADR	Responsible Agent	Management	Comments
Psychosis	Cs Tdr FQs Eto/Pto	<ol style="list-style-type: none"> <li>1. Refer to a psychiatrist for assessment.</li> <li>2. Hold suspected agent for short period of time (1-4 weeks) while psychotic symptoms are brought under control.</li> <li>3. Initiate anti-psychotic drugs (e.g., risperidone 0.5-2 mg po bd; haloperidol 1-5mg po or IV or IM repeated every hour as needed).</li> <li>4. Lower dose of suspected agent if this will not compromise the regimen.</li> <li>5. Discontinue use of suspected agents and replace accordingly.</li> </ol>	<ul style="list-style-type: none"> <li>• Some patients will need to continue anti-psychotic treatment throughout MDR-TB treatment.</li> <li>• 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.</li> <li>• Psychotic symptoms are generally reversible upon MDR-TB treatment completion or discontinuation of the offending agent.</li> </ul>
Depression	Cs Trd FQs Cm Eto/Pto	<ol style="list-style-type: none"> <li>1. Rule out side effects of concomitant medications (e.g., amoxycillin-clavulanate, penicillin, benzodiazepines)</li> <li>2. Refer to psychologist or psychiatrist for assessment.</li> <li>3. Initiate group or individual psychological therapy.</li> <li>4. Initiate anti-depressant drugs (e.g., amtryptiline, nortriptyline, fluoxetine, sertraline), but use with caution when there is a history of convulsions.</li> <li>5. Increase pyridoxine to 200 mg daily.</li> <li>6. Lower dose of the offending drug if this will not compromise the regimen.</li> <li>7. Discontinue the offending drug if this will not compromise the regimen.</li> </ol>	<ul style="list-style-type: none"> <li>• Importance of personal socioeconomic conditions and confinement to hospital should not be underestimated as contributing factor to depression.</li> <li>• Depression and depressive symptoms may fluctuate during treatment.</li> <li>• 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.</li> </ul>

ADR	Responsible Agent	Management	Comments
Nausea and vomiting	Eto/Pto PAS Cm E Z	<ol style="list-style-type: none"> <li>1. Assess for dehydration and rehydrate if indicated.</li> <li>2. Initiate anti-emetics 30 min prior to administering MDR-TB drugs.</li> <li>3. Administer ethionamide in 3 separate doses.</li> <li>4. Administer ethionamide at night with short-acting benzodiazepine.</li> <li>5. Lower dose of offending drug agent.</li> <li>6. Discontinue use of offending drug.</li> </ol>	<ul style="list-style-type: none"> <li>• Nausea and vomiting is common in the early weeks of treatment and usually abates with time on treatment or supportive therapy.</li> <li>• Electrolytes should be monitored and replenished if vomiting is severe.</li> <li>• Reversible upon discontinuation of suspected agent.</li> </ul>
Gastritis	PAS Eto/Pto E Z	<ol style="list-style-type: none"> <li>1. Administer MDR-TB drugs with a small amount of food.</li> <li>2. Caffeine, cigarettes should be avoided.</li> <li>3. Consider use of: <ul style="list-style-type: none"> <li>• Antacids (e.g., calcium carbonate, aluminium hydroxide, magnesium-hydroxide).</li> <li>• H<sub>2</sub>-blockers (e.g., cimetidine, ranitidine), proton-pump inhibitors (e.g., omeprazole).</li> </ul> </li> <li>4. Withhold offending drug (s) for short periods of time (e.g., 1-7 days).</li> <li>5. Lower dose of offending drug.</li> <li>6. Discontinue the offending drug.</li> </ol>	<ul style="list-style-type: none"> <li>• Severe gastritis or gastric ulcers as manifested by hematemesis, melena or hematechezia is rare.</li> <li>• Dosing of antacids should be carefully timed so as not to interfere with the absorption of MDR-TB drugs. Ancillary drugs should be taken 2 hours before or 3 hours after the TB medication.</li> <li>• Reversible upon discontinuation of offending drug(s).</li> </ul>

ADR	Responsible Agent	Management	Comments
Hepatitis	Z FQs Eto/Pto PAS E	<ol style="list-style-type: none"> <li>1. Stop treatment pending resolution of the hepatitis.</li> <li>2. Rule out other potential causes of hepatitis.</li> <li>3. Consider suspending the causative drug permanently.</li> <li>4. Re-introduce drugs individually while monitoring liver function, with the most likely drug introduced first.</li> <li>5. Monitor liver function every 1-2 months.</li> </ol>	<ul style="list-style-type: none"> <li>• History of prior hepatitis should be carefully analysed to determine the most likely causative drug(s); these should be avoided in future regimens.</li> <li>• Generally reversible upon discontinuation of offending drug.</li> </ul>
Renal failure and nephrotoxicity	S Km Am Cm	<ol style="list-style-type: none"> <li>1. Discontinue causative drug.</li> <li>2. Consider dosing 3 times per week and monitor creatinine clearance.</li> <li>3. Adjust dose of all the drugs according to creatinine clearance.</li> <li>4. Consider use of capreomycin if patient was on aminoglycoside.</li> </ol>	<ul style="list-style-type: none"> <li>• 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.</li> <li>• Renal impairment may be permanent.</li> </ul>
Optic neuritis	E	<ol style="list-style-type: none"> <li>1. Stop agent.</li> <li>2. Refer patient to ophthalmologist.</li> </ol>	<ul style="list-style-type: none"> <li>• Usually reverses with cessation of the drug.</li> </ul>
Arthralgia/arthritis	Z FQs	<ol style="list-style-type: none"> <li>1. Initiate therapy with non-steroidal anti-inflammatory drugs.</li> <li>2. Initiate exercise regimen/physiotherapy where necessary.</li> <li>3. Lower dose of offending drug, if this will not compromise the regimen.</li> <li>4. Discontinue offending drug, if this will not compromise the regimen.</li> </ol>	<ul style="list-style-type: none"> <li>• Symptoms of arthralgia/arthritis generally diminish over time, even without intervention.</li> <li>• Uric acid levels may be elevated in some patients but are of little therapeutic relevance.</li> <li>• Anti-gout treatment (e.g., allopurinol, colchicines) does not correct the uric acid levels in these cases.</li> </ul>

ADR	Responsible Agent	Management	Comments
Electrolyte disturbances (hypokalemia, hypomagnesemia)	Cm Km Am S	<ol style="list-style-type: none"> <li>1. Replenish potassium po or IV.</li> <li>2. Treat associated vomiting or diarrhoea.</li> <li>3. Check magnesium levels if potassium levels do not improve.</li> <li>4. Discontinue arrhythmogenic drugs (e.g., digoxin, amyltriptyline, cisapride, and haloperidol) if patient is taking them.</li> <li>5. Discontinue aminoglycosides if condition is severe.</li> </ol>	<ul style="list-style-type: none"> <li>• Hypokalemia can occur within clinical signs and symptoms and may be life-threatening</li> <li>• Amiloride 5-10 mg qid or spironolactone 25 mg qid may decrease the potassium and magnesium wasting and is useful in refractory cases.</li> </ul>

(Adapted from: World Health Organization. Guidelines for the Programmatic Management of Drug-resistant Tuberculosis (WHO/HTM/TB/2005.361), World Health Organization: Geneva, Switzerland, 2006).

\* Bold indicates the most likely offending drug

# **11. RECOMMENDED DRUGS FOR THE TREATMENT OF ADVERSE DRUG REACTIONS**



# 11. RECOMMENDED DRUGS FOR THE TREATMENT OF ADVERSE DRUG REACTIONS

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

## 11.1. Commonly Used Drugs and Supplements

The most commonly used drugs and supplements are:

### 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.

### 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. There is no evidence that one corticosteroid is better than another. Prednisone is commonly used, starting at approximately 1 mg/kg and gradually decreasing the dose by 10 mg 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.

### 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 ADRs related to cycloserine or terizidone use are experienced.

### 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 administration of fluoroquinolones, as zinc, iron and calcium can interfere with fluoroquinolone absorption.

### Respiratory Insufficiency

Oxygen can be used to alleviate shortness of breath. Generally, it is indicated in patients with a  $pO_2 < 55\text{mmHg}$  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.

### 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 be continued after completion of treatment.

### Nutritional Support

In addition to causing malnutrition, DR-TB can be exacerbated by poor nutritional status. The second-line anti-tuberculosis drugs can also decrease the appetite, making adequate nutrition a greater challenge.

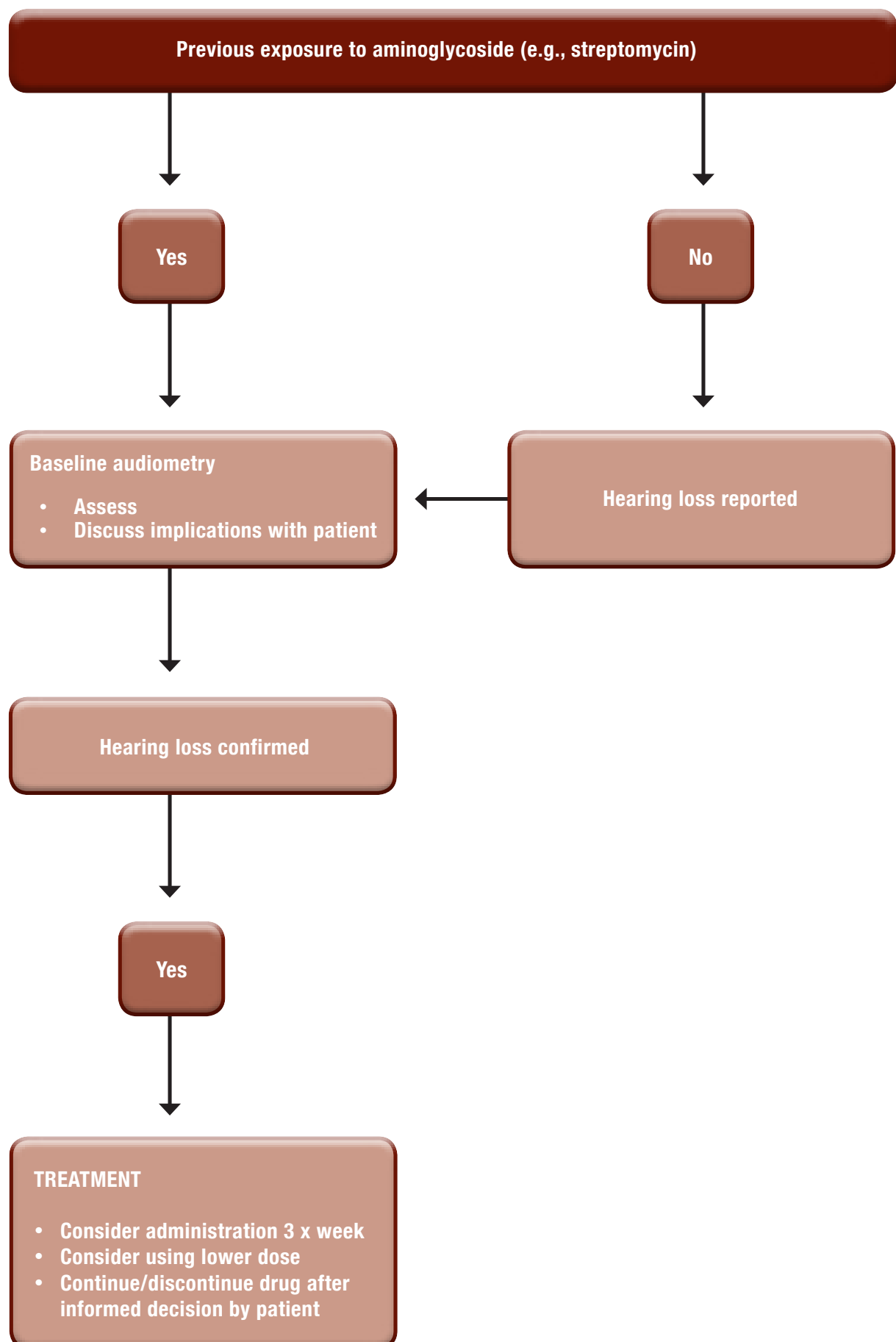
Nutritional support can take the form of providing foods parcels, and whenever possible should include a source of protein.

**Table XXIV Commonly Used Ancillary Drugs and Their Indications**

Indication	Ancillary Medication
Nausea, vomiting	Metoclopramide, cyclizine, promethazine, bismuth subsalicylate.
Gastritis, peptic ulcers	H <sub>2</sub> -blockers (ranitidine, cimetidine, famotidine, etc.), proton pump inhibitors (omeprazole, lansoprazole, etc.). <u>Avoid antacids</u> because they can decrease absorption of fluoroquinolone.
Oral candidiasis	Fluconazole, cotrimazole lozenges, nystatin oral solution.
Diarrhoea	Loperamide.
Depression	Selective serotonin reuptake inhibitors (fluoxetine), tricyclic antidepressants (amitriptyline).
Severe anxiety	Lorazepam, diazepam, clonazepam.
Insomnia	Dimenhydrinate.
Psychosis	Haloperidol, thiorazine, risperidone (consider benzotropine or biperiden to prevent extrapyramidal side effects).
Seizures	Phenytoin, carbamazepine, valproic acid, phenobarbital.
Prophylaxis of neurological complications of cycloserine or terizidone	Pyridoxine (vitamin B6).
Peripheral neuropathy	Amitriptyline.
Vestibular symptoms	Meclizine, dimenhydrinate, prochlorperazine, promethazine.
Musculoskeletal pain, arthritis	Ibuprofen, paracetamol, codeine.
Cutaneous reactions, itching	Hydrocortisone cream, calamine, caladryl lotions.
Systemic hypersensitivity reactions	Antihistamines (diphenhydramine, chlorpheniramine, dimenhydrinate), corticosteroids (prednisone, dexamethasone).
Bronchospasm	Inhaled beta-agonists (albuterol, etc.), inhaled corticosteroids (beclomethasone, etc.), oral steroids (prednisone), injectable steroids (dexamethasone, methylprednisolone).
Hypothyroidism	Levo-thyroxine.
Electrolyte wasting	Potassium and magnesium supplements.

(Adapted from: World Health Organization. Guidelines for the Programmatic Management of Drug-resistant Tuberculosis (WHO/HTM/TB/2005.361), World Health Organization: Geneva, Switzerland, 2006).

Figure III Management of Hearing Loss



## **12. TREATMENT IN SPECIAL SITUATIONS**

## 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:

### 12.2. Oral Contraception Use

Birth control is strongly recommended for all women receiving DR-TB treatment because of the potential negative consequences for both mother and foetus of frequent and/or severe ADRs.

There is no contraindication to taking oral contraceptives with second-line anti-TB 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.

If the patient opts for oral contraception, she should be made aware of the fact vomiting results in decreased absorption of the pill, and possible decreased efficacy. She 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.

### 12.3. Pregnancy

Female patients of childbearing age should be tested for pregnancy during 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. Apply the following principles:

#### **Discuss condition and treatment plan with the patient**

A discussion of risks and benefits need to take place. The benefits of initiating treatment upon diagnosis outweigh the risks of not starting treatment. Any concerns a patient may have in starting therapy or in using medicines while pregnant need to be addressed. If the patient agrees to start therapy, use three or four oral drugs with demonstrated efficacy and then reinforce the regimen with an injectable agent after the second trimester of pregnancy or immediately postpartum.

#### **Avoid injectable agents**

Aminoglycosides should not be used in the treatment of pregnant patients as they are 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.

#### **Use of ethionamide**

Ethionamide should be given with caution because it may increase the risk of nausea and vomiting associated with pregnancy and teratogenic effects have been observed in animal studies.

Table XXV shows the safety profile of the second-line drugs in pregnancy.

**Table XXV Safety of Second-Line Drugs during Pregnancy**

Medication	Safety class*	Comments
<b>Ethambutol</b>	B	Experience in gravid patients suggests safety.
<b>Pyrazinamide</b>	C	Use with caution. Most references suggest it is safe to use.
<b>Streptomycin</b> <b>Kanamycin</b> <b>Amikacin</b> <b>Capreomycin</b>	D	Documented toxicity to developing foetal ear. Risks and benefits must be carefully considered. Avoid use where possible.
<b>Fluoroquinolones</b>	C	Use with caution. No teratogenic effects seen in humans when used 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.
<b>Ethionamide</b> <b>Prothionamide</b>	C	Avoid use. Teratogenic effects observed in animal studies, and significantly worsens nausea associated with pregnancy.
<b>Cycloserine</b> <b>Terizidone</b>	C	No significant experience in gravid patients: animal studies have not documented toxicity.

(Adapted from: Partners in Health. The PIH Guide to Medical Management of Multidrug-resistant Tuberculosis. International Edition. PIH, USA: 2003)

- \* A = Safety established using human studies  
 B = Presumed safety based on animal studies  
 C = Uncertain safety, no human/animal studies show adverse effect  
 D = Unsafe, risk may only be justifiable under certain clinical circumstances.

## 12.4. Breastfeeding

### 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.

### 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.

## 12.5. Children

Children with MDR- or XDR-TB generally have primary disease transmitted from a source adult case. Since children often have paucibacillary disease, they are seldom culture-positive. Nevertheless, every effort should be made to confirm MDR- or XDR-TB bacteriologically in children.

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 source case. 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, but the child should be started on an effective regimen. 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 and many MDR-TB cases over prolonged periods 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, drug 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.

**Table XXVI Formulations and Dosages of Second-Line Drugs for Children**

Drug	Formulation	Daily Dose mg/kg/day	Frequency	Maximum Daily Dose
Streptomycin	Vials: 500 mg, 1 g	15 - 30	Once Daily	1 g
Kanamycin	Vials: 500 mg, 1g	15 - 30	Once Daily	1 g
Amikacin	Vials: 100 mg, 250 mg, 500 mg, 1 g	15 - 22.5	Once Daily	1 g
Capreomycin	Vials: 1g	15 - 30	Once Daily	1 g
Ofloxacin (for children younger 8 years)	Tablets: 200 mg or 400 mg	15-20	Once Daily	800 mg
Levofloxacin (for children younger 8 years)	Tablets: 250, 500, 750 mg	<5 yrs: 20 >5 yrs: 10	Twice Daily Once Daily	1 g
Moxifloxacin (for children older than 8 years and adults)	Tablets: 400 mg	7.5 - 10	Once Daily	400 mg
Ethionamide	Tablets: 250 mg	15 - 20	Twice daily initially but aim for once daily	1 g
Prothionamide	Tablets: 250 mg	15 - 20	Twice daily	1 g
Terizidone	Capsules: 250 mg	10 - 20	Once daily	1 g
PAS	PAS granules 4 g packets	150	Twice daily	12 g

In children who are not culture-positive at the start of treatment, failure is difficult to assess. Children, as is the case in adults, 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 advanced disease due to late diagnosis) and social factors (more problems with adherence due to peer pressure, behaviour, drug use, pregnancy, denial poor acceptance of illness). Early diagnosis, strong social support, individual and family counselling, and a close relationship with the medical provider may help improve outcomes.

## 12.6. Diabetes

The prognosis of treatment in a diabetic patient with uncontrolled glucose levels is poor. Therefore the responsibility falls on the physician and patient to ensure proper diabetic care and control. In addition, diabetes may potentiate ADRs, 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-glycaemia 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 hypoglycaemia.
  - 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 anti-TB drugs should be adjusted accordingly. Once the dose is adjusted, the creatinine should be checked weekly until it has stabilised.
  - HbA<sub>1c</sub> every three months if treatment changes or patient is not meeting target; every six months if stable. Target: HbA<sub>1c</sub><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**
  - Adjust the dose of the injectable drug based on the creatinine clearance.
  - Consider using an ACE inhibitor in patients with albuminuria >300 mg/24 hours.



## 12.7. Renal Insufficiency

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 XXVII Adjustment of Drugs in Renal Insufficiency**

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

(Adapted from: Partners in Health. The PIH Guide to Medical Management of Multidrug-Resistant Tuberculosis. International Edition.PIH, USA: 2003)

<sup>†</sup> To take advantage of the concentration-dependent bactericidal effect of many anti-tuberculosis drugs, standard doses are given unless there is intolerance.  
<sup>\*</sup> The appropriateness of 250 mg daily doses has not been established. There should be careful monitoring for evidence of neurotoxicity (if possible measure serum concentrations and adjust accordingly).

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

<sup>\*\*\*</sup> 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 (CrCl) or the glomerular filtration rate (GFR) is as follows:

Estimated Glomerular Filtration Rate (GFR):

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

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

Normal values for creatinine clearance are:

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

$$= \frac{(140 - \text{age}) \times (\text{ideal body weight in kg})}{72 \times (\text{serum creatinine, mg/dl})}$$

$$= \frac{(140 - 59) \times (53)}{72 \times 2.4}$$

$$= 24.8 \text{ ml/min}$$

**Step 2:** Refer to Table XXV 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 XXV 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:**

- For this patient, every drug in the regimen should be examined and adjusted if necessary.
- The creatinine will need to be monitored periodically (often weekly or more frequently in the patient with severe renal insufficiency) and doses readjusted for any change.

If this were a woman, the  $\text{GFR} = 24.8 \times 0.85 = 21.1$  ml/min.

Kanamycin dose: 12-15 mg/kg which works out to 636-795 mg, therefore 750 mg three times a week

(Adapted from: World Health Organization. Guidelines for the Programmatic Management of Drug-resistant Tuberculosis (WHO/HTM/TB/2005.361), World Health Organization: Geneva, Switzerland, 2006).

## 12.8. Liver Disorders

Pyrazinamide is the most hepatotoxic of the first-line anti-tuberculosis drugs. Of the second-line drugs, ethionamide, prothionamide and PAS are hepatotoxic, although less so than any of the first-line drugs. Hepatitis is quite rare with the fluoroquinolones, but may 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 judgement 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.

## 12.9. Seizure Disorders

Some patients requiring DR-TB treatment may have 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 to control them. The risks and benefits of using cycloserine/ terizidone should be considered and discussed with the patient. When seizures present for the first time whilst patient is on DR-TB treatment, there is a good chance that they are related to one of the second-line drugs.

## 12.10. Substance Dependency

Patients who abuse alcohol and drugs should be started on a rehabilitation programme and if necessary adjuvant therapy given. Although complete abstinence from alcohol or drugs 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 reactions 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.

## 12.11. Psychiatric Disorders

It is prudent to have a psychiatrist conduct a psychiatric evaluation on all patients before the start of MDR-TB treatment, or at least on 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 MDR-TB 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 reactions. Close monitoring is recommended if cycloserine or terizidone is used in patients with psychiatric disorders.

The hospital should have an organised system for management of psychiatric emergencies which include psychosis, suicidal ideation, and any situation involving the patient being a danger to him/her 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. 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 when 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. 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 ART should 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 DR-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. Furthermore, clinical presentation may be masked by the existence of other opportunistic infections.

The diagnosis of DR-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 the diagnosis of DR-TB in HIV follow the same principles as for HIV-negative patients. Sputum culture and DST should be done on all high risk groups ( i.e., non-converters, all re-treatment patients, contacts of drug resistant TB). Every effort should be made to obtain a specimen in, even if extra-pulmonary TB is suspected. Common sites of HIV-related extra-pulmonary DR-TB are the pleura, the lymph nodes and the pericardium. Blood cultures for tubercle bacilli sometimes yield positive results.

### 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 ADRs 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 ART when MDR- or XDR-TB is diagnosed should immediately be started on appropriate treatment.

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

- Timing of initiation of ART in MDR- and XDR-TB patients (i.e., 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 ART 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**

According to the National ART Guidelines 2010, all HIV co-infected TB patients should be initiated on ART when CD4 cell count is <350 cells/mm<sup>3</sup>.

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

#### ***Advantages of Starting ART Early***

1. Reduced HIV related morbidity and mortality.
2. Increased survival of co-infected DR-TB patients
3. Slower progression to AIDS.

#### ***Issues to Consider when Initiating ART***

1. Overlapping ADRs 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 ADRs that may lead to the interruption of both DR-TB and/or ART. Deferred initiation of ART may help the clinician identify the potential cause of ADRs 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**

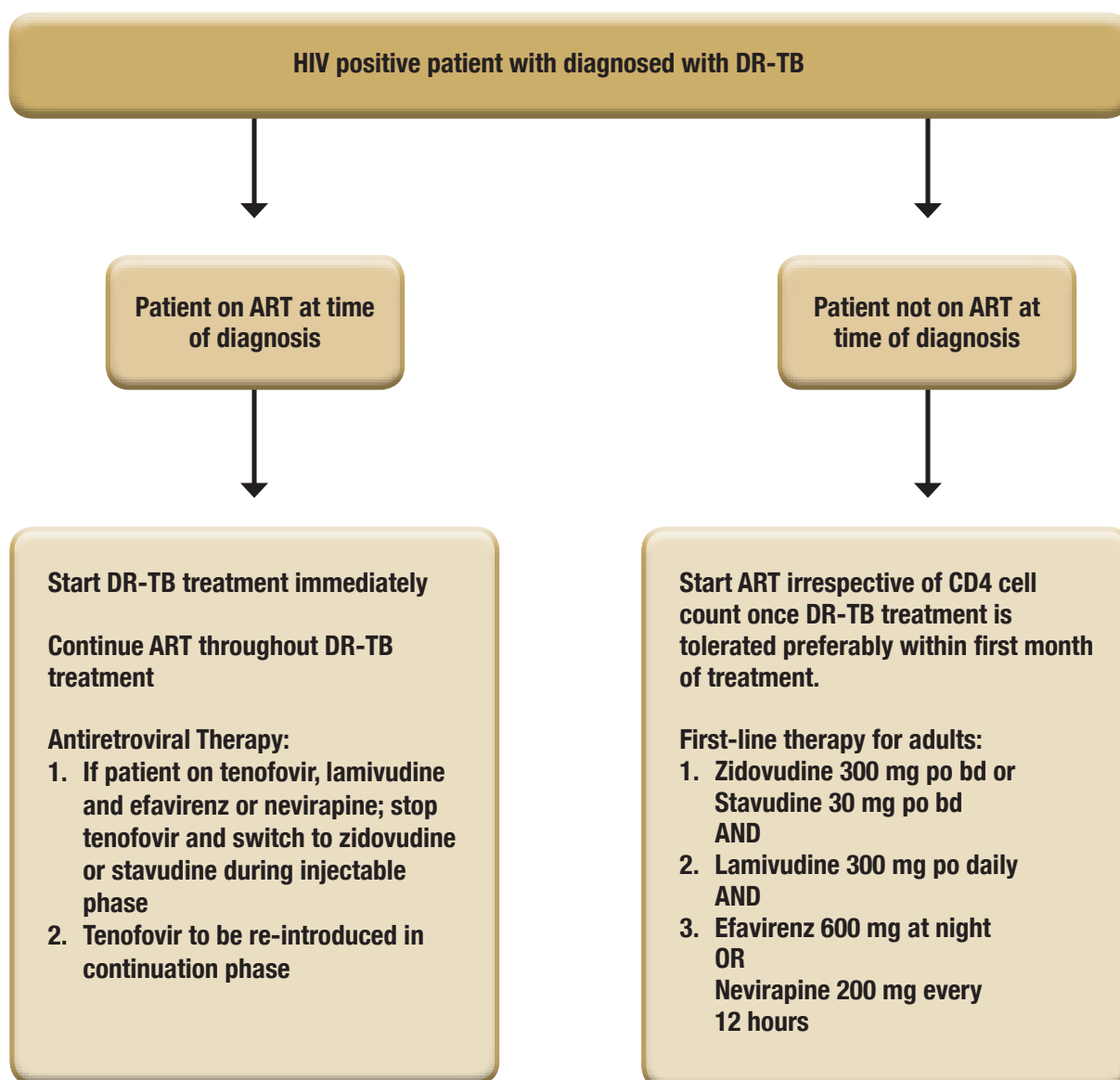
- Start DR-TB treatment immediately.
- Antiretroviral therapy should be continued throughout DR-TB treatment.
- Monitor patient for ADRs, drug-drug interactions and combined toxicities; avoid using tenofovir and aminoglycosides because they are nephrotoxic.

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**



In children abacavir, lamivudine and efavirenz at appropriate dosage constitute the first-line regimen. Lopinavir/rotonavir will replace efavirenz in children younger than 3 years. 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 ADRs 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 5 mg/kg plus sulphamethoxazole 25 mg/kg daily

#### *In Children:*

Body weight	Cotrimoxazole 40/200 mg/5ml
< 5 kg	2.5 ml
5 to 9.9 kg	5 ml
10 to 14.9 kg	7.5 ml
15 to 21.9 kg	10 ml or 1 tab 80/400 mg
> 22 kg	15 ml or 1 ½ tab 80/400 mg

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/mm<sup>3</sup> 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 ART, 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 not to be helpful.

### **13.6. Patient Monitoring**

The co-infected DR-TB/HIV 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 are particularly hard to administer, 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 Adverse Drug Reactions**

In general, HIV-positive patients have a higher rate of ADRs to both TB and non-TB medications and the risk of these increases with the degree of immunosuppression. Many of the medications used to treat DR-TB and HIV have overlapping, or in some cases additive, toxicity. Identifying the source of ADRs 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 using drugs that have overlying toxicity outweighs the risk but there is a need to increase monitoring of ADRs in HIV infected DR-TB patients.

Some of the common overlying toxicities are:

- Peripheral neuropathy
- Central Nervous System toxicity
- Depression
- Gastro-intestinal intolerance
- Hepatotoxicity
- Skin rash

- Renal toxicity
- Electrolyte disturbances
- Hypothyroidism etc.

### **13.7.1. Hepatotoxicity**

This is a common and potentially serious ADR. 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 (ddl, 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. 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 related to the disease may interfere with adherence to treatment. In addition, the long duration of DR-TB treatment, combined with ADRs, may contribute to depression, anxiety and further jeopardise treatment adherence.

Monitoring the patient throughout the treatment period is therefore essential. The symptoms of DR-TB generally improve within the first few months of treatment. However, early resolution of symptoms is not an indication of cure, and recurrence of symptoms after 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- 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 namely, 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. 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 reviewed 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 ADRs, 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 good indicator of patient progress; however, it cannot distinguish viable organisms from those that are non-viable. 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 commencement of treatment for whatever reason(s) 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 the duration of 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 ADRs.

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

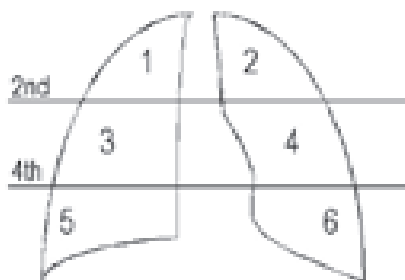
Chest x-ray films should be taken whenever the patient's clinical condition worsens, or whenever surgical intervention is being considered. The chest x-ray film results may remain unchanged or show only slight improvement, this does not mean the patient is not improving on treatment therefore; no changes in treatment should be made on the basis of chest x-ray films alone.

The chest x-ray films must be evaluated using a standardised scoring system at the following intervals:

- At diagnosis;
- After completion of the intensive phase of treatment or at six months;
- Every six months; and
- At treatment completion.

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

#### Scoring System for the Evaluation of Chest X-Rays



Disease (a)			Score
No disease	:	Leave blank	0
< 50% of area affected	:	<	1
≥ 50% of area affected	:	>	2

Cavitation (b)			Score
No cavitation		Leave blank	0
Single cavity, <2 cm diameter	:	1a	0.25
Single cavity, 2-4 cm diameter	:	1b	0.50
Single cavity, >4 cm diameter	:	1c	1.00
Multiple cavities, largest <2 cm diameter	:	2a	0.50
Multiple cavities, largest 2-4 cm diameter	:	2b	1.00
Multiple cavities, largest >4 cm	:	2c	2.00

A composite score is calculated by adding the disease and cavitation scores for each zone, as follows:

Zones affected	1	2	3	4	5	6
Disease (> / <)						
Score (a)						
Cavitation						
Score (b)						
Total score (a+b)						

Composite score

The following table presents a summary of parameters to be considered for DR-TB patient monitoring.

**Table XXVIII Monitoring and Evaluation of Patients during Hospitalisation and During Ambulatory Care**

Monitoring and Evaluation	Recommended Frequency
Evaluation by doctor	At baseline. Twice three times per week for stable patients and daily for very sick patients until conversion. Every month or bi-monthly for outpatients on continuation phase.
Evaluation by nurse	Daily.
Sputum smear and cultures	At baseline. Monthly.
Weight	At baseline and weekly during intensive phase. Monthly during continuation phase.
Height	At baseline in adults and children.
Body mass index	At baseline and then monthly.
Drug Susceptibility Testing (DST)	At baseline. For patients who remain culture-positive at six months.
Chest radiograph	At baseline. Every six months (For children every 2 to 3 months in intensive phase). At treatment completion. When requested by clinician.
Serum creatinine	At baseline, then monthly during injectable phase.
Serum potassium	Monthly during injectable phase.
Thyroid stimulating hormone	Every six months if receiving ethionamide and/or PAS. Monitor monthly for signs of hypothyroidism. In children every 2 months.
Liver serum enzymes	Periodic monitoring (every 1-3 months) in patients receiving pyrazinamide for extended periods or for patients at risk of or with symptoms of hepatitis. In children: if symptomatic or every 6 month if on ART.
HIV screening	At baseline, and repeat if clinically indicated.
Pregnancy tests	At baseline for women of childbearing age, and repeat if indicated.
Audiometry	At baseline, monthly during injectable phase and 3months after the interruption of the injectable agent.
Eye test	At baseline and when indicated.
Lung CT-scan	When indicated.

(Adapted from: World Health Organization. Guidelines for the Programmatic Management of Drug-resistant Tuberculosis (WHO/HTM/TB/2005.361), World Health Organization: Geneva, Switzerland, 2008).



### 14.3. Patient Education and Counseling

Education, counselling and emotional support are particularly important, much as in any other chronic life-threatening illness. On-going 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 informed on an on-going basis about MDR- or XDR-TB, its spread, prevention, treatment, potential ADRs, the need for treatment compliance and early testing for MDR- and XDR-TB for other family members should they develop symptoms. Information 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 more likely 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 ADRs. Monitoring 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.

Since the patients often have only one last chance for cure and there is a serious public health consequence if treatment fails, it is imperative that all patients receive their treatment under strict DOT after discharge from the hospital either in the community or at health facilities. This should be provided in such a way that it does not introduce undue 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 HCWs where possible. When human or financial resources do not permit the use of HCWs, trained community members can serve as effective treatment supporters. However, community members need intensive training, on-going 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 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 is not consistent with taking the medications, a decision should be taken to discontinue treatment.

### 14.5. Maintaining Confidentiality

The HCW and community health worker must maintain strict confidentiality at all times to ensure and maintain the patient-provider relationship, as treatment is lengthy. In some cases this may entail arranging a system where the patient receives medication without the knowledge of others.

## 14.6. Social Support

The provision of social support to patients may improve chances of adherence to therapy. The social worker must conduct an assessment of the patient's home environment and ensure that social support is provided for the family members where needed. If the patient was employed, with the patient's consent arrangements may be made with the employer to provide the necessary leave of absence from work whilst the patient is hospitalised thereby sustaining the monthly income of the patient. Patients who are substance abusers must be started on rehabilitation programmes with intensive counselling as treatment compliance tends to be poor in this group of patients. Organisations such as SANCA can assist with provision of these programmes.

Patients who qualify for social grants or disability grants should be assisted to access these grants. Those who are breadwinners, or who have lost income as a result of admission in hospital and their families are 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 the 'unemployment insurance fund' (UIF) 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 aminoglycosides 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 treatment, importance of completing the treatment and addressing the reasons for wanting to stop 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 4).

A patient is regarded as having defaulted treatment if s/he has been missed treatment for two consecutive months. Every effort should be made to recall patients who abscond or interrupt treatment for a day or two, to persuade them to resume treatment. A home visit should be conducted to find out why the patient has defaulted after two days and to ensure that treatment is resumed promptly and effectively. The situation should be addressed in a sympathetic, friendly, and non-judgmental manner. Every effort should be made to address the patients' concerns or reasons for interruption or abscondment to prevent it from happening again.

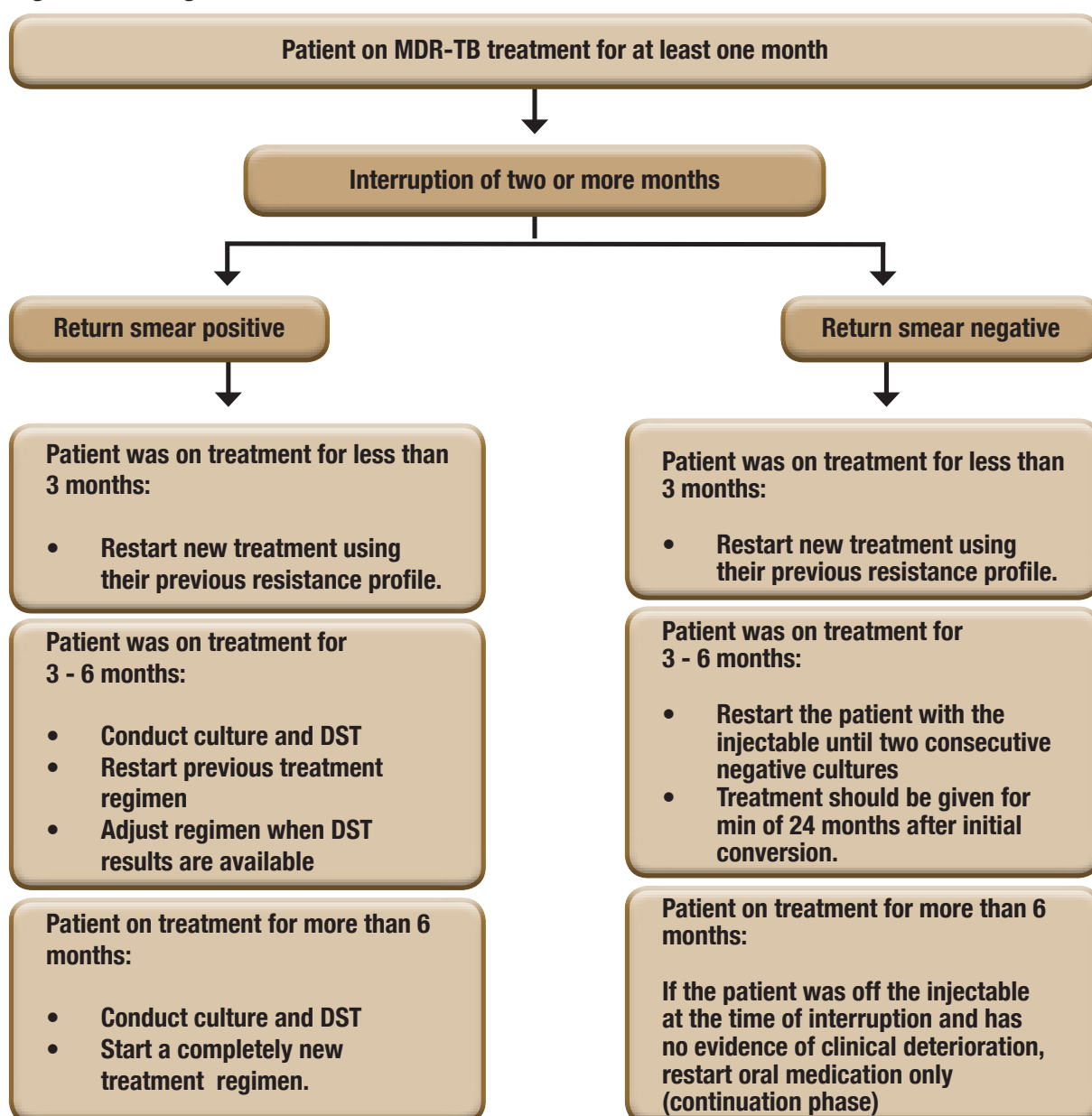
In patients where treatment has to be restarted following abscondment, default or interruption, the following should be considered:

- Commitment of patient to treatment completion;
- Clinical condition of the patient; and
- 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 interrupt 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 there is no 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 up regularly for signs of relapse.

**Figure V Management of Patients who Default Treatment**



## 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-ray films. The injectable drug can be stopped when:

- Patient has completed a minimum of six months of intensive phase treatment.
- Two consecutive negative culture results.
- At least four drugs to which the strain is still sensitive and are usable.

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 after culture conversion or throughout the treatment period.

## 14.9. If There is No Improvement at Four 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 XXIX Possible Causes of Lack of Improvement**

Problem	Possible Causes	Action
Very slow clinical improvement	<ul style="list-style-type: none"><li>• Inadequate therapy, sub-optimal dosing.</li><li>• No direct observation of treatment, or erratic pill taking by patient.</li></ul>	<ul style="list-style-type: none"><li>• Treatment is too weak: strengthen the treatment regimen, never add single drug.</li><li>• Replace injectables if patient is susceptible to the others.</li></ul>
Failure to respond to an effective treatment regimen	<ul style="list-style-type: none"><li>• Problems with bacteriology tests (specimen collection error, laboratory error, or contamination).</li><li>• Smear positive due dead bacilli.</li></ul>	<ul style="list-style-type: none"><li>• Add two new drugs that the strain is sensitive.</li><li>• Increase drug doses</li><li>• Consider surgery if disease is localised.</li><li>• If culture conversion is achieved in the following 2-3 month continue the same treatment.</li><li>• Repeat DST.</li><li>• When new DST result is available adjust treatment regimen.</li></ul>

## **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. Therefore, patients should 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 resistance amplification. 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 be modified based on 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 contamination.

## **14.11. Treatment Completion**

The patient is considered to have completed treatment when s/he has completed at least 18 months of treatment after culture conversion and 24 months for those who had extensive lung damage at the initiation of treatment. Bacteriological, clinical, and radiological information must be considered when determining the end of treatment for MDR- and XDR-TB.

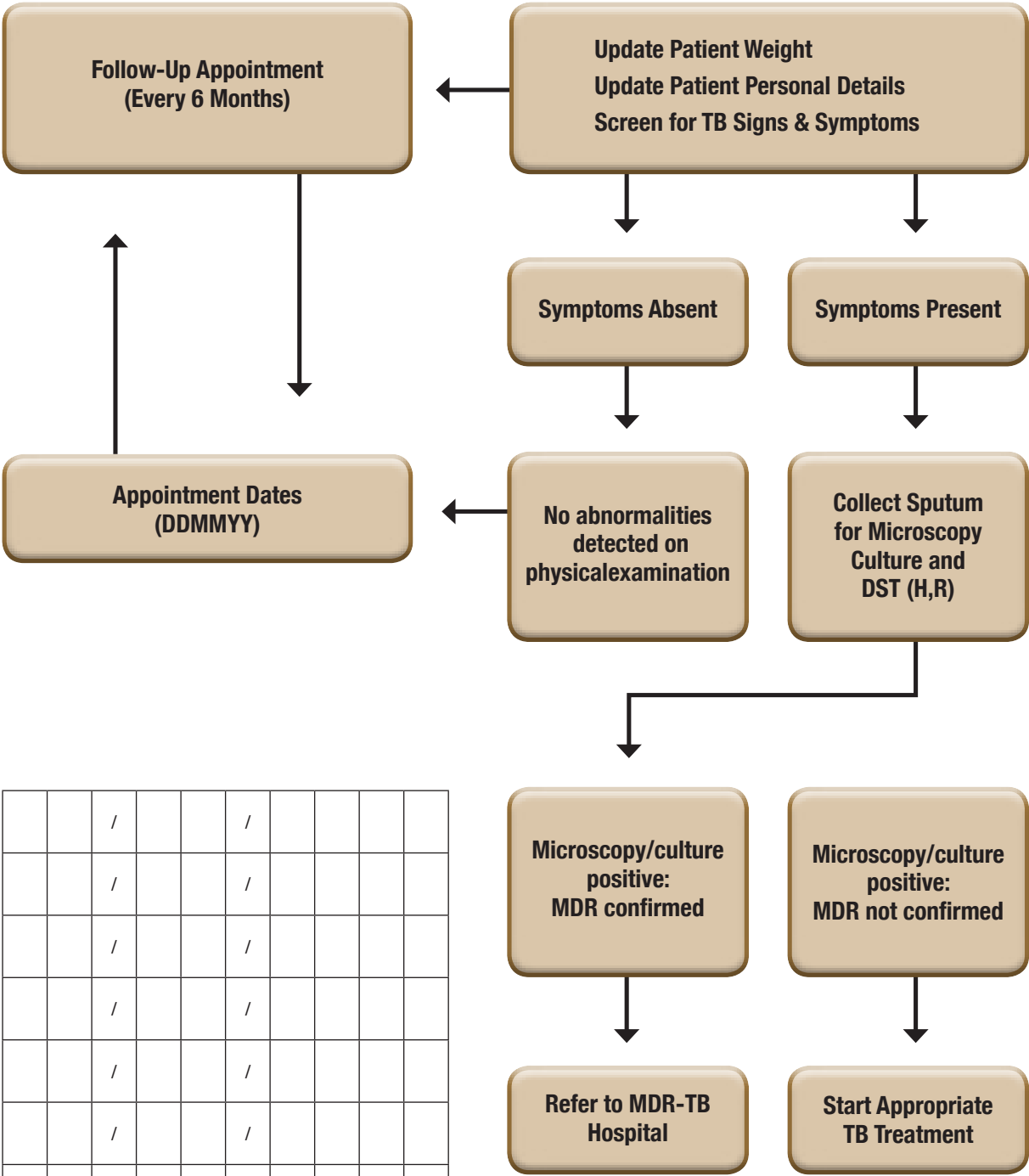
## **14.12. Follow-up After Treatment Completion**

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.
- Conducting radiographic evaluation as needed for development of respiratory symptoms.
- Monitoring response to ancillary medicines in patients who had residual lung disease.

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 of each patient's residence during the follow-up phase must be obtained.

Figure VI Post Treatment Follow-up Flow Chart



		/			/				
		/			/				
		/			/				
		/			/				
		/			/				
		/			/				
		/			/				
		/			/				

### 14.13. MDR- and XDR-TB Treatment Failures

Treatment failures are considered 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 are necessary. Avoid adding one or two drugs to an apparently failing regimen, instead redesign the regimen with four effective drugs. Once a patient gets two or more new drugs included in the regimen, with or without omission of certain drugs; this should be considered as a new regimen. The patient will receive an outcome of treatment failure and recorded in a new treatment cohort.

#### 14.13.1. Patients with Suspected MDR-TB Treatment Failure

Patients who show clinical, radiological, 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 adherence of patient to treatment. The healthcare 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 in the absence 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 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 treatment failure. Repeated negative smear and culture results in a patient with clinical and radiological deterioration may indicate that disease other than DR-TB is also affecting the patient.
- Other illnesses that may decrease absorption of medication (like chronic diarrhoea) or may result in immune-suppression (like HIV) should be excluded.

#### 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 that indicate treatment failure include:

- Persistent positive smears or cultures after 8 months of treatment;
- Extensive and bilateral lung disease with no option for surgery;
- High-grade resistance with no option to add additional agents; and
- Deteriorating clinical condition that usually includes weight loss and respiratory insufficiency.

All these signs need not 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- or XDR-TB treatment can be terminated provided that appropriate counselling 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.

Suspension of 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 decision to suspend treatment should be made by the provincial DR-TB review committee based on all evidence provided on the patient. The team should recommend a treatment plan. Conditions under which treatment may be suspended include:

- The patient's quality of life is poor, particularly when 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 take place. Both parties should be made to 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 take to minimise transmission risk 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 summarised 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, on-going 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- AND XDR-TB CONTACTS**

# 15. MDR- AND XDR-TB CONTACTS

## 15.1. Introduction

The opportunity to halt the spread of MDR- and XDR-TB in the communities, 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 who 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 be appropriately managed.

## 15.2. Evaluating the Risk of MDR-TB in Contacts

Factors that should be considered when investigating patient contacts 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-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.
- 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:** In immuno-competent persons, the risk of developing TB is highest within the first two years following infection, after which this risk declines markedly. In general, 5%-10% of infected immuno-competent persons will develop active disease within the first two years. Child contacts of patients with MDR- or XDR-TB (especially those under two years of age) are at increased risk of getting infected and develop TB disease.

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, including:

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

### **15.3. Managing Asymptomatic Contacts of MDR- and XDR-TB Patients**

The use of second-line drugs for preventive therapy in MDR- 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- or 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- and XDR-TB patients should be managed according to the standard recommendations for contacts of drug-susceptible TB patients

Asymptomatic contacts of smear-positive MDR- and 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 health status 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 be examined clinically with Mantoux tuberculin skin test and a chest radiograph done. If there is any evidence of disease, specimens (from any appropriate source) should be obtained for culture and DST before commencement of 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 radiographs are normal, all exposed and infected children (therefore irrespective of TST result) should receive preventive therapy (isoniazid 15 mg/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 3-6 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 that 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. Managing Symptomatic Contacts of MDR/XDR-TB Patients**

#### **15.4.1. Adult Contacts**

All symptomatic close contacts of MDR- or 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- and XDR-TB should be suspected in the following situations with children:

- Who are contacts of a patient with confirmed MDR- or XDR-TB.
- Who are contacts of patients who died of tuberculosis while on treatment and there are reasons to suspect it was MDR- or XDR-TB.
- With bacteriologically proven TB that are not responding to first-line drugs despite treatment compliance.

In children, the diagnosis of TB is more difficult than in adults. Symptoms of TB in young children can be non-specific (e.g. chronic cough or wheeze, failure to thrive and recurrent fevers). 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. Computerised tomography is sometimes helpful, especially in documenting complications due to 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, chest X-ray is negative and gastric aspirate or sputum culture is 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. 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 to monitor the management of DR-TB patients effectively. This information system allows the managers at different levels to monitor programme performance by following the distribution and trends in MDR-TB notification and treatment outcomes of patients started on Regimen IV. It does not include the detailed information that HCWs may need to manage individual patients, which is, however, 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 regularly by the management team 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 (EDRWeb). 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- and XDR-TB are used to:

- Allow proper patient registration and epidemiological notification;
- Facilitate case allocation to appropriate treatment categories;
- Facilitate case evaluation according to site, bacteriology and treatment history; and
- 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 commenced on MDR-TB treatment after a decision of a provincial DR-TB review committee or DR-TB practitioner on the basis of clinical presentation, radiological findings and medical history indicating a high probability of MDR-TB. It is worth noting that it is difficult to make a laboratory diagnosis of MDR-TB in children (see chapter 12).

Patients who have mono-resistance to rifampicin through GeneXpert or conventional DST will be registered as “not confirmed MDR-TB” because they receive MDR-TB treatment. These patients will later be changed to “confirmed MDR-TB” when laboratory confirmation becomes available.

**A case of XDR-TB** is defined as a patient with bacteriologically proven TB whose disease is due to bacilli showing in vitro MDR together with resistance to any fluoroquinolone plus resistance to one or more of the following injectable anti-TB drugs: kanamycin, amikacin, and capreomycin.

History of previous TB treatment allows categorisation 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 shown in the following table.

**Table XXX Patient Categories**

<b>Category I: NEW</b>	A patient who has received no anti-tuberculosis treatment for TB, MDR- or XDR-TB or received less than one month of anti-tuberculosis drugs.
<b>Category II: Previously treated with first-line drugs only</b>	Patient who has been treated for one month or more for TB with only first-line drugs
<b>Category III: Previously treated with second-line drugs</b>	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.

**Site of disease** is classified according to pulmonary or extra-pulmonary involvement:

- Pulmonary MDR- and XDR-TB refer to disease involving the lung parenchyma only.
- Extra-pulmonary MDR- and XDR-TB refer to organs other than the lungs.
- A patient with both pulmonary and extra-pulmonary MDR- and XDR-TB constitutes a case of pulmonary MDR- and XDR-TB.
- The case definition for extra-pulmonary MDR- and 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.

**Table XXXI Core Tools Used for Patient Management**

<b>Record</b>	<b>Completed by</b>	<b>Where it is Kept</b>
DR-TB Treatment Card (yellow)	Nurse/doctor	MDR-TB Hospital
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	Central MDR-TB Unit Decentralised MDR-TB unit PHC facilities allowed to do so by NDOH & provinces



### 16.3.1. DR-TB Treatment Card

HCWs administering 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 must be recorded. This must include history of previous admission to a hospital, imprisonment and working in the mines.
- **Patient category:** There are eight possible groups: new, relapse, treatment after default, treatment after failure of first treatment, treatment after failure of re-treatment, transfer in, and other (previously treated but the outcome is unknown).
- **Site of disease:** The affected organ must be specified in patients 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 and every dose of oral or injectable drugs administered to the patient is recorded in this section.
- **Adverse drug reactions:** Any ADR 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 records the same information as the treatment card but when the patient is discharged from the hospital or referred to another hospital, s/he takes this card to the receiving facility. The health care worker at the clinic updates the information on 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 patient progress while on treatment and allows for evaluation of the programme through quarterly, six-monthly and annual analysis of case finding, culture conversion and treatment outcomes.

The registers must be kept in all MDR-TB hospitals (central and peripheral). The information from the patient treatment card is entered into the register and should be updated daily for new patients registered and monthly for smear and culture results and treatment outcomes.

All patients in whom DR-TB have been confirmed must be registered in the DR-TB register, even if they have not started treatment. The following is recorded in the DR-TB register:

- **DR-TB register number:** This is a unique patient identification number for patients that enter DR-TB treatment.
- **Date registered.**
- **Name, sex, date of birth, address.**
- **District TB register number.**
- **Site of disease:** Pulmonary (vs) extra-pulmonary.
- **Registration category:** There are eight possible groups – new, relapse, treatment after default, treatment after failure of first treatment, treatment after failure of re-treatment, transfer in, and other (previously treated but the outcome is unknown).
- **Second-line drugs already received:** Yes or no.
- **DST:** Date and results. Patients may have had more than one DST. The diagnostic DST (which resulted in the patient being registered as a MDR- or XDR-TB patient) is entered. The full DST history is recorded on the treatment card. Follow-up DST results are not recorded in the register.
- **Reason for being registered as DR-TB.** Reasons include mono- or poly-resistant TB, confirmed or not confirmed MDR-TB, confirmed or not confirmed XDR-TB. If the patient is not started on treatment the reason is given in the subsequent column.
- **The DR-TB regimen:** The date and the initial regimen are recorded.
- **Smear and culture monitoring results:** Date and result.
- **Final outcomes:** At the end of treatment the outcome should be recorded on the treatment card according to the outcome definitions.
- **Comments.** This section is reserved for any additional information

#### 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 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, ADRs, clinical progress).
- Health centre where the patient will receive treatment.
- Dates of appointments.

#### 16.3.5. Request for Sputum Examination

The top of the form is identical to the form used in DOTS programmes, while the middle part is used for requesting culture and DST. The bottom part is used for reporting the results. The same form is returned to the treating unit with the results.

## 16.4. Treatment Outcome Definitions

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

- **Cure:** A patient who has converted (with 2 consecutive TB culture negative taken 30 days apart), and has remained TB culture negative, 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. This outcome is restricted to confirmed pulmonary DR-TB patients.
- **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 while 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 and are positive, or if any one of the final three cultures are positive. Treatment failure may be observed in patients who do not respond to treatment after 6 to 8 months of effective treatment. Such patients will be put on a different treatment regimen after receiving an outcome of failure and be allocated to a new treatment cohort.
- **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 ADRs:** A patient who develops ADRs while on DR-TB and could not continue treatment in spite of the management of the ADRs 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 ADRs, 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.

## 16.5. Cohort Analysis of Treatment Outcome

Details of all patients identified with DR-TB should be recorded in the register. The register must clearly identify MDR/XDR-TB patients from those with other forms of drug resistance and those that are not confirmed MDR/XDR-TB.

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 treatment start date should also be recorded 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 utilised is also useful.

The analysis of MDR/XDR-TB treatment outcomes should be performed 24 months after the last patient enrolment date in the cohort (interim outcome) and at 36 months (final outcome report). All patients should be assigned the first outcome they experience for recording and reporting purposes. The analysis at 36 months will be directed at patients who were still on treatment after 24 months of treatment. There is no need to review outcomes of the entire cohort.

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 tables. The tables report the following information:

- Table 1: Numbers of M/XDR-TB patients detected in the laboratory during the quarter.
- Table 2: Numbers of Confirmed and not-confirmed M/XDR-TB cases started on treatment during the quarter.
- Table 3: HIV and ART status of M/XDR-TB patients started on treatment during the quarter
- Table 4: Proportion of MDR-TB detected, started on treatment and reasons for not starting treatment
- Table 5: Proportion of XDR-TB detected, started on treatment and reasons for not starting treatment

This report is completed with a delay of one quarter, to allow for culture and DST results to be ready. For example, DR-TB patients registered during the first quarter of a year (01 January to 31 March) should be reported in the quarter 3 report. In this report the date when the patient first enters the DR-TB register (registration date) is used, and not the date when the patient starts DR-TB treatment.

### ***Preliminary Six-month Interim Outcome Assessment Form***

Each defined cohort should have an interim or preliminary outcome report. This report should be developed by the central DR-TB unit or the decentralised DR-TB unit. This report looks at the number of confirmed M/XDR-TB patients with a smear and/or TB culture negative by the sixth month of treatment. If there is no result at month 6, the fifth month result should be considered.

### ***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 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. 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 DR-TB**

# 17. HEALTH CARE WORKERS AND DR-TB

## 17.1. Introduction

TB is an occupational disease and HCWs have the legal right for a safe working environment where adequate protection is provided against infection. The onus rests on the employer to provide a safe working environment or alternative employment for HCWs 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, including:

- 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 employees 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 OHSA.

### Hazardous Biological Agents Regulations

These regulations were passed in December 2001 and they legally entrench infection control. A hazardous biological agent (HBA) is defined as any micro-organism, cell culture, and human endo-parasite, genetically modified which may cause infection, allergy, toxicity, or create hazard to human health. These are classified into four groups as shown in the following table.

**Table XXXII Hazardous Biological Agents**

HBA	Definition
<b>Group 1</b>	Unlikely to cause human disease.
<b>Group 2</b>	May cause human disease. Hazard to exposed persons. Unlikely to spread to community. Effective prophylaxis and treatment.
<b>Group 3</b>	May cause severe human disease. Serious hazard to exposed persons. Risk of spread to community. Effective prophylaxis/treatment.
<b>Group 4</b>	Causes severe human disease. Serious hazard to exposed persons. Risk of spread to community. No effective prophylaxis/treatment.

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 this ranges 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 monitored on a regular basis and medical surveillance of the employees are 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.

Section 15 deals with special measures for health facilities, to prevent spread of infection in instances where patients may present with unknown or undiagnosed infections by implementing regulated infection control measures.

### **Compensation for Occupational Injuries and Diseases Act, 130 of 1993**

*The Compensation for Occupational Injuries and Diseases Act* provides for compensation of HCWs who contract 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 found 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.

## 17.2. Infection Prevention and Control

Nosocomial infections are mainly due to delayed diagnosis of TB and confirmation of DR-TB and delayed start of appropriate treatment, which contributes to prolonged infectiousness. Inadequate or delayed isolation of suspects and patients, poor ventilation, lack of respiratory protective equipment and inadequate sputum collection procedures can result in exposure of HCWs, other patients and visitors to infection.

### ***Priorities of Infection Control (for in-patients and out-patients)***

There are three levels of infection control measures:

- **Administrative (managerial):** Aims to reduce health care worker and patient exposure.
- **Environmental:** Aims 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 practices;
- Educating, training and counselling HCWs about TB; and
- Screening HCWs 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 infectious 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 the following principles:

#### **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.

#### **Air Sanitisation**

Air sanitisation is 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 sufficiently exposed to UV light. For UVGI to be effective, 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 or 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. Also, it is 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 measured regularly with a radiometer. In addition, care must be taken to minimise risk to HCWs and patients who, if inadequately protected, may get skin and eye irritation due to exposure to UV light if not properly installed.

### 17.2.3. Personal Respiratory Protection Equipment

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.

### ***Surgical masks***

Surgical masks are meant to prevent the spread of micro-organisms from the person wearing the mask to others by trapping 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.

### ***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 re-used if well maintained (i.e., 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, such that a tight seal can no longer be maintained between the edge of the mask and the face. The main factors responsible for their deterioration are humidity, dirt, and crushing. The durability of these devices varies among designs and products, and the extent of use. There is often a trade-off between durability and cost. If respirators are to be re-used, they should be stored in an open, clean, dry location. Plastic bags should never be used since they retain humidity.

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**

Specific measures for preventing the spread of nosocomial infection:

- Assign infection control officers who will be responsible for developing, implementing, monitoring and evaluating infection control plans.
- Establish a multidisciplinary infection control committee comprising of an infection control officer, microbiologist, medical practitioner/physician, pharmacist, housekeeping supervisor/manager food service manager, laundry service manager, maintenance manager and hospital manager.
- Conduct 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 infection control 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*.

- Develop an infection control plan based on the risk assessment. This should include the development and implementation of policies or protocols for early identification, diagnosis and treatment of patients who may have infectious TB.
- Provide prompt triage for and appropriate management of patients who may have infectious TB in the outpatient department. Ensure that staff:
  - Vigorously identify patients with active TB disease.
  - Conduct symptomatic screening of symptomatic patients.
  - Develop and use symptomatic screening tool.
  - Maintain a separate waiting area for TB suspects.
  - Provide tissues to cover the mouth when coughing and sneezing.
  - Use surgical masks to prevent spread of infectious particles when coughing or sneezing into the immediate surrounding areas.
- Promptly initiate and maintain TB isolation for persons who may have infectious TB and admitted in the wards.
  - Include indications for isolation in policies for initiating isolation.
  - Designate a person to decide on initiation and termination of isolation.
  - Implement isolation practices in the facility.
  - Monitor isolation practices.
  - Manage patients who do not adhere to isolation practises.
  - Development and adhere to criteria for discontinuing isolation.
- Effectively plan for discharge, which 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.
- Plan, install and evaluate ventilation and other engineering controls to reduce the risk of exposure to *M. tuberculosis*.
- Plan, implement, maintain and evaluate a respiratory protection programme.
- Educate and train HCWs about TB, effective methods for preventing transmission of infection and the benefits of medical surveillance programmes.
- Develop and implement a programme for periodic counselling and screening for HCWs for latent infection and active disease.
- Ensure that all HCWs know the importance of compliance to infection control interventions to minimise risk of exposure to infectious agents.
- Offer alternative employment to HCWs who have a health condition that compromises cell mediated immunity when placed in high risk areas.
- Ensure that information provided by HCWs regarding their HIV status is treated confidentially.
- Ensure prompt evaluation of nosocomial transmission, including PPD test conversions or active TB in HCWs, epidemiological association of cases among workers, patients, contacts of patients or HCWs 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 MDR-TB have 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 terminated.
- Report all people confirmed with DR-TB and ensure adequate discharge follow up and the continuum of care.

## 17.4. Conducting Risk Assessment

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 summarised as follows:

Risk category	Definition
High risk	HCWs in prolonged close contact with infectious (smear-positive) MDR-TB cases (e.g., nursing staff and other medical staff in MDR-TB hospitals and wards).
	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.
	HCWs who are immuno-compromised and who are involved in regular MDR tuberculosis patient management.
Medium risk	HCWs in primary health care centres who are involved in sputum collection procedures from tuberculosis suspects.
	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.
Low risk	HCWs in primary health care centres involved in management of tuberculosis patients on therapy.
	Health care facility support staff, such as porters, cleaners and administrative staff.
	HCWs in general hospitals and community health centres.

## 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:

- Provide on-going education and training on the transmission and pathogenesis of TB, the consequences of DR-TB, the infection control measures implemented in the facilities and importance of compliance to these.
- Stress a continuous awareness of risk situations and avoidance thereof.
- Promote HIV testing due to the increased risk of acquiring tuberculosis among HIV- positive people.
- Offer alternative employment to staff who are immuno-compromised.
- Implement universal infection control procedures (including safe waste disposal) in all health care facilities.
- Strictly adhere to cough hygiene.
- Collect sputum in an open area or cough booths where available.

- Ensure that in-patients who are coughing are 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 a handkerchief, surgical mask or a tissue when 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.

HCWs 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 minimise droplet infection exposure.
- Ensure that the patient holds the container as close as possible to the mouth.
- Ask the patient to close the container immediately after expectoration.
- Ensure that all sputum jars are labelled prior to collection taking place to minimise handling of specimens.
- Wear gloves when handling specimens.
- Wash hands with appropriate disinfectant if hands have contacted sputum without gloves.
- Ensure that the lids of sputum containers are properly closed to avoid spillage.
- Follow correct procedures 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, area then should be wiped with hypo-chlorite solution.
- Ensure that all specimens are placed in a plastic bag.

The HCW should also follow these protective measures:

- Wear disposable apron, gloves and particulate filter respirators during cough inducing procedures.
- Follow correct hand washing before and after each patient contact.
- Wash all instruments in the ward to remove respiratory secretions before being sent to CSSD.
- Ensure that all resuscitation equipment is in order and no mouth-to-mouth resuscitation is conducted.
- Supply each patient with a disposable sputum mug with a lid and sputum mugs must be replaced three times per day.

### 17.5.3. Isolation Practices

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 patients.
- Children should be kept separate from adults.
- Very sick patients should be admitted in a ward separate 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- 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 visualised during microscopy.

### 17.5.4. Medical Surveillance Programme

Medical surveillance programmes are in existence for all employees. The objectives of surveillance programmes are to:

- Establish the baseline of TB infection status of the workers;
- Identify those with latent TB infection and offer them preventive therapy to decrease their risk of developing active TB;
- Identify workers with active TB disease and initiate TB treatment immediately;
- Document conversion rates, those who are initially negative and then later become positive;
- Investigate the possible source of infection for all converters;
- Notify district and provincial health authorities; and
- Monitor the effectiveness of the infection control program.

The elements of the medical surveillance programme include the following:

- Pre-placement.
- On-going surveillance.
- Exit.
- Post-employment.

#### **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, including the following baseline tests:

- Chest X-ray
- Mantoux tuberculin skin test (TST)
- Lung function tests
- Glucose blood and urine levels
- Hepatitis B



### ***Provider-Initiated Counselling and Testing (PICT)***

HCWs 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.

On-going Surveillance

Table XXXIII shows the recommended frequency of on-going medical surveillance based on the facility, and activity risks

**Table XXXIII Frequency of On-going Medical Surveillance**

Activity risk	Health Care Facility Risk	
	High	Low
High	Six-monthly	Annually
Intermediate	Annually	Post-exposure
Low	Post-exposure	Post-exposure

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 (i.e., 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 <10mm should be re-tested. Strongly positive reactors with skin test diameters of >15 mm and recent skin converters should be evaluated clinically and microbiologically.

### ***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.

### ***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.
- Results of post-exposure screening.
- Management plans for treatment and follow-up of workers with confirmed disease
- Management and follow-up of workers on preventive therapy.
- Counselling provided to the HCW.

As a general rule, HCWs 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.



# ANNEXURES

# ANNEXURE 1: ADVERSE DRUG REACTION FORM

## ADVERSE DRUG REACTION AND PRODUCT QUALITY PROBLEM REPORT FORM



health

Department:  
Health  
REPUBLIC OF SOUTH AFRICA

(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:

M	F
---	---

DOB: ..... / ..... / .....

Height (cm) : .....

### ADVERSE REACTION/PRODUCT QUALITY PROBLEM

Adverse  
reaction<sup>1</sup>

☐

and/or Product Quality  
problem<sup>2</sup>

☐

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)

Trade Name & Batch No. (Asterisk Suspected Product)	Daily Dosage	Route	Date Started	Date Stopped	Reasons for use

## ADVERSE REACTION OUTCOME (Check all that apply)

<input type="checkbox"/>	death	<input type="checkbox"/>	life-threatening	Event reappeared on rechallenge:	Recovered:	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/>	disability	<input type="checkbox"/>	hospitalisation			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	congenital anomaly	<input type="checkbox"/>	Other.....	<input type="checkbox"/>	Rechallenge not done	Sequelae:	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	required intervention to	.....		Treatment (of reaction)		Describe Sequelae:.....		
	prevent	.....		.....		.....		
	permanent	.....		.....		.....		
	impairment/ damage	.....		.....		.....		

**COMMENTS:** (e.g. relevant history, allergies, previous exposure, baseline test results/lab data)

## 2. PRODUCT QUALITY PROBLEM:

Trade Name	Batch No	Registration No	Dosage form & strength	Expiry Date	Size/ Type of container

Product available for evaluation:

☐

☐

## REPORTING DOCTOR/PHARMACIST:

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.*

**PLEASE USE ADDRESS PROVIDED BELOW- JUST FOLD IN THIRDS, TAPE and MAIL**

Geen posseël nodig nie indien in die  
Republiek van Suid-Afrika gepos.  
Posgeld sal deur die geadreseerde

No postage stamp necessary if posted in  
the Republic of South Africa  
Postage will be paid by the addressee

BUSINESS REPLY SERVICE  
BESIGHEIDSANTWOORDDIENS  
Free Mail Number:  
Vryposnommer: **BNT 178**

DEPARTEMENT VAN GESONDHEID  
REGISTRAR OF MEDICINES  
REGISTRATEUR VAN MEDISYNE  
PRIVATE BAG/ PRIVAATSAK X828  
PRETORIA

# ANNEXURE 2: 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 antiretroviral 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)?

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 HCWs, 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.

## What happens to a report?

All ADR reports are entered into a national ADR database. Each report is evaluated to assess the causal relationship between the event and the medicine. A well-completed adverse drug reaction/product quality form submitted could result in any of the following:

- Additional investigations into the use of the medicine in South Africa
- 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)
6. Can this reaction be explained by other causes (e.g. underlying disease/s; other medicine/s; toxins or foods)? (It is essential that the patient is thoroughly investigated to decide what the actual cause of any new medical problem is. A medicine-related cause should be considered when other causes do not explain the patient's condition)

## **What types of reactions should be reported?**

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 3: 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 be hospitalised for the duration to be determined by my doctor if hospitalisation is deemed necessary to facilitate administration of the treatment and clinical monitoring
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 practises 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: .....

### UNDERTAKING BY HEALTH CARE WORKER

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 4: GUIDELINES FOR REFERRAL OF DR-TB PATIENTS FOR REVIEW BY THE PROVINCIAL DR-TB REVIEW COMMITTEE**

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 these 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  
And set dates for submission for next scheduled meeting of the committee.

All paperwork must be completed at the referring institution by delegated nurse, doctor. This will include:

- The MDR-MRB application form
- The MDR form
- The contract signed by patient and relevant HCWs on initiation of treatment

The MDR-TB co-ordinator of the MDR-TB 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 5: STANDARD ADMISSION/DISCHARGE/ REFUSAL OF HOSPITAL TREATMENT FORM

TPH 3 (81/500909)

HOSPITAL ..... Ward .....

..... Gender ☐ M ☐ F Age .....  
*Patient*

Patients' No.  Classification .....

ADDRESS  
.....  
*Doctor*  
Phone .....

## ADMISSION

Admitted by ..... Date ..... Time .....

Provisional diagnosis .....

Doctor's signature (if available) .....

## DISCHARGE

Date of discharge ..... Time .....

Final diagnosis .....

Doctor's signature .....

## REFUSED HOSPITAL TREATMENT

I, 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 .....

I, the undersigned, take the patient ..... out of the  
..... Hospital on my own responsibility and against the advice  
of the attending doctor.

Witnesses: 1 ..... Signature .....

2 .....

Date ..... Time ..... Capacity .....

For particulars of treatment use from TPH 3 (a).

## ANNEXURE 6: 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: .....

Name of Nurse/ Doctor: ..... Signature: .....

Date: .....

Witness 1: ..... Date:.....

Witness 2: ..... Date:.....

# **ANNEXURE 7: 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 advise and recommend appropriate clinical management of individual DR-TB patients within available resources.
- To address the dilemma posed to the individual clinician by offering multidisciplinary technical input and shared moral responsibility.

## **Mandate**

- To advise and recommend appropriate clinical management of individual patients.
- 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 retreatments, salvage regimens, withdrawal of treatment:*

- MDR- and XDR-TB patients who revert to culture positive after having had 2 negative cultures.
- MDR- and XDR-TB patients who remain culture positive for longer than 6 months after treatment is initiated. These would include true failures.
- Patients who default or interrupt treatment and patients with limited treatment options due to side-effects.
- MDR-TB 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-TB patients failing on standard regimens.
- Patients with sensitive strains, but phenotypical MDR- or XDR-TB.
- 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 or isolation:*

- Any of the above cases, where applicable.
- MDR- and XDR-TB patients who refuse therapy, remain smear positive and pose a risk to contacts.

## Method of Referral

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.

**Table XXXIV Documentation Required**

Information	Document	Whom
Counselling	<ul style="list-style-type: none"> <li>• Patient education and counselling form sheet</li> <li>• Social worker assessment report</li> </ul>	MDR counsellor/social worker, patient
Contract	<ul style="list-style-type: none"> <li>• Patient Consent Form</li> </ul>	MDR counsellor/social worker, patient
Socio-economic, environment report	<ul style="list-style-type: none"> <li>• Patient's family social assessment report</li> </ul>	Social worker/clinic staff
DR – TB patient history	<ul style="list-style-type: none"> <li>• Patient profile summary.</li> <li>• Baseline assessment results.</li> <li>• Summary of treatment and adherence.</li> </ul>	MDR-TB nurse, / clinic doctor / Info officer
Interview with patient and family	<ul style="list-style-type: none"> <li>• Home visit report</li> </ul>	Social worker/doctor, counsellor
Clinical records and results of investigations conducted	<ul style="list-style-type: none"> <li>• Patient treatment folder including CXRs, CT scans, etc.</li> </ul>	Hospital staff
Original patient adherence record	<ul style="list-style-type: none"> <li>• Patient treatment folder</li> </ul>	Hospital staff

## Proceedings

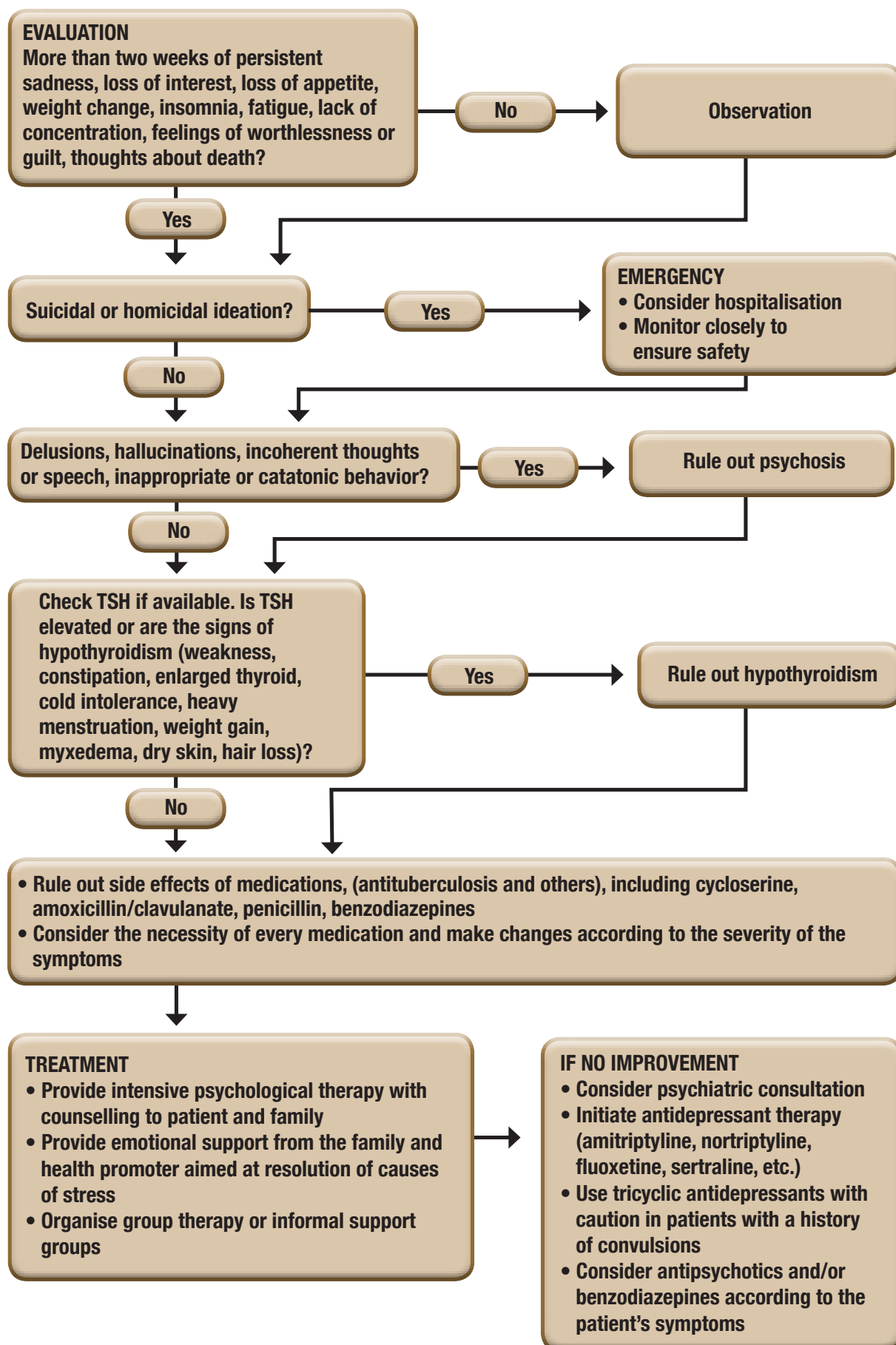
The quorum must constitute 50% of committee members plus one should the key specialist consultant not be available on the day of the meeting. They must be consulted on an ad hoc basis prior to meeting for their written recommendations on the patients to be presented.

Meeting proceedings will include:

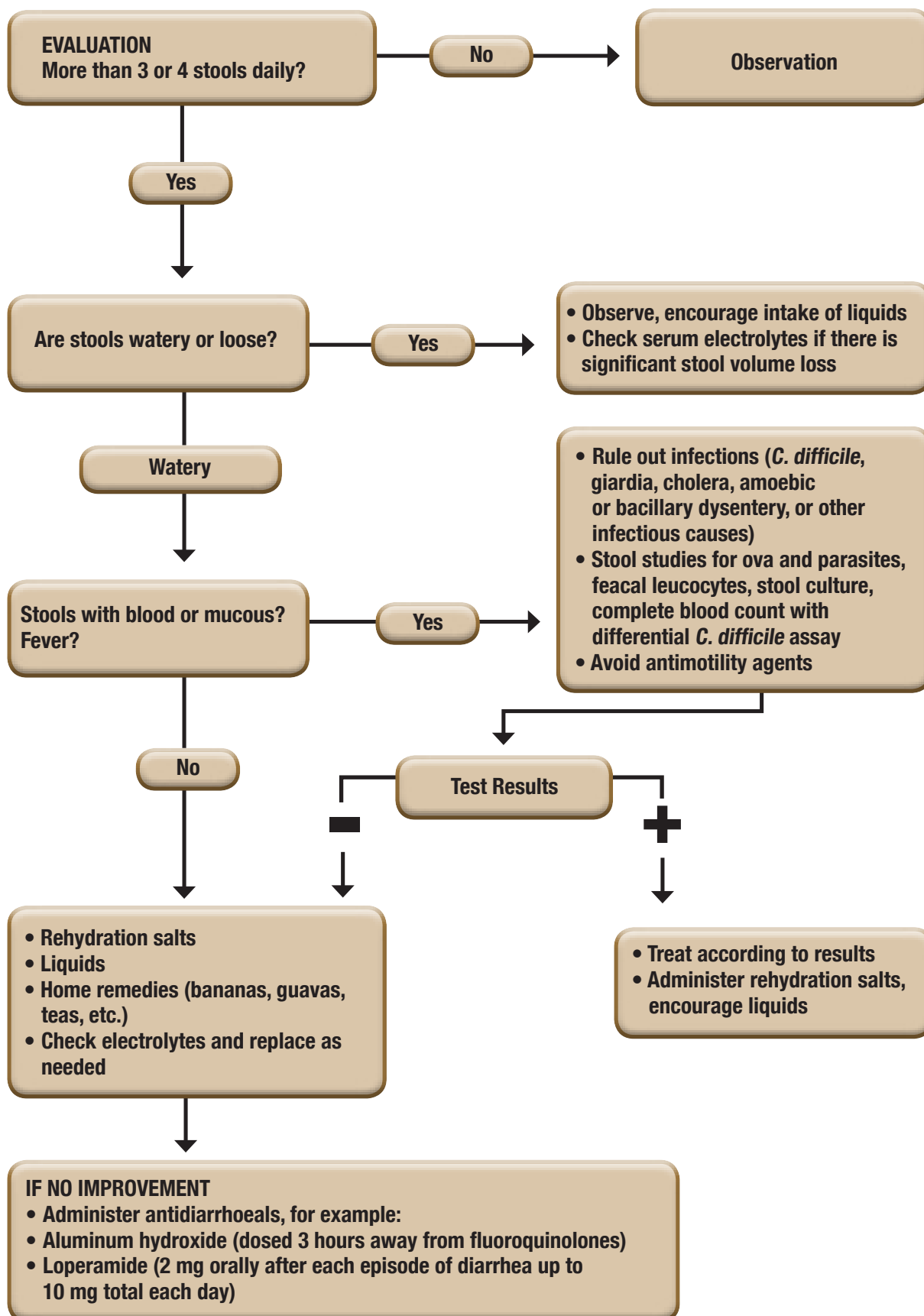
- Presentation by the treating medical officer.
- Structured discussion by committee, with minutes taken.
- Decisions or recommendations [or deferment of decision if further input/information is needed].
- A report is compiled by the Secretariat and signed off by the chairperson of the committee, and 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.
- Copies of referrals and committee decisions must be kept by the Secretariat.

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

## ANNEXURE 8: MANAGEMENT ALGORITHM FOR DEPRESSION

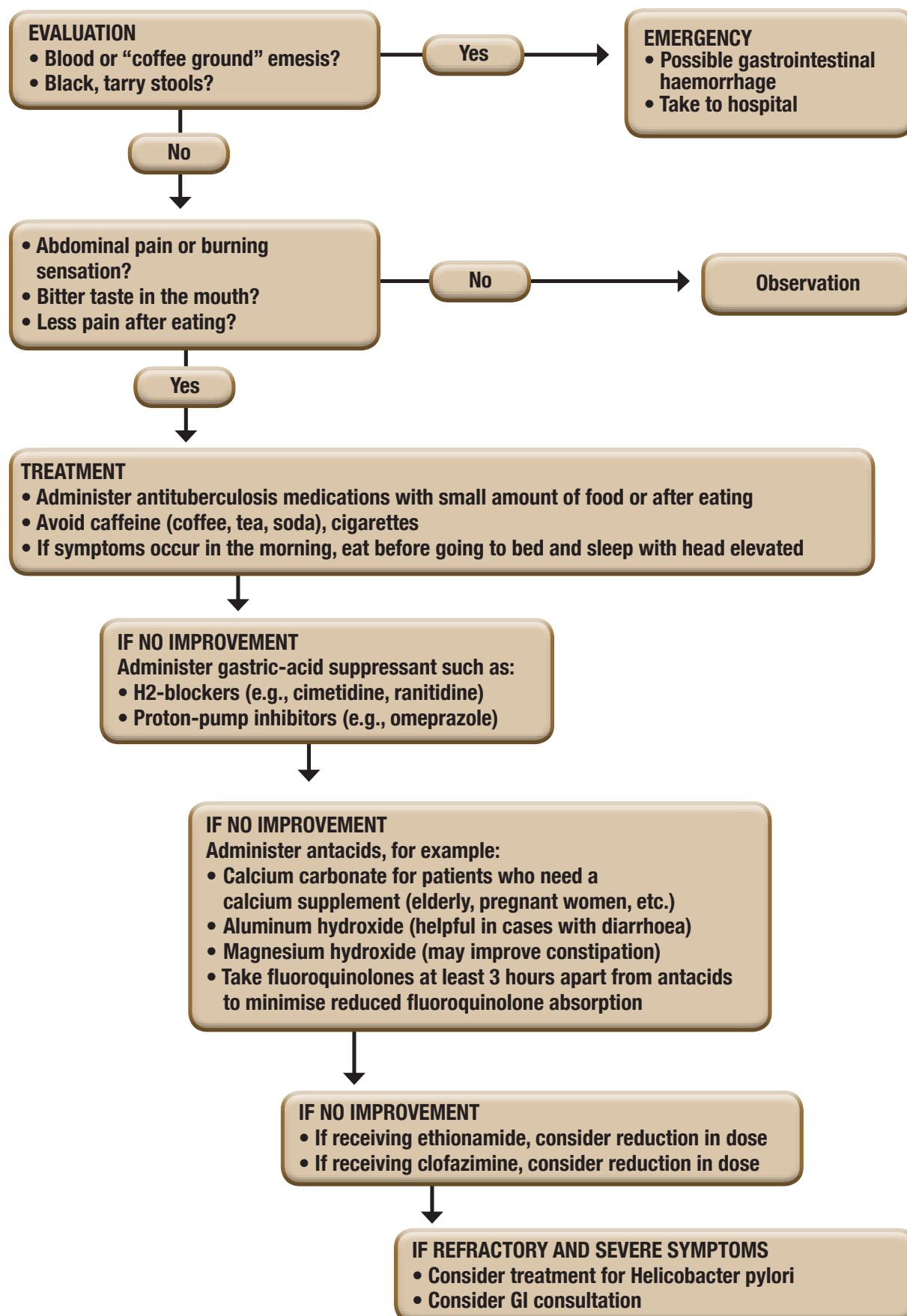


## ANNEXURE 9: MANAGEMENT ALGORITHM FOR DIARRHOEA

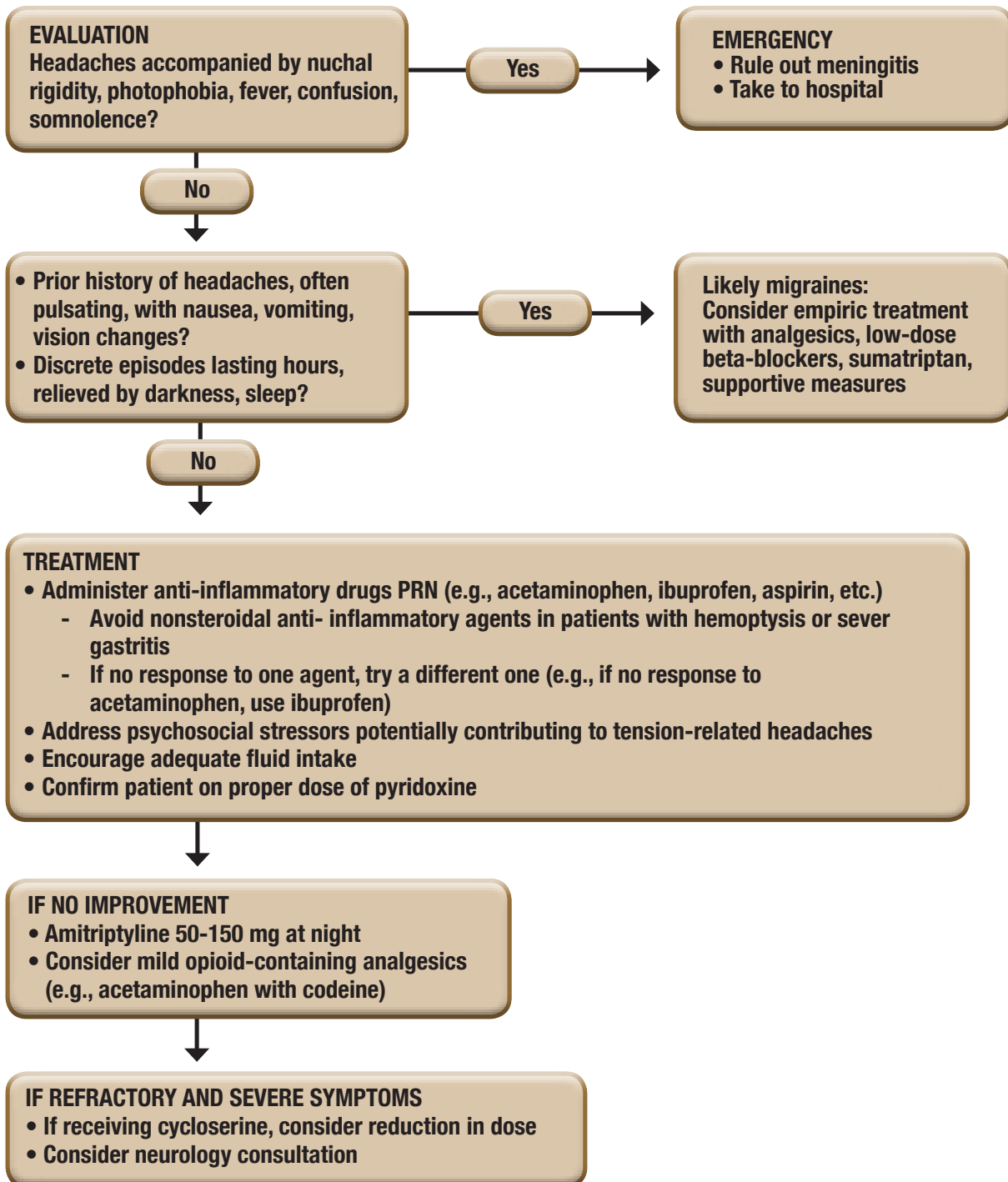




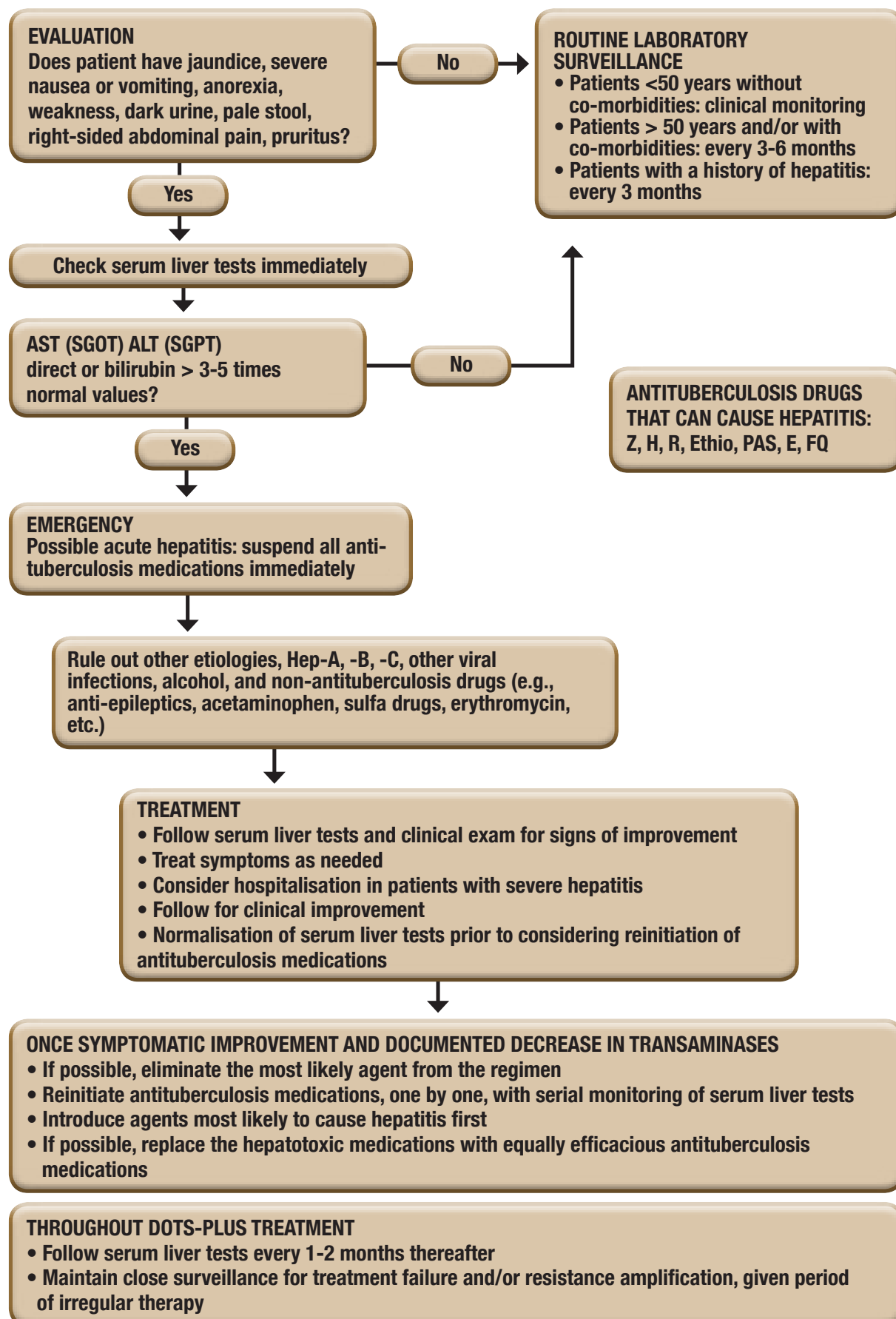
## ANNEXURE 10: MANAGEMENT ALGORITHM FOR GASTRITIS



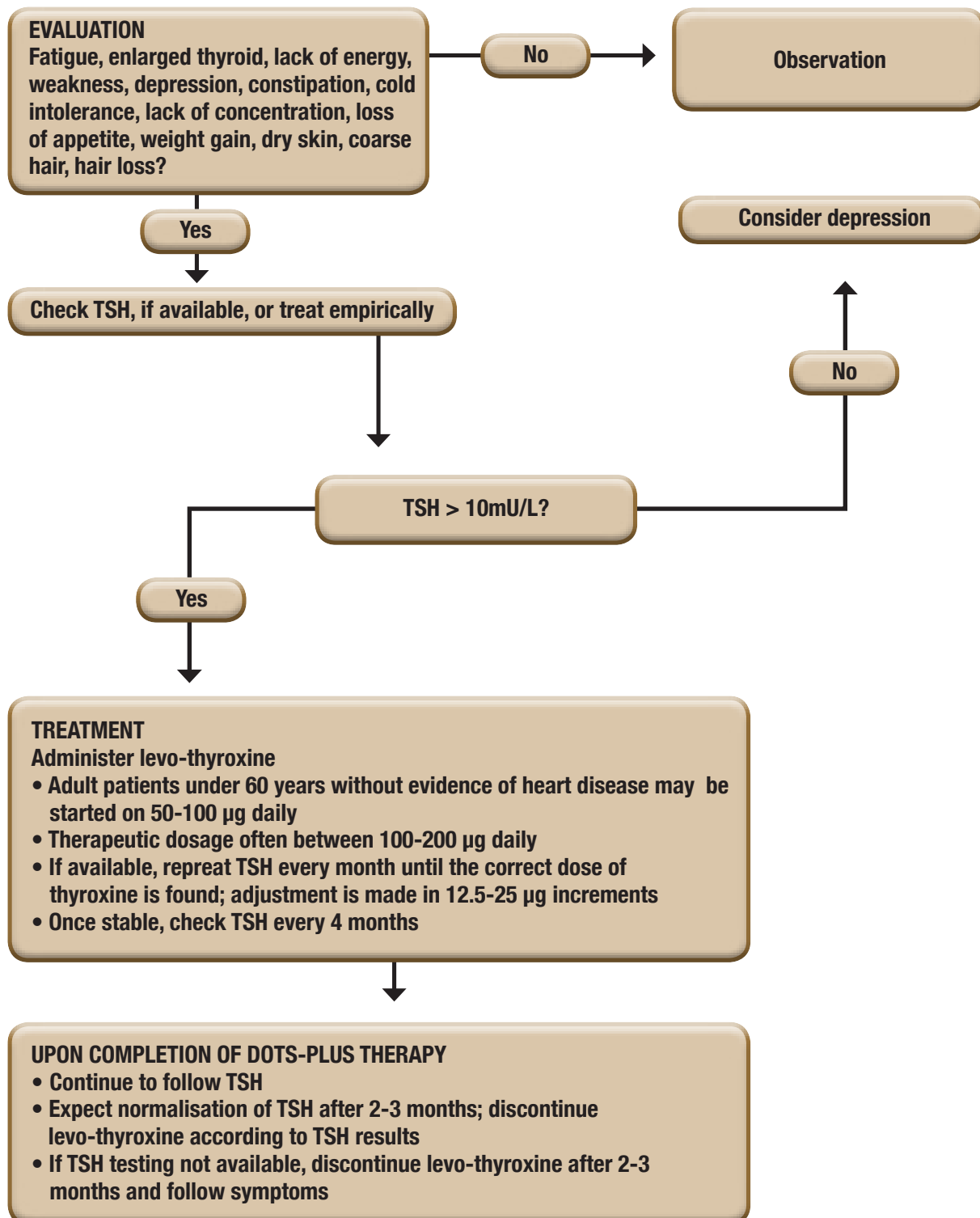
## ANNEXURE 11: MANAGEMENT ALGORITHM FOR HEADACHE



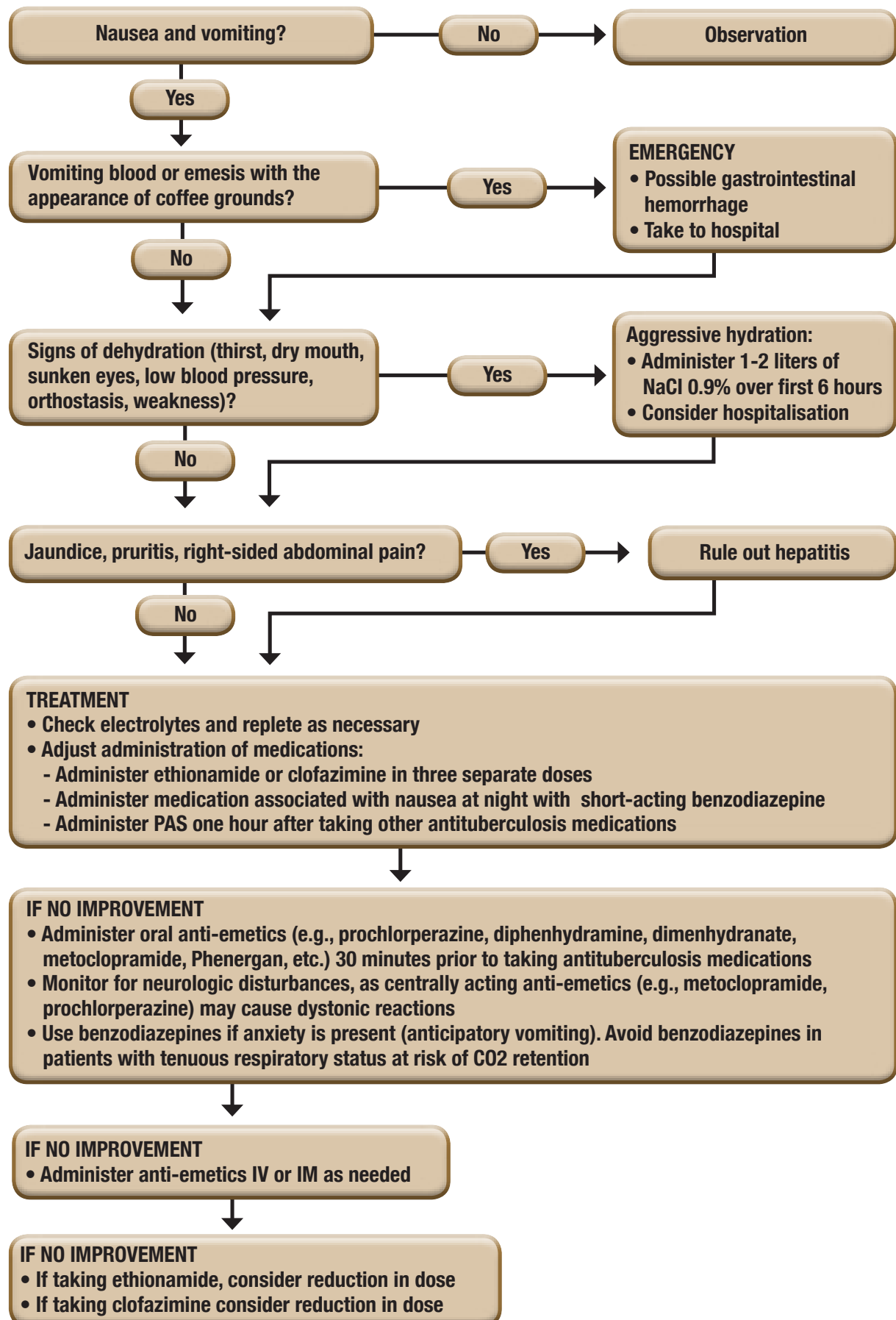
## ANNEXURE 12: MANAGEMENT ALGORITHM FOR HEPATITIS



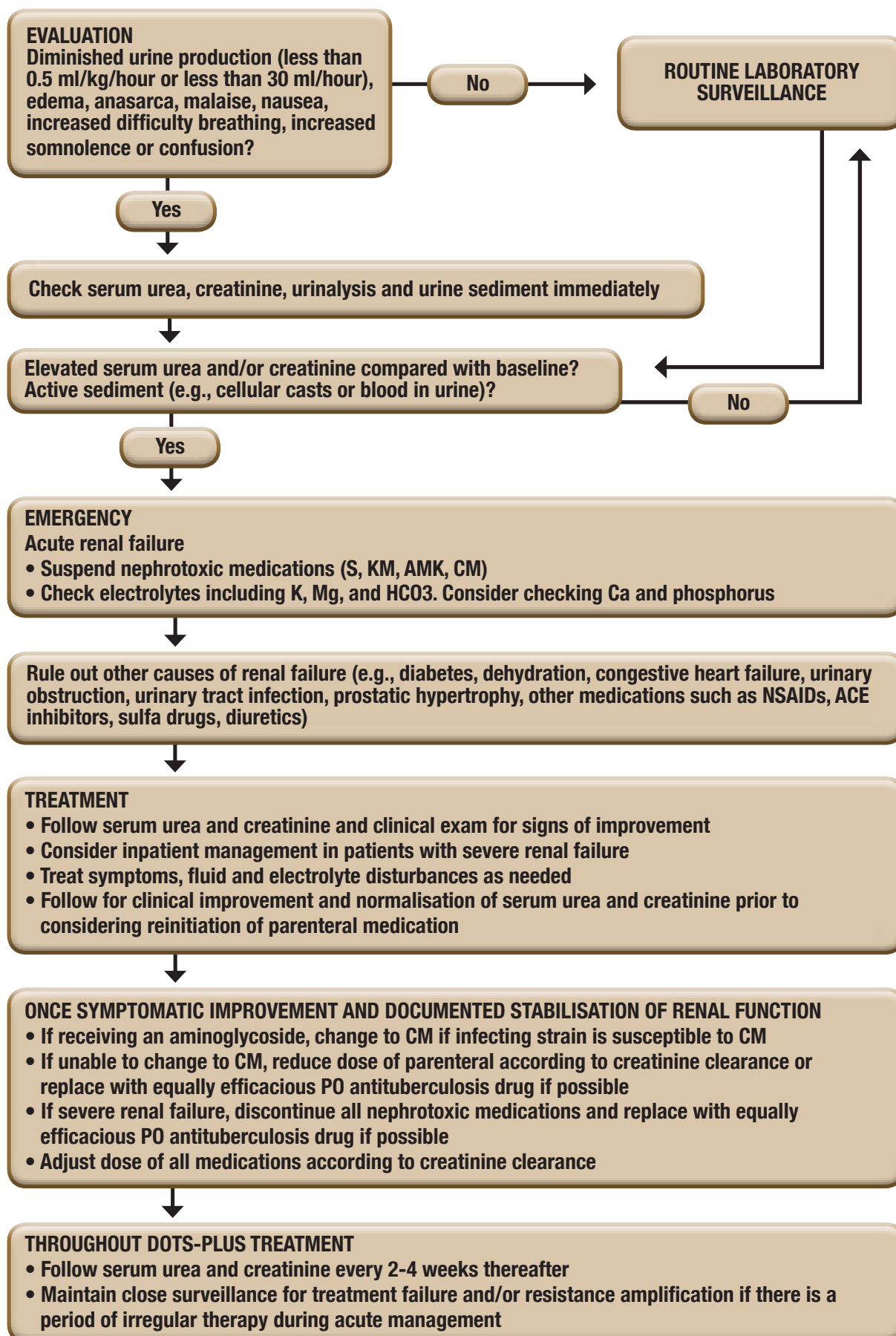
## ANNEXURE 13: MANAGEMENT ALGORITHM FOR HYPERTHYROIDISM



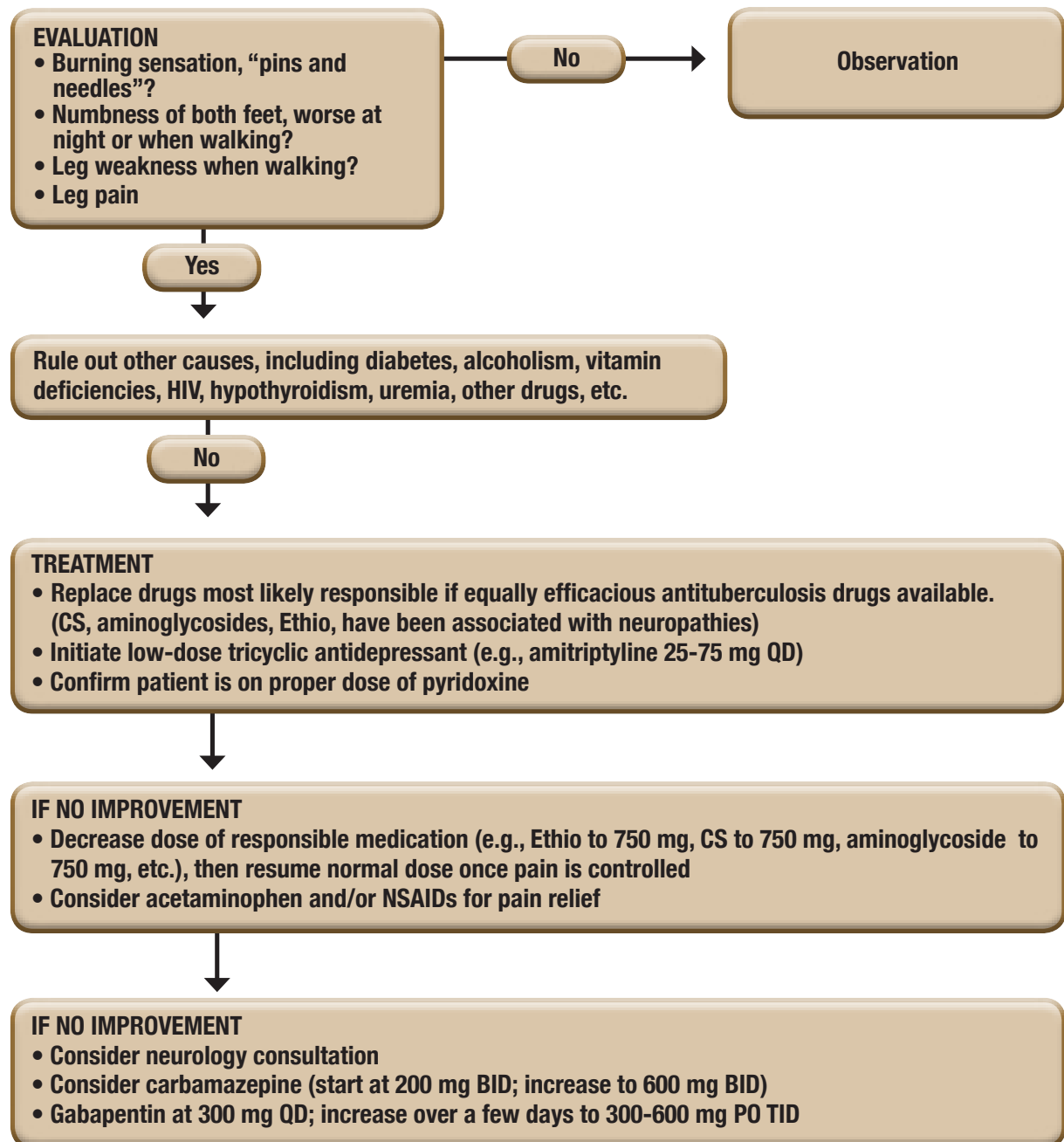
## ANNEXURE 14: MANAGEMENT ALGORITHM FOR NAUSEA AND VOMITING



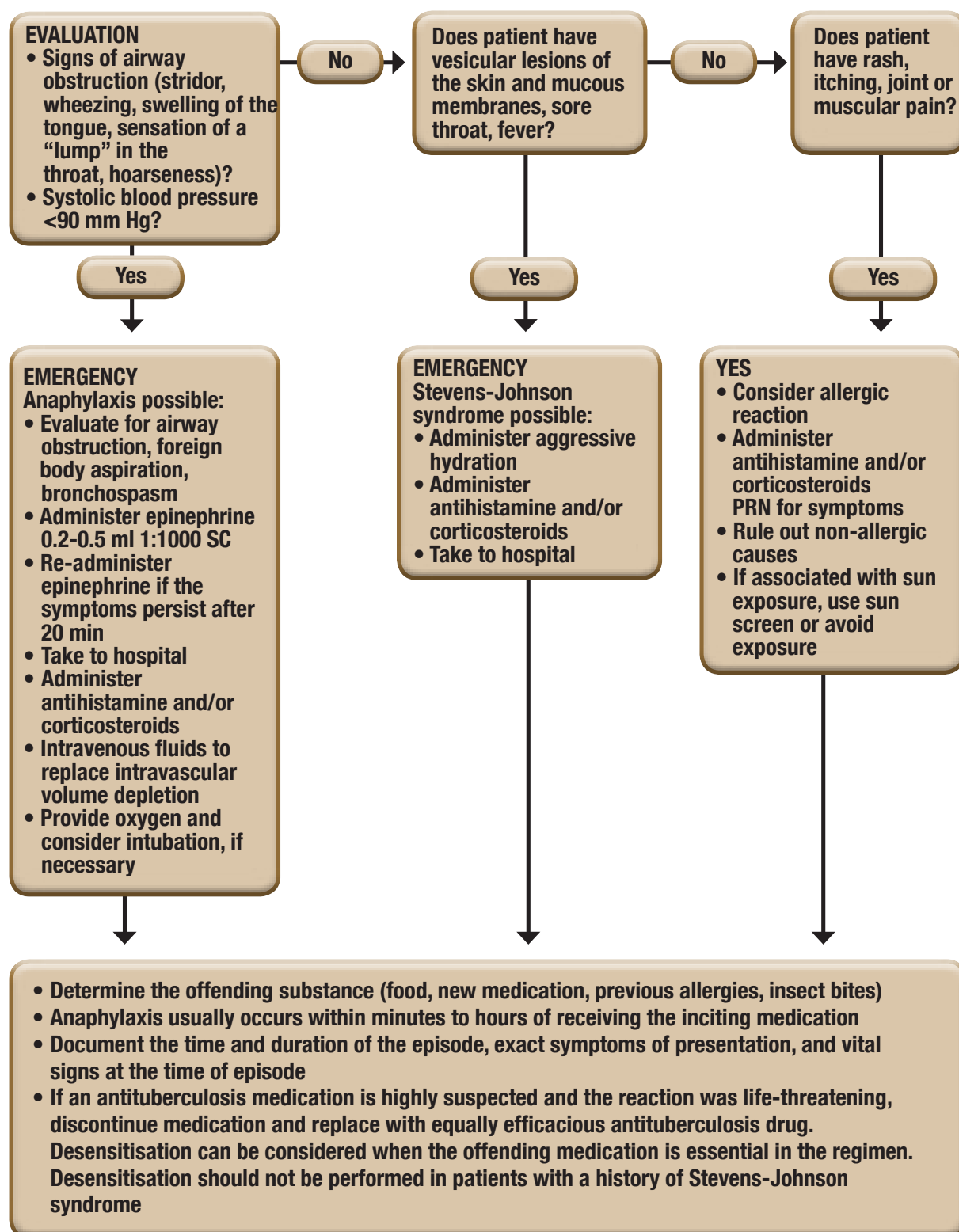
## ANNEXURE 15: MANAGEMENT ALGORITHM FOR NEPHROTOXICITY AND RENAL FAILURE



## ANNEXURE 16: MANAGEMENT ALGORITHM FOR PERIPHERAL NEUROPATHY

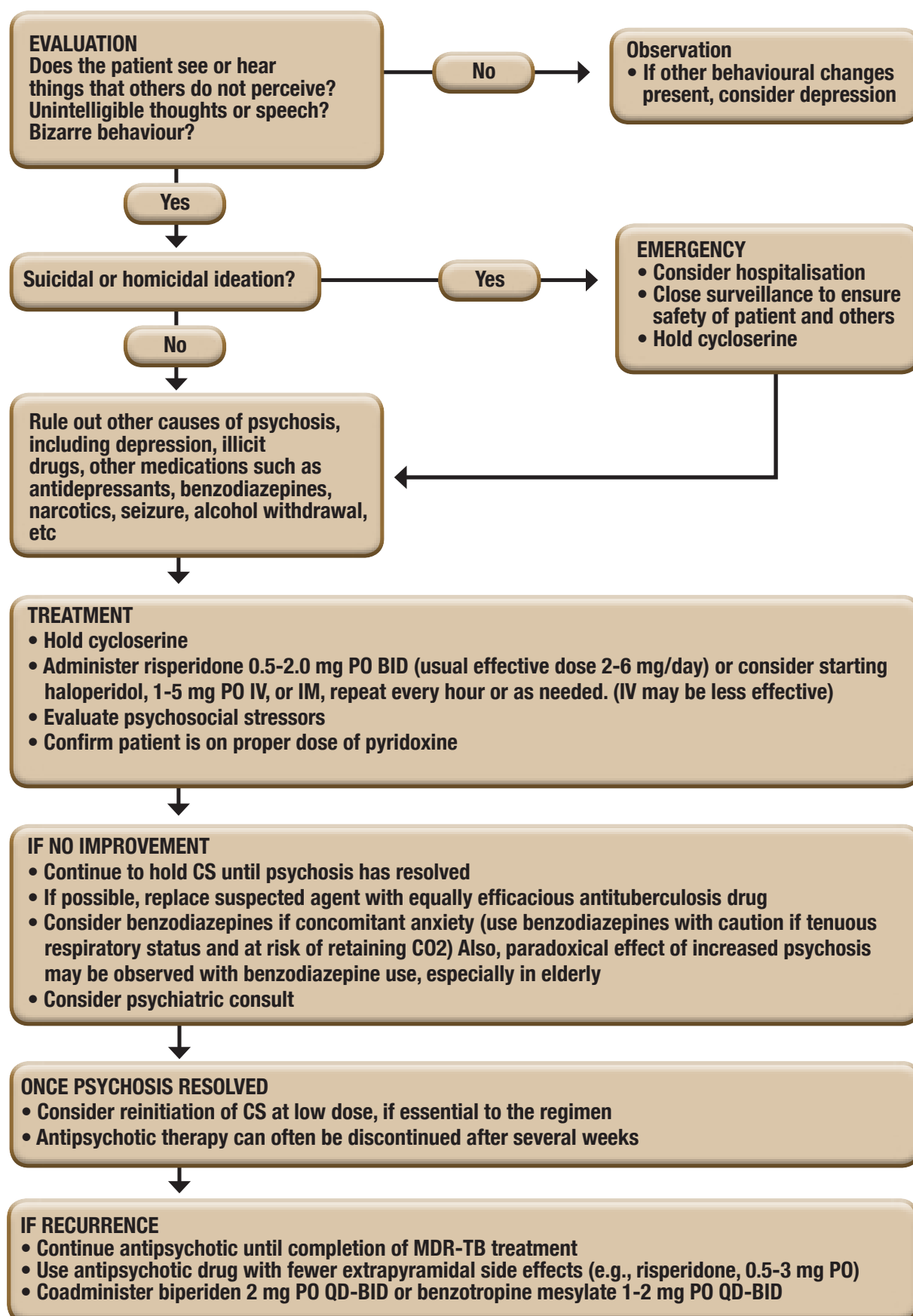


## ANNEXURE 17: MANAGEMENT ALGORITHM FOR ANAPHYLAXIS AND ALLERGIC REACTIONS

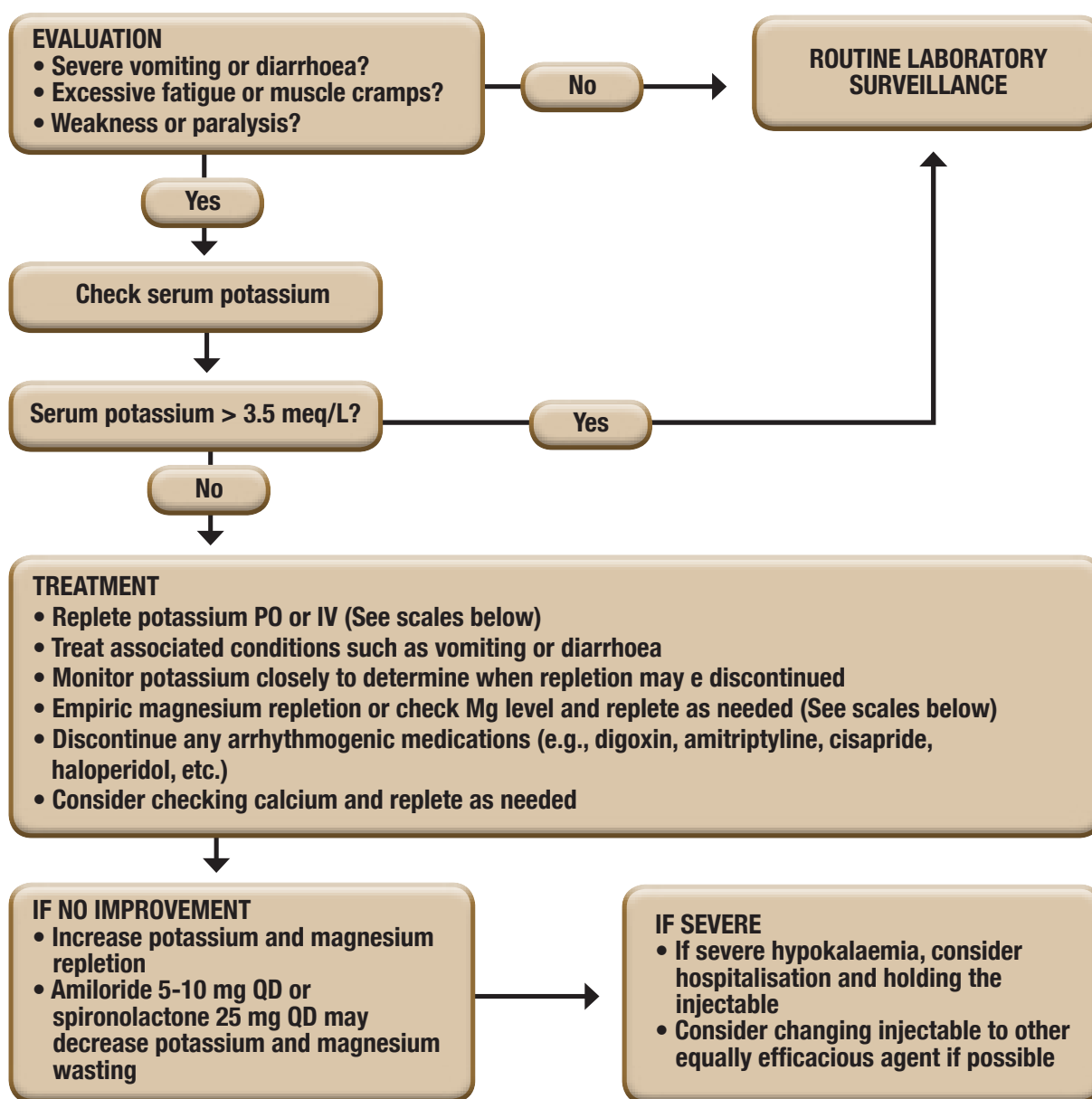




## ANNEXURE 18: MANAGEMENT ALGORITHM FOR PSYCHOSIS



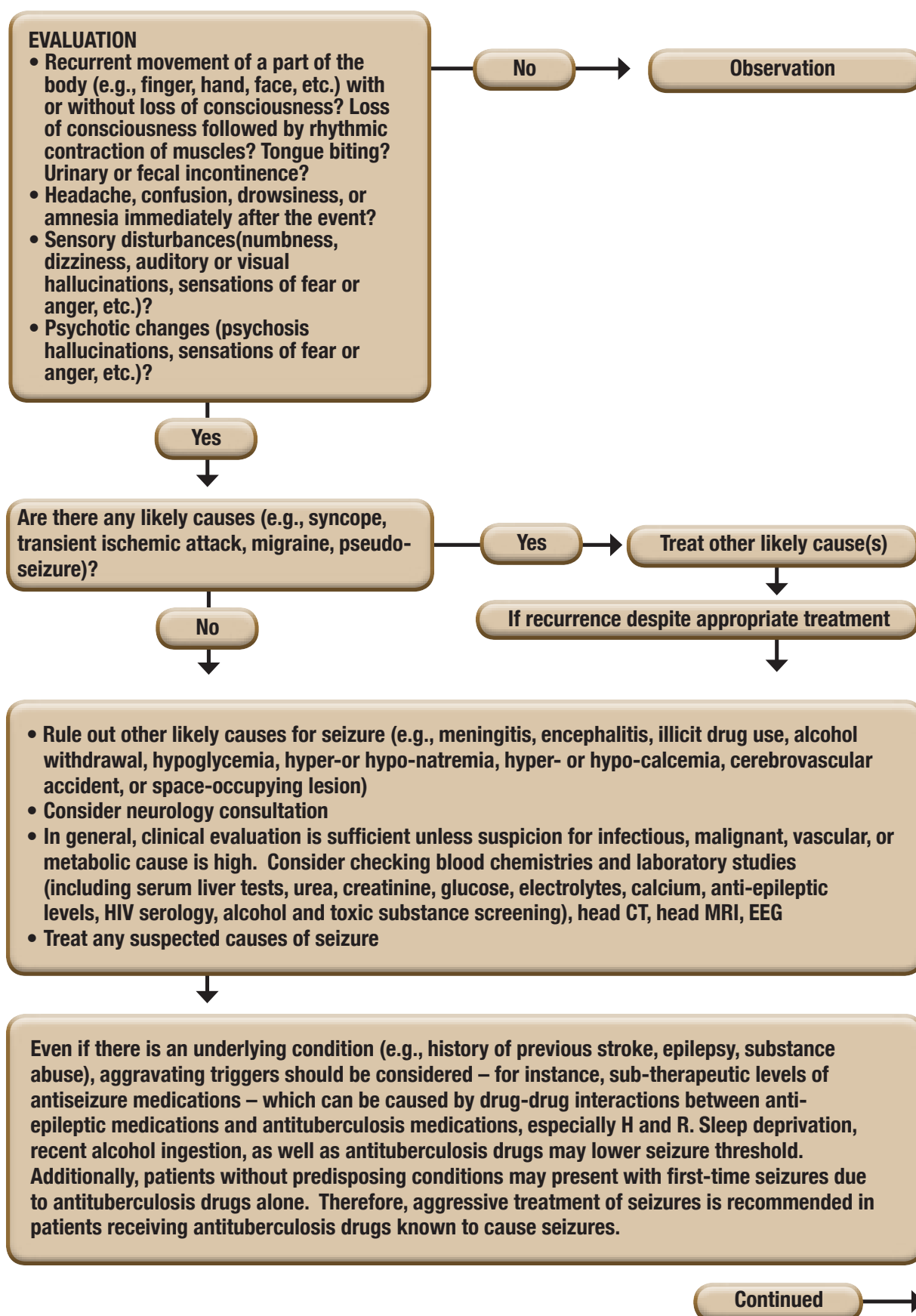
## ANNEXURE 19: MANAGEMENT ALGORITHM FOR HYPOKALAEMIA



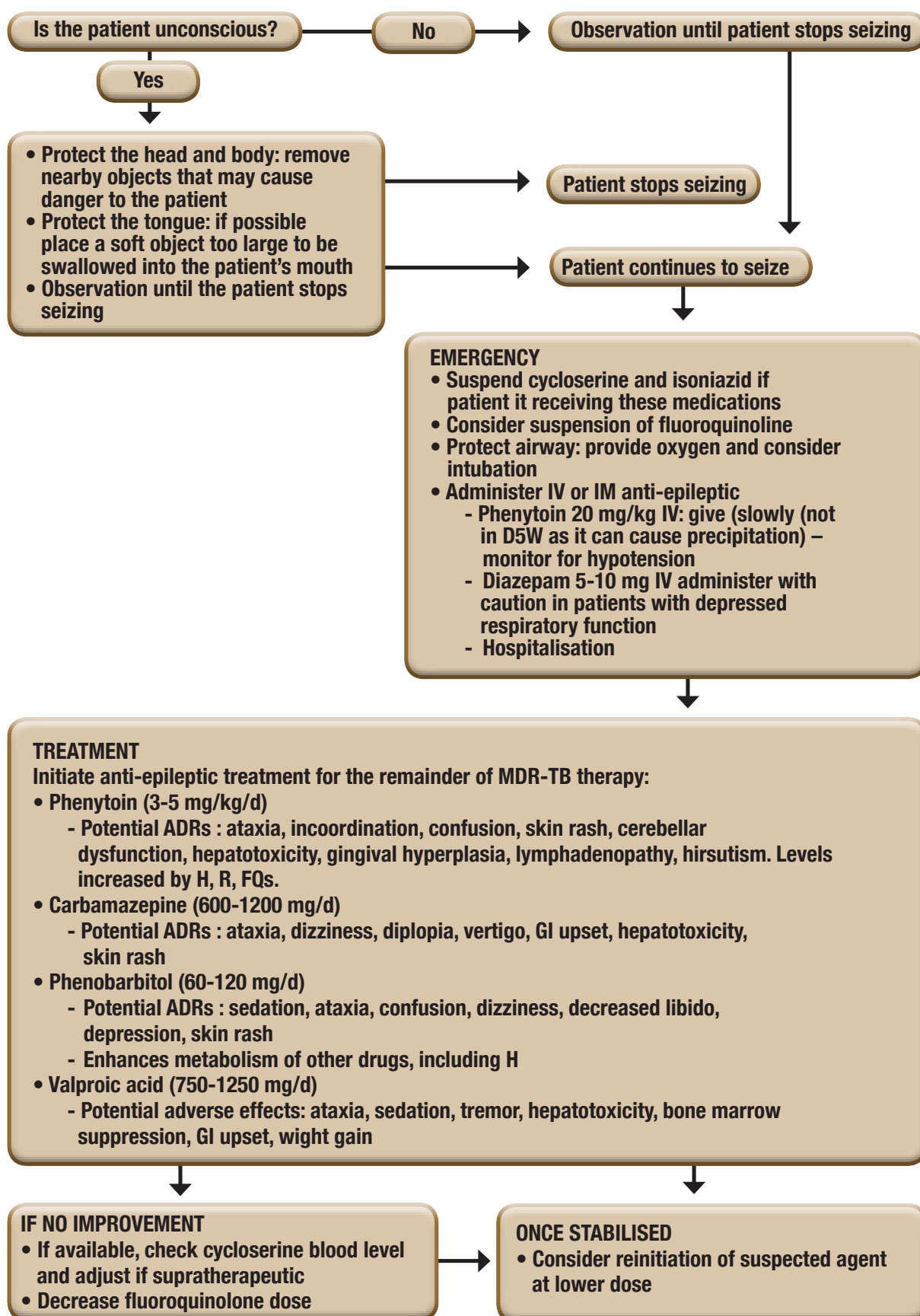
Potassium level Normal value (3.5-5.0 meq/L)	Quantity of KCl
3.7 or more	None
3.4-3.6	40 meq
3.0-3.3	60 meq
2.7-2.9	80 meq
2.4-2.6	80-120 meq
2.0-2.3	60 meq IV and 80 meq PO
<2.0	60 meq IV and 100 meq PO

Magnesium level Normal value (1.5-2.5 meq/L)	Quantity of Magnesium (Total daily dose)
1.5 or more	None
1.1-1.4	1000 mg – 1200 mg
0.8-1.0	2000 mg (consider IM)
<0.8	3000 mg – 6000 mg (give IV or IM)

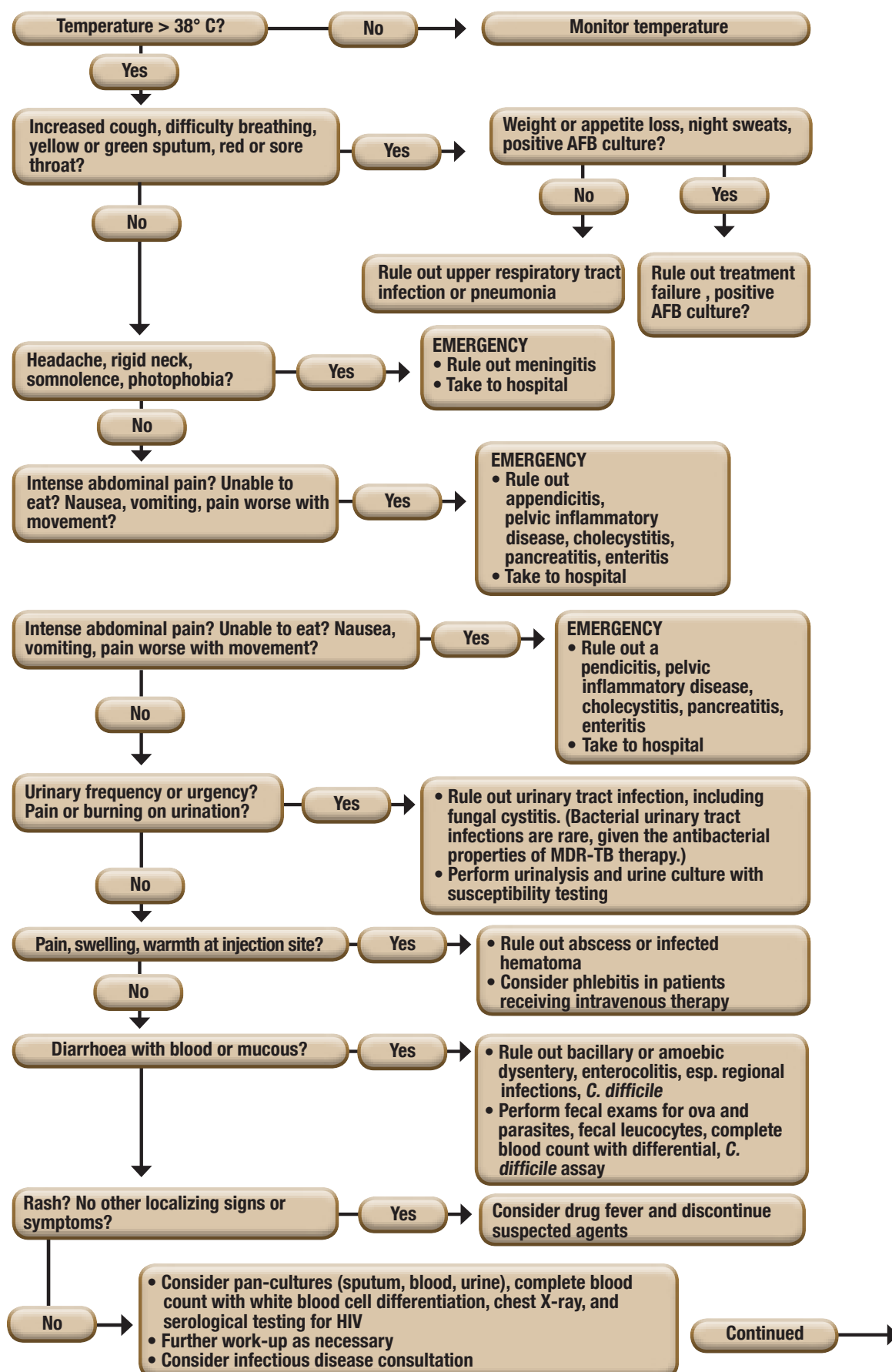
## ANNEXURE 20: MANAGEMENT ALGORITHM FOR SEIZURES – PART I



## ANNEXURE 20: MANAGEMENT ALGORITHM FOR SEIZURES – PART II



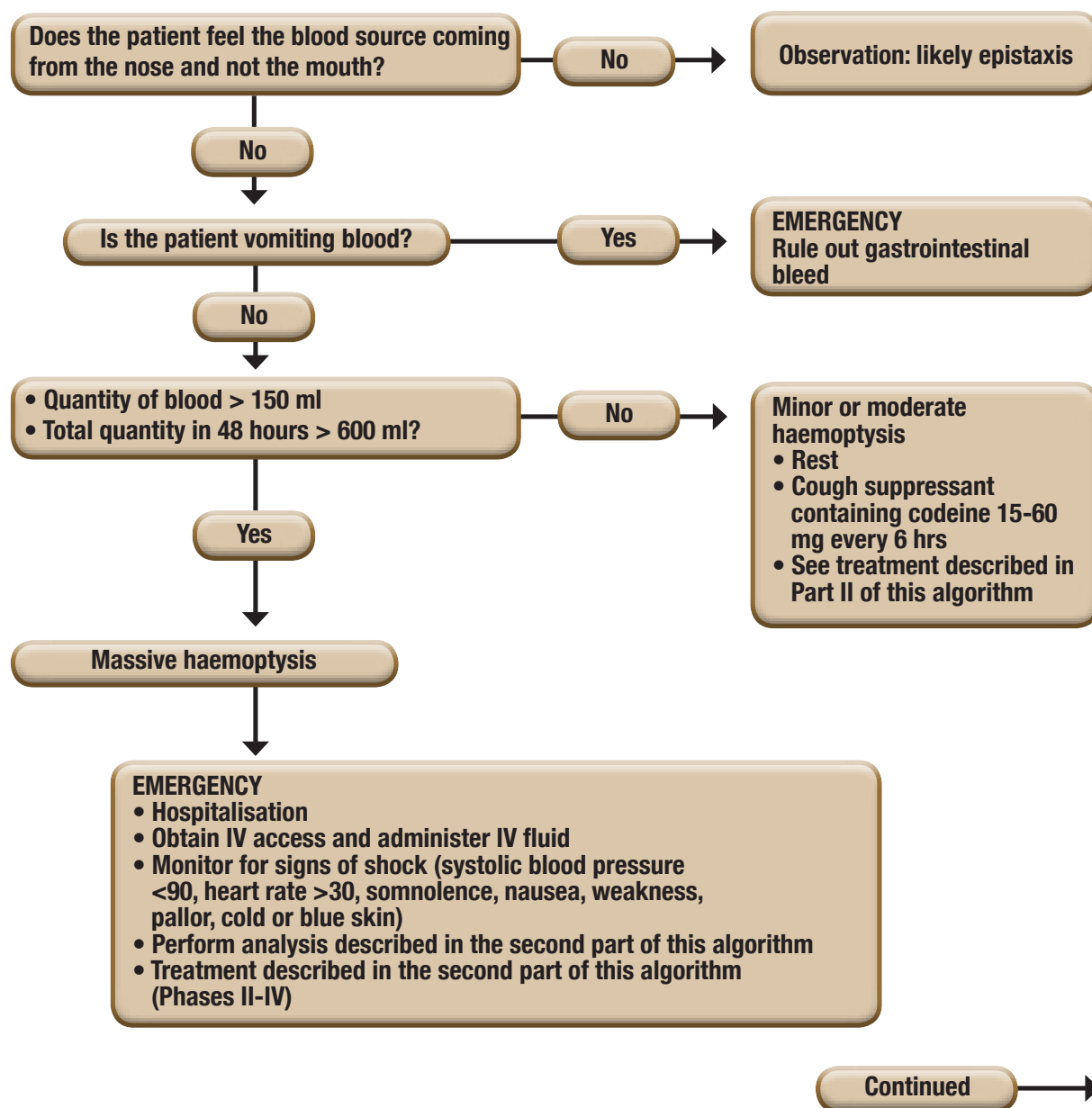
## ANNEXURE 21: MANAGEMENT ALGORITHM FOR FEVER – PART I



## ANNEXURE 21: MANAGEMENT ALGORITHM FOR FEVER – PART II

POSSIBLE CAUSE	PRESENTATION	TREATMENT
<b>URINARY TRACT INFECTION</b>		
<b>Bacterial</b>	<ul style="list-style-type: none"> <li>• Urine leucocytes</li> <li>• Positive Gram stain</li> <li>• Positive urine culture</li> </ul>	<ul style="list-style-type: none"> <li>• Treat according to susceptibility testing</li> </ul>
<b>Fungal</b>	<ul style="list-style-type: none"> <li>• Urine leucocytes</li> <li>• Negative bacterial urine culture</li> </ul>	<ul style="list-style-type: none"> <li>• Treat with fluconazole 200 mg QD first dose, then 100 mg QD for 4 days</li> </ul>
<b>ABSCCESS, HEMATOMA</b>		
	Injection Site: <ul style="list-style-type: none"> <li>• Pain</li> <li>• Warmth</li> <li>• Swelling</li> <li>• Fluctuance</li> </ul>	<ul style="list-style-type: none"> <li>• Aspirate with 18-gauge needle or incise and drain</li> <li>• If abscess, treat with dicloxacillin 500 mg four times a day (or other anti staphylococcal therapy)</li> </ul>
<b>GASTROENTERITIS, ENTEROCOLITIS</b>		
<b>Viral</b>	<ul style="list-style-type: none"> <li>• Diarrhoea, usually without mucous or blood</li> <li>• Negative fecal studies</li> </ul>	<ul style="list-style-type: none"> <li>• Oral rehydration therapy</li> </ul>
<b>Bacterial/Parasitic</b>	<ul style="list-style-type: none"> <li>• Diarrhoea, can be with mucous or blood</li> <li>• Positive fecal leukocytes</li> <li>• Possible <i>C. difficile</i> if positive fecal leukocytes elevated white blood count, fever</li> </ul>	<ul style="list-style-type: none"> <li>• Oral rehydration therapy</li> <li>• Treat according to fecal study results</li> <li>• If <i>C. difficile</i> suspected or confirmed, treat with metronidazole 500 mg TID for 10-14 days</li> </ul>

## ANNEXURE 22: MANAGEMENT ALGORITHM FOR HAEMOPTYSIS – PART I

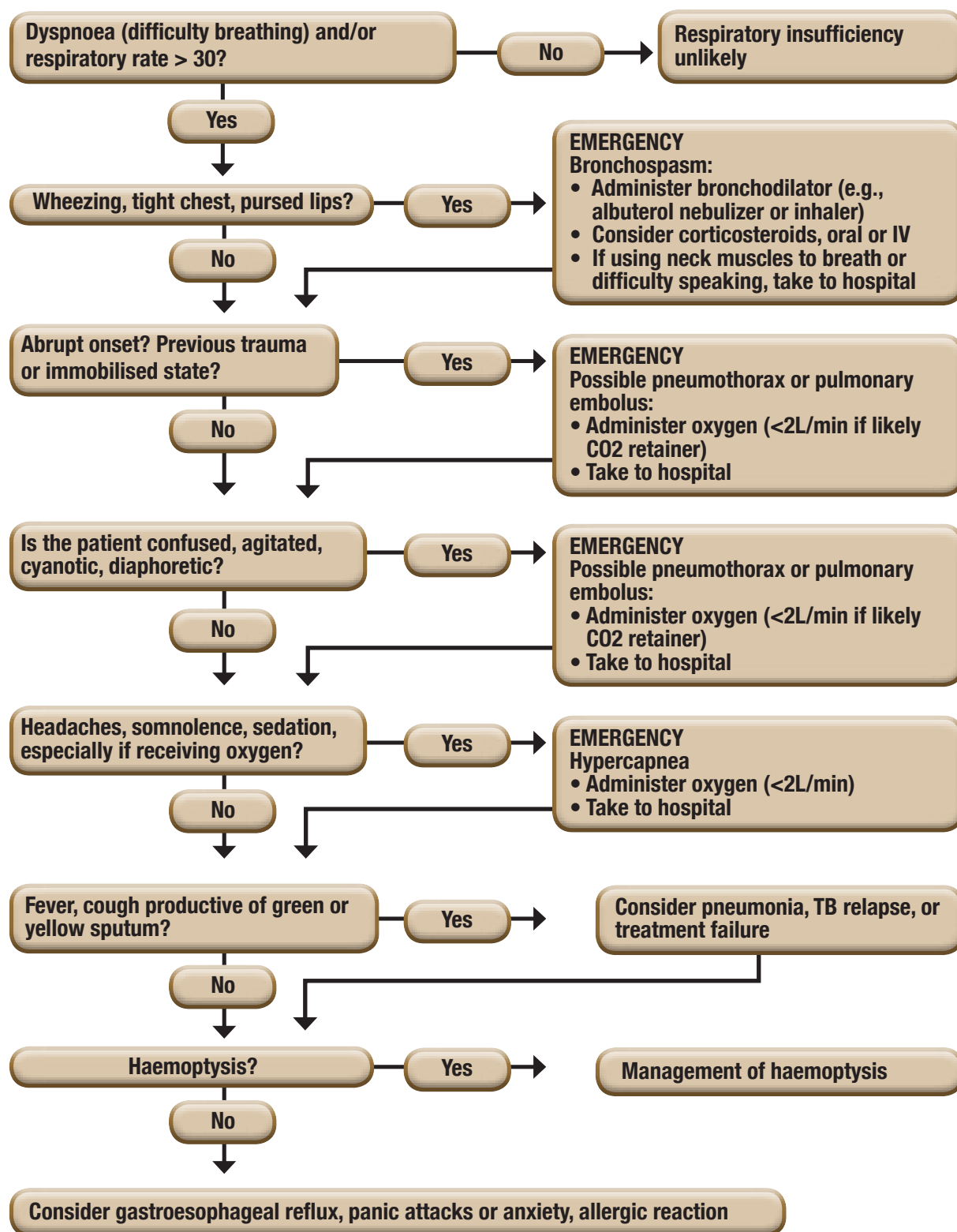


## ANNEXURE 22: MANAGEMENT ALGORITHM FOR HAEMOPTYSIS – PART II

ANALYSIS	
<ul style="list-style-type: none"> <li>• Chest radiograph</li> <li>• Haematocrit (Hct)</li> <li>• Type and cross match blood for possible transfusion</li> <li>• If fever and productive sputum: AFB and culture, sputum Gram stain and culture</li> </ul>	
TREATMENT	
<b>Phase I</b> Minor or moderate haemoptysis	<ul style="list-style-type: none"> <li>• Prescribe bed rest</li> <li>• Monitor patient closely</li> <li>• Avoid NSAIDs and aspirin</li> <li>• If evidence of respiratory super infection, initiate appropriate antibiotic treatment</li> <li>• Use cough suppressant containing codeine, 15-60 mg every 6 hrs</li> </ul>
<b>Phase II</b> For massive haemoptysis	<ul style="list-style-type: none"> <li>• Place large bore IV and resuscitate with 1-2 liters of normal saline within the first hour</li> <li>• Thereafter, maintain fluid (normal saline 0.9%)</li> <li>• Lay patient with likely source of haemorrhage in dependent position</li> <li>• Provide O<sub>2</sub> if needed</li> <li>• Check vital signs frequently</li> <li>• Administer vitamin K 5 mg SC QD for three days if malnutrition or coagulopathy present</li> </ul>
<b>Phase III</b> If Hct < 30%	<ul style="list-style-type: none"> <li>• Transfuse with matched blood</li> <li>• Follow Hct closely</li> </ul>
<b>Phase IV</b> If recurrent episodes without improvement	<ul style="list-style-type: none"> <li>• Consider bronchoscopy to localise the bleeding site</li> <li>• Consider surgical evaluation: bronchiectasis, cavities, or coin-shaped lesions may be haemorrhagic sources (e.g., tuberculosis destruction, erosion of blood vessels, aspergilloma) and may require surgical resection</li> </ul>



## ANNEXURE 23: MANAGEMENT ALGORITHM FOR RESPIRATORY INSUFFICIENCY – PART I



## ANNEXURE 23: MANAGEMENT ALGORITHM FOR RESPIRATORY INSUFFICIENCY – PART II

ANALYSIS			
<ul style="list-style-type: none"> <li>• Chest radiograph</li> <li>• Complete blood count with differential</li> <li>• Sputum AFB and culture, Gram stain and culture</li> </ul>			
POSSIBLE CAUSE	PRESENTATION	TREATMENT	
Bronchospasm	<ul style="list-style-type: none"> <li>• Wheezing, prolonged expiration</li> <li>• May be associated with respiratory super infection</li> </ul>	Phase I	<ul style="list-style-type: none"> <li>• Inhaled bronchodilators</li> <li>• Treat for infection if suspected</li> </ul>
		Phase II	<ul style="list-style-type: none"> <li>• Administer oral or intravenous steroids</li> </ul>
		Phase III	<ul style="list-style-type: none"> <li>• Consider long-term use of inhaled bronchodilators and/or inhaled steroids</li> </ul>
		Phase IV	<ul style="list-style-type: none"> <li>• Nebulized bronchodilators</li> </ul>
Pneumothorax	<ul style="list-style-type: none"> <li>• Sharp pain, sudden onset of respiratory insufficiency, previous trauma</li> <li>• Positive chest X-ray</li> </ul>	<ul style="list-style-type: none"> <li>• Administer O<sub>2</sub></li> <li>• Take to hospital</li> <li>• Thoracic survey consult and chest-tube placement</li> </ul>	
Pulmonary embolus	<ul style="list-style-type: none"> <li>• May have fever, chest pain, tachycardia, positive EKG, positive chest X-ray and/or diminished O<sub>2</sub> sat/pO<sub>2</sub></li> </ul>	<ul style="list-style-type: none"> <li>• Administer O<sub>2</sub></li> <li>• Take to hospital</li> <li>• Perform V/Q scan, if available</li> <li>• Anticoagulation, if no contraindication</li> </ul>	
Respiratory infection	<ul style="list-style-type: none"> <li>• Fever, productive cough</li> <li>• May have bronchospasm</li> <li>• Infiltrate on chest X-ray</li> <li>• Leucocytosis, positive sputum</li> </ul>	<ul style="list-style-type: none"> <li>• Treat with antibiotics according to sputum Gram stain/culture results</li> <li>• Administer O<sub>2</sub> as needed</li> </ul>	
Tuberculosis relapse	<ul style="list-style-type: none"> <li>• Productive cough, fever, night sweats, weight loss, diminished appetite</li> <li>• Chest radiograph may reveal new infiltrate</li> <li>• Positive AFB and/or culture</li> </ul>	<ul style="list-style-type: none"> <li>• Confirm positive AFB and/or culture</li> </ul>	



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## NOTES



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