

**DOTS-Plus FOR STANDARDISED MANAGEMENT OF
MULTIDRUG-RESISTANT TUBERCULOSIS IN SOUTH AFRICA**

- POLICY GUIDELINES -



January 2004

PREFACE

The following policy guidelines are intended for use by health care professionals involved in the complex and difficult task of management of multidrug-resistant (MDR) tuberculosis patients in South Africa. The World Health Organization (WHO) recommends that MDR tuberculosis be managed on the principles of the DOTS strategy, using second-line reserve drugs, directly observed treatment and standardised recording and reporting to accommodate the need for complex outcome definitions. This strategy, called 'DOTS-Plus' has also been adapted by the National Tuberculosis Control Programme of the SA Department of Health and has now been implemented in all nine Provinces.

This document draws heavily from guidelines by the WHO DOTS-Plus Initiative, the Centres for Disease Control and Prevention (CDC) and Partners in Health (PIH) from Harvard University. However, South Africa has a unique blend of health care services and resources requiring innovative adaptations to accommodate the diversity in the country. These guidelines also reflect our growing experience in managing MDR tuberculosis and it is becoming clear that a programmatic approach to the problem of MDR tuberculosis can be successful, even in resource-poor settings.

The guidelines have been written for use by health professions caring for patients with MDR tuberculosis within South Africa's DOTS-Plus programme. The document has a strong clinical focus in order to ensure adequate standards of health care for MDR tuberculosis patients; however, background information on the development and pathogenesis of MDR tuberculosis, strategies for prevention and control, and management of health care worker risks have also been provided, strengthening our public health approach to the problem of MDR tuberculosis. Legal issues around the management of MDR tuberculosis in South Africa are complex and will be addressed in a separate document, guided by rapidly evolving health legislation and the Constitution of South Africa.

DOTS-Plus is still an evolving strategy, and needs to be adapted through evidence-based information. Comments and suggestions from those in the field is essential to ensure a dynamic process, aimed towards optimal control of MDR tuberculosis in South Africa. Please forward these to: The Director, Tuberculosis Control, Department of Health, Private Bag X828, Pretoria, 0001.

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EXECUTIVE SUMMARY

CRUCIAL ISSUES IN THE MANAGEMENT OF MDR TUBERCULOSIS

The following principles have been accepted as policy by the Provincial Health Restructuring Committee (PHRC) and implemented in all Provinces:

1. Multidrug-resistant (MDR) tuberculosis is defined as tuberculosis disease where there is *in vitro* resistance to both isoniazid and rifampicin, with or without resistance to other anti-tuberculosis drugs. As isoniazid and rifampicin are the two most important first-line tuberculosis drugs, their removal (via resistance) from the anti-tuberculosis drug armamentarium has serious implications. Based on current estimates, there are at least 6 000 newly active cases of MDR tuberculosis in South Africa each year.
2. Prevention is the key to effective control of MDR tuberculosis. There is no point using scarce health care resources for the treatment of MDR tuberculosis while neglecting to properly implement the DOTS strategy, since most cases of MDR tuberculosis arise as a result of a poorly applied Tuberculosis Control Programme. The district and provincial Health Departments must aim at a cure rate of over 85% for at least all new smear-positive cases.
3. Rifampicin should not be available as a single drug for the routine treatment of tuberculosis in hospitals or clinics.
4. Laboratory results are sometimes wrong. Remember to treat the patient, not the laboratory result. The most common mistake is a wrongly labelled specimen or result. If the patient is getting better clinically on first-line treatment and the laboratory result seems to contradict this, contact the laboratory for verification and, if necessary, repeat the specimen. Do not neglect to get expert advice.
5. Provinces are not advised to embark on programmes for the treatment of MDR tuberculosis unless they are able to furnish a properly staffed referral centre and ensure a regular supply of appropriate drugs, with treatment taken under direct supervision.
6. Counselling of patients and families is important. Offer emotional support and education about prevention to ensure that patients are given the best chance of cure.
7. A standardised approach to treatment is the national policy. The standardised regimen is based on *in vitro* susceptibility of the diagnostic strain to ethambutol, and consists of a four-month intensive phase with five drugs followed by a continuation phase of between 12 and 18 months with three drugs. Treatment should be given daily (at least five times per week).

8. Patients with MDR tuberculosis are ideally treated in hospital, at least until two consecutive monthly sputa are culture negative. The most cost-effective way of doing this is to provide dedicated, well-ventilated wards in existing tuberculosis hospitals. Separate MDR hospitals built far from the patient's social support network are not recommended.
9. Clinic-based care for MDR tuberculosis patients without hospitalisation is possible provided that the conditions outlined in these guidelines are met.
10. Contact management is the same as for the contacts of drug susceptible pulmonary tuberculosis. There is, as yet, no evidence to support other, expensive and often poorly tolerated chemoprophylaxis regimens for contacts.
11. Reducing the risk of the spread of tuberculosis especially when many patients are HIV positive, is an essential part of clinic and hospital management. In the absence of negative pressure wards, MDR tuberculosis patients should be treated in wards with doors closed and windows open. Sputum collection should take place outside if at all possible. Inside the ward it should be mandatory for ward staff to wear particulate respirators that are impermeable to droplet nuclei when nursing patients. Patients should wear ordinary surgical masks to contain aerosols.

The positioning and installation of extraction fans is a specialised activity and expert help should be obtained. The value of ultraviolet lights is, as yet, not determined.

12. Health care workers in tuberculosis laboratories and MDR tuberculosis wards should be well informed about the risks of their becoming ill with MDR tuberculosis, as well as ways of minimising this risk. They should be medically examined at employment and encouraged to report any illness to facilitate early diagnosis and treatment. A baseline medical examination will make compensation easier. Health workers who suspect that they are HIV positive should be encouraged to request transfer to areas where the risk of tuberculosis infection is low.
13. Every tuberculosis hospital must use one of their most competent nurses as an infection control practitioner. This person should have special skills in monitoring procedures and communication skills.

A register of all health workers who develop MDR tuberculosis should be kept at the provincial MDR referral centre in order to help determine the risk involved and to inform future policy.

14. Every case of MDR tuberculosis should be reviewed as to the reasons for the case developing. Annual reviews should be compiled for each MDR referral centre on the probable causes of MDR tuberculosis, the outcome of treatment and the costs involved. A

report should be forwarded for the personal attention of the Provincial Head of Health, outlining the problems which led to the development MDR tuberculosis.

15. All laboratories that perform tuberculosis drug susceptibility tests must be part of an external quality assurance system.
 16. Periodic surveys of MDR tuberculosis incidence and prevalence must be undertaken in each province.
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DOTS-Plus FOR STANDARDISED MANAGEMENT OF MULTIDRUG-RESISTANT TUBERCULOSIS IN SOUTH AFRICA

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INTRODUCTION

At no time in recent history has tuberculosis been as widespread a concern as it is today. Despite highly effective drugs, disease and deaths due to *Mycobacterium tuberculosis* are increasing worldwide and are being fuelled by the widespread HIV epidemic. A most serious aspect of the problems has been the emergence of multidrug-resistant (MDR) tuberculosis, which poses a threat to individual patients as well as to communities.

MDR tuberculosis is defined as tuberculosis disease caused by strains of *M. tuberculosis* that are resistant *in vitro* to both rifampicin and isoniazid, with or without resistance to other drugs. As with other forms of drug resistance, MDR tuberculosis is a man-made problem, being largely the consequence of human error in any or all of the following:

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

Most common medical errors leading to the selection of resistant bacilli

- Prescription of inadequate chemotherapy (eg. three drugs during the initial phase of treatment in a new patient smear-positive with bacilli resistant to isoniazid);
- Adding one extra drug in the case of treatment failure, and often adding a further drug when the patient relapses after what amounts to monotherapy.

Most common errors observed in the management of drug supply

- Frequent or prolonged shortages of antituberculosis drugs due to poor management;
- Use of two or three drugs when four or five first-line drugs should be given;
- Use of tuberculosis drugs (or drug combinations) of unproven bioavailability.

Poor management practices multiplying the risk of successive monotherapies and selection of resistant bacilli

- Health care workers not ensuring that a good relationship is built with the patient from the start, eg. not taking time to show an understanding of the patient's situation nor taking a problem-solving approach;
- Patient's lack of knowledge due to poor information, or not repeatedly checking on patient understanding and practice;

- Poor case-management, eg. careless attitudes, lack of friendly support, treatment not directly observed;
- Frequent staff changes, with no focal point for ensuring correct clinical practice;
- Poor staff morale, compounded by lack of regular support and supervision;
- Poor record keeping and follow-up of patients, compounded by poor referral systems.

Patient-related factors

Patient cooperation or adherence is most often a problem when the patient is homeless, has an alcohol or drug problem, is unemployed, looking for a job, when a family member has been unsuccessfully treated previously or when access to health care is difficult. An in-depth discussion with the patient at the initiation of treatment, clarifying the expectations of both the patient and the health care staff, helping the patient try to solve barriers to adherence and building a supportive relationship would help decrease these constraints.

Since the mid-eighties, patients with MDR tuberculosis have been diagnosed in each of the nine provinces in South Africa, and a recent national survey by the Medical Research Council indicated a rate of 1.6% MDR in new tuberculosis cases and 6.6% in previously treated cases. This translates into at least 6 000 new cases of MDR tuberculosis in South Africa each year. MDR tuberculosis is difficult and expensive to treat. The social and economic burden of this problem is already evident in South Africa, where the cost of treating a case of MDR tuberculosis is up to 25 times the cost of treating an uncomplicated drug-susceptible case. There is also ample reason to believe that the full brunt of MDR tuberculosis is still to be faced in the country: Several epidemiologic and genetic studies have confirmed ongoing transmission of drug-resistant tuberculosis. Nosocomial outbreaks of MDR tuberculosis associated with HIV infection have been documented, while HIV-infected patients being treated in hospitals for drug susceptible tuberculosis have been re-infected with MDR strains. Experience in other countries has shown that patients with active, untreated MDR tuberculosis can infect large numbers of HIV-positive individuals, leading rapidly to significant outbreaks of MDR tuberculosis with high case-fatality rates.

It is therefore of the utmost importance that MDR tuberculosis be prevented by rigorous adherence to the principles of the Tuberculosis Control Programme (the DOTS* strategy) and by patiently and consistently building partnerships with patients, their families and communities to cure tuberculosis at the first attempt.

To achieve tuberculosis control world-wide, the World Health Organization (WHO) considers the implementation of sound tuberculosis control based on the DOTS strategy a top priority. However,

*DOTS: Directly Observed Treatment, Short Course; a comprehensive strategy to manage tuberculosis effectively.

recognising that MDR tuberculosis poses a considerable risk to the effectiveness of DOTS programmes, WHO strongly encourages pilot projects to assess the feasibility and cost effectiveness of DOTS-Plus** interventions in tuberculosis control programme settings, provided that DOTS is in place.

The National Tuberculosis Control Programme (NTCP) of the Department of Health developed a strategy in 2000 to treat patients with MDR tuberculosis in South Africa. This policy recommended that MDR tuberculosis treatment be provided as part of the NTCP in areas where the DOTS strategy has been implemented successfully. Each of the nine provinces currently provides MDR tuberculosis treatment through NTCP structures.

Mycobacteria other than tuberculosis

It should be emphasised that MDR tuberculosis is not the same as disease due to mycobacteria other than tuberculosis (MOTT). The latter are commonly resistant to both isoniazid and rifampicin but should not be confused with MDR tuberculosis. These guidelines are relevant for the management of MDR tuberculosis only and not for disease caused by MOTTs. The incidence of MOTTs in patients with a positive culture is less than 2% in South Africa. This proportion is, however, likely to increase as those who are HIV positive are more susceptible, also to MOTTs. MOTT infection is also more common in miners with silica dust disease.

Identification of MOTT disease is made after culture has been referred for special investigation. MOTTs are often contaminants in the sputum and are only of clinical significance if the patient is not responding to first-line treatment. If the disease is not responding to treatment and MOTTs are reported in the sputum culture, the patient should be referred to a respiratory physician for advice.

**DOTS-Plus: A strategy under development, designed to manage MDR tuberculosis using second-line drugs within the DOTS strategy in low- and middle-income countries

MECHANISMS OF TUBERCULOSIS DRUG RESISTANCE

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 the individual antituberculosis drugs is as follows:

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

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

Drug resistance, therefore, is the result of selection of resistant mutants in the bacterial population, due to killing of susceptible bacilli by tuberculosis drugs. The problem is greatly exacerbated by inadequate treatment, such as direct or indirect monotherapy, resulting from intake of a single antituberculosis drug or from intake of a combination of drugs where the minimal inhibitory concentration of only one drug may be optimal. Susceptible cells are killed rapidly and resistant mutants are then able to multiply.

MDR tuberculosis occurs either through infection by *M. tuberculosis* already resistant to isoniazid and rifampicin (primary resistance) or through the selection of drug-resistant mutants of the original (susceptible) strain as a consequence of inadequate therapy or poor patient adherence (acquired resistance).

Since the early 1990's, several outbreaks of MDR tuberculosis have been reported in different regions of the world, as a consequence of inappropriate use of essential antituberculosis drugs. Usually MDR tuberculosis occurs in chronic cases after failure of retreatment regimens and represents a significant proportion of tuberculosis patients with acquired resistance. Exceptionally, MDR tuberculosis is observed in new cases, ie. in patients who have never taken antituberculosis drugs, and who have been infected by MDR bacilli. In the recent South African survey, between 1% (Western Cape) and 3% (Mpumalanga) of new culture-positive tuberculosis patients were found to have MDR tuberculosis.

DEFINITIONS

Drug resistant tuberculosis:	Disease (usually pulmonary) caused by <i>M. tuberculosis</i> bacilli resistant to one or more antituberculosis drugs. Drug resistance is further classified according to history of previous tuberculosis treatment.
Resistance in new patients:	Resistance in cultures from patients with no history of previous tuberculosis treatment or patients who had received tuberculosis treatment for less than one month.
Resistance in previously treated patients:	Resistance in cultures from patients with one or more previous tuberculosis treatment episodes of more than one month.
Treatment failure:	A tuberculosis patient who is still excreting bacilli at the end of treatment (at five to six months for new cases or seven to eight months for retreatment cases).
Chronic case:	Failure of a <i>fully supervised retreatment regimen</i> . A chronic case has received at least two courses of chemotherapy, and sometimes more than two courses (complete or incomplete). Chronic cases are often, but not always, excretors of MDR bacilli. Likewise, patients with retreatment failure are more likely to be harbouring multidrug-resistant organisms.

RELEVANCE OF DRUG RESISTANCE IN TUBERCULOSIS CONTROL

During the early stages of implementation of an effective national tuberculosis control programme, retreatment cases may represent up to half of registered cases and the rate of resistance in this group of patients is usually high. The top priority, therefore, is to standardise treatment for new and retreatment cases of tuberculosis.

Drug resistance differs in terms of prevalence and severity between new and retreatment cases. The rate of resistance in new patients is always lower than the rate in retreatment patients. In well-functioning control programmes the rate among new patients is usually below 5%; in new programmes implemented after a period of disorganised and chaotic tuberculosis chemotherapy the rate often exceeds 15%. Drug resistance in new patients is also usually less serious than resistance in retreatment patients because fewer drugs are usually involved and the level of resistance is lower.

The South African National Tuberculosis Control Programme cannot afford drug susceptibility testing on all tuberculosis patients; also, with the current low levels of MDR tuberculosis, testing every patient's strain for drug resistance is not cost-effective and is unnecessary. Drug susceptibility testing should however routinely be done for the following individuals:

- All retreatment cases, including failure and interruption cases;
- Patients who remain sputum smear-positive after two to three months' of intensive therapy;
- Close contacts of MDR tuberculosis cases who have signs and symptoms of tuberculosis;
- High-risk individuals with signs and symptoms of tuberculosis, eg. health care workers, laboratory workers.

MANAGEMENT OF PATIENTS WITH MONODRUG RESISTANT TUBERCULOSIS

In the group of patients previously treated with one or several courses of chemotherapy and who remain smear/culture positive, three sub-populations can be observed:

- patients excreting bacilli still susceptible to all antituberculosis drugs;
- patients excreting bacilli resistant to at least isoniazid, but susceptible to rifampicin;
- patients excreting bacilli resistant to isoniazid and rifampicin.

The respective proportions of the three sub-populations vary according to the chemotherapy applied in the community during the preceding years. It varies also with the number of courses of chemotherapy received by patients:

- In patients who are still smear-positive after the *first course of chemotherapy*, the proportion of patients excreting bacilli still susceptible to all drugs is usually higher than the proportion of the two other sub-populations. For this reason, the standard *retreatment* regimen of eight months given under direct observation can cure the majority of patients, including those still harbouring susceptible bacilli, and those having bacilli resistant to isoniazid, streptomycin or ethambutol, but still susceptible to rifampicin.
- In patients whose treatment had failed after *two courses of chemotherapy* (the second being the fully supervised standard *retreatment* regimen), the majority (up to 80%) will harbour isoniazid and rifampicin resistant bacilli. The proportion of patients with MDR tuberculosis can be as high as 50%. For this reason, a second application of the standard retreatment regimen is likely to fail and these patients should be considered eligible for MDR treatment.
- Standardised short course tuberculosis drug therapy is the best way to prevent MDR tuberculosis. Standardised regimens are also effective in patients with bacilli mono-resistant to isoniazid and/or streptomycin. Rifampicin mono-resistance occurs very rarely. If the patient is deteriorating clinically, culture and drug susceptibility testing should be repeated and MDR tuberculosis treatment considered.

It cannot be emphasised strongly enough that a patient improving clinically and radiologically with a drug-resistant laboratory report should be considered to have an abnormal laboratory report and investigated again, rather than be put on MDR tuberculosis treatment immediately. Patients with strains showing mono-resistance to isoniazid, streptomycin or ethambutol should receive standard first-line treatment.

PREVENTION OF MULTIDRUG-RESISTANT TUBERCULOSIS

Standardised first-line regimens for new and retreatment patients

Ensuring cure of (especially) new smear-positive patients the first time around will prevent significant development and subsequent spread of MDR tuberculosis. This is only possible on a national scale by the use of standard regimens. Every effort should be made to ensure that patients on the retreatment regimen complete it, as their risk of developing MDR tuberculosis is especially high.

Health system compliance

Compliance refers here to how well the health care system (doctors and nurses) comply with management guidelines as laid down by the National Tuberculosis Control Programme. It is essential that adequate drugs, in the correct combinations and dosages, be prescribed for the correct period of time. In a high proportion of MDR tuberculosis cases either a single drug is added when a patient does not respond or a “shot gun” approach is used whereby a range of drugs are prescribed in an *ad hoc* fashion, often leading to side effects and eroding the patient’s confidence in the treatment.

It is also important that clinicians and nurses make efficient use of resources. The ordering of expensive drugs and investigations in an unsystematic manner leaves fewer resources available for more important interventions such as tracing patients who have missed treatment appointments.

Patient adherence

Here, adherence refers to how well patients manage to complete the full course of prescribed medication. This often depends on adequate counseling, accessibility of the service, and the attitudes and ongoing support 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 MDR tuberculosis. 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 tuberculosis drugs to treatment points is crucial in preventing drug resistance. Forecasting of consumption at the district level should be done based on the numbers of new and retreatment patients seen and registered during the preceding ordering period. These should be approximately equal to previous consumption plus 10%. Inventory should fluctuate between one

and four months' supply. If inventory is to be reduced, then the re-order interval will need to be shortened. Much will depend on the reliability and cost of transport so that more remote districts might settle for fewer orders per year and larger inventory holdings, while metropolitan districts might prefer to order monthly.

Treatment for tuberculosis should always be free of charge.

Supervision of therapy

Directly observed therapy is considered the optimal form of drug administration for the majority of patients especially during the intensive phase of treatment, and preferably for the entire treatment period. If rigorously applied, especially for sputum smear-positive patients, retreatment patients and patients with MDR tuberculosis, it will make a major contribution to the control of MDR tuberculosis in South Africa.

DIAGNOSIS OF MULTIDRUG-RESISTANT TUBERCULOSIS

- MDR tuberculosis is a laboratory diagnosis; showing *in vitro* resistance to isoniazid and rifampicin, with or without resistance to additional drugs;
- MDR should be suspected in a patient who fails to respond to treatment despite good documented adherence, but must always be confirmed by sputum culture and drug susceptibility testing;
- Usually the first indication that a patient may be harbouring drug-resistant organisms is when s/he fails to respond to treatment despite documented good adherence. This is often supported by the smear at two/three months being positive, which should prompt a culture and drug susceptibility test to be done;
- If the smear at two months is negative and treatment continued and the smear done at five months is positive, culture and drug susceptibility should be requested. If the smear is negative but the patient has not responded clinically, culture and drug susceptibility should also be requested;
- Do not add any single drug to a failed regimen. Always await laboratory confirmation of drug resistance;
- If there is a history of close contact with an MDR tuberculosis patient, culture and drug susceptibility testing should be requested on the initial sputum from contacts.

The diagnosis of MDR tuberculosis is indicated by resistance to at least rifampicin and isoniazid. When requesting drug susceptibility testing, ethambutol should be included in order to guide the selection of the appropriate standardised MDR tuberculosis regimen (see later).

The classification of a patient as MDR tuberculosis carries very serious consequences and should only be made by (or at the very least in consultation with) a physician experienced in managing MDR tuberculosis patients. These patients must be referred to a provincial MDR treatment centre. A list of names and contact details is available from the Provincial or National Tuberculosis Control Programme.

A person with bacteriologically proven pulmonary tuberculosis who continues to produce positive smears despite regularly observed swallowing of first line treatment, and who is not improving clinically, with at least one positive culture and drug susceptibility result which shows resistance to rifampicin and isoniazid should be started on treatment for MDR tuberculosis.

LABORATORY ASPECTS

Identification of MDR strains of *M. tuberculosis* can only be established through culture and susceptibility testing of the organism. Routine susceptibility testing should be carried out for patients at risk of harbouring MDR strains, eg. patients in whom retreatment has failed.

The so-called 'proportion method' is commonly used for determining drug susceptibility of *M. tuberculosis* isolates in the laboratory. The results of this method are reported as the percentage of the total bacterial population resistant to a specific drug, which is defined as the amount of growth on a drug-containing medium as compared with growth on a drug-free control medium.

When 1% or more of the bacillary population become resistant to the critical concentration of a drug, the *M. tuberculosis* isolate is regarded as resistant to that drug. The critical concentration is the concentration that inhibits the growth of most cells of susceptible strains of *M. tuberculosis*.

Drug concentrations for susceptibility testing

The quality of laboratory susceptibility testing is of paramount importance and impacts directly on tuberculosis treatment. Laboratory methodology and reporting must be standardised and appropriate controls must be used. Each drug should be tested at its critical concentration, ie. the concentration that inhibits growth of the majority of wild strains of *M. tuberculosis* without markedly affecting the growth of resistant mutants present. Some critical concentrations are listed in Table 1.

Table 1: Critical drug concentrations ($\mu\text{g/ml}$) for routine drug susceptibility testing

Drug	Radiometric	Conventional	
	Bactec 12B	Middlebrook 7H10	Löwenstein-Jensen
Isoniazid	0.1	0.2	0.2
Rifampicin	2.0	1.0	40.0
Ethambutol	2.5	5.0	2.0
Streptomycin	2.0	2.0	4.0

The quality of susceptibility tests carried out in provincial laboratories should be checked regularly as errors are not uncommon. A single report of MDR tuberculosis without additional clinical evidence should be regarded with caution. Laboratories detecting MDR should fax and/or telephone the results to the requesting facility immediately. **All laboratories performing culture and drug susceptibility testing must be part of a recognised external quality assurance system.**

MANAGEMENT OF PATIENTS WITH MULTIDRUG-RESISTANT TUBERCULOSIS

Dedicated referral facilities and specialised management teams

Treatment of patients with MDR tuberculosis involves second-line, reserve drugs. These are much more expensive, less effective and have more side effects than first-line tuberculosis drugs. Treating MDR patients requires experience and special expertise, which are available at the provincial MDR treatment centres. Patients with MDR tuberculosis should be admitted for at least the first four months or preferably until they have produced two consecutive monthly culture-negative sputa. During this time, plans should be made for the provision of treatment at designated clinics which should be supplied with the drugs required prior to the patient's discharge from hospital, on a patient-named basis.

Specialised management teams should (at the least) consist of a respiratory physician or a specially trained medical officer, supported by a dedicated MDR tuberculosis-trained nurse, a social worker or trained counselor and an administrative assistant. These teams should oversee all aspects of MDR tuberculosis management and should be collectively responsible for decisions about treatment and surgery. The main functions of the management teams are the evaluation of patients, prescribing of treatment, follow-up, specialised counseling, training of staff and problem solving for special cases.

Particular attention must be paid to **full documentation** of patient particulars and every effort must be made to ensure that all patients are seen by the management team regularly during the course of the disease to ensure an adequately detailed management plan. Routine treatment of MDR tuberculosis patients at primary health care clinics should not be attempted. However, supervision of therapy for these patients being treated as outpatients may be available at dedicated clinics. In these instances the required drugs should be made available to the approved clinic on a named-patient basis only, and on prescription from the MDR tuberculosis referral centre. Provincial health authorities should restrict the use of second-line reserve drugs in order to contain the development of incurable tuberculosis.

Home care of MDR tuberculosis patients

After discharge from the MDR referral facility, patients could be managed on ambulatory treatment, **provided that DOT is ensured**. This should reduce costs, free up hospital beds and enable patients to remain in employment. Patients must be educated on basic infection control procedures such as safe coughing and sputum disposal, separate sleeping place, adequate ventilation and sunlight. If any of the following criteria are applicable, discharge should not be considered:

- Poor clinical condition;
- Previous history of treatment interruption;
- Complications (ie. haemoptysis);

- Major adverse drug effects.

Management of MDR tuberculosis patients at dedicated clinics (closest to patients) should be prioritised by:

- Provision of dedicated staff for counseling and support;
- Provision of key nursing staff to provide continuity and direct observation of treatment;
- Keeping updated information for incorporation into the DOTS-Plus electronic register;
- Monitoring compliance;
- Developing measures for rapid recall if patients interrupt their treatment;
- Ongoing education and motivation of patients;
- Tracing and evaluating contacts rapidly.

With the foregoing considerations in mind, specialised facilities and management teams for dealing with MDR tuberculosis may be regarded as an expensive luxury which are only affordable where national/provincial resources are adequate and after full implementation of the DOTS strategy has been achieved. A gross waste of resources will occur unless these facilities/teams consist of skilled and experienced staff who are given long-term responsibility. Treatment decisions should not be made by untrained and unsupervised persons on an *ad hoc* basis. Provincial protocols for referral, assessment and management of MDR tuberculosis patients should be done in consultation with all role players.

Counseling of patients

Patients with MDR tuberculosis face the prospect of lengthy and often unpleasant treatment as well as the real possibility of premature death. Therefore, counseling and emotional support are particularly important, much as in any other chronic life-threatening illness (eg. malignancies or HIV-related diseases). Proper early counseling will also help to ensure good adherence to the treatment regimen and increase the likelihood of a successful outcome.

All MDR tuberculosis patients should receive voluntary counseling and testing (pre- and post test) for HIV.

Once the patient is on treatment, further support will be required in order to maintain adherence and to help identify social and emotional problems early so that they may be addressed before they interfere with the treatment programme. If treatment has been unsuccessful and further therapy becomes futile it becomes very important that the patient is not merely abandoned, but continue to receive sympathetic and palliative care from the health team.

It should be clear, therefore, that skilled counseling services are an essential part of the team approach to the management of MDR tuberculosis. All staff, however, should show empathy with patients and should provide support at every contact.

Training and review

Specific training programmes should be ongoing and practice should be reviewed annually. This should be facilitated by the Provincial Tuberculosis Coordinator in close co-operation with the head of the specialised MDR centre.

Every case of MDR tuberculosis should be reviewed and the reasons for the case developing should be documented.

Each centre should conduct an annual review on the probable causes of MDR tuberculosis, the outcome of treatment and the costs involved. Each centre should provide a report to the Provincial Head of Health annually.

STANDARDISED TREATMENT REGIMEN

Treatment of patients with MDR tuberculosis involves second-line reserve drugs. In designing treatment regimens, the limited number of reserve drugs available imposes obvious limitations on the potential range of effective drug combinations that may be utilised. It has been shown that, regardless of drug susceptibility profiles, the most successful treatment regimens for MDR tuberculosis are those that include multiple drugs which the patient had not previously received. An individualised treatment approach (whereby treatment regimens are designed according to individual strain drug susceptibility patterns) requires considerable medical and microbiological expertise, sophisticated laboratory support and particularly tight management. One of the most pressing problems of individualised treatment regimens is the problematic nature of *in vitro* drug susceptibility testing of the second-line drugs. Internationally, the methodology has not been standardised and some of the drugs (eg. cycloserine) are so difficult to test that *in vitro* testing has been abandoned.

Because of the problems associated with an individualised approach to MDR tuberculosis treatment, a standardised second-line regimen has been proposed by WHO and adopted by the NTCP in South Africa. This regimen is based on country-specific profiles of drug resistance and expected to yield particularly good results in countries (like South Africa) where second-line drugs have not been previously used for tuberculosis treatment. The standardised approach requires much less medical and microbiological expertise and access to culture facilities only.

Second-line drugs for MDR tuberculosis are classified according to their bacteriological activity, toxicity and patient tolerance. The ranking of available drugs for MDR tuberculosis treatment is presented in Table II. A description of these drugs is provided in Annexure 1. The standardised treatment regimen used in South Africa has been designed from the highest-ranking categories and is presented in Table III. It is based on drug susceptibility testing at diagnosis to confirm resistance to isoniazid and rifampicin, and testing for ethambutol resistance to guide its use in the regimen. The standardised regimen consists of a four-month daily (at least five times per week) intensive phase with five drugs (kanamycin, pyrazinamide, ofloxacin, ethionamide and either terizidone or ethambutol, followed by a 12-18 months daily (at least five times per week) continuation phase with three drugs (ofloxacin, ethionamide and either ethambutol or terizidone). The continuation phase may be shortened provided that 12 months of treatment is given after sputum conversion, defined as two consecutive negative cultures, taken at least 30 days apart. Administration of the standardised regimen has been simplified across three weight bands, as indicated in Table III, to accommodate the limited formulations available in South Africa while complying with the international requirements for minimum, maximum and average dose per kg.

A description of drug administration and adverse effects is provided in Annexure 2.

GENERAL MANAGEMENT PRINCIPLES

- MDR tuberculosis treatment should be implemented only in districts where the DOTS strategy is functional;
- Measures to curtail the availability of MDR tuberculosis drugs must be taken at provincial level, eg. removing these drugs from provincial/district hospitals and centralising their procurement to the provincial MDR tuberculosis referral centre;
- Management structures must be in place. These include formal referral mechanisms for MDR tuberculosis patients, dedicated MDR tuberculosis wards/centres and MDR tuberculosis management teams with clear management responsibilities. Management teams should have the necessary capacity and expertise to take collective decisions on managerial issues such as termination of treatment, refusal of treatment and dealing with habitual defaulters;
- MDR tuberculosis treatment logistics must be in place. These include hospitalisation of MDR tuberculosis patients in dedicated wards/centres at least during the intensive phase of treatment and preferably until sputum culture conversion has been achieved. Patients eligible for discharge must be managed through a dedicated clinic system where the second-line drugs are available on a patient-named basis only and controlled by the provincial MDR tuberculosis referral centre.

Table II. Ranking of available drugs for treatment of MDR tuberculosis

(Source: World Health Organization. *Guidelines for the management of drug-resistant tuberculosis. WHO/TB/96.210(Rev.1). WHO, Geneva: 1997*)

Rank	Drugs	Activity	Dosage (daily)			Acceptability	Tolerance	Toxicity
			Average	Minimum	Maximum			
1	Aminoglycosides <ul style="list-style-type: none"> Streptomycin Kanamycin Amikacin Capreomycin 	Bactericidal (actively multiplying organisms)	15mg/kg 15mg/kg 15mg/kg 15mg/kg	750mg 750mg 750mg 750mg	1000 mg 1000 mg 1000 mg 1000 mg	Injection Injection (painful) Injection (painful) Injection	Moderate Poor Poor Moderate	Medium Medium Medium Medium
2	Thioamides <ul style="list-style-type: none"> Ethionamide Prothionamide* 	Bactericidal	10-20 mg/kg 10-20 mg/kg 10-20 mg/kg	500 mg 500 mg 500 mg	750 mg 750 mg 750 mg	Good Good	Moderate Moderate	Medium Medium
3	Pyrazinamide	Bactericidal (acid pH)	20-30 mg/kg	1200 mg	1600 mg	Good	Moderate	Low
4	Fluoroquinolones <ul style="list-style-type: none"> Ofloxacin Ciprofloxacin 	Weakly bactericidal Weakly bactericidal	7.5-15 mg/kg 7.5-15 mg/kg	600 mg 1000 mg	800 mg 1500 mg	Good Good	Good Good	Low Low
5	Ethambutol	Bacteriostatic	15-20 mg/kg	1000 mg	1200 mg	Good	Good	Low
6	Terizidone Cycloserine	Bacteriostatic Bacteriostatic	15-20 mg/kg 10-20 mg/kg	500 mg 500 mg	750 mg 750 mg	Good Good	Moderate Moderate	High High
7	PAS*	Bacteriostatic	10-12g	10g	12g	Bad (bulk, taste)	Poor	Low

*Not available in South Africa

Table III. Standardised regimen for treatment of MDR tuberculosis in South Africa

Intensive phase: 4 months (daily)

Patient weight	Drug	Dosage
<50 kg	Kanamycin	750 mg
	Ethionamide	500 mg
	Pyrazinamide	1000 mg
	Ofloxacin	600 mg
	Ethambutol	800 mg
	or Terizidone*	750 mg
50 – 65 kg	Kanamycin	1000 mg
	Ethionamide	750 mg
	Pyrazinamide	1500 mg
	Ofloxacin	600 mg
	Ethambutol	1200 mg
	or Terizidone*	750 mg
>65 kg	Kanamycin	1000 mg
	Ethionamide	750 mg
	Pyrazinamide	2000 mg
	Ofloxacin	800 mg
	Ethambutol	1200 mg
	or Terizidone*	750 mg

Continuation phase: 12 – 18 months (daily), depending on culture conversion

Patient weight	Drug	Dosage
<50 kg	Ethionamide	500 mg
	Ofloxacin	600 mg
	Ethambutol	800 mg
	or Terizidone*	500 mg
50 – 65 kg	Ethionamide	750 mg
	Ofloxacin	600 mg
	Ethambutol	1200 mg
	or Terizidone*	750 mg
>65 kg	Ethionamide	750 mg
	Ofloxacin	800 mg
	Ethambutol	1200 mg
	or Terizidone*	750 mg

* Ethambutol to be used if strain still susceptible
 Terizidone to be used if strain resistant to Ethambutol; reduce dose to 500 mg if weight ≤ 35 kg
 Pyridoxine (B6) 150 mg to be given daily to patients on terizidone

In exceptional instances:
 Kanamycin may be substituted with amikacin
 Ofloxacin may be substituted with ciprofloxacin

PATIENT MONITORING AND FOLLOW-UP

Designations and responsibilities

South African DOTS-Plus Group

This Group comprises of individuals directly involved in the management of MDR tuberculosis patients, designated staff from the provincial MDR tuberculosis referral centers, provincial Tuberculosis Managers and researchers from the MRC. The Group meets twice a year to review progress and address operational issues.

National Coordinator

The national coordinating centre is based at the MRC in Pretoria. Dr Karin Weyer of the MRC represents South Africa on the DOTS-Plus Working Group of the WHO and is the National Coordinator. She assumes overall responsibility for coordination and support of activities at the different MDR referral centres, for monitoring of progress, for drug adverse effect reporting to the Medicines Control Council, for analysis of data and providing regular feedback to the NTCP.

Local Investigators

One person (preferably a medical officer or nursing sister) from each of the MDR referral centres should assume overall responsibility for patient management and for monitoring progress at centre level. This person should preferably be represented on the provincial MDR tuberculosis management team. Specific responsibilities include compliance of centre staff with the DOTS-Plus policy, reporting of drug adverse events to the National Coordinator, decisions on DOTS-Plus policy violations, monitoring of data accuracy and completeness and organisation of data flow to the National Coordinator.

Referral centres

MDR referral centres are regarded as centres of expertise and therefore remain overall responsible for treatment of MDR tuberculosis patients, even after discharge. Second-line drugs should only be available through these centres. Mechanisms for regular feedback on patient progress must be established with designated clinics before patient discharge, including adherence monitoring. Final treatment outcomes must be recorded at the referral centres.

Recording and reporting

Recording in DOTS-Plus differs from recording in conventional tuberculosis control programmes. Differences include a different time frame (longer duration of treatment); monitoring of bacteriological conversion using both smear and culture; and using results of drug susceptibility testing to guide drug choices, even in the standardized regimen. The importance of collecting more information for operational research is a priority. In addition, the definitions used both in classification of patients and evaluation of outcome of treatment (failure, cure, etc.) are more complex. Documentation of adverse

effects needs to be addressed. Thus, classical DOTS recording and reporting forms need to be adapted considerably.

In order to comply with international DOTS-Plus requirements and facilitate monitoring and follow-up of patients, standardised forms have been designed. These are presented in Annexures 3 to 10. It is essential that all relevant information be accurately recorded, either directly on these forms or by transferring the required data from existing patient medical files.

Data collection should be done according to the standardised data collection forms that contain the following patient information (Annexures 3 –10):

- DOTS-Plus number
- Age and sex
- Previous tuberculosis treatment
- MDR treatment details
- HIV status at diagnosis, completion of therapy and end of 60-months follow-up
- Chest radiography at diagnosis, after the intensive phase of treatment, after 9 months and at completion of therapy
- Dates and results of monthly sputum smear investigations
- Dates and results of monthly culture investigations
- Monthly body weight
- Number of directly-observed doses of each drug
- Number of treatment doses interrupted for each drug
- Adverse effects
- Treatment outcome and date outcome assigned
- Follow-up information at six-monthly intervals for a total period of 60 months

Patients considered eligible for MDR tuberculosis treatment according to NTCP policy should be registered using the Patient Record Form (Annexure 3). Upon discharge the patient referral form (Annexure 4) should be completed and forwarded to the designated clinic. At the clinic, patient monitoring should be recorded using the clinic card and treatment record presented in Annexure 5. Data should be forwarded to the MDR referral centre at quarterly intervals.

Data should be collated into the DOTS-Plus electronic register which has been developed by the MRC and implemented at all participating centres. Data collected electronically at these centres should be forwarded to MRC at six-monthly intervals, from where validated and checked data will be forwarded to the NTCP.

Laboratory Investigations

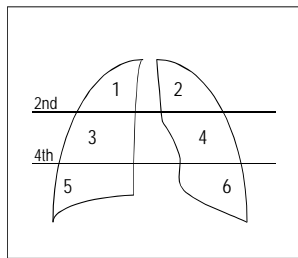
At patient intake one sputum specimen should be collected and sent to the MRC laboratories in Pretoria for confirmation of MDR tuberculosis. During treatment one sputum specimen should be collected monthly for smear and culture examination at the MRC.

Chest x-ray evaluation

Chest x-rays should be evaluated using a standardised scoring system at the following intervals:

- at diagnosis;
- after completion of the intensive phase of treatment;
- after nine months of treatment;
- at completion of treatment.

Chest x-rays should be evaluated using the standardised grading system (developed by Prof Paul Willcox at Brooklyn Chest Hospital). The chest x-ray is divided into six zones by the mediastinum and horizontal lines through the 2nd and 4th anterior rib shadows. Each zone is described according to disease and cavitation, as follows:



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

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

Treatment administration

All treatment must be given under direct observation on at least five days a week and the Patient Adherence Record (Annexure 6) completed and initialed by the person observing drug intake. All patients must receive a minimum of 16 months' treatment (four months of intensive and at least 12 months of continuation phase therapy, based on culture conversion). Anecdotal evidence from South Africa seems to suggest that patients who do not achieve culture conversion after nine months of fully supervised therapy are likely to be treatment failures; this observation has guided some provinces to consider termination of treatment if cultures remain positive after nine months. The exact duration of treatment required for MDR tuberculosis is, however, not known. Therefore, all patients must complete the required full course of 16 - 22 months of treatment.

Additional investigations

Cultures from patients who fail to convert at nine months should be subjected to a full drug susceptibility investigation (including second- and third-line drugs) at the MRC. Subsequent chemotherapy is adjusted according to the drug resistance profile and availability of drugs in the individual provinces. Changes are made in consultation with the MRC, the DOTS-Plus Group and the relevant provincial MDR management team.

Monitoring of drug adverse effects

During the intensive phase of treatment, patients must be interviewed *weekly* about adverse effects to the drugs and these recorded utilising the Drug Adverse Effect Monitoring Form (Annexure 7). In the continuation phase the incidence of adverse effects must be monitored *monthly* utilising the same Form. Line listings of these effects must be provided *quarterly* to the National Coordinator. Serious adverse events which necessitate discontinuation of drugs must be noted in the Serious Adverse Drug Effect Report (Annexure 8) and a report forwarded within *five calendar days* to the National Coordinator for notification to the Medicines Control Council. Drug intolerance and patient sensitisation should be managed according to the recommendations contained in these guidelines.

Management of treatment interruption, default and death

A patient is regarded as having defaulted from MDR tuberculosis treatment if s/he does not take treatment for a consecutive period of two months. Every effort must be made to rapidly recall MDR tuberculosis patients who interrupt and to persuade them to resume treatment. Subsequent management of patients who continue to interrupt treatment should be done according to legal policy guidelines and in consultation with the provincial MDR management teams.

If a patient dies, a Death Report (Annexure 9) should be submitted to the National Coordinator documenting the date of death, the manner of death and details of the cause of death.

Patient follow-up after treatment completion

Patients who complete a full course of MDR tuberculosis treatment should be followed up at six-monthly intervals for a total duration of 60 months. They should be questioned about signs and symptoms of tuberculosis and two sputum specimens collected at each interval if indicated. Active follow-up of patients failing an appointment is essential and knowledge about each patient during follow-up must be secured. The required follow-up documentation is presented in Annexure 10.

TREATMENT OUTCOMES

The following mutually exclusive MDR tuberculosis treatment outcome definitions have been designed internationally to fit the wide range of country-specific regimens and treatment durations currently in use. These definitions rely on the use of culture; smears should only be used in the absence of culture.

Cure: A patient who has completed MDR tuberculosis treatment, is culture-negative in the last month of treatment, and has been culture-negative during the preceding 11 months of treatment, with a maximum of only one positive culture during that time. A minimum of five cultures must be performed within the last 12 months of treatment. For any patient who have one positive culture in the last 12 months, the positive culture must be followed by a minimum of three consecutive negative cultures.

Treatment completed: A patient who has completed MDR tuberculosis treatment but does not meet the definition for cure or failure due to lack of bacteriologic results.

Death: A patient who dies for any reason during the course of MDR tuberculosis treatment.

Treatment default: A patient whose MDR tuberculosis treatment was interrupted for two or more consecutive months.

The following algorithms should be followed for patients returning after default:

- If the individual has taken ≥ 1 month of MDR tuberculosis treatment, and upon return is smear (positive), then he/she will receive a final outcome of default and will need to be re-registered and reinitiated on a new MDR tuberculosis regimen;
- If the individual has taken ≥ 1 month of MDR tuberculosis treatment, and upon return is smear (negative), then MDR treatment should continue, and a culture should be performed.
- If the culture returns positive, then he/she will receive a final outcome of default and will need to be reinitiated on a new MDR tuberculosis treatment regimen.

Treatment failure:¹ A patient who has more than one positive culture² in the last 12 months of treatment, with a minimum of five cultures performed during the last 12 months. A patient will also be considered a treatment failure if one of the last three cultures taken during treatment is positive, or if he/she is persistently culture-positive and, on a case-by-case basis, a clinical decision has been made to terminate treatment.

¹ This is a programmatic definition for cohort analysis; thus after a patient fails treatment, drug susceptibility testing of second-line drugs should be performed in order to find a successful treatment option for the patient. Treatment may continue after a programmatic outcome has been assigned.

² A positive culture requires >10 colonies; two consecutive positive cultures must be obtained if <10 colonies are detected in the first culture; if second culture also shows <10 colonies, the culture should be interpreted as positive.

Transferred out: A patient who has been officially transferred to another reporting and recording unit which has a documented MDR tuberculosis treatment program and for whom the treatment outcome is unknown.

SPECIAL SITUATIONS

Children

There is limited reported experience using the second-line antituberculosis medications for extended periods in children. Careful consideration of the risks and benefits of each drug should be made. Frank discussion with the patient and family members is critical, especially at the outset of therapy. Given the life-threatening aspects of MDR tuberculosis, there are no drugs that are absolutely contraindicated in children. Children who have received treatment for MDR tuberculosis have generally tolerated the second-line drugs, including the aminoglycosides, cycloserine, and ethionamide.

It should be noted that while fluoroquinolones have been shown to retard cartilage development in beagle puppies, experience in the treatment of children with cystic fibrosis has failed to demonstrate similar effects in humans. Additionally, ethionamide, cycloserine and kanamycin have been used effectively in children and are tolerated well. In general, drugs should be dosed according to weight. Monitoring monthly weights is therefore especially important in paediatric cases, with adjustment of doses as the child gains weight.

Pregnancy and lactation

Since drugs are on purpose not tested in pregnant and nursing mothers, available data on safety and efficacy are anecdotal. All female patients of childbearing age should be tested for pregnancy upon initial evaluation; birth control is strongly recommended for all women receiving MDR tuberculosis therapy. Since oral contraceptives may have decreased efficacy due to potential drug interactions, other options include the use of medroxy-progesterone (Depo-Provera) intramuscular every 14 weeks or barrier methods (eg. diaphragm or condom) throughout the course of treatment. All patients should be encouraged to use condoms to protect against sexually transmitted diseases.

Table IV lists the safety during pregnancy of medications used in the standardised treatment of MDR tuberculosis. Pregnancy is not an absolute contraindication to the treatment of active MDR tuberculosis, since active disease poses great risks to the life of the mother and fetus.

Gravid patients should be carefully evaluated, taking into consideration gestational age and severity of MDR tuberculosis. The risks and benefits of MDR tuberculosis treatment should be considered carefully, with the primary goal being smear conversion in order to protect the health of the mother and child, both before and after birth.

- Since the majority of teratogenic effects occur in the first trimester, therapy should be delayed until the second trimester unless life-threatening symptoms occur.

- Patients in the third trimester have reduced risk of teratogenicity, although aminoglycosides may still damage the fetal ear. For the most part, aminoglycosides are not used in the regimens of pregnant patients.
- If possible, begin treatment in the second or third trimester without the aminoglycoside and then reinforce the regimen with kanamycin immediately postpartum.

Table IV: Safety of antituberculosis medications during pregnancy

(Source: Partners in Health. *The PIH guide to medical management of multidrug-resistant tuberculosis. International Edition. PIH, USA: 2003*)

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

* A = safety established using human studies;

B = presumed safety based on animal studies;

C = uncertain safety, no human studies and animal studies show an adverse effect;

D = unsafe, evidence of risk that may be justifiable under certain clinical circumstances.

Newborn infants are at high risk of developing disseminated MDR tuberculosis. If possible, smear-positive mothers should avoid close contact with infants, leaving the care of the infant to a family member until the mother is smear-negative. Alternatively, N-95 respirators may be used by the mother; the degree of protection conferred in this setting, however, has not been studied. Mothers and babies should be isolated from other MDR tuberculosis patients if possible.

Effects of MDR tuberculosis medications on the nursing infant have not been fully studied. Therefore, the use of infant formula is a 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. Table V gives a summary of information concerning breast-feeding and MDR tuberculosis medications. In most cases, the amount of drug delivered to the infant is small; therefore, these drugs are not absolutely contraindicated in mothers who choose to breastfeed. Quinolones should be avoided because of the possible risk to cartilage development in the nursing infant. Patients should be told of the limited facts available, and allowed to make an informed decision.

Table V: Breast-feeding and anti-MDR tuberculosis medications

(Source: *Partners in Health. The PIH guide to medical management of multidrug-resistant tuberculosis. International Edition. PIH, USA: 2003*)

Drug	Compatible with breast-feeding	% Concentration in breast milk compared with therapeutic doses for infants
Ethambutol	Yes	2.8 - 6.9%
Pyrazinamide	Not known	0.75 - 1.5%
Amikacin	Yes. Poorly absorbed by GI tract	Not reported
Kanamycin	Yes. Poorly absorbed by GI tract	0.9 - 18%
Cycloserine	Yes	11 - 28%
Terizidone	Unknown	Unknown
Ethionamide	Unknown	Unknown

Diabetes

The treatment of MDR tuberculosis in the diabetic will result in poorer outcomes if glucose is not well controlled. The responsibility often falls on the physician treating the patient for MDR tuberculosis to ensure proper diabetic care. In addition, diabetes may potentiate adverse effects, especially renal dysfunction and peripheral neuropathy. The following guidelines are suggested to assist in the management of the diabetic with MDR tuberculosis:

Medical follow-up

Diabetes must be managed closely throughout treatment. The physician should be in close communication with a physician who manages the patient's diabetes.

Patient education

Patients should be educated about the required diabetic diet (all nurses with diabetic patients should be familiar with the basics of the diabetic diet), weight control, exercise, foot care and symptoms of hypo- and hyperglycemia.

Glucose monitoring

- Goals for capillary blood testing: 80-120 mg/dl before meals; 100-140 mg/dl before bedtime; the range should be higher if patient has a history of hypoglycemia;
- Patients may need a period of intensive glucose monitoring until these goals are met;
- Once a patient is on a stable dose of insulin, his or her blood sugar may be monitored four times weekly to ensure that targets are being maintained;
- If a patient is on oral antidiabetic agents, his or her blood sugars 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, a creatinine clearance should be checked and antituberculosis medications should be adjusted according to Table VI. Once the dose is adjusted, the creatinine should be checked weekly until it has stabilized;
- HbA_{1C} every three months if treatment changes or patient is not meeting goals; every 6 months if stable;
- Goal for HbA_{1C}<7;
- Retinal examination annually.

Screening and treatment for hypertension

- Blood pressure checks every month;
- Hypertensive patients with diabetes should be started on an ACE-inhibitor.

Prevention of diabetic nephropathy

- Dosing of kanamycin according to Table VI;
- Consider using an ACE inhibitor for patients with albuminuria (> 300 mg/24 h).

Renal insufficiency

Renal insufficiency due to longstanding tuberculosis disease is not uncommon. Second-line drugs that rely on renal clearance for most of their elimination include the aminoglycosides, ethambutol, terizidone and cycloserine. Cirpofloxacin is about 50% cleared by the kidneys, while ofloxacin is more than 90% cleared by the kidneys. Metabolites of pyrazinamide are also primarily cleared by the kidneys. Great care should be taken in the administration of second-line drugs in patients with renal insufficiency, and the dose and/or the interval between dosing should be adjusted according to Table VI.

Since the creatinine clearance approximates the glomerular filtration rate (GFR), knowledge of the blood urea nitrogen and serum creatinine concentrations allows for the estimation of residual renal function. The formula to calculate the creatinine clearance (CrCl) or the glomerular filtration rate (GFR) is as follows:

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

A correction for females (0.85 times the result of the formula) is recommended.

Normal values for the creatinine clearance are:

Men: 97 to 137ml/min

Women: 88 to 128ml/min

Table VI: Dosing of MDR tuberculosis drugs in renal failure

(Source: *Partners in Health. The PIH guide to medical management of multidrug-resistant tuberculosis. International Edition. PIH, USA: 2003*)

Drug	Change in frequency	Recommended dose and frequency for patients with creatinine clearance < 30 ml/min or for patients receiving hemodialysis ¹⁻⁶
Pyrazinamide	Yes	25-35 mg/kg/dose 3 x wk
Ethambutol	Yes	15-25 mg/kg/dose 3 x wk
Ciprofloxacin	Yes	1000-1500 mg/kg/dose 3 x wk
Ofloxacin	Yes	600-800 mg/kg/dose 3 x wk
Cycloserine	Yes	250 mg once daily, or 500 mg/dose 3 x wk ^{ll}
Terizidone	Yes	250 mg once daily, or 500 mg/dose 3 x wk
Ethionamide	No	250-500 mg/dose daily
Kanamycin	Yes	12-15 mg/kg/dose 2 or 3 x wk**
Amikacin	Yes	12-15 mg/kg/dose 2 or 3 x wk**

- 1 To take advantage of the concentration-dependant bactericidal effect on many antituberculosis drugs, standard doses are given unless there is intolerance.
- 2 The medications should be given after haemodialysis on the day of haemodialysis (this also allows for the easy administration of DOT three times per week).
- 3 Monitoring of serum drug concentrations should be considered to ensure adequate drug absorption, without excessive accumulation, and to assist in avoiding toxicity.
- 4 Data are currently not available for patient receiving peritoneal dialysis. Until data become available, begin with doses recommended for patients receiving hemodialysis and verify adequacy of dosing using serum concentration monitoring.
- 5 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).
- 6 Caution should be used with the injectable agents in patients with renal function impairment because of the increased risk of both ototoxicity and nephrotoxicity.

Consideration may also be given to extension of the dosing interval in chronic renal failure, as it takes longer for a drug to leave the body when renal clearance is reduced. Aminoglycoside doses must be adjusted in renal failure, as the kidneys excrete essentially of the drug. The dosing interval may be extended as creatinine clearance declines. Patients with decreased renal function may accumulate ethambutol, as renal elimination accounts for about 80% of the dose. Ofloxacin is particularly dependant on renal clearance and its half-life is significantly prolonged in renal failure. Ciprofloxacin has less renal excretion than ofloxacin and is therefore preferred in cases of chronic renal failure.

Below is 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 be the dose of kanamycin?

Step 1: Calculate the Glomerular Filtration Rate (GFR) =

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

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

$$= \frac{4217}{172.8}$$

$$= 24.4 \text{ ml/min}$$

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

Step 2: Refer to Table VI and make the appropriate adjustment in dose. In this case the 24.8 ml/min falls below 30 ml/min. The dose of kanamycin given from Table VI is 12-15 mg/kg. The dose to prescribe would be between (12)(53) = 636 mg and (15)(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.

Step 3: Check creatinine periodically (often weekly or more frequently in the patient with severe renal insufficiency) and readjust medications for any change.

Note: For this patient, every drug in the regimen should be examined and adjusted if necessary. If this were a woman, the GFR = 24.8 x 0.85 = 21.1 ml/min.

Central nervous system infections

There is a high baseline incidence of depression and anxiety in patients with MDR tuberculosis, often connected to chronicity and socioeconomic stressors related to the disease. Any psychiatric illness identified at the start of or during treatment should be addressed fully.

Treatment with psychiatric medications, individual counseling, and/or group therapy may be needed to manage the patient suffering from a psychiatric condition or adverse effect. The physician treating tuberculosis should be involved in all management modalities. Group therapy has been very successful in providing a supportive environment for the MDR tuberculosis patient and may be helpful for patients with or without psychiatric conditions.

The patient with a substance dependency poses a difficult challenge. Treatment for addiction should be offered if possible. Complete abstinence from alcohol or drugs should be strongly encouraged. However, active alcohol or drug use is not an absolute contraindication to treatment. If treatment is

repeatedly interrupted due to the patient's addiction, MDR tuberculosis therapy should be suspended until treatment for the addiction is successful. Good DOT gives the patient contact with and support from health care providers that often aids greatly in being successful in reducing substance dependency.

Terizidone and cycloserine will have a higher incidence of adverse effects in both the psychiatric patient and the alcohol or drug dependent patient. However, if terizidone or cycloserine is required in the regimen, it should be used in these patients and the patients closely observed for adverse effects.

All physicians treating MDR treatment should work closely with a psychiatrist and have a system in place for psychiatric emergencies, including psychosis, suicidal indication, and any situation that involves the patient posing a danger to himself or to others.

HIV co-infection

The full link between HIV and MDR-TB is not yet fully understood. Nevertheless, outbreaks of MDR-TB involving HIV-infected patients have been associated with extremely high mortality rates (more than 70%). Nosocomial transmission of MDR-TB to HIV-positive individuals due to prolonged hospitalization (and therefore exposure to circulating MDR-TB strains) has also been well described.

HIV patients in general have a higher rate of adverse drug reactions, both to TB and non-TB drugs. Known adverse effects of increased magnitude include peripheral neuropathy, cutaneous reactions, gastro-intestinal effects, renal toxicity and neuropsychiatric effects. Gastrointestinal side effects (already a major problem in patients receiving MDR-TB treatment) may be further potentiated by antiretroviral agents with similar side-effect profiles. Also, malabsorption of MDR-TB drugs (including ethambutol, pyrazinamide, ethionamide and cycloserine) has been reported in patients with HIV-related enteropathology. Given that HIV also poses a risk for increased mortality in MDR-TB patients, routine HIV counseling and testing is recommended for all patients diagnosed with MDR-TB.

The positive impact of highly active antiretroviral therapy (HAART) in MDR-TB patients has been shown in a small study in Argentina, where mortality in MDR-TB patients with AIDS was reduced to 31%, compared to 91% in co-infected MDR-TB patients not receiving antiretroviral therapy. Given that fact that MDR-TB patients have only one more chance of cure and that there may be distinct benefits to HAART, it is recommended that all MDR-TB patients be considered for HAART. However, it should be recognized that the initiation of HAART is also associated with adverse events that may lead to interruption of both MDR-TB and HIV therapy. Also, a significant proportion of patients who receive HAART during treatment for TB (and conceivably also MDR-TB), may experience immune-reconstitution syndromes resulting in a paradoxical worsening of TB (and conceivably also MDR-TB). This is due to the ability of the treated HIV patient to mount a stronger immune response, resulting in an inflammatory reaction against TB that may lead to clinical worsening of the patient's condition. However, this remains a controversial area that requires further study.

Currently, very limited information is available on drug-drug interactions between MDR-TB drugs and those used in antiretroviral treatment. Nonenteric-coated didanosine contains an aluminium/magnesium based antacid which, when given together with quinolones, may result in decreased absorption of the quinolones. The combination of cycloserine or terizidone and efavirenz may increase the rate of neuropsychiatric effects; however, this has not been formally studied. Peripheral neuropathy has been associated with the use of ethionamide, cycloserine and pyrazinamide and may be exacerbated in patients receiving stavudine and/or didanosine. It is therefore recommended that MDR-TB drugs and antiretroviral treatment be given at least two hours apart.

The appropriate time to initiate antiretroviral treatment in MDR-TB co-infected patients is not known. Currently, the timing of antiretroviral treatment is a subject of much debate in co-infected drug-susceptible TB patients, requiring extensive study. Weighing the risks and benefits of beginning antiretroviral therapy in MDR-TB patients, it is recommended that HAART be started within the first four months of MDR-TB treatment in patients with advanced AIDS (CD4 count < 50), depending on the clinical status of the patient and provided that the MDR-TB treatment is tolerated. HAART should be delayed until the continuation phase of MDR-TB treatment in clinically stable patients, especially if the CD4 count is more than 100. Patients already on HAART when diagnosed with MDR-TB should be started on MDR-TB treatment immediately.

In patients receiving antiretroviral therapy, 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 loads 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. On appropriate therapy, viral load usually reaches undetectable levels (<50 RNA copies/ml) by 16-20 weeks, although this outcome is affected by baseline CD4 count, baseline viral load, regimen potency, adherence, prior exposure to antiretrovirals and intercurrent opportunistic infections. Viral loads should not be measured during or within four weeks of any intercurrent infection, immunization or symptomatic illness.

The complexity of both antiretroviral and MDR-TB treatment, each with its own toxicity profiles (which may be potentiated during concomitant therapy), demands even more rigorous monitoring in co-infected MDR-TB patients. In addition, other opportunistic infections will have to be prevented, monitored and treated. Prophylaxis will depend on the patient's MDR-TB and HIV status. Given the higher likelihood of sulfa-related adverse reactions in HIV-positive patients (6-8 times greater than in the general population) sulfa-based prophylaxis should be started at least two weeks apart from MDR-TB and/or HIV therapy.

The MDR-TB patient with HIV infection poses a great challenge and will require intensive monitoring of drug interactions and additive drug toxicities. Management of the patients should therefore take place by health care staff who are well-versed in both conditions.

MANAGEMENT OF DRUG ADVERSE EFFECTS

Of equal importance to the treatment strategy used is the proper management of adverse effects. Special attention should be given to the management of adverse effects and to the systemic collection of data on adverse effects. The timely and aggressive management of adverse effects of the second-line drugs greatly facilitates patient adherence.

Adverse effects may be classified under the following categories:

- Minor side effects
- Toxic reactions
- Hypersensitivity reactions
- Idiosyncratic reactions
- Reactions not classified in any of the above

Since patients receive combination chemotherapy, it is often difficult to determine which drug is the source of the undesired effect as drug-drug interactions may also produce adverse effects. Some adverse effects disappear within a short period after treatment begins. Given these considerations, the following sequential steps for the management of adverse effects are suggested:

1. Direct management of adverse effects with standardised algorithms;
2. Reduced dosage of suspected drug(s) on an individual drug basis;
3. Removal of drugs from regimen.

Some adverse effects can be managed with over-the-counter and common prescription drugs. If adverse effects cannot be managed through such means, and the adverse effects are not deemed serious, then patients should be encouraged to tolerate the effects until they subside. If it is determined that a patient cannot tolerate the regimen, the dosage of the suspected drug(s) may be reduced until the adverse effects subside. If it is not clear which drug is the cause of the adverse effects(s), dosages 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 adverse effects(s), then it may be necessary to reduce the dosage of multiple drugs simultaneously. If this does not alleviate the adverse effects(s) then 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.

Nausea and vomiting

Suspected drugs: Ethionamide (most common), Ofloxacin, Ethambutol

Nausea (often associated with vomiting) is ubiquitous during the early weeks of therapy and usually abates with supportive therapy. While the majority of patients experience nausea and/or vomiting as an adverse effect these symptoms rarely prevent delivery of adequate therapy. Symptoms should be controlled and any medications lost to emesis replaced. Electrolytes should be monitored and replaced in cases of severe vomiting. Refractory nausea and vomiting suggest the need for further investigation, including the possibility of hepatitis. Nausea and vomiting are reversible upon discontinuation of the suspected drug.

A management algorithm for nausea and vomiting is provided in Annexure 11.

Hearing loss

Suspected drugs: Kanamycin, Amikacin

Patients with prior exposure to aminoglycosides (eg. streptomycin) may have baseline hearing loss. In these patients it is useful to obtain audiometry at the start of MDR tuberculosis therapy. Hearing loss is generally not reversible. The risk of further hearing loss must be weighed against the risk of stopping kanamycin/amikacin, as these drugs are the most potent for treatment of MDR tuberculosis. The risk should be discussed with the patient in order to allow him/her to make an informed choice about continuation of the drug.

A management algorithm for hearing loss is provided in Annexure 12.

Depression

Suspected drugs: Cycloserine, Terizidone, Ofloxacin, Ciprofloxacin, Ethionamide

Although the word 'depressed' is often used to describe sadness, clinical depression refers to a specific psychiatric diagnosis. Symptoms of major depressive disorder can include changes in sleep pattern, loss of interest in usual activities, feelings of guilt, diminished energy, decreased concentration, lack of appetite, slowed movement and thought, and suicidal thoughts. Sadness may be considered a normal reaction for a patient with a chronic illness such as MDR tuberculosis, however, additional factors (including drug adverse effects, loss of work or social factors associated with MDR tuberculosis) may exacerbate this condition and result in clinical depression. If a patient presents with significant changes in behaviour or mood that affect his/her daily activities, s/he should be evaluated for depression.

The importance of socio-economic conditions as a contributing factor to depression should not be underestimated. Group or individual supportive counseling may offer some help. Depression symptoms may fluctuate during MDR tuberculosis therapy and may improve as illness is successfully treated. A history of prior depression is not a contra-indication to MDR tuberculosis treatment; however such patients may be at increased risk for developing depression during therapy. Depression associated with MDR tuberculosis treatment is fully reversible upon discontinuation of suspected drugs; however, usually there is no need to suspend suspected agents.

A management algorithm for depression is provided in Annexure 13.

Peripheral neuropathy

Suspected drugs: Terizidone, Cycloserine, Kanamycin, Amikacin, Ethambutol, Ofloxacin, Ciprofloxacin

Neuropathy refers to a degenerative, infectious or inflammatory process that cause damage to the nerves. Peripheral neuropathy refers to those neuropathies located outside the central nervous system. Patients with co-morbid disease (eg. diabetes, alcoholism, HIV) may be more likely to develop peripheral neuropathy. It is therefore important to consider causes other than anti-tuberculosis drugs (including other medications) in patients presenting with peripheral neuropathy. Neuropathy is generally not reversible; however, some patients may experience improvement when the offending agent(s) are suspended. Usually, a minority of patients (<10%) require continued intervention to keep symptoms under control once MDR tuberculosis treatment has been completed.

A management algorithm for peripheral neuropathy is provided in Annexure 14.

Gastritis

Suspected drugs: Ethionamide, Ethambutol, Pyrazinamide

Gastritis refers to inflammation of the stomach. Multiple causes (including infection, diet, alcohol, and medications, including nonsteroidal anti-inflammatory drugs and anti-tuberculosis medications) should be considered. If left untreated, gastritis can progress to ulcers and gastro-intestinal bleeding. Emesis that has the appearance of ground coffee can represent coagulated blood from a bleeding gastro-intestinal source.

Severe gastritis, as manifested by hematemesis, melena or hematechezia is rare. Dosing of anti-acids should be carefully timed so as not to interfere with the absorption of anti-MDR tuberculosis drugs (administer two hours before or after drugs).

Gastritis is reversible upon discontinuation of suspected agent(s).

A management algorithm for gastritis is presented in Annexure 15.

Psychosis

Suspected drugs: Cycloserine, Terizidone, Ofloxacin, Ciprofloxacin, Ethionamide

Psychotic symptoms refer to a constellation of symptoms that indicate a disintegration of personality or loss of contact with reality. Patients tend to present with hallucinations or delusions. The cause of psychosis in patients with MDR tuberculosis may be related to underlying psychiatric disorders, anti-MDR tuberculosis medications (particularly cycloserine and terizidone) and other drugs. Decompensation may occur in the context of stressors such as socio-economic problems, additional medications, substance abuse, etc.

Some patients will need to continue anti-psychotic treatment throughout MDR tuberculosis therapy. Prior history of psychiatric disease is not a contraindication to the use of anti-MDR tuberculosis drugs, but may increase the likelihood of development of psychotic symptoms. Psychosis is generally reversible upon discontinuation of the suspected agent(s) or upon completion of MDR tuberculosis treatment.

A management algorithm for psychosis is presented in Annexure 16.

Fever

Fever is defined as an elevation in body temperature in excess of the normal range, although temperatures within 1 degree of normal (37°C) are not generally considered significant. In a patient receiving MDR tuberculosis treatment, various sources must be ruled out.

A management algorithm for fever is provided in Annexure 17.

Headache

Although headaches are often an adverse effect of MDR tuberculosis treatment, it is important to rule out other causes, including meningitis, migraine and cluster headaches.

A management algorithm for headaches is provided in Annexure 18.

Arthralgia

Suspected drugs: Pyrazinamide, Ofloxacin, Ciprofloxacin

Symptoms of arthralgia usually diminish over time, even without intervention. Uric acid levels may be elevated in some patients but are of little therapeutic relevance and anti-gout therapy (eg. allupurinol, colchicines) is of little benefit in these patients.

Therapy with non-steroidal anti-inflammatory drugs and initiation of an exercise regimen are usually adequate to alleviate symptoms.

Diarrhoea

Diarrhoea is characterized by frequent watery bowel movements. Since many patients use the term diarrhoea to describe bowel movements that are more frequent or loose than normal, it is important to note whether the stool is truly watery and more than three times a day. Both loose stool and diarrhoea are frequent side effects of MDR tuberculosis medications. Antimotility agents should be avoided in patients with fever or if blood is present in the stool.

A management algorithm for diarrhoea is provided in Annexure 19.

Nephrotoxicity and renal failure

Suspected drugs: Kanamycin, Amikacin

A history of diabetes or renal disease is not a contraindication to the use of MDR tuberculosis drugs; however, patients with these co-morbidities may be at increased risk for developing renal failure.

Renal impairment may be permanent. Serum urea and creatinine should be documented at the beginning of MDR tuberculosis treatment and renal function followed regularly throughout. In general, however, routine testing of creatinine clearance of non-hospitalised patients is not recommended due to the difficulties of ambulatory 24-hour urine collection.

A management algorithm for nephrotoxicity and renal failure is provided in Annexure 20.

Hepatitis

Suspected drugs: Pyrazinamide, Ofloxacin, Ciprofloxacin, Ethambutol

Hepatitis refers to inflammation of the liver. Diverse causes include infection (viral, amoebic, etc), autoimmune disease, alcoholism, medications (including anti-tuberculosis drugs). For this reason, it is advisable to obtain serum liver tests at the start of treatment and at intervals during treatment for at-risk patients. Any signs and symptoms of hepatitis (including nausea, severe vomiting, scleralicterus, jaundice, dark urine, pale stool) merit immediate evaluation of liver function tests.

A history of prior hepatitis should be carefully analysed to determine the most likely causative agent(s); these should be avoided in future regimens.

Hepatitis is usually reversible upon discontinuation of the suspected agent.

A management algorithm for hepatitis is provided in Annexure 21.

Seizures

Suspected drugs: Cycloserine, Terizidone, Ofloxacin, Ciprofloxacin

The term seizure refers to a paroxysmal neurological dysfunction caused by abnormal electrical activity of the brain. While epilepsy describes the syndrome of recurrent episodes, a seizure may also occur as an isolated episode. Prompt identification of a seizure is essential for timely management, however, the spectrum of presentations is diverse and sometimes subtle. While convulsive seizures present with motor activity disturbances, other seizures may manifest as mere sensory or cognitive changes.

History of previous seizures is not a contraindication to the use of MDR tuberculosis treatment if seizures are well-controlled and/or the patient is receiving anti-convulsant therapy. The latter is usually

continued until MDR tuberculosis treatment is completed, or until the suspected agent has been discontinued.

The goals of seizure management are the stabilisation of the patient during an acute episode and prevention of seizure recurrence.

Seizure is not a permanent sequelae of MDR tuberculosis treatment.

A management algorithm for seizures is provided in Annexure 22.

Haemoptysis

Haemoptysis is the expectoration of blood originating from the larynx, trachea, bronchia or lungs. Because haemoptysis may present as anything from blood-streaked sputum to a large quantity of blood, it is essential to specify the quantity of blood loss and the period of time over which the loss occurred. During an episode of haemoptysis the blood pressure, heart rate and respiratory rate should be quickly obtained and documented. All patients who have a history of haemoptysis should have their blood type identified at the start of MDR tuberculosis treatment as blood transfusion may be required.

A management algorithm for haemoptysis is provided in Annexure 23.

Respiratory insufficiency

In patients with MDR tuberculosis the adjuvant use of corticosteroids has been shown not to increase mortality and can help alleviate the symptoms of severe respiratory insufficiency. There is no evidence that one corticosteroid is better than another. Prednisone is commonly given, starting at approximately 1mg/kg and gradually increasing the dose 10mg per week. However, in patients dependent on corticosteroids, stopping the prednisone abruptly can be dangerous.

Corticosteroids may also alleviate symptoms in patients with an exacerbation of obstructive pulmonary disease. In these cases, prednisone may be given in a short taper over one to two weeks, starting at approximately 1mg/kg and decreasing the dose by 5-10mg per day.

A management algorithm for respiratory insufficiency is provided in Annexure 24.

Hypokalemia

Hypokalemia signifies a low level of potassium in the blood (<3.5 meq/L). It can also be associated with other electrolyte abnormalities, such as hypomagnesemia. Persistent vomiting and diarrhea is a common cause of hypokalemia. Aminoglycosides cause renal wasting of potassium and magnesium. In most patients with MDR tuberculosis and hypokalemia the cause of the electrolyte abnormality is likely to be multifactorial. Because hypokalemia can occur without clinical signs and symptoms (ventricular fibrillation, excessive muscle weakness, suppressed muscle reflex) and can be life-threatening, it is recommended that potassium levels be checked every 3 to 6 months and if the patient has severe vomiting or diarrhea.

Normal values for potassium = 3.5 – 5.0 meq/L

Normal values for magnesium = 1.5 – 2.5 meq/L

A management algorithm for hypokalemia is provided in Annexure 25.

Anaphylaxis and allergic reactions

There are many types of adverse effects, but it is very important to promptly identify anaphylaxis. The anaphylactic response can be fatal and appears within minutes. Symptoms include: difficulty breathing (often with wheezing, shock, pruritis, urticaria (with or without angioedema), nausea, vomiting, cramps and diarrhea). Sometimes the patient can also present with fever, arthralgia (joint pain) and myalgias (muscle pain).

A management algorithm for anaphylaxis and allergic reactions is provided in Annexure 26.

THE ROLE OF SURGERY

The treatment of MDR tuberculosis is first and foremost chemotherapeutic. There are, however, limited indications for surgery; all presume that disease is mainly unilateral and that there is adequate cardiopulmonary reserve.

Definite 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.

Lesser indications

- In a patient who has undergone sputum conversion but the original profile of drug resistance is so great (ie. four or more drug resistance) 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 if at all feasible. The decision to perform surgery and the extent of surgery (lobectomy or pneumonectomy) should be made after anatomical localisation of disease by CT scan. Often the apex of a lower lobe is involved together with a corresponding upper lobe and the former should also be removed. Perfusion scans are useful in establishing how much functioning lung is likely to be removed. Basic spirometry (FEV1 and FVC) is adequate in assessing lung function in the majority of patients. The electrocardiogram is useful for excluding pulmonary hypertension which would contraindicate surgery.

The resected specimen 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-positive at the time of surgery the treatment should continue for 12 months after culture conversion.

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. There is no place for segmental/limited resection.

CONTACTS OF MDR TUBERCULOSIS PATIENTS

The effectiveness of preventive therapy in persons exposed to or infected with MDR tuberculosis organisms is not known. Factors which should be considered in the management of contacts include the likelihood of infection with MDR tuberculosis among contacts thought to be newly infected and the likelihood that the contact, if infected, will develop active tuberculosis. Contacts who have had exposure to a patient with MDR tuberculosis and are likely to be newly-infected should be evaluated to assess the likelihood of the actual infection being an MDR strain of *M. tuberculosis*.

Factors that should be considered include:

- the infectiousness of the MDR tuberculosis source case;
- the closeness and intensity of the exposure;
- the likelihood of exposure to persons with drug-susceptible tuberculosis.

Infectiousness of the source case

Tuberculosis patients (including MDR cases) who cough and have smear-positive sputum are substantially more infectious than those do not cough or who have smear-negative sputum.

Closeness and intensity of MDR tuberculosis exposure

Persons who share air space with an MDR tuberculosis patient for a prolonged time (eg. a household member, hospital room mate) are at higher risk for infection than those with a brief exposure. Further, exposure in a small, enclosed, poorly-ventilated space is more likely to result in transmission than exposure in a large, well-ventilated space. Finally, exposure during cough-inducing procedures (eg. sputum induction, bronchoscopy) may greatly enhance transmission.

Contact history

Persons exposed to several sources of *M. tuberculosis*, including infectious tuberculosis patients with drug-susceptible strains, are less likely to become infected with an MDR tuberculosis case.

Recentness of infection also contributes to the risk of developing active tuberculosis: Persons with recently acquired *M. tuberculosis* infection are at relatively high risk of developing active disease: in immunocompetent persons, the risk of developing tuberculosis is highest within the first two years following infection, after which this risk declines markedly. In general, 5%-10% of infected immunocompetent persons will develop active disease within the first two years. Child contacts of MDR tuberculosis patients (especially those under two years of age) are therefore at increased risk.

The most potent factor, however, that increases the probability that a person infected with MDR tuberculosis will develop active disease is impaired immunity. Impaired immunity is increasingly seen in persons infected with HIV. It should be remembered, however, that there are many other medical causes of impaired immunity, including malnutrition, some congenital syndromes, certain haematological diseases, and endocrine, or renal disease (notably diabetes mellitus). In addition, patients who are receiving immunosuppressive drugs (steroids, anti-cancer chemotherapy) or radiation therapy may also be at increased risk.

Management of contacts of MDR tuberculosis patients

- Manage contacts of sputum smear-*negative* MDR tuberculosis patients according to the standard recommendations for infected contacts of drug-susceptible tuberculosis patients;
- Identify contacts of sputum smear-*positive* MDR tuberculosis cases rapidly;
- Child contacts aged five years and younger should be placed on preventive therapy irrespective of state of health and tuberculin response. In the absence of information on the effectiveness of preventive therapy for MDR tuberculosis the national guidelines for contacts of susceptible tuberculosis cases apply;
- In children older than five years as well as in adult contacts, a strongly reactive tuberculin test indicates infection but not necessarily disease. The decision to start these persons on treatment depends on clinical history, examination and investigation. Routine preventive therapy in contacts is not considered appropriate. Patients should report the first signs of possible tuberculosis and a careful risk assessment should be made. Sputum should be sent for smear, culture and drug susceptibility testing. A chest X-ray should also be done. Presumptive MDR tuberculosis treatment should be avoided. Contacts who are HIV-positive should be followed up three-monthly and encouraged to report symptoms and signs as soon as they become evident.

HEALTH CARE WORKERS AND MDR TUBERCULOSIS

Transmission of tuberculosis

Transmission of tuberculosis, including MDR tuberculosis, is a recognised risk for health care workers (HCWs). In addition, persons with HIV are at greater risk for disease as evidenced by explosive and lethal outbreaks of MDR tuberculosis in HIV-infected patients and HCWs in hospital environments elsewhere in the world.

The infectious source of *M. tuberculosis* (and by implication also MDR tuberculosis) is mainly adults with pulmonary disease, especially where cavitation is present. Infective particles are usually derived from moist particles discharged into the air by forced expiration through the mouth and nose, eg. coughing, sneezing, spitting or by procedures liberating aerosols. Once aerosolised materials dry out to form droplet nuclei about 1-5 µm in size, infective particles are formed. Droplet nuclei remain airborne and are inhaled and trapped in resident lung alveolar macrophages, where they initiate infection.

The risk for an individual of becoming infected with tubercle bacilli depends on the concentration of organisms in the source case, the duration of exposure to air contaminated with tubercle bacilli and the aerodynamics of the droplet nuclei: Patients with infectious tuberculosis may have between 10^7 and 10^8 organisms in a cavitating lesion. A 10 µm droplet nucleus may carry three to ten tubercle bacilli. In indoor environments, droplet nuclei can remain suspended in the air for long periods of time, unless they are removed by ventilation or filtration. Virtually all transmission occurs in enclosed environments. The infective dose is very low and may constitute fewer than 10 tubercle bacilli. Only about 6% of inhaled organisms reach the lung alveoli; the majority of inhaled particles settle in the upper respiratory track and are expelled or harmlessly swallowed and digested. The probability of a person becoming infected during a one-hour exposure period has been estimated to range from 1 in 600 (0.2%) to 1 in 4 (25%).

Contaminated clothing, bedding, eating utensils, books etc. are not involved in the spread of tuberculosis infection and need no special attention. Infection rarely occurs when bacilli are introduced through the skin. This is occasionally seen among pathologists and laboratory workers handling infected specimens. Human sputum is, however by far, the most important source of infection and other infected body fluids present no practical risk to the majority of HCWs.

Contact therefore does not mean infection.

Pathogenesis of tuberculosis

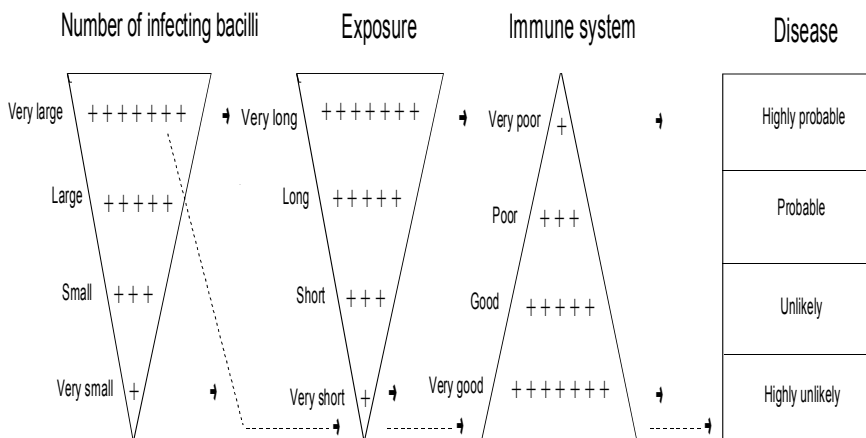
It is useful to understand the pathogenesis of tuberculosis, in order to understand the risk: Most people do not develop tuberculosis disease following infection, since specific cell-mediated immunity usually develops within two to ten weeks after the initial infection. In most cases, his/her immunity

arrests multiplication and averts clinical disease. In immunocompetent persons who are exposed to infectious tuberculosis for a prolonged period (hours or days rather than minutes), 20% to 50% may become infected. In 90% of infected individuals the organisms become dormant and cause no clinical disease. 5% may develop early tuberculosis (usually within two years after infection). A further 5% may develop disease at some point during their lifetime, usually as a result of physical or emotional stress that adversely affects the immune system. Infection with HIV is presently the most important risk factor for developing disease following infection. HIV kills T-helper cells (T4 lymphocytes), which reduces the infected individual's defence against *M. tuberculosis*. HIV infection therefore increases the risk of reactivation of dormant tuberculosis infection, as well as the risk of progressive disease following new infection.

The relationship between tuberculosis infection and disease and the associated risk factors are illustrated in Figure 1. Putting the risk into perspective means that, for the establishment of a tuberculosis infection sufficient to produce tuberculosis disease, exposure must be close and prolonged, the environment heavily laden with infectious droplet nuclei and the prospective host unprotected by his/her own immune mechanisms. Over-crowded living conditions with poor housing and sanitation increase the ease of transmission of *infection*, while factors adversely affecting the immune status of individuals (eg. HIV, alcohol abuse, diabetes, cancer) increase the likelihood of the development of *disease*. The declining cellular immunity caused by HIV is also associated with reactivation of old, endogenous tuberculosis foci and increases susceptibility to new tuberculosis infection.

Infection therefore does not mean disease.

Figure 1: Probability of developing tuberculosis disease following infection: Influence of the number of infecting bacilli, the duration of exposure and the competence of the individual's immune system



Risk assessment

It has been well established that the risk of infection with tuberculosis depends on the severity of disease in the source case and on prolonged, intensive exposure to this case. It follows, therefore,

that all HCWs are not at equal risk of acquiring infection, and that for many cadres of HCWs the risk is almost equal to that of the general community. The following categories of risk may be surmised:

High risk

1. HCWs in *prolonged close* contact with infectious (smear-positive) MDR tuberculosis cases, eg. nursing staff and other medical staff in MDR tuberculosis wards/centres;
2. HCWs involved in aerosol-producing procedures, eg. pulmonary physicians, respiratory technicians and other medical staff performing bronchoscopy, sputum induction, tracheal intubation, aerosolised pentamidine therapy and autopsy procedures;
3. HCWs who are HIV-positive 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.

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

- HCWs should receive ongoing education and training on the transmission and pathogenesis of tuberculosis and the consequences of MDR tuberculosis.
- The importance of a continuous awareness of risk situations and their avoidance should be stressed.
- HCWs should be informed about the increased risk of acquiring tuberculosis (and MDR disease) should they become HIV positive. Confidential HIV testing should be standard practice and alternative employment should be offered to those testing HIV positive.

- Universal infection control procedures should be implemented in all health care facilities, including safe waste disposal.
- Coughing behaviour should be strictly controlled. Sputum collection is especially dangerous. Patients who are coughing should be isolated as far as possible. In clinics and outpatient settings, these patients should not be allowed to sit in waiting rooms for any length of time. Consideration should be given to setting up an adult cough clinic at hospitals where patients can be rapidly assessed, entered into a cough register for proper follow-up and encouraged to come for re-evaluation.
- Inpatients who are coughing should be in a single ward with good outside ventilation and large windows if at all possible. They should be nursed with the door shut and the windows open as far as possible if the ward is not under negative pressure.

In high risk environments only, the following additional principles apply:

Disease monitoring programme for HCWs

Health care workers should be encouraged to report the first symptoms and signs of tuberculosis disease (tiredness, weight loss, persistent cough and loss of appetite). These symptoms tend to come on gradually and may be passed off as flu or stress. Many health workers have put off being investigated until the disease has caused permanent lung damage. Health workers should encourage colleagues to report at the first suspicion. Two sputum specimens, collected on successive days, should be investigated for tuberculosis by microscopy and culture.

Each HCW should have a confidential disease monitoring file in which screening procedures for tuberculosis as well as other health-related data are recorded. The elements of a disease monitoring programme include the following:

Employment profiles and baseline screening of employees

A standardised health questionnaire should be completed for each employee for purposes of compensation. This questionnaire should relate past tuberculosis disease. BCG vaccination status, underlying medical conditions which may increase susceptibility of HCWs to tuberculosis and previous contact with confirmed tuberculosis cases. A baseline chest x-ray and a Mantoux tuberculin skin test (TST) should be performed.

A baseline blood serum sample should be collected and stored untested. The taking of such specimens should be optional but may be useful should improved serum testing for tuberculosis become available. These samples could also be tested for HIV antibodies or hepatitis B, at the request of the employee after counseling. HCWs should be made aware of the serious consequences which may occur in HIV positive individuals who become infected with MDR tuberculosis strains.

Annual screening for those who continue to work in high risk situations

HCWs should be offered an annual full size x-ray examination for evidence of recent tuberculosis disease. Individuals exhibiting changes on serial examination or recent skin test converters should be evaluated for tuberculosis, both clinically and microbiologically.

HCWs with TST reactions of <10mm should be re-tested. Strongly positive reactors with skin test diameters of >15 mm should be evaluated clinically and microbiologically.

Quarterly record of health status in high risk situations

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, anorexia, night sweats and the frequent occurrence of colds or other respiratory infection episodes in recent weeks.

The HCW's weight should be recorded quarterly and an unexplained loss of 10% or more of body weight during the previous quarter should be followed up with clinical and microbiological investigations for tuberculosis. Quarterly information on health status can be obtained by using a simple structured questionnaire.

Post-exposure monitoring

If any HCW has been exposed to an infectious MDR patient for more than two hours or to aerosolised infected material (eg. 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.

Preventive measures in medium to high risk situations

The prevention of MDR tuberculosis focuses on both the infectious patient (or infected material) and on the HCW who is at risk of becoming infected.

All patients should be instructed to cover their mouths and noses with gauze or a tissue during coughing and other forms of forced expiration. Wearing an ordinary surgical mask is another option to prevent widespread droplet dispersal. Immediately 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, a synthetic phenolic such as 2% Hycolin or 5% concentrations of an iodine-containing solution or a hypochlorite solution containing 10 000 ppm active chlorine should be used for disinfection and disposal.

HCW's should wear especially designed masks (particulate respirators) which are impermeable to droplet nuclei when nursing patients or collecting sputum. An industrial mask with a 1µm particle size

and a filter efficiency of more than 95% is recommended (3M Health Care 1860 Particulate Respirator Type N95 or equivalent). These masks should be discarded after eight hours of use.

Collection of sputum specimens should take place if at all possible in the open air on the sunny side of the ward. A special veranda should be built for this purpose. The correct procedure for sputum collection has been described in the Practical Guidelines of the National Tuberculosis Control Programme. These must be read carefully and followed to decrease the risk for everyone in that area.

Worker's compensation

Relevant legislation dealing with contamination by any infectious substance includes the Occupational Health and Safety Act (Act 85 of 1993) and the Compensation for Occupational Injuries and Diseases Act (Act 130 of 1993). All HCWs are covered by these Acts, with compensation provided at an amount determined by the Compensation Commissioner.

Tuberculosis and infections by mycobacteria other than *M. tuberculosis* (MOTTs) are covered by the Act, but employees have to keep records of baseline and follow-up procedures in order to show that infections were acquired during the course of duties carrying a risk of contracting these infections. Compensation under the Act is payable whether or not there was negligence on the part of the employer. The right to compensation shall lapse if the Commissioner is not informed within 12 months from the start of the disease. It should be noted that HCWs may acquire subclinical tuberculosis infection (as shown by TST conversion) and may only become ill with reactivation tuberculosis many years later. These cases are also covered by the Act, subject to proof that the initial infection was acquired in the workplace.

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 willful misconduct or neglect of either the HCW or the employer could be proven.