MULTIDRUG-RESISTANT TUBERCULOSIS

Despite highly effective drugs and disease control strategies, morbidity and mortality due to Mycobacterium tuberculosis *are rising worldwide, being fuelled in many countries by widespread HIV epidemics.*

KARIN WEYER

DSc (Microbiology)

Director

Unit for Tuberculosis Operational & Policy Research
Medical Research Council
Pretoria

Karin Weyer has been involved in tuberculosis research for 22 years. Research experience covers basic (laboratory-based), clinical and epidemiological activities. Current interests include multidrug-resistant tuberculosis (MDR-TB) and HIV-associated tuberculosis, particularly related to national and international evidence-based policy. She is the author of several scientific papers and international policy documents, and serves on various international tuberculosis expert committees.

Although the vast majority of TB cases worldwide are drug susceptible, multidrug-resistant TB (MDR-TB) is an emerging threat to TB control, having been found in all countries surveyed.[1] MDR-TB strains are, by definition, resistant to the two most potent anti-TB drugs (isoniazid and rifampicin), making MDR-TB much more difficult and expensive to treat.

MDR-TB is a man-made phenomenon, almost always due to inadequate therapy. Although patient non-adherence is often thought to be the most common cause of drug resistance, many studies have shown that organisational failure of TB control programmes, lack of available drugs, and clinical error are responsible for much of the MDR-TB problem existing today. Human error resulting in inadequate therapy includes incorrect drug prescription, lack of patient education and supervision, and patient non-adherence to treatment. Common clinical errors include addition of a single drug to a failing regimen, inadequate primary regimens, failure to recognise existing drug resistance, failure to provide directly observed therapy and failure to manage non-adherence.

Sound TB control based on the directly observed therapy – short course (DOTS) strategy of the World Health Organization (WHO) is a top priority in public health, with the focus of DOTS programmes on cure of infectious TB patients and prevention of drug resistance. The DOTS strategy on its own is, however, not effective to treat patients with MDR-TB. Recognising that MDR-TB poses a considerable risk to public health, WHO now recommends that established DOTS programmes consider implementation of MDR-TB treatment using second-line reserve drugs through so-called 'DOTS-Plus' programmes.[2] South Africa currently has one of the largest DOTS-Plus programmes in the world, implemented in 2001 by the National TB Control Programme (TBCP) of the Department of Health and encompassing a standardised approach to MDR-TB management through dedicated provincial MDR-TB centres.[3]

Although the term MDR-TB has been used to describe resistance to any two or more anti-TB drugs, the correct definition is *resistance to at least isoniazid and rifampicin*. MDR-TB is always a laboratory diagnosis, requiring *in vitro* confirmation of bacterial resistance. MDR-TB most often occurs in chronic patients, i.e. those who had received multiple courses of first-line TB treatment and remain sputum-positive. To a lesser extent, MDR-TB may also occur in patients who fail a single course of (observed) first-line treatment. Exceptionally, MDR-TB occurs in patients who have never taken anti-TB drugs.

MDR-TB is not the same as disease due to non-tuberculous mycobacteria (NTM). The latter are commonly resistant to both isoniazid and rifampicin and are sometimes confused with MDR-TB. Treatment of NTM is even more complicated, requiring mycobacterial species identification and selection of multiple drugs to which a specific isolate has been shown to be susceptible. NTM are often contaminants in sputum and are clinically significant only if repeated isolation shows

the same organism, supported by clinical and radiographic presentation.

EPIDEMIOLOGY

Outbreaks of MDR-TB in different regions of the world and reports of increasing numbers of MDR-TB cases prompted worldwide surveillance by WHO since 1994. Three global surveys covering 106 countries and more than 250 000 patients have been completed,[1] showing MDR-TB to be ubiquitous. The public health threat of MDR-TB is particularly evident in Eastern Europe and the Russian Federation, where rates in retreatment patients exceed 50%.[1] Although median values for global MDR-TB levels are low at 1% in new patients and 7% in retreatment patients,[1] the overall burden is considerable at an estimated 185 000 – 414 000 cases.[4] MDR-TB rates in Africa are among the lowest recorded globally, being ascribed to the late introduction of rifampicin and its limited use in TB control programmes.[1]

Patients with MDR-TB have been diagnosed in all provinces of South Africa since the mid-eighties. A recent national survey by the Medical Research Council indicated an overall MDR-TB prevalence of 2.9%, arising from 1.6% of new TB cases and 6.6% of previously treated cases.[5] Given the high TB burden, these relatively low prevalence levels translate into a high burden of at least 6 000 MDR-TB cases estimated per year.[5] The economic burden of the MDR-TB epidemic is already severe, given that a case of MDR-TB costs up to 100 times more to treat than an uncomplicated drug-susceptible case. Furthermore, suboptimal TB control, together with the rapidly progressing HIV epidemic, creates a fertile environment for transmission of MDR-TB. Epidemiological and genetic studies have confirmed ongoing transmission of drug-resistant TB.[6,7] Nosocomial transmission of MDR-TB associated with HIV infection has been documented,[8] while HIV-positive patients being treated in hospital for drug-susceptible TB have been re-infected with MDR strains (with 100% case fatality).[9] There is ample reason, therefore, to believe that the full brunt of MDR-TB still has to be faced in South Africa.

DEVELOPMENT OF MDR-TB

M. tuberculosis undergoes spontaneous, slow but constant mutation, resulting in resistant mutant organisms. This natural phenomenon varies for different anti-TB drugs and is genetically determined. Anti-TB drugs therefore constitute a two-edged sword — while they destroy TB bacilli, they also select for organisms that are naturally resistant. Selection of these mutants is greatly facilitated by inadequate treatment, with susceptible bacilli being killed rapidly and resistant mutants being selected over time. Chromosomal location of bacterial resistance to the different drugs is not linked and spontaneously occurring MDR mutants are extremely rare. A high bacterial load and several cycles of inappropriate treatment are therefore needed for significant numbers of MDR-TB bacilli to emerge (acquired MDR). These strains can also be transmitted to individuals who have never before had TB and they can present with MDR-TB (primary MDR).

DIAGNOSIS OF MDR-TB

MDR-TB should be suspected in patients with persistently positive acid-fast bacilli (AFB) smears or cultures despite adequate treatment adherence. MDR-TB should also be suspected in close contacts of MDR-TB patients, particularly those who are immune-compromised. MDR-TB can, however, only be diagnosed by *in vitro* confirmation of resistance. Inadequate clinical response in an adherent patient is often supported by a positive smear at 2/3 months, which should prompt a request for culture and drug susceptibility testing (DST) against isoniazid, rifampicin and ethambutol (results for ethambutol guiding the appropriate standardised MDR-TB regimen: see later). If sputum remains positive at the end of treatment or the patient does not show adequate clinical response, culture and DST should also be done. Laboratory confirmation of MDR-TB should always be awaited. *Never add a single drug to an apparently failing regimen.* Close contacts of an MDR-TB patient should have sputa investigated by culture and DST as soon as possible, particularly if TB signs and symptoms are present.

Clinical presentation of patients with MDR-TB is identical to that of patients with drug-susceptible disease, and radiological features are indistinguishable. The diagnosis of MDR-TB is critically dependent on the quality of laboratory methodology. DST for TB drugs is a complicated procedure and errors are not uncommon. A single laboratory report of MDR-TB without supporting clinical evidence should therefore be treated with caution and follow-up investigations requested. A diagnosis of MDR-TB carries very serious consequences and should only be made by (or at the very least in consultation with) a clinician experienced in managing MDR-TB patients. These patients must be referred to a provincial MDR-TB treatment centre for initial work-up, access to treatment and registration. Full details are available from the provincial or national TBCP.[3]

TREATMENT

Management principles

Treatment of MDR-TB involves second-line, reserve drugs that are much more expensive, more toxic and less effective than first-line TB drugs. Patients with MDR-TB face the prospect of lengthy and often unpleasant treatment as well as the real possibility of premature death. Therefore, counselling and emotional support are particularly important, much as in any other chronic life-threatening illness.

The standardised approach to DOTS-Plus in SA comprises the following:

- Treatment at dedicated MDR-TB referral facilities. Patients should be admitted for at least the first 4 months of therapy or preferably until sputum conversion, defined as two consecutive negative cultures,

Table I. **Ranking of available drugs for treatment of MDR-TB**[11]

Rank	Drugs	Activity	Dosage (daily)			Acceptability
			Average	Minimum	Maximum	
1	Aminoglycosides					
	Streptomycin	Bactericidal	15 mg/kg	750 mg	1 000 mg	Injection
	Kanamycin	(actively multiplying	15 mg/kg	750 mg	1 000 mg	Injection (painful)
	Amikacin	organisms)	15 mg/kg	750 mg	1 000 mg	Injection (painful)
	Capreomycin		15 mg/kg	750 mg	1 000 mg	Injection
2	Thioamides		10 - 20 mg/kg	500 mg	750 mg	
	Ethionamide	Bactericidal	10 - 20 mg/kg	500 mg	750 mg	Good
	Prothionamide*		10 - 20 mg/kg	500 mg	750 mg	Good
3	Pyrazinamide	Bactericidal (acid pH)	20 - 30 mg/kg	1 200 mg	1 600 mg	Good
4	Fluoroquinolones					
	Ofloxacin	Weakly bactericidal	7.5 - 15 mg/kg	600 mg	800 mg	Good
	Ciprofloxacin	Weakly bactericidal	7.5 - 15 mg/kg	1 000 mg	1 500 mg	Good
5	Ethambutol	Bacteriostatic	15 - 20 mg/kg	1 000 mg	1 200 mg	Good
6	Terizidone	Bacteriostatic	15 - 20 mg/kg	500 mg	750 mg	Good
	Cycloserine	Bacteriostatic	10 - 20 mg/kg	500 mg	750 mg	Good
7	PAS*	Bacteriostatic	10 - 12 g	10 g	12 g	Bad (bulk, taste)

* Not available in South Africa.

at least 30 days apart.[10] Discharge planning during this time involves arrangements for treatment at designated clinics, with supply of the required drugs on a patient-named basis.

- Specialised teams overseeing all aspects of MDR-TB management at the referral centres.
- A standardised treatment regimen, based on the ethambutol resistance profile of the diagnostic strain, with drug administration standardised across three patient weight bands (see later).
- Regular monitoring of patients during treatment, involving extensive documentation. All MDR-TB patients must be registered in the DOTS-Plus Electronic Register at the MDR-TB referral centres. This database contains all information necessary for patient management and follow-up, drug adverse effect monitoring, and final treatment outcomes. It also serves as the formal notification and registration system for MDR-TB in SA.
- Ambulatory treatment after discharge, provided that directly observed treatment is ensured.
- Patient follow-up for 5 years after treatment completion. Six-monthly visits are required to assess symptoms and signs of recurrence.

Treatment principles

First-line TB drugs (isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin) are the mainstay of modern treatment given their high efficacy, low toxicity and low cost. Second-line TB drugs are not typically used in the treatment of drug-susceptible disease, having less effective anti-TB activity and increased toxicity, while also being much more expensive.

Design of MDR-TB regimens poses several challenges, complicated by a limited choice of second-line agents. The use of multiple drugs is imperative to avoid amplification of resistance. Available MDR-TB drugs have been ranked according to efficacy, toxicity and tolerability and are summarised in Table I. Drugs from the highest ranking groups are used to optimise efficacy; however, due to cross-resistance only one drug from a particular group can be selected. Because of the limited number of drugs available, pyrazinamide and ethambutol are used again in second-line TB treatment. Resistance to pyrazinamide is neither easy to acquire nor to prove by DST. Ethambutol resistance prevalence in SA is less than 3% overall, and more than 60% of MDR-TB patients have strains that are still ethambutol susceptible.[5]

Other oral medications (sometimes referred to as 'third-line' drugs) that have been used for treatment of MDR-TB include thioacetazone, clofazimine, amoxicillin-clavulanate, macrolides (clarithromycin and azithromycin) and other rifamycin agents (rifabutin and rifapentine). Thioacetazone has been associated with the development of erythema multiforme in HIV-infected TB patients and is no longer recommended. Clofazimine, an antileprosy drug, has *in vitro* activity against *M. tuberculosis* but no clinical efficacy has been proven. Amoxycillin-clavulanate and the macrolides have high minimal inhibitory concentrations for most strains of *M. tuberculosis* relative to achievable serum concentrations, but clinical efficacy has again not been proven. Rifabutin exhibits cross-resistance with rifampicin in up to 80% of

patients, while rifapentine has complete cross-resistance with rifampicin. None of the aforementioned drugs are therefore recommended for routine MDR-TB treatment. They are, however, used as salvage drugs as a last resort in patients failing conventional MDR-TB therapy. Novel therapies currently under investigation include new-generation fluoroquinolones (moxifloxacin and gatifloxacin), inhaled aminoglycosides, oxazolidinones (linezolid), nitroimidazopyrans (PA-824) and inhaled gamma interferon. Although a few show promising results in animal models (notably PA-824), clinical studies have not yet been done.

Standardised treatment regimen

A major problem with the design of MDR-TB treatment regimens relates to inherent problems in DST of the second-line drugs. Methodology is not standardised, drug powders are highly unstable and available techniques provide variable results, even on repeat testing of the same strain. Treatment based on individual DST patterns therefore requires sophisticated laboratory support, and initiation is often delayed due to methodological problems. Clinical expertise is another problem, as previous DST patterns and treatment details need to be meticulously analysed and regimens designed within the constraints of limited drug choices as described above.

Countries where second-line drugs have been used extensively invariably have high resistance levels, making the use of individualised regimens unavoidable. Second-line drugs have not previously been used for treatment of TB in SA and current availability is restricted to treatment for MDR-TB. Drug resistance is therefore almost non-existent, greatly facilitating the implementation of a standardised approach, not requiring second-line DST results or individualised patient regimens.

The standardised treatment regimen used in SA has been designed from the highest-ranking drug categories. Ethambutol resistance of the diagnostic strain determines its use: The regimen consists of a 4-month daily intensive phase with five drugs (kanamycin, pyrazinamide, ofloxacin, ethionamide and either terizidone or ethambutol), followed by a 12 - 18-month daily continuation phase with three drugs (ofloxacin, ethionamide and either ethambutol or terizidone), as outlined in Table II. Administration is simplified across three patient weight bands to accommodate the limited formulations available in SA while complying with international requirements for minimum, maximum and average dose per kilogram. Drug dose is adjusted as patients gain (or lose) weight. The continuation phase may be shortened provided that 12 months of treatment is given after culture conversion.

Treatment must be given under direct observation on at least 5 days a week. Patients must receive a minimum of 16 months' treatment (4 months of intensive and at least 12 months of continuation phase therapy, based on culture conversion) and must complete the full course. Short interruptions of treatment must be corrected by adding the number of drug doses missed.

Outcomes of treatment for the first cohort of MDR-TB patients treated with the standardised regimen in SA showed high culture conversion rates (79%), indicating good potential for eventual cure. Treatment was successful in 90% of patients who remained on the regimen, confirming excellent efficacy; however, high default rates (30%) after discharge from hospital reduced overall DOTS-Plus effectiveness to around 50%[12]. Risk factor analysis showed that default was not associated with the regimen but with patient perception of negative health care provider attitude, indicating the need for effective, patient-orientated case holding strategies.[13]

Ancillary treatment

Pyridoxine 150 mg/day is given as adjuvant therapy with terizidone to prevent neurological toxicity, and may be increased to 300 mg/day when drug-related adverse effects are experienced.

Headache is a frequent adverse effect of MDR-TB treatment; however, other causes should always be ruled out. Codeine with acetaminophen relieves mild to moderate pain and helps control cough. Stronger analgesics should be used as appropriate.

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

Adjuvant use of corticosteroids in patients on MDR-TB treatment can help alleviate symptoms associated with severe respiratory insufficiency and has not been associated with increased mortality.[14] Prednisone is recommended, starting at 1 mg/kg and gradually decreasing the dose by 10 mg per week. Corticosteroids may also alleviate symptoms in patients with exacerbation of obstructive pulmonary disease. In these cases, prednisone may be given over 1 - 2 weeks, starting at approximately 1 mg/kg and decreasing the dose by 5 - 10 mg per day.

Oxygen is indicated in patients with a pO_2 < 55 mmHg or O_2Sat < 89%, and should be titrated to raise the O_2Sat to more than 90%.[3] Oxygen is usually started at 2 - 4 l/min via nasal cannula. If more than 5 l/min is needed, the oxygen should be delivered through a mask. Retention of CO_2 can occur in some patients and should be checked when starting oxygen or increasing oxygen delivery.

PATIENT EVALUATION AND MONITORING

Documentation

The DOTS-Plus programme contains standardised forms (available from the MDR-TB referral centres) to ensure that all relevant data are collected. These forms encompass international standards of care for MDR-TB patients and ensure compliance with international DOTS-Plus requirements.[2,3]

Table II. **Standardised regimen for treatment of MDR-TB in South Africa**

Patient weight	Drug	Dosage
Intensive phase: 4 months (daily)		
< 50 kg	Kanamycin	750 mg
	Ethionamide	500 mg
	Pyrazinamide	1 000 mg
	Ofloxacin	600 mg
	Ethambutol	800 mg
	or	
	Terizidone*	750 mg
50 - 65 kg	Kanamycin	1 000 mg
	Ethionamide	750 mg
	Pyrazinamide	1 500 mg
	Ofloxacin	600 mg
	Ethambutol	1 200 mg
	or	
	Terizidone*	750 mg
> 65 kg	Kanamycin	1 000 mg
	Ethionamide	750 mg
	Pyrazinamide	2 000 mg
	Ofloxacin	800 mg
	Ethambutol	1 200 mg
	or	
	Terizidone*	750 mg
Continuation phase: 12 - 18 months (daily), depending on culture conversion		
< 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	1 200 mg
	or	
	Terizidone*	750 mg
> 65 kg	Ethionamide	750 mg
	Ofloxacin	800 mg
	Ethambutol	1 200 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 (B_6) 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.

Table III. **Common drug adverse reactions and strategies for management[2]**

Adverse reaction	Suspected agent(s)	Management	Comments
Seizures	Cy, Te Of, Ci	Rule out other likely causes Treat any suspected causes Initiate anticonvulsant therapy (e.g. phenytoin 3 - 5 mg/kg/day; valproic acid 750 - 1 250 mg/kg/day; carbamazepine 600 - 1 200 mg/day; phenobarbitol 60 -120 mg/kg/day) Increase pyridoxine to 300 mg daily Lower dose of suspected agent Discontinue suspected agent	Clinical evaluation generally sufficient unless suspicion high for infectious, malignant, vascular or metabolic cause Anticonvulsant generally continued until MDR-TB treatment completed or suspected agent discontinued History of prior seizure disorder not a contraindication to the use of agents listed here if patient's seizures are well controlled and/or patient is receiving anticonvulsant therapy Patients with history of prior seizures may be at increased risk for development of seizures during MDR-TB therapy Seizures not a permanent sequelae of MDR-TB treatment
Peripheral neuropathy	Cy, Te, Ka, Am, E, Of, Ci	Increase pyridoxine to 300 mg daily Begin exercise regimen, focusing on affected regions Initiate therapy with tricyclic antidepressant drugs Lower dose of suspected agent Discontinue suspected agent Initiate therapy with gabapentin (300 mg QHS; increase by 600 mg every 3 - 7 days; max dose 1 200 tid)	Patients with co-morbid disease (e.g. diabetes, HIV, alcoholism) more likely to develop peripheral neuropathy, but these conditions are not contraindications to the use of the agents listed here Neuropathy is generally not reversible, although only a minority (approximately 10%) of patients require continued intervention to keep symptoms controlled once MDR-TB treatment completed
Hearing loss	Ka, Am	Consider administration 3x per week Lower dose of suspected agent Discontinue suspected agent	Patients with prior exposure to aminoglycosides may have baseline hearing loss Hearing loss is generally not reversible
Psychosis	Cy, Te, Of, Ci, Et	Initiate antipsychotic drugs (e.g. risperidone 0.5 - 2 mg po bid; haloperidol 1 - 5 mg po IV or IM repeated every hour as needed) Hold suspected agent for short period of time (1 - 4 weeks) while psychotic symptoms brought under control Lower dose of suspected agent Discontinue suspected agent	Some patients will need to continue antipsychotic treatment throughout MDR-TB therapy Prior history of psychiatric disease not a contraindication to the use of agents listed here but may increase the likelihood of development of psychotic symptoms Psychotic symptoms generally reversible upon MDR-TB treatment completion or discontinuation of offending agent
Depression	Cy, Te, Of, Ci, Et	Rule out side-effects of concomitant medications, e.g. amoxycillin-clavulanate, penicillin, benzodiazepines Institute psychological therapy Group or individual supportive counselling Initiate antidepressant drugs (e.g. amitriptyline, nortriptyline, fluoxetine, sertraline), but use with caution when history of convulsions Increase pyridoxine to 300 mg daily Consider anti-psychotics Lower dose of suspected agent Discontinue suspected agent	Importance of socioeconomic conditions should not be underestimated as contributing factor to depression Depression and depressive symptoms may fluctuate during therapy History of prior depression is not a contraindication to the use of the agents listed here; however, these patients may be at increased risk for developing depression during MDR-TB treatment

Table III. **Common drug adverse reactions and strategies for management[2] (continued)**

Adverse reaction	Suspected agent(s)	Management	Comments
Nausea and vomiting	Et (most common), Of, Ci, E	Rehydration Initiate anti-emetics 30 min prior to MDR-TB drugs Administer Et in 3 separate doses Administer Et at night with short-acting benzodiazepine Lower dose of suspected agent Discontinue suspected agent	Nausea and vomiting ubiquitous in early weeks of therapy and usually abate with supportive therapy Electrolytes should be monitored and repleted if vomiting severe Reversible upon discontinuation of suspected agent
Gastritis	Et, E, Z	Administer MDR-TB medications with small amount of food Avoid caffeine, cigarettes Antacids (e.g. calcium carbonate, aluminium hydroxide, magnesium-hydroxide) H_2-blockers (e.g. cimetidine, ranitidine), proton-pump inhibitors (e.g. omeprazole) Hold suspected agent(s) for short periods of time (e.g. 1 - 7 days) Lower dose of suspected agent Discontinue suspected agent	Severe gastritis possible, as manifest by haematemesis, melaena or hematechezia Dosing of antacids should be carefully timed so as not to interfere with the absorption of MDR-TB drugs Take fluoroquinolones at least 3 hours apart from antacids Reversible upon discontinuation of suspected agent(s)
Hepatitis	Z, Of, Ci, E	Stop therapy Rule out other potential causes of hepatitis Re-introduce drugs individually while monitoring liver function, with most likely agent introduced first Monitor liver function every 1 - 2 months	History of prior hepatitis should be carefully analysed to determine most likely causative agent(s); these should be avoided in future regimens Generally reversible upon discontinuation of suspected agent
Nephrotoxicity and renal failure	Km, Am	Follow serum urea and creatinine, treat symptoms Reduce dose of medication according to creatinine clearance Discontinue suspected agent	History of diabetes or renal disease not a contraindication to the use of the agents listed here, although patients with co-morbidities may be at increased risk for developing renal failure Renal impairment may be permanent
Optic neuritis	E	Stop agent	
Arthralgias	Z, Of, Ci	Initiate therapy with non-steroidal anti-inflammatory drugs Initiate exercise regimen Lower dose of suspected agent Discontinue suspected agent	Symptoms of arthralgia generally 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 (e.g. allopurinol, colchicines) is of no proven benefit in these patients
Hypokalaemia	Ka, Am	Replete potassium orally or IV Treat associated vomiting or diarrhoea Check magnesium levels if potassium levels do not improve Discontinue arrhythmagenic medications (e.g. digoxin, amitriptyline, cisapride, haloperidol) Discontinue aminoglycocides if severe	Hypokalaemia can occur within clinical signs and symptoms and may be life-threatening

Cy = cycloserine; Te = terizidone; Et = ethionamide; E = ethambutol; Ka = kanamycin; Am = amikacin; Of = ofloxacin; Ci = ciprofloxacin; Z = pyrazinamide.

MDR-TB is a man-made phenomenon, almost always due to inadequate therapy.

Common clinical errors include addition of a single drug to a failing regimen, inadequate primary regimens, failure to recognise existing drug resistance, failure to provide directly-observed therapy and failure to manage non-adherence.

Although the term MDR-TB has been used to describe resistance to any two or more anti-TB drugs, the correct definition is resistance to at least isoniazid and rifampicin.

MDR-TB should be suspected in patients with persistently positive acid-fast bacilli (AFB) smears or cultures despite adequate treatment adherence.

Never add a single drug to an apparently failing regimen.

Management approach

A standardised but comprehensive approach to patient evaluation and monitoring is followed, as outlined in Fig. 1. Full medical, social and psychiatric history should be recorded, as well as current medications, substance use and allergies. Prompt detection of co-morbidities is required as these may affect treatment tolerance.

Treatment progress is monitored by monthly AFB smear and mycobacterial culture. Patients who fail to convert after 9 months should have cultures subjected to second- and third-line DST and subsequent chemotherapy adjusted according to the resistance profile and availability of drugs at provincial level. Changes to the regimen should be made in consultation with an experienced MDR-TB clinician. Chest X-rays are evaluated according to the standardised DOTS-Plus grading system,[3] at the intervals specified in Fig. 1. National TBCP policy calls for routine HIV counselling and testing as outlined in Fig. 1, in order to identify MDR-TB patients who qualify for antiretroviral treatment (see later).

During the intensive phase of treatment, patients must be interviewed weekly about adverse effects. These are graded according to severity and the need for intervention.[3] Adverse effects are monitored monthly during the continuation phase of treatment utilising the same grading system. Serious adverse events that require drug withdrawal must be reported to the MDR-TB referral centre for notification to the Medicines Control Council.[3]

Management of drug adverse events

Timely and aggressive management of drug adverse effects greatly facilitates patient adherence. Most adverse effects respond well to palliative care and disappear within a short period. Sequential steps for the management of adverse effects are therefore recommended: firstly, palliative management using standardised algorithms; secondly, reduced dosage of suspected drug(s); and thirdly, removal of drug(s) from the regimen (as a last resort). Table III presents the most common adverse reactions and management strategies. Detailed standardised management algorithms are available from the provincial MDR-TB referral centres.

Management of treatment interruption and default

MDR-TB patients who interrupt treatment must be recalled rapidly and the duration of treatment extended by the number of doses missed. Once patients meet the definition of default, i.e. having missed treatment for two consecutive months, a management approach based on smear results upon return applies:

- if the smear is positive, MDR-TB treatment needs to be restarted
- if the smear is negative, MDR-TB treatment should continue and a culture investigation be requested; if the culture is also negative, treatment should be extended to cover the period of default; if the culture is positive, MDR-TB treatment needs to be re-initiated.

Treatment outcomes

Defining treatment outcomes for MDR-TB patients is complex due to the long duration of treatment and the need for extensive bacteriological monitoring. Six mutually exclusive MDR-TB treatment outcome definitions apply, based on the use of culture as prognostic indicator.[10]

SPECIAL SITUATIONS

Children

Evidence on the use of second-line drugs for extended periods in paediatric MDR-TB is limited. Given the toxicity profile of these drugs, careful consideration of the risks and benefits is necessary as MDR-TB can be life-threatening if left untreated. In a few studies involving children with MDR-TB, adequate tolerance to second-line treatment has been noted;[15] however, informed consent from the guardian of a paediatric MDR-TB patient is required before treatment is initiated. Drug doses should be according to weight and adjusted as required.

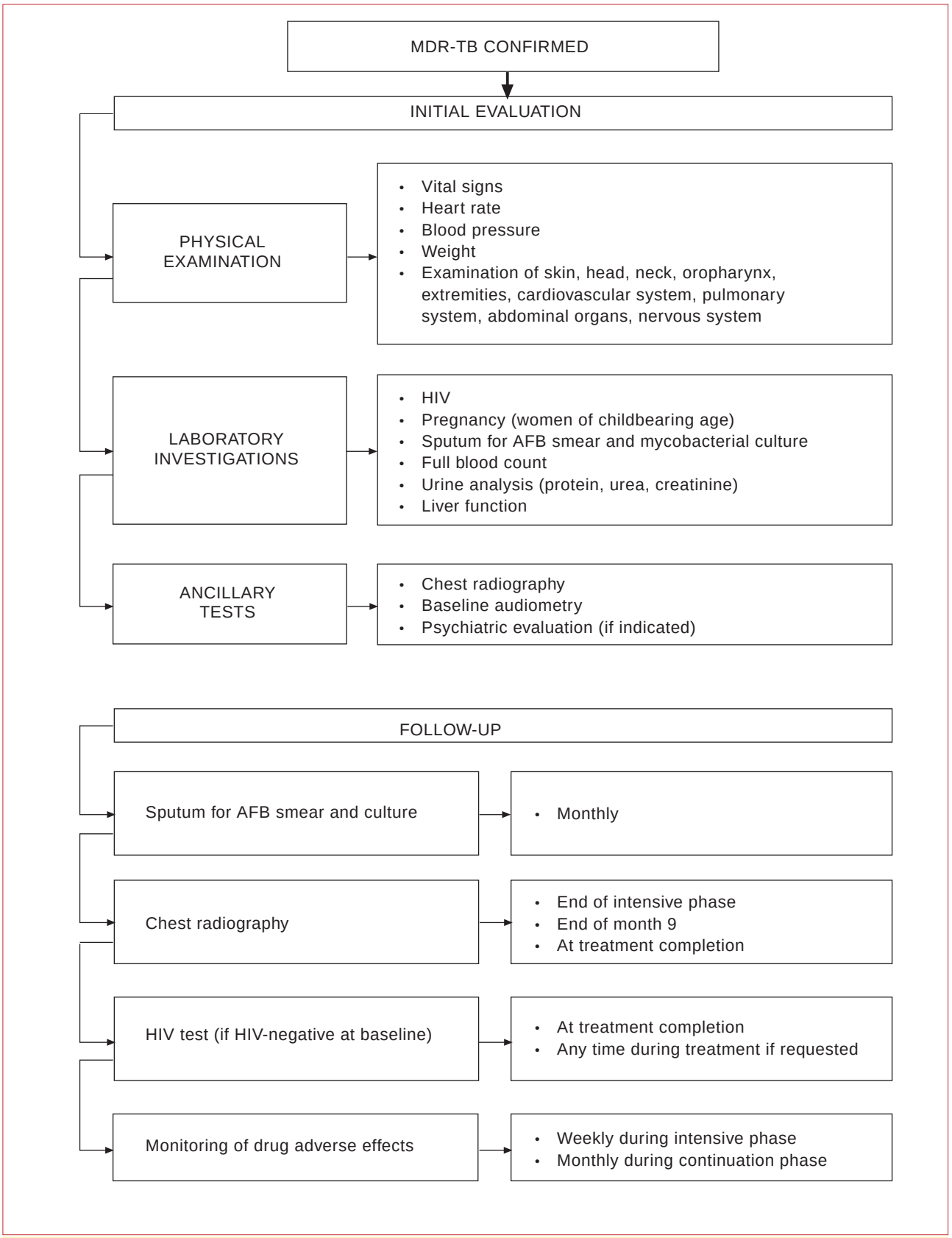

Fig. 1. Standardised approach to evaluation and follow-up of MDR-TB patients.

Pregnancy and newborn babies

Birth control is strongly recommended for all female patients on MDR-TB therapy; however, alternatives to oral contraceptives should be used due to potential drug interactions. Pregnancy is not an absolute contraindication to the treatment of active MDR-TB, since active disease poses great risks to the mother and fetus. Gravid patients should, however, be carefully evaluated, taking into consideration gestational age and MDR-TB disease severity. The majority of second-line drug teratogenic effects occur in the first trimester and MDR-TB treatment should therefore be delayed, unless life-threatening symptoms occur. Aminoglycosides are contraindicated during pregnancy; therefore, if treatment is initiated (preferably in the second or third trimester), aminoglycosides should be withheld until delivery and given immediately postpartum.

Newborn infants are at high risk of developing disseminated MDR-TB if exposed. Smear-positive mothers should avoid close contact with infants if at all possible, at least until smear-conversion has occurred.

Effects of MDR-TB medications on the nursing infant have not been appropriately studied and formula use is a reasonable way to avoid any unknown adverse effects. However, this will depend on multiple factors including the patient's resources and safety of water supply, and breast-feeding may be the only option if the setting is not appropriate for infant formula.

Diabetes

Diabetes may potentiate drug adverse effects, especially renal dysfunction and peripheral neuropathy, and close management is required throughout MDR-TB treatment. Annual retinal examination is required, as is monthly monitoring of blood pressure and creatinine levels. Intensive glucose monitoring is needed to ensure that patients maintain stable blood goals.

Renal insufficiency

Renal insufficiency due to longstanding TB disease is not uncommon. Great care must be taken in administering MDR-TB drugs to these patients, with the dose and/or interval between dosing adjusted as required.[3]

Psychiatric patients and substance dependency

MDR-TB patients have a high baseline incidence of depression and anxiety, often connected to disease duration and socio-economic stressors. MDR-TB drugs may exacerbate psychological problems and any psychiatric illness identified at the start of or during treatment should be addressed fully. Psychiatric medications, individual counselling, and/or group therapy may be needed. Systems should be in place for psychiatric emergencies including psychosis, suicidal indication, and any situation that involves the patient posing a danger to him/herself or to others.

The patient with 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 MDR-TB treatment.

MDR-TB AND HIV CO-INFECTION

The complete link between HIV and MDR-TB is not yet fully understood. Nevertheless, outbreaks of MDR-TB in HIV-infected patients have been associated with extraordinarily high mortality rates. HIV patients also tend to have a higher rate of adverse drug reactions, notably peripheral neuropathy, cutaneous reactions, gastrointestinal disturbances, renal toxicity and neuropsychiatric effects.[14] Malabsorption of MDR-TB drugs has been reported in patients with HIV-related enteropathology.[14] Routine HIV counselling and testing for MDR-TB patients is therefore strongly recommended by TBCP policy guidelines.[3]

Dramatic impact of highly active antiretroviral therapy (HAART) on MDR-TB mortality has been reported in co-infected patients.[14] Current TBCP policy in SA calls for ART in all MDR-TB patients, irrespective of CD4 count or clinical staging, using the same regimens recommended for drug-susceptible TB.[3] The appropriate time to initiate ART in MDR-TB patients is, however, not known. Weighing risk and benefit, it is currently recommended that ART be started within the first 4 months of MDR-TB treatment in patients with CD4 count < 50, provided that the MDR-TB treatment is tolerated.[3] ART should be deferred until the continuation phase in clinically stable patients, especially if the CD4 count is more than 100. Patients already on ART when diagnosed with MDR-TB should be started on MDR-TB treatment immediately.[3]

Patients on ART should have CD4 counts done at baseline and every 6 months thereafter. Viral loads should be measured at baseline and at 6-monthly intervals. If virological goal (defined as a 1-log or 10-fold decrease) is not achieved, virological failure (due to patient adherence, regimen potency, drug absorption or viral resistance) should be assessed.[3]

Information on ART and MDR-TB drug-drug interactions is lacking. Peripheral neuropathy has been associated with the use of ethionamide, cycloserine and pyrazinamide and may be exacerbated in patients receiving stavudine and/or didanosine.[13] Nonenteric-coated didanosine contains an aluminium/magnesium-based antacid that may result in decreased absorption of the quinolones when administered together. The combination of terizidone and efavirenz may increase the rate of neuropsychiatric effects, although this has not been formally studied.

The MDR-TB patient with HIV infection poses a great challenge and requires intensive monitoring of drug interactions and additive drug toxicities. The complexity of the regimens, each with its own toxicity profiles (which may be potentiated during concomitant therapy), demands rigorous monitoring of patients. In addition, other oppor-

tunistic infections need to be prevented, monitored and treated.

MANAGEMENT OF MDR-TB CONTACTS

Factors which should be considered in the management of contacts include the likelihood of infection with MDR-TB and the likelihood of active disease. Related aspects include infectiousness of the MDR-TB source case (smear-positive cases being substantially more infectious), closeness and intensity of the exposure (prolonged exposure in confined spaces posing a higher risk), and the recentness of exposure (recently acquired infection having a higher risk of active disease). In immune-competent individuals, the lifetime risk of developing active MDR-TB is 5 - 10%, with the highest risk within the first 2 years following infection.[3] Child contacts of MDR-TB patients (especially those under 2 years of age) are therefore at risk of developing active MDR-TB soon after infection.

The most potent risk factor for active disease, however, is impaired immunity, the risk increasing to 5 - 10% per year.[3] Although HIV is the most common reason for immune deficiency in SA, it should be kept in mind that impaired immunity can also result from malnutrition, congenital syndromes, haematological diseases, endocrine or renal disease and diabetes mellitus. Patients who are receiving immunosuppressive drugs or radiation therapy may also be at increased risk of active MDR-TB after exposure.

The effectiveness of preventive therapy in persons exposed to or infected with MDR-TB bacilli is not known. No controlled clinical trials have been conducted to assess the efficacy of treatment to latent MDR-TB infection. Small studies conducted with experimental regimens (pyrazinamide and high-dose ethambutol; pyrazinamide and fluoroquinolones) indicated significant rates of toxicity, including asymptomatic hepatitis, arthralgias, musculoskeletal, gastrointestinal, dermatological, and central nervous system side-effects.[14] A 'watchful waiting' approach may therefore be more appropriate. Presumptive MDR-TB treatment should be avoided.

Contacts of sputum smear-positive MDR-TB patients should be rapidly screened. Those with HIV co-infection should be followed up regularly and encouraged to report TB symptoms and signs as soon as they appear. Child contacts aged 5 years and younger should receive preventive therapy with isoniazid (15 mg/kg for 6 months), as infection may have preceded the development of MDR in the source patient, i.e. TB disease in the child contact may be drug-susceptible. In children older than five years, as well as in adult contacts, a careful risk assessment is required and MDR-TB must be confirmed before treatment is started.

References available on request.

IN A NUTSHELL

Multidrug-resistant TB (MDR-TB) is an emerging threat to TB control.

Although patient non-adherence is often thought to be the most common cause of drug resistance, many studies have shown that organisational failure of TB control programmes, lack of available drugs, and clinical error are responsible for much of the MDR-TB problem existing today.

Although the term MDR-TB has been used to describe resistance to any two or more anti-TB drugs, the correct definition is *resistance to at least isoniazid and rifampicin*.

MDR-TB rates in Africa are among the lowest recorded globally, being ascribed to the late introduction of rifampicin and its limited use in TB control programmes.

A recent national survey by the Medical Research Council indicated an overall MDR-TB prevalence of 2.9%, arising from 1.6% of new TB cases and 6.6% of previously treated cases.

MDR-TB should be suspected in patients with persistently positive acid-fast bacilli (AFB) smears or cultures despite adequate treatment adherence.

Clinical presentation of patients with MDR-TB is identical to that of patients with drug-susceptible disease, and radiological features are indistinguishable.

Treatment of MDR-TB involves second-line, reserve drugs that are much more expensive, more toxic and less effective than first-line TB drugs.

Design of MDR-TB regimens poses several challenges, complicated by a limited choice of second-line agents. The use of multiple drugs is imperative to avoid amplification of resistance.

Treatment must be given under direct observation on at least 5 days a week. Patients must receive a minimum of 16 months' treatment (4 months of intensive and at least 12 months of continuation phase therapy, based on culture conversion) and must complete the full course. Short interruptions of treatment must be corrected by adding the number of drug doses missed.

AU MDR-TB patients with HIV co-infection should receive antiretroviral treatment, irrespective of CD4 count.