Course on Multidrug-Resistant Tuberculosis MDR-TB

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COURSE ON MULTIDRUG-RESISTANT TUBERCULOSIS MDR-TB

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World Medical Association
13, Chemin du Levant - 01212 Ferney-Voltaire, France
Tel.: + 33 450 40 75 75 • Fax: + 33 450 40 59 37
e-mail: wma@wma.net
www.wma.net

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COURSE ON
MULTIDRUG-RESISTANT
TUBERCULOSIS
MDR-TB

THE WORLD MEDICAL ASSOCIATION
WITH SUPPORT FROM
THE LILLY MDR-TB PARTNERSHIP

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INTRODUCTION

Treatment of multidrug-resistant tuberculosis (MDR-TB) is now regarded as an essential component of international standards of TB care, with MDR-TB treatment currently being integrated into expanded Directly Observed Treatment, Short-course (DOTS) programmes for TB control. However, unlike DOTS, treatment of MDR-TB is complicated and expensive, requiring considerable expertise and resources. This Course is aimed at medical practitioners involved in the management of MDR-TB patients, under the guiding principles of the expanded DOTS framework.

The Course presupposes essential knowledge of TB transmission, pathogenesis, and the international DOTS strategy for TB control. The Course aims to facilitate self-study by medical practitioners of contemporary, evidence-based standards for diagnosis and clinical management of MDR-TB in a variety of geographical, economic and social settings.

Since MDR-TB treatment is a programmatic activity and treatment of patients should preferably be conducted under guidance of National TB Control Programmes, electronic links to relevant international policy guidelines have been provided.

MODULE 1

TB-MDR Strategies

1   Learning Objectives

At the end of this module you should be able to:

- Understand the DOTS strategy as the key to prevent MDR-TB
- Identify microbial, clinical and programmatic causes of MDR-TB
- Describe clinical practices leading to development of MDR-TB
- Understand the programmatic approach to MDR-TB management
- Describe the different components of MDR-TB strategies

2   INTRODUCTION

Anti-tuberculosis drugs constitute a two-edged sword – while they destroy tuberculosis (TB) organisms, they also select for organisms that are naturally resistant. In this way strains can become sequentially resistant to several agents and patients become more vulnerable to the acquisition of further resistance. One of the gravest public health examples of this phenomenon has been the global emergence of multidrug-resistant TB (MDR-TB), defined as resistance to isoniazid and rifampicin (the two most potent first-line anti-TB agents), with or without resistance to other first-line drugs. The rise of extensively drug-resistant TB (XDR-TB), defined as MDR-TB that is resistant as well to any one of the fluoroquinolones and to at least one of three injectable second-line drugs (amikacin, capreomycin or kanamycin), has heightened this threat.

3   DEVELOPMENT OF MDR-TB

QUESTION
What are the main reasons for the development of MDR-TB?
a. Ongoing bacterial mutation.
b. Selective pressure of naturally-occurring drug resistant mutants.
c. Preventive therapy.
d. Inactive metabolism of drugs in TB cavities.
e. Inefficient macrophage activity.
f. Early discontinuation of treatment.

ANSWER
The correct answers are a and f . The reasons for the development of MDR-TB are as follows:
- Selection of resistant mutants in the bacterial population, due to killing of susceptible bacilli by anti-TB drugs.
- Inadequate treatment such as direct or indirect monotherapy.
- *Mycobacterium tuberculosis* has the ability to undergo spontaneous, slow but constant mutation, resulting in resistant mutant organisms.
- Failure the full course of treatment for primary TB.

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

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

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

Usually, the chromosomal location of resistance to different drugs is not linked; therefore, spontaneously occurring multidrug resistance is extremely rare. For example, the probability of mutation resulting in resistance to isoniazid is 10^{-6} and for rifampicin it is 10^{-9}. The likelihood of spontaneous resistance to both isoniazid and rifampicin is the product of the two probabilities, ie. 10^{-15}. Since the probability of naturally occurring resistant mutants is very low, a large bacterial load (eg. in lung cavities) is needed for MDR-TB strains to emerge.
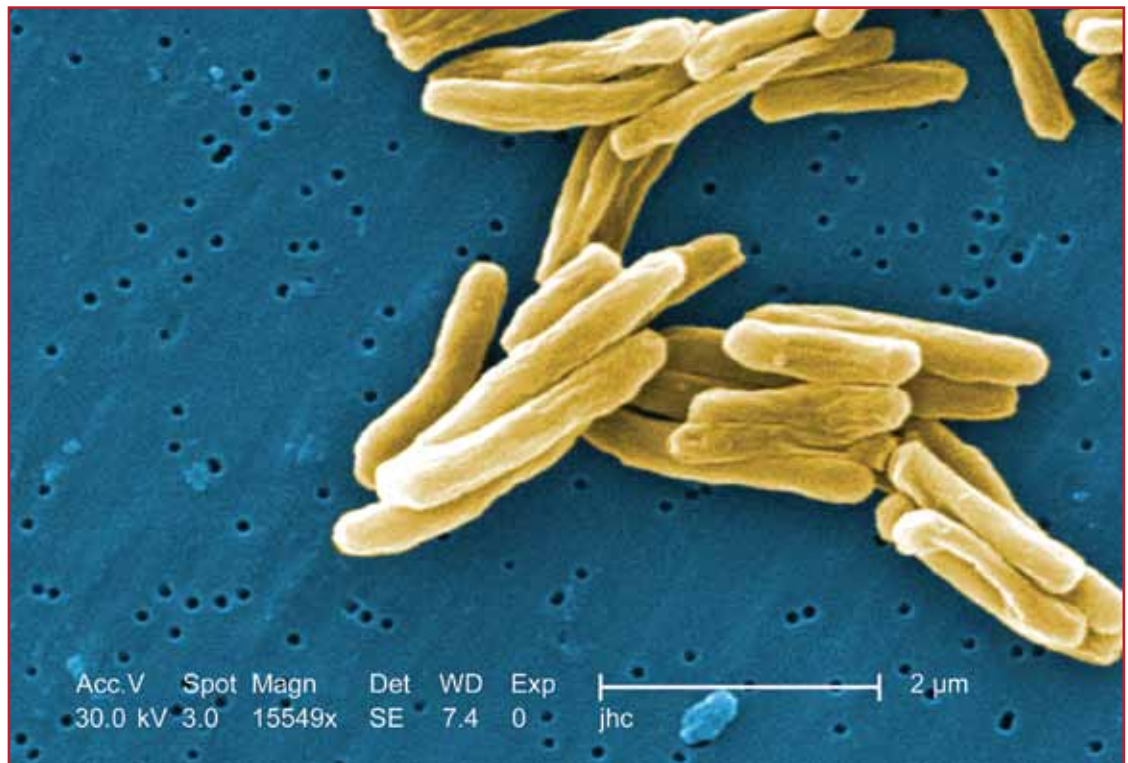
MDR-TB is not the same as disease due to non-tuberculous mycobacteria (NTM). The latter are commonly resistant to both isoniazid and rifampicin but should not be confused with MDR-TB. This training course is relevant for the management of MDR-TB only and not for disease caused by NTM. Identification of NTM disease is made after the culture has been referred for specialised identification. NTM are often contaminants in the sputum and are only of clinical significance when several bacteriological, radiological and clinical criteria have been met.

4   THE DOTS STRATEGY AS THE CORNERSTONE TO PREVENT MDR-TB

QUESTION
Which of the following should be regarded as the cornerstone of the DOT approach to the management of MDR-TB?
a. The patient receives a monthly supply of medication for self-administration.
b. A health worker completes the patient's treatment record.
c. A health worker counts the remaining tablets in medication bottles.
d. A health worker calculates the number of drug doses taken.
e. The patient is watched swallowing the prescribed medication.

ANSWER:
The correct answer is e.
In the other alternative answers there is no direct supervision of the taking of medication and patients may refrain from taking the medication often due to unpleasant side-effects.

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The essential services needed to control TB, based on diagnosis and treatment of infectious cases and incorporating essential management tools, were packaged by the World Health Organization (WHO) as the DOTS strategy in the early 1990s and have been promoted as a global strategy for TB control since then. The DOTS strategy has now been implemented in more than 200 countries worldwide. Countries applying DOTS on a wide scale have witnessed remarkable results and improvements in TB control over relatively short periods of time. Despite initial skepticism and reluctance by many countries to revise their TB control strategies to comply with DOTS principles, DOTS programmes have over the last 10 years shown consistent good performance (see the WHO 2008 Report on Global tuberculosis control for more information: http://www.who.int/tb/publications/global_report/2009/update/en/index.html). As yet, no strategy has been identified that provides comparable results.

Supervision of drug intake in the Sergio Bernales Hospital hospital in Lima, Perú

QUESTION

What are the essentials of the DOTS Strategy to prevent MDR-TB ?

a. Sustained political commitment to increase human and financial resources.
b. Access to quality-assured TB bacteriology.
c. Standardised short-course chemotherapy.
d. Uninterrupted supply of quality-assured drugs.
e. Recording and reporting system.
f. Repeated home visit by healthcare personnel.
g. Continuous information to family members.

ANSWER

The correct answers are a ,b, c, d and e.

• Home visits play no part in the DOTS Strategy.
• Informing the patient's family, while advantageous, is not essential.
• Political and financial assistance are essential factors for a successful program.

QUESTION
The five essential elements of the DOTS strategy are essential parts to prevent the development of MDR-TB. List the five essential elements of the DOTS Strategy.

ANSWER
1. Sustained political commitment to increase human and financial resources and make TB control a nation-wide priority integral to the national public health system.
2. Access to quality-assured TB bacteriology for case detection among persons presenting with, or found through screening to have, symptoms of TB.
3. Standardised short-course chemotherapy to all cases of TB under proper case-management conditions including direct observation of treatment.
4. Uninterrupted supply of quality-assured drugs with reliable drug procurement and distribution systems.
5. Recording and reporting system enabling outcome assessment of each and every patient and assessment of overall TB control programme performance.

PROPORTION OF ESTIMATED CASES NOTIFIED UNDER DOTS (GREY PORTION OF BARS) AND NON-DOTS (BLUE PORTION OF BARS) IN 2006. The number of notified cases (in thousands) is shown in or above each portion or each bar. The grey portion of the bars is cases notified in DOTS programmes. The blue portion is the number notified outside DOTS programmes.

(a) New smear-positive
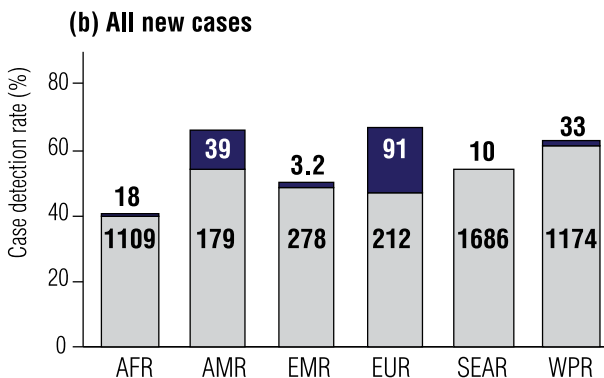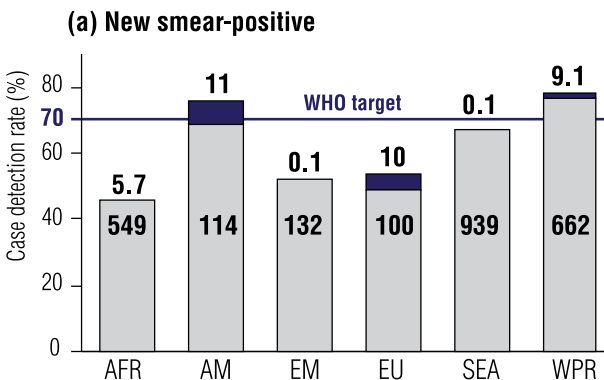
WHO REGIONS		
AFR	African Region	
AMR	Region of the Americas	
EMR	Eastern Mediterranean Region	
EUR	European Region	
SEAR	South-east Asia Region	
WPR	Western Pacific Region	

(b) All new cases

World Health Organization. WHO Report 2008. Global tuberculosis control: surveillance, planning, financing (WHO/HTM/TB/2008.393). Geneva, Switzerland: World Health Organization; 2008.

The DOTS strategy consists of five essential elements:

It is worth reviewing the detail the five essential elements of the DOTS strategy as the cornerstone of good TB control. (These same five elements can be applied to a the programmatic control of MDR-TB – see Section 5 of this module).

- **Sustained political commitment** to increase human and financial resources and make TB control a nation-wide priority integral to the national public health system.
- **Access to quality-assured TB bacteriology** for case detection among persons presenting with, or found through screening to have, symptoms of TB (most importantly, prolonged cough of more than two weeks). The use of sputum smear microscopy to identify patients with infectious TB constitutes the cornerstone of case detection, being the most cost-effective method of screening pulmonary TB suspects. A specific requirement is the rapid communication and dissemination (within 24 to 48 hours) of microscopy results. Culture is necessary for case detection amongst HIV infected individuals and other high-risk groups such as child contacts of infectious cases, while individuals in congregate settings in high MDR-TB burden areas need drug susceptibility testing in addition.
- **Standardised short-course chemotherapy to all cases of TB under proper case-management conditions including direct observation of treatment.** Proper case management conditions imply technically sound and socially supportive treatment services, using appropriate treatment regimens for different categories of TB patients (see the WHO Treatment of tuberculosis: guidelines for national programmes, 3rd edition for more information: http://whqlibdoc.who.int/hq/2003/WHO_CDS_TB_2003.313_eng.pdf).

  Direct observation of treatment is a crucial important element in the DOTS strategy to ensure patient adherence to treatment and prevent the development of drug resistance. Directly observed treatment (DOT - not be confused with DOTS, which refers to the comprehensive management strategy -) means that an observer watches the patient swallowing the tablets, in a way that is sensitive and supportive to the patient's needs. This ensures that a TB patient takes the right drugs, in the right doses, at the right intervals. In practice, it means providing a treatment observer acceptable to the patient, to enable him/her to complete treatment. The observer may be a health worker or a trained and supervised community member. It is important to ensure that directly observed treatment is acceptable to the patient and that his/her privacy is protected, ie that treatment takes place in a positive environment <u>TB drugs always remains with the treatment observer and are given to the patient at the time of intake.</u>

  DOT helps to reinforce a patient's motivation to continue treatment and to counter the human tendency to interrupt treatment, as it is impossible to predict which patients will or will not comply. DOT also ensures accountability of health care workers and helps to prevent the emergence of drug resistance.

  DOT is recommended whenever rifampicin is used to prevent the emergence of drug resistance, including MDR.
- **Uninterrupted supply of quality-assured drugs with reliable drug** procurement and distribution systems. TB drugs are procured by health authorities at the most favourable prices. However, planning and maintaining drug stocks at all levels of care can be a challenge for general health services. Where DOTS is implemented, however, an accurate recording and reporting system provides the information needed to plan and maintain adequate drug stocks, such as the number of cases in the different treatment categories notified the previous year, the standardised treatment regimen used, and existing and buffer stock availability.
- **Recording and reporting system enabling outcome assessment** of each and every patient and assessment of overall TB control programme performance. The recording and reporting system is used to systematically evaluate patient progress and treatment outcome, as well as overall control programme performance. The system consists of:
  * <u>A Laboratory Register</u> that contains information of all patients who have had a smear test done.
  * <u>Patient Treatment Cards</u> that detail the regular intake of medication and follow-up sputum examinations.
  * <u>A Facility TB Register,</u> which lists patients starting treatment and monitors their individual and collective progress towards cure.

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- **Cohort analysis** is the key management tool used to evaluate the effectiveness of TB control activities in any given area. A cohort of TB patients consists of patients registered during a certain time period and cohort analysis refers to the systematic follow-up and reporting on specific indicators of treatment progress and treatment success. Interim performance indicators are obtained through quarterly smear conversion reports, while quarterly and annual treatment success rates provide timely, concrete indicators of health service achievement or of problems requiring action. The DOTS recording and reporting system allows for targeted, individualised follow-up to identify patients who may not be making satisfactory progress, as well as rapid managerial assessment of the overall performance of institutions, districts, regions, provinces or of a country.

Supervision and on-going training are necessary to ensure the quality of DOTS services throughout the health care system. Since TB control is an integral component of public health services, all primary health care workers should receive basic training in the DOTS strategy and mechanisms for effective TB control.

The full participation by doctors in the private sector is required for more widespread use of DOTS. Physicians must support the implementation of DOTS and become full partners in TB control efforts.

TB treatment supporters talk to TB patients outside a clinic

Lung Health Image Library

4.1 Causes of inadequate first-line TB treatment

QUESTION
What are the main causes of inadequate first line TB treatment?
a. No monitoring of treatment.
b. Non-adherence.
c. Poorly organized or funded TB control programs.
d. Unavailability of certain drugs.
e. DOT not done.
f. Non compliance of patients due to various reasons.

ANSWER
All the statements are correct.

QUESTION
What are the causes of inadequate first line anti-TB treatment which leads to MDR-TB?

ANSWER
Drug-resistant TB has microbial, clinical, and programmatic causes. Table 1.1. summarizes the common causes of inadequate treatment.

QUESTION
What are the main causes of inadequate treatment of MDR-TB ?
a. No monitoring of treatment.
b. Poor quality of drugs.
c. Wrong doses of drugs.
d. DOT not properly done.
e. Side effects of drugs.
f. Non-adherence.
g. Ignorance and lack of information.
h. Associated diseases eg HIV.

ANSWER
The above statements are all correct and sometimes combine in a specific patient.

Table 1.1. Causes of inadequate treatment		
Doctors/TB Programmes: Inadequate regimens	**Drugs:** Inadequate supply/quality	**Patients:** Inadequate drug intake
• Inappropriate guidelines • Non-compliance with • guidelines • Absence of guidelines • Poor training • No monitoring of treatment • Poorly organized or funded • TB control programs	• Poor quality • Unavailability of certain • drugs • Stock-outs • Distribution and delivery • disruptions • Poor storage conditions • Wrong dose or combination	• Poor adherence (or poor DOT) • Lack of information • Lack of money (No treatment • available free of charge) • Lack of transportation • Adverse effects • Social barriers • Malabsorption • Substance dependency disorders

Source: Lambregts-van Wezenbeek CSB, Veen J. Control of drug-resistant tuberculosis. Tubercle and Lung Disease. 1995; 76:455-459

Weak TB control programs enable undesirable clinical practices to continue, multiplying the number of drug-resistant TB cases in the community, e.g.

- Drug shortages may force clinicians to use inadequate treatment regimens.
- Poor quality drugs result in inadequate regimens.
- Inadequate supervision of treatment results in erratic drug intake favouring the growth of drug-resistant bacilli.
- TB control programme policies may be suboptimal.
- Clinical practices do not always follow policies. Private medical practitioners, who do not work under the TB control programme's authority, may use practices that result in the development of drug resistance at high rates.

Quality-assured laboratories with adequate capacity to identify patients with MDR-TB strains are a key element to avoid inadvertently placing patients on inadequate regimens (See Module 4).

Strong infection control measures can help stop the spread of MDR-TB in health care facilities, prisons, and other institutions (See Module 15).

Lung Health Image Library

4.2 Primary and secondary MDR-TB

Once MDR-TB strains are well-established in a population, even well-run TB control programmes that use standardized short course chemotherapy (SCC) will fail to cure a growing proportion of TB patients. Repeating SCC for patients infected with drug-resistant strains creates even more resistance to the drugs in use. Ongoing primary transmission of established MDR-TB strains in a population is also a significant source of new drug resistant cases.

Antonio Tito Puma, 9, contracted primary MDR-TB from a brother

5   MDR-TB TREATMENT

5.1   MDR-TB FRAMEWORK APPROACH

In order to control drug resistant TB worldwide, WHO and its partners recommend the treatment of MDR-TB as a priority in expanded DOTS programmes, now called the Stop TB Strategy. The STOP TB Strategy calls for strengthened TB control, thereby preventing the emergence of drug resistance, and underpins the Stop TB Partnership's Global Plan to Stop TB 2006-2015 (http://www.who.int/tb/features_archive/global_plan_to_stop_tb/en/), with the aim of treating 50 million patients and preventing 14 million TB deaths.

The Stop TB Strategy continues to emphasize the basic components of the DOTS strategy while addressing additional constraints and challenges to TB control. The Stop TB Strategy has six principal components:

1. **Pursuing high-quality DOTS expansion and enhancement**
   - Secure political commitment, with adequate and sustained financing.
   - Ensure early case detection, and diagnosis through quality-assured bacteriology.
   - Provide standardized treatment with supervision, and patient support.
   - Ensure effective drug supply and management.
   - Monitor and evaluate performance and impact.
2. **Address TB-HIV, MDR-TB, and the needs of poor and vulnerable populations**
   - Scale-up collaborative TB/HIV activities.
   - Scale-up prevention and management of multidrug-resistant TB (MDR-TB).
   - Address the needs of TB contacts, and of poor and vulnerable populations.
3. **Contribute to health system strengthening based on primary health care**
   - Help improve health policies, human resource development, financing, supplies, service delivery and information.
   - Strengthen infection control in health services, other congregate settings and households.
   - Upgrade laboratory networks, and implement the Practical Approach to Lung Health (PAL).
   - Adapt successful approaches from other fields and sectors, and foster action on the social determinants of health.
4. **Engaging all care providers**
   - Involve all public, voluntary, corporate and private providers through Public-Private Mix (PPM) approaches.
   - Promote use of the International Standards for Tuberculosis Care (ISTC).
5. **Empower people with TB, and communities through partnership**
   - Pursue advocacy, communication and social mobilization.
   - Foster community participation in TB care.
   - Promote use of the Patients' Charter for Tuberculosis Care.
6. **Enable and promote research**
   - Conduct programme-based operational research, and introduce new tools into practice.
   - Advocate for and participate in research to develop new diagnostics, drugs and vaccines.

Emphasis on expanding laboratory capacity (sputum smear microscopy first, then culture and drug susceptibility testing (DST)) and the use of quality assured drugs across all programmes are important aspects of this comprehensive approach to TB control.

World Health Organization, Stop TB Department

In the past, MDR-TB was often a disconnected activity separate from the TB control programme; however, new international guidelines promote integration of DOTS and MDR-TB within a framework approach, consisting of an essential core of five components based on fundamental principles of TB control and flexible options for country-specific implementation. The core components are comprehensive, ensuring that all essential elements of MDR-TB treatment are included. The design and implementation may vary from one country or region to another depending on the local situation. The WHO website of TB publications (http://www.who.int/tb/publications/en/) dating from 1988 up to the present is helpful in providing more information about these new international guidelines.

Guidelines for the programmatic management of drug-resistant tuberculosis have recently been updated by the WHO and are based on the best evidence currently available

World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency update 2008 (WHO/HTM/TB/2008.402). Geneva, Switzerland: World Health Organization; 2008.).
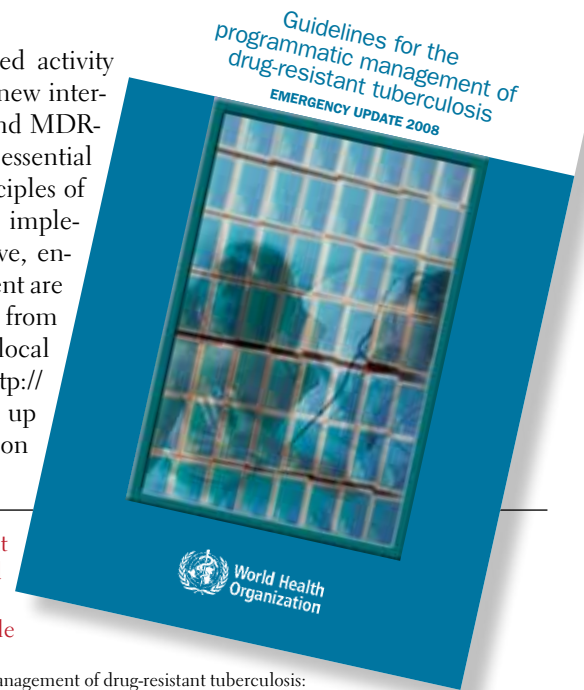
QUESTION

Which treatment approaches for MDR-TB are the most successful?
a. Treatment must be tailored to country circumstances.
b. Proper selection of patients is essential.
c. A repeat of the treatment for primary TB may be attempted.
d. Laboratory facilities must be considered.
e. Financial circumstances need to be taken into consideration.
f. Known resistance of Mycobacterium should be considered.

ANSWER

a , b , d , e and f are correct.

Repetition of Primary TB treatment should not be attempted as this action may encourage the emergence of resistant strains.

First line therapy is strongly contra-indicated as the organism will be resistant should tests indicate MDR-TB.

Patient-selection is important and many factors should be taken into account.

Treatment must be tailored to country circumstances and often requires different combinations of second-line drugs, depending on resistance patterns.

No one protocol or plan fits all countries, programs or health providers.

MDR-TB TREATMENT IS MUCH MORE COMPLEX THAT DOTS. Unlike DOTS, a single standardized regimen cannot be recommended for all MDR-TB patients. Treatment must be tailored to country circumstances and often requires different combinations of second-line drugs, depending on resistance patterns. Many health care providers have little or no experience with these drugs and their side effects, especially in combinations of many drugs at a time. No one protocol or plan fits all countries, programs or health providers. Therefore, private physicians are strongly encouraged to follow their specific country policies for management of MDR-TB patients.

Factors to consider in the MDR-TB framework approach are:

- The magnitude and distribution of drug-resistant TB.
- Existing infrastructure.
- Possibilities for case-finding.
- Selection of patients to be treated.
- Prevailing drug-resistance patterns.
- Available laboratory capacity.
- Resources available for directly observed treatment over a long period of time.
- The availability of human and financial resources.

Despite a wide range of acceptable strategies, certain essential requirements have to be met under all conditions to ensure the proper management of MDR-TB cases and prevent the emergence of drug-resistance to second-line drugs. MDR-TB treatment should be fully integrated with the TB control programme in the country. If many of the MDR-TB cases are treated in the private sector, integration can be accomplished through a public-private mix.

5.2 MDR-TB TREATMENT COMPONENTS

QUESTION
What do you think are essential components for MDR-TB strategies?

ANSWER
MDR-TB strategies are organized around five components like DOTS, because the underlying principles are the same and enable the programmes to be fully integrated:
- Sustained government commitment;
- Accurate, timely diagnosis through quality assured culture and drug susceptibility testing;
- Appropriate treatment utilizing second-line drugs under strict supervision;
- Uninterrupted supply of quality assured second-line drugs;
- Standardized recording and reporting system.

Government commitment is essential to establish and maintain the other four components. However, each of these components involves more complex and expensive operations than the DOTS strategy. Therefore, adding an MDR-TB component to a DOTS-programme usually strengthens the existing TB control programme.

5.2.1 Sustained government commitment

Sustained government commitment is crucial, requiring both long term investment and leadership in ensuring an appropriate environment for MDR-TB treatment, which should include:
- Adequate infrastructure.
- Development and retention of human resources.
- Inter-agency cooperation.
- Enactment of necessary legislation.
- TB control policies enabling rational implementation of MDR-TB treatment, while strengthening the DOTS programme to prevent the emergence of MDR-TB.
- Facilitation of the procurement of quality-assured second-line drugs.

Folang MDR-TB clinic in Pretoria, South Africa

South African Medical Research Council

Government commitment means more than economic support, though an adequate budget is necessary. Government commitment expresses itself in adequate infrastructure including facilities and trained human resources. Coordination among the different dimensions of public and private health programs/organizations is essential for successful implementation of an MDR-TB program. Sufficient training and retention of medical and public health personnel depend on long-term government planning and support.

5.2.2 Diagnosis of MDR-TB through culture and DST

QUESTION

Which factors are important in the diagnosis of MDR-TB ?
a. Timely diagnosis.
b. Quality assured culture and DST is indispensable.
c. Internal quality control and external quality assurance.
d. A link for proficiency testing with a recognized reference laboratory.
e. Reliance on positive TB sputum smears.

ANSWER

 a ,b ,c and d are correct.
Reliance should not be placed on an apparently positive TB sputum smears as the finding of TB bacilli does not indicate an active infection.

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Accurate and timely diagnosis is the backbone of an MDR-TB programme (see Module 4).

MDR-TB must be diagnosed correctly before it can be treated effectively. Quality assured culture and DST is indispensable. Nonviable cultures, culture contamination, and unreliable DST results have major consequences for both individual patients and the TB control programme as a whole. Therefore, internal quality control and external quality assurance should be in place, including a link for proficiency testing with a recognized reference laboratory or one of the WHO Supranational Reference Laboratories.

In areas where XDR-TB threatens TB control, laboratories will have to develop the capacity for DST to second-line injectable agents and to a fluoroquinolone in order to diagnose XDR-TB.

Nurse collecting sputum samples, Lima, Perú. Correct diagnosis is key in fighting MDR-TB

5.2.3 *Appropriate treatment strategies utilizing second-line anti-TB drugs*

QUESTION
Name the appropriate treatment strategies in the use of second-line anti-TB drugs.
a. Representative drug-resistance surveillance data of well-defined local groups of TB.
b. The specific array of available second-line drugs.
c. The availability of DST to first and selected second-line drugs.
d. Chart the migration of MDR-TB diagnosed patients.
e. The availability of hospital beds with adequate infection control measures.
f. The availability of trained personnel at hospitals and clinics.

ANSWER
a, b, c and f are correct.
It would be impossible to keep track of diagnosed patients.
Patients often do not have a permanent address and effective means of communication with them is not always possible.

An appropriate treatment strategy consists of:

- A rational approach to designing an optimal treatment regimen;
- Methods to deliver this regimen under direct observation;
- Plans for monitoring and managing adverse drug reactions.

Designing an optimal treatment requires the professional expertise to consider several factors simultaneously, including:

- Representative drug-resistance surveillance data of well-defined local groups of TB patients, distinguishing susceptibility patterns and prevalence of drug resistance in new cases and different types of re-treatment cases;
- The history of drug-use in the country and in the individual patient;
- The specific array of available second-line drugs;
- The availability of DST to first- and selected second-line drugs;
- Reliable options for administering treatment for up to two years, including directly observed treatment (DOT);
- Plans and protocols for addressing MDR-TB patients infected with HIV;
- Proper infection control measures in place.

A standardized regimen for certain groups of patients may be more appropriate than an individualized regimen in one country and vice versa in another (see Module 5 for more information on treatment strategies).

The choice between hospitalization and ambulatory treatment depends on several factors other than the severity of the disease. Such factors include:

- The availability of hospital beds with adequate infection control measures to prevent nosocomial transmission;
- The availability of trained personnel at hospitals and clinics to administer treatment and manage adverse drug reactions;
- The availability of a social support network to facilitate adherence to treatment; and the presence of other clinical or social conditions in patients.

5.2.4 Uninterrupted supply of quality-assured drugs

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MDR-TB drug management is complex, especially when individualized treatment regimens are used. Drugs are frequently changed due to side effects, delayed DST results, and poor response to treatment. In addition, most second-line drugs have a short shelf life, global production of quality-assured drugs is limited, and drug registration may be a lengthy and costly process that is not attractive to drug manufacturers. Procurement must begin six or more months in advance of the anticipated need, and projected drug needs must be estimated as accurately as possible. Only quality-assured second-line drugs should be used.

A secure supply of quality second-line drugs is vital for treatment of MDR-TB

5.2.5 A recording and reporting system designed for MDR-TB

The specific characteristics of an MDR-TB programme require a recording system with differently defined categories for patient registration, culture and DST results, and monitoring treatment delivery and treatment response for 24 months. Cohort analysis in MDR-TB includes interim indicators and treatment outcomes after two or more years, and treatment outcomes by treatment regimen and DST results. Case registration groups and treatment outcome definitions for MDR-TB are recommended by WHO (see Module 3). These should be used for conducting cohort analyses under the MDR-TB strategy. The recording and reporting system (See Module 6) is essential for evaluating program performance and treatment effectiveness.

FIVE MDR-TB STRATEGY COMPONENTS

1. Sustained political commitment.
   - Long term investment of staff and resources.
   - Coordination efforts between community, local governments, and international agencies.
   - A well functioning DOTS program.
   - Addressing the factors leading to the emergence of MDR-TB.
2. Diagnosis of MDR-TB through quality-assured culture and drug susceptibility testing.
   - Proper triage of patients into DST and the MDR-TB program.
   - Relationship with Supranational Reference Laboratory.
3. Appropriate treatment strategies utilizing second-line drugs under proper management.
   - Rationale and evidence-based treatment design.
   - Monitoring and management of drug side effects.
   - Adequate human resources.
4. Uninterrupted supply of quality-assured second-line drugs.
5. Recording and reporting system designed for MDR-TB programs that ensures performance monitoring and evaluation of treatment outcome.

Patient education is vital in MDR-TB management

HELP Design Group

5.3 MDR-TB PROGRAMME REQUIREMENTS

5.3.1 *Political commitment*

QUESTION
Which public governance and industry involvement are important for a successful MDR-TB prevention and treatment programme?
a. Regional government departments of health.
b. The pharmaceutical industry.
c. Government ministries.
d. Academic and research institutions.
e. Municipal and regional health clinics.
f. Private practitioners.

ANSWER
All the above are correct.

Sustained government commitment and leadership are the foundation for any sound TB control programme. Government commitment must be expressed at all stages of the health intervention process, from planning and implementation to monitoring and evaluation. Key stakeholders must garner such political support, including:

- Government ministries,
- Regional departments responsible for TB control,
- Non-governmental organizations (NGOs),
- The private sector,
- The pharmaceutical industry,
- Academic and research institutions,
- Professional medical societies,
- The donor community.

Commitment comes in the form of:

- Financial and human resources,
- Training,
- Legal and regulatory documents,
- Infrastructure,
- Coordination of all stakeholders.

5.3.2 *Sufficient economic support*

The TB control programme budget must be sufficient for development and retention of an adequate work force with interest and expertise in MDR-TB without weakening the workforce in the rest of the TB programme.

The necessary financial resources to support the MDR-TB framework should be provided.

The patient should have no financial barrier to appropriate care for MDR-TB.

TB control programmes will need physicians, managers, nurses, engineers, microbiologists, information technology specialists, pharmacists, and other specialists with expertise in managing drug-resistant TB.

5.3.3 Regulatory and operational requirements

Before embarking on an MDR-TB programme, the national and regional authorities must shape the policies that provide the foundation for any subsequent legal, administrative and technical support necessary for the initiation, implementation, and monitoring of the MDR-TB programme.

Regulatory document(s) should consider how the program will integrate with the basic DOTS program. The following examples of using regulatory and operational documents can be helpful:

- Legislation can be drafted to assure proper registration, availability, use, and distribution of second-line drugs.
- A local Steering Committee or expert committee can be formed to meet periodically to consult on individual patients in addition to addressing program problems.
- A Memorandum of Understanding delineating responsibilities and funding is often necessary if multiple organizations are involved. In settings where MDR-TB management programmes involve different ministries or departments, eg. the prison system, or the social security system, an inter-ministerial or inter-departmental agreement should be signed which codifies the mechanism for integrating TB services between all authorities.
- A Programme Manual can be the vehicle for disseminating operational and clinical protocols to ensure consistency. It should be officially endorsed by the relevant authorities. The manual not only describes treatment protocols but defines responsibilities for different health care providers and delineates the human resources that will be needed. It specifically describes how patients will be diagnosed, registered, reported, treated, and followed, in addition to program monitoring and evaluation.

AIDS Training and Information Centre members perform a play depicting the symptoms and treatment of TB on World TB Day in Port Elizabeth, South Africa

Lung Health Image Library

5.3.4 Coordination

As organizations and governments in various parts of the world embark on MDR-TB programmes, coordination of activities at all levels is critical. Key stakeholders and organizations that will need to establish good coordination include the following:

- **National TB Control Programme:** The National TB Control Program (NTP) is the central coordinating body for the activities described in the framework. Commitment of the necessary resources,

particularly towards a strong central management team, assures that all aspects are in place from the procurement of second line anti-TB drugs to the proper implementation and monitoring of the MDR-TB programme. Where appropriate, the NTP may need to build partnerships with the private sector.

- **Local health system:** MDR-TB programmes should be tailored to fit into the local infrastructure. The exact organizational structure of the program may vary greatly between different settings depending on how local health care is provided. Transfer between hospitals to outpatient settings or between DOT centres requires great care, advance planning and good communication. Given the nature of care required in the treatment of MDR-TB, a team of health workers including physicians, nurses, and social workers is often used.

- **Community level:** Community involvement and communication with community leaders can greatly facilitate implementation of MDR-TB programmes and fill needs that cannot be met by the medical community alone. Community education, involvement, and organization around TB issues can instil a feeling of community ownership of TB programs and reduce stigma. In some circumstances, communities have helped address the patient's interim needs including the provision of DOT, food and/or housing. Fairly- compensated and well-trained community health workers often play a critical role in ambulatory care and treatment of MDR-TB patients.

- **Coordination with prisons:** Transmission in prisons is an important route of spread of MDR-TB in some countries, and infection control measures can reduce incidence substantially. In many cases, inmates and detainees are released from prison before they finish treatment. Close coordination and communication with the civilian TB control programme, advance planning, targeted social support, and specific procedures for transferring care will help to ensure that the patient completes treatment.

- **Professional societies and the public sector:** In some countries private practitioners manage most of the MDR-TB patients. In these settings it is important to involve the private sector in the design and technical aspects of the program. Many programmes known as public-private mix (PPM) have demonstrated effective and mutually beneficial cooperation. In PPM systems, patients and information move both ways. For example, private providers are compensated fairly through negotiated systems of reimbursement and the public health system may provide clinic- or community-based DOT as well as registering patients and their outcomes. Similar public-private mixes can be set up for MDR-TB, but they require exceptional coordination. The public health system may also get involved in training on national guidelines for the management of MDR-TB, which would apply to all health-care providers.

- **International level:** International technical support through the WHO, Supranational Reference Laboratories (SRL) and other technical agencies is recommended. The collaboration between such entities requires effective coordination and communication on an ongoing basis.

In summary, MDR-TB programmes require:

- Adequate financial support,
- An enabling regulatory environment,
- Sufficient human resources,
- Physical infrastructure,
- Coordination.

A TB control program in Cuzco depends heavily on community volunteers

Lung Health Image Library

From the earliest planning stage, the full range of issues needs to be addressed. With so many components, no single strategy will fit all circumstances. A checklist for MDR-TB Managers can be found on page 18 of the WHO Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency Update 2008, available at (http://whqlibdoc.who.int/publications/2008/9789241547581_eng.pdf).

1. Which of the following describes directly-observed treatment (DOT)?
a) The patient receives a monthly supply of medication for self-administration
b) A health worker completes the patient's treatment record
c) A health worker counts the remaining tablets in medication bottles
d) A health worker calculates the number of drug doses taken
e) The patient is watched swallowing the prescribed medication daily

2. Drug resistance in TB occurs through:
a) Ongoing bacterial mutation
b) Selective pressure of naturally-occurring drug resistant mutants
c) Preventive therapy
d) Inactive metabolism of drugs in TB cavities
e) Inefficient macrophage activity

3. A patient with MDR-TB is defined as:
a) A TB patient on treatment who is not responding
b) A TB patient who has failed treatment
c) A TB patient with confirmed resistance to more than one drug
d) A TB patient with confirmed resistance to isoniazid and rifampicin
e) A TB patient who is a close contact of a known MDR-TB case

4. The most important reason for a patient to develop acquired resistance and MDR-TB is:
a) Patient immune status
b) Preventive therapy
c) Inadequate TB therapy
d) Transmission of MDR-TB strains
e) BCG vaccination

ANSWERS

1: e
2: b
3: d
4: c

Module 2   Epidemiology of MDR-TB

MODULE 2
EPIDEMIOLOGY OF MDR-TB

1   LEARNING OBJECTIVES

At the end of this module you should be able to:

- Define essential terminology
- Describe the global epidemiology of MDR-TB
- Understand the epidemiological impact of MDR-TB
- Define risk factors for MDR-TB

2   Introduction

The term **MDR-TB** has a very specific definition in the field of medicine. A strain of *Mycobacerum tuberculosis* that is resistant to the effects of at least isoniazid and rifampicin is defined as a MDR-TB, with or without resistance to any other drugs. Insoniazid and rifampicin are the two most potent drugs available for TB treatment.

Extensively drug-resistant tuberculosis (XDR-TB) is defined as resistance to any fluoroquinolone, and at least one of three injectable second-line drugs (capreomycin, kanamycin, and amikacin), in addition to being MDR-TB.

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

The **epidemiology of MDR-TB** is the study of the spread of MDR-TB and the factors determining the spread of disease in human populations. Epidemiology is also the basic science for preventive medicine and public health.

The epidemiologic framework for understanding the dynamics of MDR-TB in a community pertains to three types of epidemiologic questions:

- **Analytic epidemiology** (also called etiologic epidemiology), aimed at disentangling and identifying factors that increase the likelihood of infection and the development of disease;
- **Descriptive epidemiology,** that outlines the frequency and distribution of infection, disease and death from MDR-TB in different populations;
- **Predictive epidemiology,** using modelling techniques to forecast the likely course of a MDR-TB epidemic in a given community, based on historical observations.

3   Epidemiological definitions

Question
What is the difference between the "infected" and "infectious" pool of MDR-TB cases?

Answer
Individuals who are actively excreting MDR strains of *M. tuberculosis* and thereby infecting others (usually sputum smear-positive, but may also be smear-negative, culture-positive).

MDR-TB morbidity
Usually measured by the **incidence or prevalence** of the disease in a given population.

Prevalence
The number of cases of MDR-TB, both new and old, present at a given time in a defined population. Prevalence is usually expressed as a proportion (%) or as a number per 100 000 population.

Prevalence of MDR-TB can only be determined accurately through complicated and costly population surveys. Prevalence of MDR-TB in a country or particular area is largely determined by the quality of chemotherapy and the TB treatment program which can be further fuelled by the conditions of the country such as extensive malnutrition, poverty, and HIV. In countries where there is not adequate treatment of MDR-TB, the prevalence of MDR-TB may be two to three times higher than the annual incidence.

INCIDENCE

The number of **new cases** of MDR-TB diagnosed during the course of one year. Incidence is expressed as a proportion of the mid-year population and as a standardised rate per 100 000 population.

True incidence is almost impossible to determine, as incidence is directly related to case finding and notification; as a result of limitations of case finding and notification systems, incidence is frequently referred to as 'notified incidence' or 'estimated incidence', derived from epidemiological models using mortality, prevalence, and risk of infection.

MORTALITY

The number of MDR-TB deaths occurring in a population during one year, usually expressed as a rate per 100 000 population.

CASE FATALITY

The proportion of MDR-TB patients who die as a result of the disease within a given period, usually reported on an annual time period.

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

QUESTION
Does previous TB treatment play a role in determining drug resistance?

ANSWER
Drug resistance is classified according to history of previous TB treatment, as follows:
- Resistance in new patients (previously called 'primary resistance') is resistance in cultures from patients with no history of previous TB treatment or patients who had received TB treatment for less than one month.
  Resistance in new patients provides a measure of the degree of transmission of *M. tuberculosis* strains.
- Resistance in previously treated patients (previously called 'acquired resistance') refers to resistance in cultures from patients with one or more previous TB treatment episodes, of more than one month each. Previously treated patients are also often referred to as retreatment cases. Resistance levels in retreatment are always higher than in new patients, and provide an indication of the extent to which patients were appropriately treated, ie. the quality of TB control.

The terms 'primary' and 'acquired' have been discontinued as epidemiological terminology, as the exact causative nature of drug resistance in a patient is not always possible to assess. Patients may be erroneously labeled as having primary resistance if they do not disclose previous treatment for TB, while patients who fail treatment (and are therefore labeled to have acquired resistance) may do so because the initial strain was resistant and not because it acquired resistance during treatment.

For example, chronic cases of TB (defined by the WHO as cases of tuberculosis that have failed a supervised retreatment regimen) often have MDR-TB. However, there is no way to know if a chronic case of TB has acquired TB or primary TB unless drug susceptibility testing (DST) to the strain was performed at the start of the patient's treatment and then documented to acquire resistance.

Global Project Coverage 1994-2007

* Sub-national coverage in India, China, Russia, Indonesia.

Legend:
- Never previously reported
- New data report 4
- Previous reports
- No data

* shaded areas indicate survey planned or ongoing
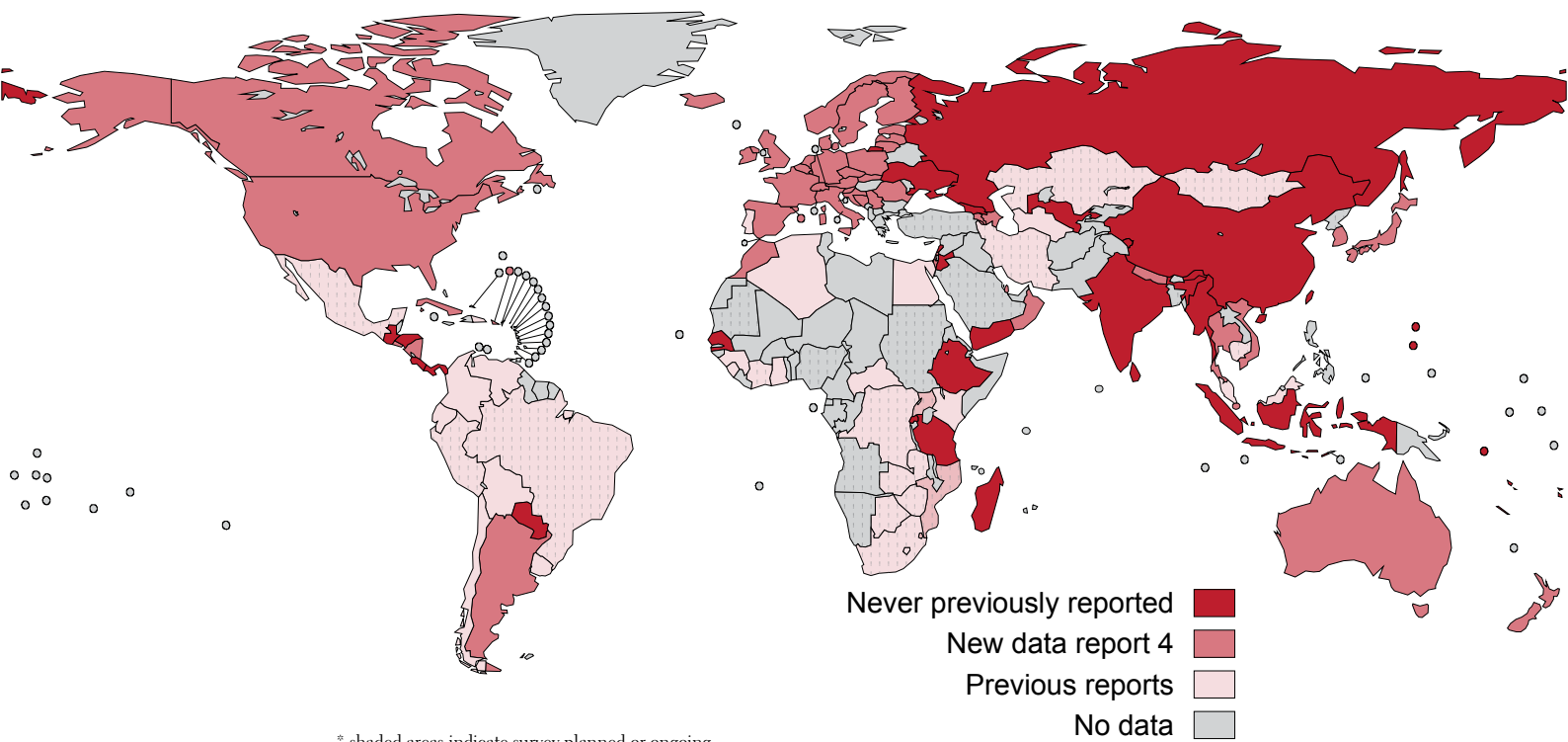
4. MAGNITUDE OF THE GLOBAL MDR-TB PROBLEM

The epidemiology of MDR-TB is complicated by the fact that *Mycobacterium tuberculosis*, unlike many other infectious diseases, causes disease in only a minority of patients infected and has a lifetime potential for activation after infection. MDR-TB incidence varies considerably in different populations and geographical regions. Most of these differences can be attributed to underlying variation in the prevalence of infection; however, very often the underlying reasons for increased incidence are difficult to entangle. Descriptive epidemiology then becomes helpful in identifying populations and risk groups that need particular attention for targeting scarce resources.

Reports of MDR-TB have been increasingly rapidly in different areas of the world, reflecting an unprecedented public health threat. Initially, efforts to ascertain the extent of drug resistance were hampered by problems with laboratory methodology and epidemiological methods. As a result, the WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD) established a Global Project on Anti-TB Drug Resistance Surveillance in 1994. The aim of the project is to determine the levels of resistance to first-line TB drugs (isoniazid, rifampicin, streptomycin and ethambutol) in nationally representative populations using standardised methods. Emphasis is placed on epidemiological methods to ensure patient representativeness and on differentiating new and retreatment TB cases (for more information see the WHO Guidelines for the surveillance of drug resistance in tuberculosis: http://whqlibdoc.who.int/publications/2003/9241546336.pdf). A network of Supranational Reference Laboratories (SRL) was simultaneously established to provide quality assurance through validation of drug susceptibility data. For a list and contact details for the 20 SRLs worldwide, look on the WHO website (http://www.who.int/drugresistance/tb/labs/en/index.html).

The most authoritative documentation describing the global epidemiology of MDR-TB is the series of monographs on anti-TB drug resistance surveillance issued by WHO/IUATLD. By 2007, four rounds of the global survey have been completed and all are available online:

- The first report 1994-1996 (http://whqlibdoc.who.int/hq/1997/WHO_TB_97.229.pdf)
- The second report 1996-1999 (http://whqlibdoc.who.int/hq/2000/WHO_CDS_TB_2000.278_intro.pdf)
- The third report 1999-2002 (http://www.who.int/tb/publications/who_htm_tb_2004_343/en/index.html)
- The fourth report 2002-2007 (http://www.who.int/tb/publications/2008/drs_report4_26feb08.pdf)

A total of 116 countries or regions within countries have been surveyed and isolates from over 250 000 patients have been tested between 1994 and 2007. Forty-seven countries participated in more than one survey, allowing trends in drug resistance to be determined.

Of particular concern is the fact that the magnitude of drug resistance is not known in many areas of the world with high burdens of TB, such as most of China, India, the former Soviet Union, Nigeria, and Indonesia. These gaps must be filled before the magnitude of drug resistance is fully known. Nevertheless, evidence from one-half the world's nations confirms that MDR-TB is a serious problem in many countries.

Results from the WHO surveys showed that the problem of MDR-TB is ubiquitous; China, India and the Russian Federation are estimated to carry the highest number of MDR cases.

- Among new patients, the median prevalence of MDR-TB in new patients in the latest WHO Report (2007) was 2.9%;
- In patients previously treated for TB, the median prevalence of MDR-TB was 15.3%.

The geographical distribution of MDR-TB in the world can be found in the *WHO fourth report on Anti-tuberculosis drug resistance in the world*, showing that many areas face endemic and epidemic MDR-TB, with rates in several settings being alarmingly high.

The WHO estimates that the number of incident MDR-TB cases (including both new and retreatment cases) occurring worldwide in 2003 was 424 000 (95% confidence interval 297000 to 639 000 cases). MDR-TB patients often live a number of years before succumbing to the disease. Therefore, MDR-TB prevalence may be three times greater than its incidence, suggesting that the actual number of MDR-TB cases in the world today may approach or exceed **one million cases.**

All MDR TB Cases by Regions (2003)

152,018	Western Pacific Region
114,967	South-east Asia
65,853	Eastern Europe
48,141	Africa high HIV incidence
18,330	Eastern Mediterranean Region
11,301	Latin America
10,449	Africa low HIV incidence
1,681	Established Market Economies
1,462	Central Europe
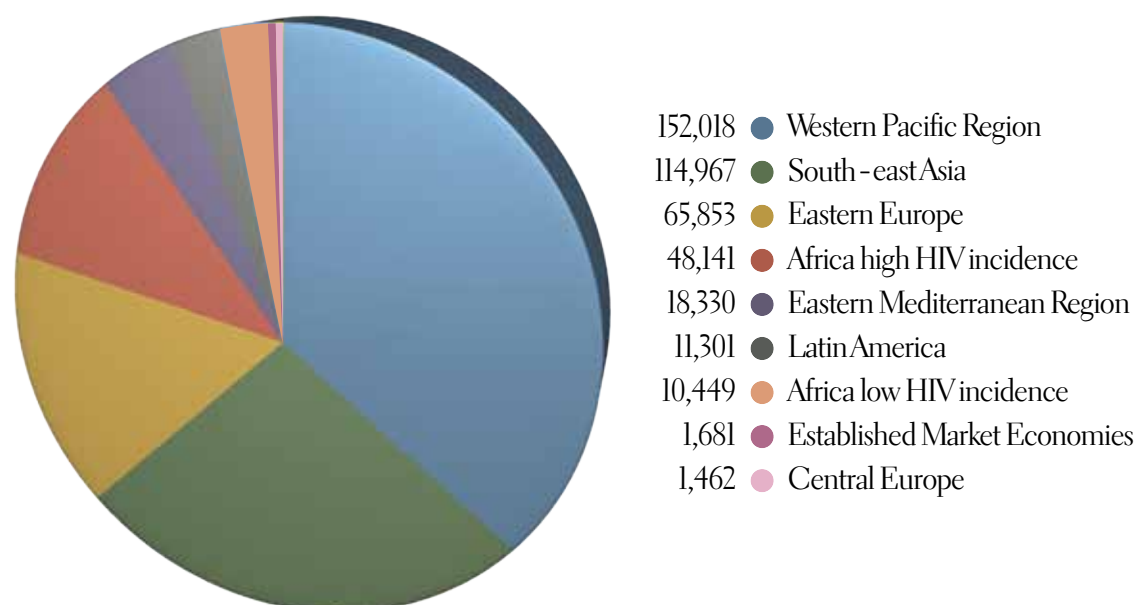
Rates of MDR among new TB cases 1994-2007

☐	< 3%
☐	3-6%
☐	>6%
☐	No estimate
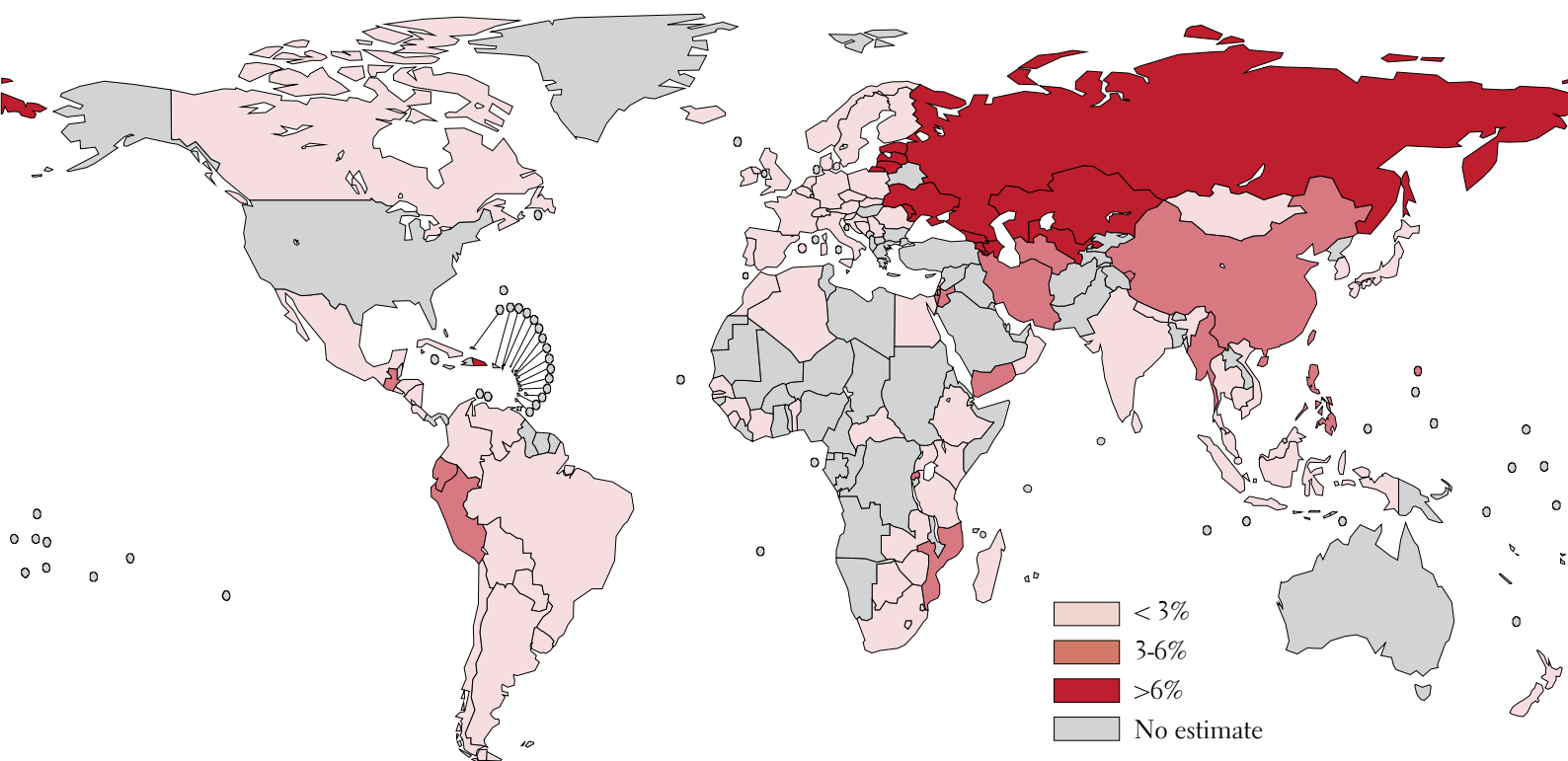
Rates of MDR among previously treated TB cases1994-2007

☐	< 6%
☐	6-20%
☐	20-40%
☐	>40%
☐	No estimate
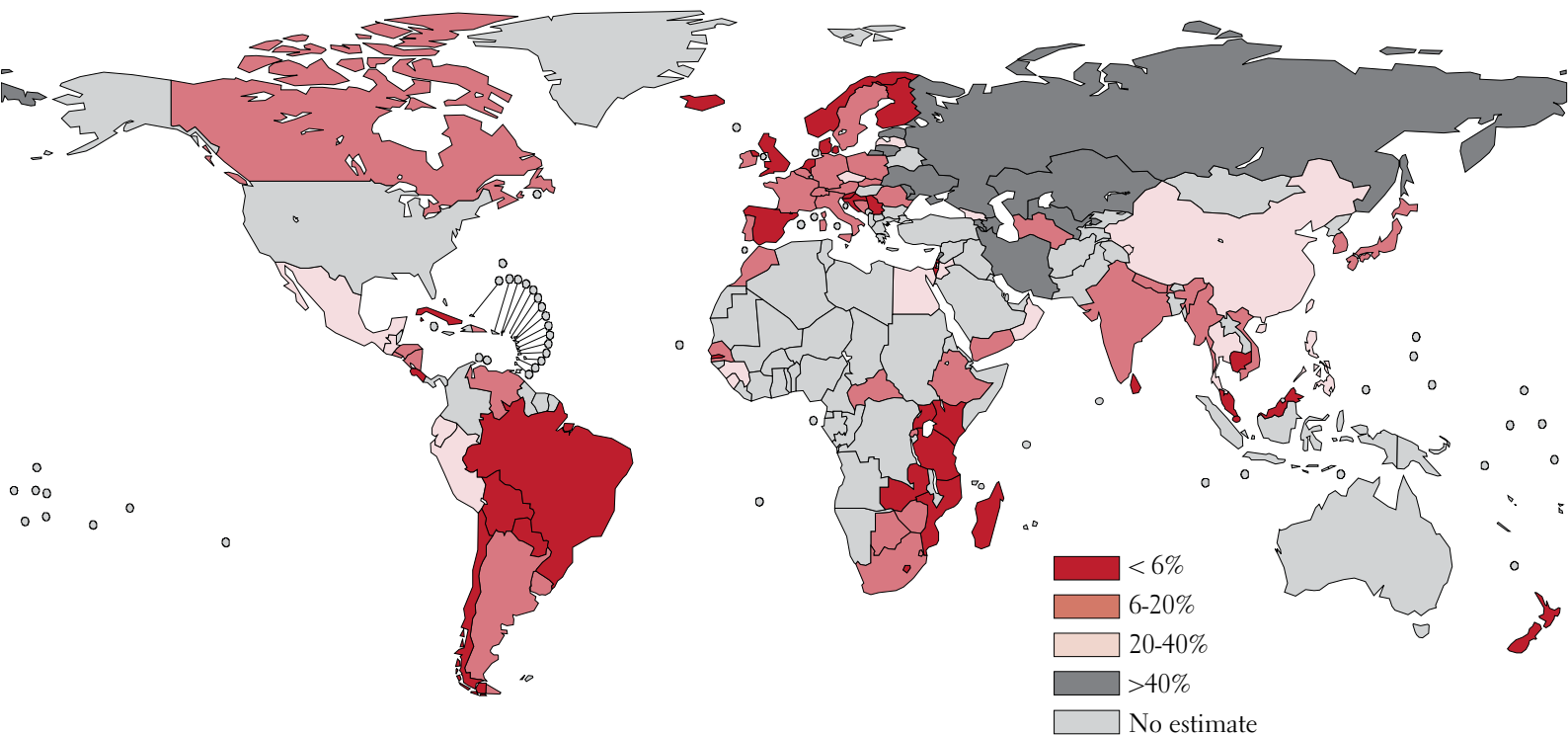
The social and economic burden of this problem is already evident, given that the cost of treating a case of MDR-TB is **up to 100 times** the cost of treating an uncomplicated drug-susceptible TB case.

Many identified MDR-TB cases have resistance to other drugs in addition to rifampicin and isoniazid. In the global survey, one third of MDR-TB cases had resistance to all four first-line drugs drugs tested (isoniazid, rifampicin, streptomycin and ethambutol).

Since the early 1990's, several outbreaks of MDR-TB have been reported in different regions of the world, often associated with HIV infection. Experience in many countries has shown that patients with active, untreated MDR-TB can infect large numbers of HIV-positive individuals, leading rapidly to significant outbreaks of MDR-TB with high case-fatality rates. Epidemiologic and genetic studies have confirmed ongoing transmission of drug-resistant TB and nosocomial transmission of MDR-TB associated with HIV infection has been documented. Although HIV has not yet been shown as an independent risk factor for MDR-TB, sub-optimal TB control, together with the rapidly progressing HIV epidemic, has created a fertile environment for transmission of MDR-TB in many countries, and there is ample reason to believe that the full brunt of MDR-TB is still to be faced worldwide.

In 2006, a resistance survey was conducted by the CDC and the WHO to determine the extent of resistance to second-line drugs. Surveying the WHO/IUATLD network of SRLs, over 17,000 isolates from 49 countries were included, all of which had been tested for resistance to at least three classes of second- line drugs. These are not population-based data, as second-line drug testing is not routine in most countries. The survey found that of the isolates tested against second-line drugs in the 49 contributing countries, 20% were found to be MDR-TB, and 2% to be XDR-TB.(7) Strains of XDR-TB have been reported in every region of the world, with as many as 19% of MDR strains found to be XDR, a proportion which has more than tripled in some areas since 2000. When capacity allows, these guideline recommend testing all MDR-TB isolates for resistance to a fluoroquinolone and the second-line injectable agents to define the proportion XDR-TB among MDR-TB.

Despite the association with previous treatment, drug-resistant strains including XDR-TB are readily transmissible and outbreaks have been reported, often in populations with high HIV prevalence. In one outbreak of XDR-TB in Kwazulu-Natal, half of the patients had never received anti-tuberculosis treatment. The overlapping epidemics of HIV and TB are significantly worsened by XDR-TB, as outbreaks of these strains appear to cause higher and more rapid mortality in HIV-infected patients. Such strains pose a serious threat to global TB control, as detection is challenging in settings where laboratory resources and treatment options are severely limited.

5. RISK FACTORS FOR MDR-TB

The WHO Global Reports showed the following significant risk factors for MDR-TB:

- Previous treatment for TB.
- Exposure to MDR-TB patients.
- Recent emigration from a geographic area with high drug resistance prevalence.

Module 3 provides more detail on risk factors for MDR-TB and strategies for case-finding.

1. The frequency and distribution of MDR-TB infection, disease and death is provided by:
a) Analytic epidemiology
b) Predictive epidemiology
c) Population epidemiology
d) Descriptive epidemiology
e) Modelling epidemiology

2. Which of the following statements are true
a) The Western Pacific Region has the largest number of estimated MDR-TB cases globally
b) Generally new TB cases will have higher levels of MDR-TB then previously treated cases
c) Many MDR-TB have resistance to other anti-TB drugs as well
d) all of the above
e) a) and c)

3. True/False:
(   ) MDR-TB is uniformly spread throughout the world
(   ) MDR-TB incidence is highest in countries with highest HIV prevalence
(   ) Previous TB treatment is a major risk factor for MDR-TB
(   ) MDR-TB transmission is facilitated in the presence of HIV infection
(   ) The incidence of MDR-TB is always lower than the prevalence

ANSWERS

1: d
2: e
3: F,F,T,T,T.

MODULE 3

CASE FINDING STRATEGIES AND CASE DEFINITIONS

1 LEARNING OBJECTIVES

At the end of this module you should be able to:

- Identify risk groups for MDR-TB
- Apply case finding strategies in different resource settings
- Understand the purpose of case definitions
- Apply case registration categories and case definitions
- Understand the concept and purpose of cohort analysis

2 Introduction

This course assumes a general understanding of case-finding and diagnosis of active TB. This information can be reviewed in reference books on TB, including WHO TB publications such as Treatment of tuberculosis: Guidelines for national programmes, 3rd edition (http://whqlibdoc.who.int/hq/2003/WHO_CDS_TB_2003.313_eng.pdf). This module emphasizes aspects that will allow the health care professional to identify TB patients that may have MDR-TB.

There is no single strategy for case finding of MDR-TB. Country-specific strategies must be developed based on the burden of MDR-TB cases and the resources available.

3 Risk groups for MDR-TB

The prevalence of MDR-TB in specific risk groups can vary greatly across different settings. Local data are best for characterizing risk groups accurately, eg. prisoners with TB in one country may have a high rate of MDR-TB, while in other countries, the risk of MDR-TB among prisoners with TB may be no different than other TB patients.

Most TB control programmes do not have the resources to perform culture and test drug susceptibility testing (DST) in all TB patients; these tests can be used selectively for patients at risk for MDR-TB based on a careful history.

QUESTION

Which features in the history of a patient with TB would suggest MDR-TB?

a. Persistent nausea while on TB treatment.

b. Failure of TB treatment in the private sector.

c. History of other medications that interfere with TB drug absorption.

d. Patients who, while on SCC treatment, are sputum smear positive at 5 months or later during the course of treatment.

e. The presence of more than one person in the same household with active TB.

ANSWER

b, c and d are correct.

TB regimens from the private sector can vary greatly. A detailed history of drugs used is essential. If both isoniazid and rifampicin were used, the chances of MDR-TB may be high. Sometimes second-line TB drugs may have been used and this is important information for designing MDR-TB treatment regimens.

Antacids containing aluminium or magnesium selectively compete with TB drugs, particularly with isoniazid and fluoroquinolones.

The most important feature in the history of a TB patient which would suggest MDR-TB is the patient who is sputum positive at 5 months or later during the course of treatment.

Specific elements of the history that suggest an increased risk for drug resistance are described listed in Table 3.1.

Table 3.1. Risk factors for MDR-TB	
Risk factor	**Comments**
Failure of retreatment regimens and chronic TB cases	Chronic TB cases are defined as patients who are sputum positive at the end of a re-treatment regimen. These patients have the highest MDR-TB rates of any other group, often greater than 80%.
Exposure to a known MDR-TB case	Most studies have shown close contacts of MDR-TB patients to have very high rates of MDR-TB. How to address MDR-TB contacts is described in Module 13.
Failure of first-time short course chemotherapy (SCC)	Failures for SCC are patients who, while on treatment, are sputum smear positive at 5 months or later during the course of treatment. Not all patients who fail a regimen have MDR-TB and the percentage may depend on a number of factors, including whether rifampicin was used in the continuation phase and whether DOT was used throughout the treatment course.
Failure of TB treatment in the private sector.	TB regimens from the private sector can vary greatly. A detailed history of drugs used is essential. If both isoniazid and rifampicin were used, the chances of MDR-TB may be high. Sometimes second-line TB drugs may have been used and this is important information for designing MDR-TB treatment regimens.
Relapse and return after default without recent treatment failure	Evidence suggests that most relapse and return after default cases do not have MDR-TB. However, certain histories may point more strongly to possible MDR-TB, eg. erratic drug use or early relapses. Relapses with in the first six months post-treatment may have similar MDR-TB rates as failures.
Exposure in institutions that have MDR-TB outbreaks or a high MDR-TB prevalence	Patients that frequently stay in homeless shelters, prisoners in many countries, and healthcare workers from clinics and hospitals tend to have higher rates of MDR-TB.
Residence in areas with high MDR-TB prevalence	MDR-TB rates in many areas of world in new cases can be high enough to justify routine MDR-TB testing in all new cases.
History of using poor or unknown quality TB drugs	The percentage of MDR-TB caused by use of poor quality drugs is unknown but considered significant. It is known that poor quality drugs are used in many countries. Just because drugs come from a national TB program does not assure they are of adequate quality. All drugs should be quality-assured.
History of other medications that interfere with TB drug absorption	Antacids containing aluminium or magnesium selectively compete with TB drugs, particularly with isoniazid and fluoroquinolones.
Use of drugs that compete with or alter the metabolism of TB drugs, resulting in reduced serum levels	Antifungal agents in the azoles family interfere with each other; rifamycins will lower azole levels. In addition, ketoconazole can lower rifampicin levels by 40%-50%.
Treatment in programs that operate poorly (especially recent and/or frequent drug stock outs)	These are usually non-DOTS programs or DOTS programs with poor drug management and distribution systems.
Co-morbid conditions associated with Malabsorption or rapid transit diarrhoea	Malabsorption may result in selective low serum drug levels and may occur in either HIV-negative or -positive patients.
HIV in some settings	Numerous MDR-TB outbreaks have been documented in HIV patients, and in some areas of the world having HIV is risk factor for MDR-TB (see module 10)

(Source: World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency update 2008 (WHO/HTM/TB/2008.402). Geneva, Switzerland: World Health Organization; 2008.)

The prevalence of MDR-TB in specific risk groups can vary greatly across different settings.

Congregate settings may pose a great risk for MDR-TB outbreaks

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4 Case-finding strategies

Identification and treatment of patients with or at high risk of MDR-TB can be based on a range of strategies. *In vitro* DST plays a key role in virtually all of these strategies and the recommended standard of care is to start MDR-TB treatment upon laboratory confirmation; however this may not always be possible in resource-poor areas or in areas with low laboratory capacity. A strong emphasis should always be for programmes to have access to DST capacity to identify MDR-TB and when it is not there, to develop it. When adequate laboratory infrastructure and resources to conduct DST on all patients suspected of having MDR-TB do not exist, there are strategies for which patients can be empirically treated for MDR-TB (see Modules 5 and 6 for information on treatment design).

4.1 Strategies for programmes with no access to DST

Question

Which case finding strategies could be followed in settings with no access to DST?
a. Regard all failures of first-line retreatment and chronic TB cases as MDR-TB.
b. Regard all HIV+ patients with TB as MDR-TB.
c. Patients in whom first-line re-treatment failed in well-run DOTS programmes almost always have MDR-TB and in most instances can enter MDR-TB treatment directly.
d. First-line SCC failures can be regarded as MDR-TB.
e. All prisoners with TB should be regarded as MDR-TB.

Programs that do not have sufficient laboratory capacity or resources to do DST in all patients could consider strategies that enrol patients with a high risk of MDR-TB into the MDR-TB programme, without individual DST. Three groups that fall under consideration for this strategy are as follows:

Failures of first-line retreatment and chronic TB cases:
- **Symptomatic close contacts of MDR-TB cases:** Regimens for symptomatic close contacts of MDR-TB cases are recommended. See Module 13 for more information and definitions of close contacts.
- **First-line SCC failures:** Since the MDR-TB rate in this group of patients can vary greatly, it is best to document the rate of MDR-TB in first-line SCC failures before deciding if enrolment into MDR-TB treatment can take place without DST.

Groups other than the three mentioned above are unlikely to have such high rates of MDR-TB to justify entry into a MDR-TB treatment without DST. In groups with low or moderate rates of MDR-TB, at least screening to document MDR-TB is necessary before enrolment into MDR-TB programmes.

4.2 STRATEGIES FOR PROGRAMMES WITH ACCESS TO DST

4.2.1 General considerations

No less than two sputum specimens should be obtained for culture, and DST should be performed with the best culture. DST does not routinely need to be done in duplicate. Procedures for collecting and managing specimens for culture and DST are described in Module 4. Different techniques, limitations, quality assurance requirements and other issues of culture and DST are also addressed in Module 4.

Previously treated patients may have had DST results in the past that may no longer reflect the resistant pattern of the strain they have at the time of MDR-TB enrolment. DST should therefore be performed again in all patients who have received treatment since the date of their last DST result.

Paediatric cases require adjustments in diagnostic criteria and treatment. Young children in particular may not be able to produce sputum specimens. More aggressive measures such as nasal gastric aspiration may be considered for culture and DST (Note: gastric aspiration should only be undertaken where culture facilities are available due to the low yield from microscopy and the distress involved for the child. Culture specimens need to be processed within the hour because the acidic juices will kill the bacteria relatively quickly). MDR-TB programmes should not exclude children from treatment solely because sputum specimens are not available; children with active TB who are close contacts of patients with MDR-TB can be started on regimens designed for MDR-TB treatment. See Module 13 for more detail on the diagnostic work-up and management of children and MDR-TB contacts.

Cases of HIV infection also require adjustment in diagnostic criteria and indications for treatment. The diagnosis of TB in HIV-infected people is more difficult and may be confused with other pulmonary or systemic infections. HIV-infected persons are more likely to have smear-negative TB or extrapulmonary TB. WHO Guidelines (*Improving the diagnosis and treatment of smear-negative pulmonary and extrapulmonary tuberculosis among adults and adolescents: Recommendations for HIV-prevalent and resource-constrained settings: http://whqlibdoc.who.int/hq/2007/WHO_HTM_TB_2007.379_eng.pdf*)

recommend the use of clinical algorithms that include the use of chest X-ray and culture to improve the ability to diagnose TB in smear-negative HIV-infected patients. Because unrecognized MDR- and XDR-TB are associated with such high mortality in HIV-infected patients, many programmes perform culture and DST testing for all HIV-infected patients with active TB. Programmes without facilities or resources to screen all HIV-positive patients for DR-TB should put significant efforts into obtaining them, especially if DR-TB rates are moderate or high. Some programmes may adopt a strategy of targeted DST for patients with increased risk of DR-TB or low CD4 (See Module 10). Rapid diagnostic techniques for the HIV-infected with active TB can be very useful to promptly identify those with DR-TB (see page 32 of the *Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency Update* 2008). If XDR-TB is prevalent, HIV-infected patients with MDR-TB should be screened for XDR-TB with the use of liquid media or another validated rapid technique for DST to second-line injectable agents and a fluoroquinolone (Section 4.2.3 of this Module). In some cases (also see Module 10) smear-negative HIV-infected patients may need to be enrolled empirically into regimens designed to treat MDR-TB.

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4.2.2 Use of rapid DST testing

When possible, it is recommended that an accurate rapid DST test be used in patients suspected of having MDR-TB. If the test identifies MDR-TB, the patient can be started on an empiric treatment regimen until full DST results are available. Different types of rapid tests are discussed in Module 4. To date, large-scale use of rapid DST tests in poor resource areas has not been feasible; however, research at WHO and other institutions aims to bring rapid testing on a large-scale level to these countries.

In most cases a rapid test that tests only for rifampicin resistance can be used to determine whether or not a patient should be started on a MDR-TB regimen; however, the correlation between rifampicin resistance and MDR-TB is not 100%.

Page 33 of the latest WHO *Guidelines for the programmatic management of drug-resistant tuberculosis* (http://www.who.int/entity/tb/publications/2008/programmatic_guidelines_for_mdrtb/en/index.html) have an algorithm for use to rapid drug-resistance testing that is available online.

4.2.3 Use of second-line DST

Not all MDR-TB programmes have the capacity to do DST to second-line drugs, and therefore many programs design diagnostic and treatment strategies that are not dependent on them. Commonly, programs recommend DST for second-line drugs after the strain has been identified as MDR-TB; however, in some programs DST to second-line drugs is recommended at the initial evaluation if the suspicion of MDR-TB is very high and most cases of MDR-TB in the area also have resistance to second-line drugs.

This will enable programmes to perform case-finding for XDR-TB and to assure proper treatment. The two strongest risk factors for XDR-TB are:

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

For HIV-infected individuals with risk factors for XDR-TB, because of the high and rapid risk of death with co-infection, liquid or other validated rapid techniques for DST of first- and second-line drugs is recommended.

DST of second-line drugs and how to interpret them are discussed in Modules 4, 5 and 6.

5 CASE DEFINITIONS FOR MDR-TB

5.1 WHY USE CASE DEFINITIONS?

QUESTION
What is the purpose of using case definitions in MDR-TB ?
a. To allow proper patient registration and epidemiological notification;
b. To facilitate case allocation to appropriate treatment categories;
c. To facilitate case evaluation according to site, bacteriology and treatment history;
d. To evaluate new treatment regimes for MDR-TB;
e. To evaluate MDR-TB programme performance through cohort analyses.

ANSWER:
a,b, c and e are correct.
Case definitions are used to identify, record and control patients and their treatment and to allow proper patient registration and epidemiological notification.
Case definitions are used to facilitate case evaluation according to site, bacteriology and treatment history and resistance to rifampicin may be used to indicate a diagnosis and estimation of the relevance of MDR-TB.

MDR-TB case definitions are used for the following reasons:

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

Question

Which of the following statements describe MDR-TB?

a. A case of MDR-TB is defined as a patient with bacteriologically proven TB whose disease is due to bacilli showing in vitro resistance to rifampicin and isoniazid.
b. Pulmonary MDR-TB refers to disease involving the lung parenchyma only.
c. Site of MDR-TB disease is classified according to pulmonary or extra-pulmonary involvement
d. MDR-TB cannot be diagnosed by x-ray alone.
e. Severity of disease is classified according to bacteriological status (smear or culture, positive or negative) at diagnosis.

Answer:

Statements a, b, and c describe the disease and the principles of diagnosis of MDR-TB i.e. the resistance of tuberculosis bacteria to rifampicin and isoniazid.

Statements d and e deal with diagnostic and classification matters and do not contribute to the definition of the disease or answer the set question.

A case of MDR-TB is defined as a patient with bacteriologically proven TB whose disease is due to bacilli showing in vitro resistance to rifampicin and isoniazid.

Case definitions for MDR-TB are determined by three aspects, ie:

- Site of disease.
- Severity of disease.
- History of previous treatment.

Site of MDR-TB disease is classified according to pulmonary or extra-pulmonary involvement: Pulmonary MDR-TB refers to disease involving the lung parenchyma only. Extra-pulmonary MDR-TB refers to organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, and meninges.
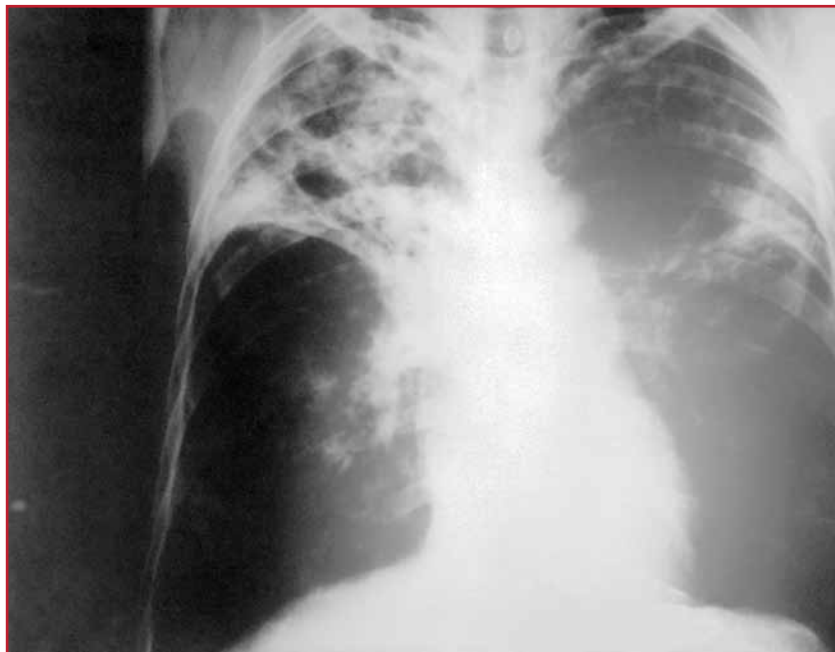
An anteroposterior X-ray of a patient diagnosed with advanced bilateral pulmonary TB. MDR-TB cannot be diagnosed by X-ray alone.

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A patient with both pulmonary and extra-pulmonary MDR-TB constitutes a case of pulmonary MDR-TB. The case definition for extra-pulmonary MDR-TB in several sites depends on the site with the most severe form of disease.

Severity of disease is classified according to bacteriological status (smear or culture, positive or negative) at diagnosis. Previously confirmed MDR-TB patients may be smear and culture-negative at the start of MDR-TB treatment. Commonly, this is due to delays between obtaining the sputum specimen and the start of MDR-TB treatment, intermittent excretion of mycobacteria, and anti-TB treatment in the interim period.

History of previous TB treatment allows categorization of MDR-TB patients into three categories. These categories are essential for epidemiological monitoring of the MDR-TB epidemic at the regional and country level, and help identify patients that may be at risk failing a MDR-TB regimen. These groups refer explicitly to previous treatment and do not purport to explain the reason for resistance. Patient categories are as follows:

- New: Patients with no history of previous TB or MDR-TB treatment (or less than one month of anti-tuberculosis treatment).
- Previously treated with first-line drugs only: Patients with a history of previous TB treatment, ie. with first-line TB drugs.
- Previously treated with second-line drugs: Patients with a history of previous MDR-TB treatment, ie. with second-line TB drugs.

5.3 Case registration for cohort analysis

All patients who are identified with MDR-TB should be entered into a registry. The registry is described in more detail in Module 12, but must clearly identify MDR-TB patients from other forms of drug resistance (or from patients with suspected, but not confirmed MDR-TB).

QUESTION:
What is meant by an "MDR-TB cohort"?

ANSWER:
An MDR-TB cohort is defined as a group of patients registered with MDR-TB during a specified time period (eg. one year). The date of confirmation of MDR-TB and the date when treatment was started should also be entered in the registry (see Module 12) but it is the date when the patient is registered that determines the cohort to which the patient belongs.

Cohort analysis should be performed on all registered MDR-TB patients. National TB Programmes are encouraged to provide MDR-TB treatment for all diagnosed MDR-TB patients.

Examples of reasons for exclusion from treatment include the following:

- Died before treatment initiated
- Patient unwilling to be treated
- Drug supply shortage
- Limited health facility access
- Clinically and/or socially related reasons

Some patients may be registered twice during one cohort period, e.g. failure or default patients who are re-registered; therefore, the cohort analysis should identify the total number of patients as well as the total number of treatment episodes. Stratifying cohort analyses by the three patient registration categories will decrease the repeated inclusion of a patient in a single analysis.

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Self Assessment Questions and Exercises:
Case finding strategies and case definitions

1. MDR-TB case definitions are used to:
a) Allow appropriate treatment of patients
b) Monitor epidemiological trends
c) Conduct cohort analyses of control programme performance
d) Allow correct disease notification
e) All of the above

2. A case of MDR-TB is defined as:
a) A TB patient on treatment who is not responding
b) A TB patient who has failed treatment
c) A TB patient with confirmed resistance to isoniazid and streptomycin
d) A TB patient with confirmed resistance to isoniazid and rifampicin
e) A TB patient who is a close contact of a known MDR-TB case

3. A case of XDR-TB is defined as:
a) A TB patient with comfirmed resistance to Ethionamide and Kanamycin
b) A TB patient with confirmed MDR-TB and confirmed resistant to any two second-line drugs
c) A TB patient with confirmed resistance to 4 TB drugs
d) A TB patient with confirmed resistance to isoniazid and rifampicin, a second-line injectable agent and a fluoroquinolone
e) A TB patient who is a close contact of a known MDR-TB case

4. A patient with MDR-TB and previous history of TB treatment is defined as a:
a) New MDR-TB patient
b) Retreatment patient
c) Category II MDR-TB patient
d) Treatment failure
e) Chronic case

5. MDR-TB case definitions are determined by:
a) Site of disease
b) Severity of disease
c) History of previous TB treatment
d) All of the above
e) None of the above

6. A patient with pulmonary MDR-TB complicated by MDR-TB meningitis is classified as
a) A case of extra-pulmonary MDR-TB
b) A case of MDR-TB meningitis
c) A case of pulmonary MDR-TB
d) A case of central nervous system MDR-TB
e) A case of mixed MDR-TB

		ANSWERS
1:	e	
2:	d	
3:	d	
4:	c	
5:	d	
6:	c	

MODULE 4

DIAGNOSIS OF MDR-TB

1   LEARNING OBJECTIVES

At the end of this module you should be able to:

- Identify signs and symptoms of MDR-TB
- Outline the examinations required when assessing a patient for MDR-TB
- Understand the laboratory diagnosis of MDR-TB
- Make rational use of drug susceptibility testing

2   INTRODUCTION

In the majority of cases the development of disease due to MDR-TB is insidious and takes place over weeks and months. Because this happens, patients often ignore the symptoms or accept them as symptoms from being overworked, experiencing a lack of sleep or simply related to the daily stresses of life. Many patients therefore delay in seeking health care.

MDR-TB may also be associated with other serious disorders, including HIV infection, alcoholism, renal failure, diabetes mellitus, neoplastic diseases and drug abuse, to name but a few. The signs and symptoms of these conditions and their complications can easily obscure or modify those of MDR-TB and can result in considerable delays in diagnosis or in misdiagnosis for extended periods, especially in patients with HIV infection. It is therefore important that clinicians in high-burden countries have a high index of suspicion for MDR-TB.

3   RISK GROUPS FOR MDR-TB

QUESTION
What are the signs and symptoms of MDR-TB?

ANSWER
Signs and symptoms of MDR-TB are the same as in drug-susceptible TB.

Cough is the most common symptom of pulmonary MDR-TB. Early in the course of the illness, the cough may be nonproductive, but subsequently, as inflammation and tissue necrosis ensue, sputum is usually produced. A cough is not specific to MDR-TB; however, most acute respiratory infections resolve within a week or two.

Chest pain due to infiltration in the lung parenchyma is common in active pulmonary MDR-TB. Spontaneous pneumothorax may also occur, often causing chest pain. Inflammation of the lung parenchyma adjacent to a pleural surface may cause pleuritic pain. A dull, nagging chest pain is common in advanced disease; the sharp pleuritic pain due to pleural involvement is less common.

Dyspnea as a result of parenchymal lung involvement usually manifest in advanced pulmonary MDR-TB disease. Dyspnea is caused by severe lung fibrosis or lung destruction, or by tuberculous bronchopneumonia. MDR-TB may cause severe respiratory failure.

Haemoptysis may be a presenting symptom of pulmonary MDR-TB but does not necessarily indicate an active disease process. Haemoptysis may result from residual tuberculous bronchiectasis, rupture of a dilated vessel in the wall of an old cavity (Rasmussen's aneurysm), bacterial or fungal infection (especially Aspergillus in the form of a fungus ball or mycetoma) in a residual cavity, or erosion of calcified lesions into the lumen of an airway (broncholithiasis). In active pulmonary MDR-TB, haemoptysis presents a late sign and may be profuse.

Systemic symptoms of MDR-TB include fever, chills, night sweats, tiredness, anorexia and weight loss. Systemic manifestations such as fever, malaise and weight loss are likely mediated by cytokines, especially tumour necrosis factor (TNF-α). **Fever** is most easily quantified, usually presenting a low-grade fever that may be remittent or intermittent. **Anorexia** and **weight loss** usually start early in the illness and become worse as the disease progresses. **Chills** and **night sweats** are general complaints by MDR-TB patients but too nonspecific to render a definitive diagnosis.

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

Extra-pulmonary MDR-TB presents more of a diagnostic challenge, in part because it is far less common and therefore less familiar to most clinicians. In addition extra-pulmonary MDR-TB involves relatively inaccessible sites, and because of the nature of the sites involved, fewer bacilli can cause much greater damage.

A young husband brings his wife and sister-in-law to see Dr Praveen at the MCD Chest Clinic in Patparganj in East Delhi. The sister-in-law has TB and has now been diagnosed with MDR-TB. She has had TB for 2 years and not gotten better. In those 2 years, the family has spent 100 000 rupees (2000 USD) on her treatment; drugs, injections, home care, nursing home etc. They have finally come to the clinic where they have told her she has MDR-TB. The family spent the money to avoid stigma and because they thought that by paying for a private practitioner, they were getting better services

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4   Assessing a patient for MDR-TB

An initial evaluation for MDR-TB should include:

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

More detail on patient evaluation and monitoring once the diagnosis has been made is provided in Module 11.

4.1 Medical history

It is important to ask patients suspected of having MDR-TB about their history of MDR-TB exposure and disease as well as history of past TB treatment. If previous TB treatment was erratic or interrupted, MDR-TB may be the result.

It is also important to establish whether other medical conditions are present, e.g:

- HIV infection;
- Diabetes mellitus;
- Renal disease;
- Malignancies;
- Chronic malabsorption syndrome;
- Prolonged corticosteroid therapy;
- Other immunosuppressive therapy.

All patients who do not know their current HIV status should be offered provider-initiated HIV testing and counseling. Given the high levels of HIV and TB co-infection in many settings, provider-initiated HIV counseling and testing is the recommended method of HIV testing for all TB suspects and patients. This is more efficient and more likely to be successful than referring patients elsewhere for HIV testing and counseling. Provider-initiated counseling and testing can serve as a gateway to life-saving prevention, care and treatment interventions.

4.2 Physical examination

A physical examination is an essential part of the evaluation of any patient. It cannot be used to confirm or rule out MDR-TB, but can provide valuable information about the patient's overall condition and other factors that may affect patient management.

Physical signs of MDR-TB are often nonspecific. The patient may be thin and pale, body temperature may be high, slightly increased or normal, and the pulse is usually rapid. Finger clubbing is associated with extensive lung damage and superinfection with non-TB organisms, often found in bronchiectasis, lung cancer, empyema and lung abscess.

During chest examination, crackles are common, and there may be dullness to percussion or bronchial breathing with a localized wheeze. Amphoteric breathing over a large cavity can often be heard. The trachea may be pulled over due to fibrosis or scarring. For details on the examinations required once a diagnosis of MDR-TB has been made please refer to Module 11.

Dr Praveen examines one of his TB patients at the MCD Chest Clinic in Patparganj in East Delhi

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5   LABORATORY DIAGNOSIS OF MDR-TB

MDR-TB is often suspected clinically when a patient has a persistently positive acid-fast bacilli (AFB) smear or mycobacterial culture or when progress on first-line TB therapy is unsatisfactory, despite good adherence. MDR-TB can also be suspected epidemiologically when a person has had exposure to a confirmed MDR-TB patient (see Module 3). The symptoms and signs of MDR-TB are, however, non-specific and many diseases may mimic MDR-TB and vice versa.

A confirmed diagnosis of MDR-TB can only be made by demonstrating *in vitro* **resistance to isoniazid and rifampicin** in the *M. tuberculosis isolate* from the patient; therefore, **MDR-TB is a laboratory diagnosis**. Nonetheless, there are circumstances where patients will be treated for empirically for MDR-TB without a confirmed diagnosis (see Modules 5 and 6). Empirical treatment for MDR-TB without a confirmed diagnosis is far from optimal and all programs should strive for quality-assured/quality-controlled laboratories with DST

The clinical presentation of patients with MDR-TB is similar to those of patients with drug-susceptible TB. Because MDR-TB patients in resource poor areas are often initially placed on first-line regimens and the diagnosis is made only after non-response to therapy. Because of this many patients present with cavitary lung lesions, advanced lung parenchyma damage, and smear-positive sputum. Efforts should be made to diagnose MDR-TB early to avoid late presentation of the disease which is more difficult to treat (see Modules 5 and 6).

MDR-TB cannot be diagnosed on physical presentation or signs and symptoms alone. Definitive diagnosis of MDR-TB requires culture and drug susceptibility results

Often 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 usually supported by consistently positive smears and/or cultures, which should undergo drug susceptibility testing (DST) to confirm MDR-TB. The quality of laboratory susceptibility testing is of paramount importance and impacts directly on treatment. TB drug susceptibility testing is a complicated procedure and errors are not uncommon. A single laboratory report of MDR-TB without supporting clinical evidence should be regarded with caution and follow-up investigations requested.

The classification of a patient as MDR-TB carries very serious consequences and should only be made by (or at the very least in consultation with) a health care professional experienced in managing MDR-TB patients. Aspects that allow health care professionals to diagnose MDR-TB patients are discussed in more detail below.

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5.1 Microscopy

Because of the high lipid content of the cell wall of mycobacteria, special stains are needed to observe the bacilli microscopically. The stains used most commonly are the **Ziehl-Neelsen** and **Auramine-O fluorescent** stain. The primary stain binds to mycolic acid in the mycobacterial cell wall, and acid alcohol subsequently applied fails to remove the stain, hence the term 'acid-alcohol-fast', or as they are more commonly termed, 'acid-fast bacilli' or 'AFB'. A counter-stain is then applied and the acid-fast bacilli appear as red, often beaded bacilli against a blue background (with Ziehl-Neelsen staining), or as fluorescent bacilli (auramine O staining).
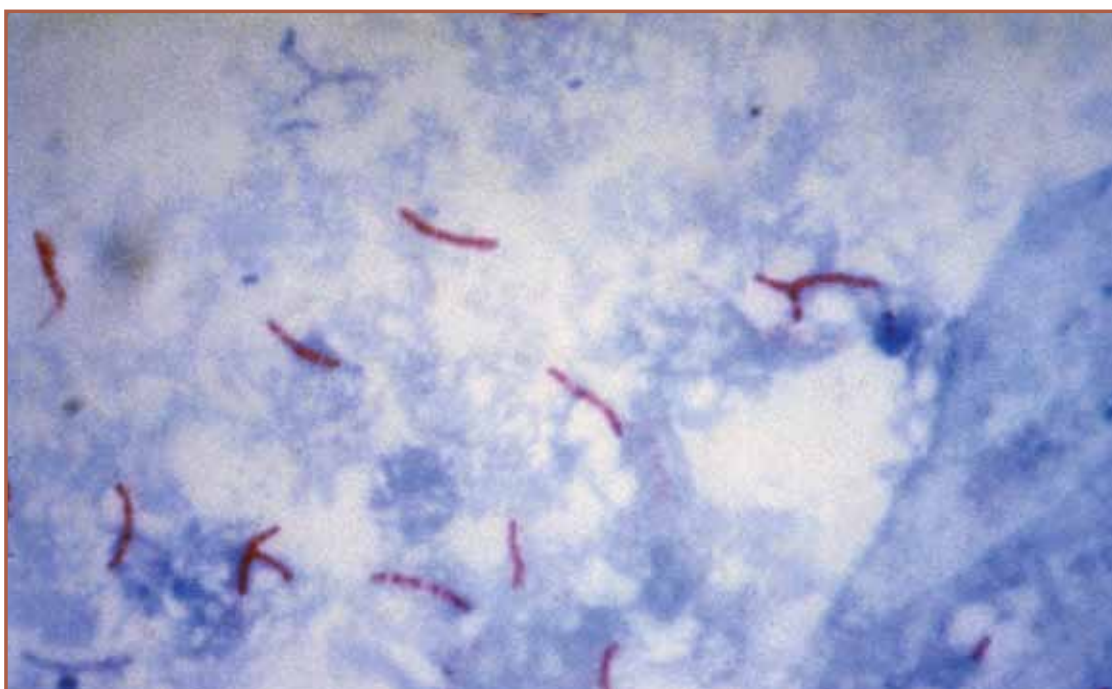
*his photomicrograph
reveals Mycobacterium
tuberculosis bacteria
using acid-fast
Ziehl-Neelsen stain;
Magnified 1000 X.*

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All mycobacteria have the property of acid-fastness. Slides stained with Ziehl Neelsen methodology are viewed under a light microscope and afford the microscopist good observation of cell morphology. Auramine-O stained slides are viewed using a fluorescent microscope, and allow the microscopist to view a much larger field in a shorter time; hence this method, although more expensive, is favoured when large numbers of smears have to be viewed.

QUESTION:
What is the value of direct microscopy for acid-fast bacilli in the diagnosis of MDR-TB?

ANSWER:
Although direct microscopy is the cornerstone of diagnosis of drug-susceptible pulmonary TB, microscopy cannot distinguish between drug-susceptible and drug-resistant *M. tuberculosis*, or between different species of mycobacteria. The chief uses of microscopy in relation to MDR-TB are therefore limited to:
- Evaluating the infectiousness of patients;
- Triaging specimens to different methods of culture and DST;
- Confirming that microbes growing on (or in) artificial media are acid-fast bacilli rather than contaminants.

The direct sputum smear detects AFB in only 30-60% of tuberculosis cases, but culture can improve diagnosis by 20-50%. The reason for this is because in order for sputum smear to be positive 5 000 to 10 000 organisms per millilitre of sputum are needed to be present to allow visualisation. This compared to solid culture where 100 organisms per millilitre of sputum, or liquid culture where 10 organisms per millilitre of sputum, are required to result in a positive identification of mycobacteria.

Nevertheless, the infectiousness of MDR-TB patients, like drug-susceptible TB patients, correlates roughly with the number of AFB in the sputum smear as measured by conventional semi-quantitative methods, other factors being equal.

AFB smear microscopy, however, cannot distinguish viable from nonviable bacilli, so its utility for monitoring of MDR-TB treatment is limited. For example, even with adequate treatment, specimens from MDR-TB patients may remain smear positive after they become culture negative suggesting that the bacilli are non-viable.

The **turnaround time** for microscopy results should be **less than 48 hours**, depending on work load and the transport time to the laboratory. Results are reported as 'positive/negative for acid fast bacilli' and quantified, as quantification may serve as an indication of disease severity. Quantification of smear results is internationally standardised as follows:

Number of AFB seen on a smear	Result reported
No AFB per 100 oil immersion fields	Negative
1 – 9 AFB per 100 oil immersion fields	Scanty "Exact number of AFB"
10 – 99 AFB per 100 oil immersion fields	1+
1 – 10 AFB per field	2+
>10 AFB per field	3+

A low number of bacilli (fewer than 10 AFB per 100 fields, sometimes referred to as 'scanty') are often difficult to interpret, as microscopy cannot distinguish between viable and dead bacilli. The result may be due to actual MDR-TB, or may reflect dead bacilli (common during follow-up smears when patients are on treatment), due to environmental AFB that are not colonizations and not *M. tuberculosis*, or rarely, to laboratory contamination. Results of such investigations have also not been well-correlated with culture

Mycobacteria are slow growing organisms with a mean generation time of 12 to 18 hours, so results of culture investigations for MDR-TB may take **several weeks.** Mycobacteria also require special culture media. A variety of suitable culture media and differential tests for species identification are available and the choice depends on the resources and expertise available to countries implementing MDR-TB programmes.

Egg-based solid culture medium (eg. Löwenstein-Jensen or Ogawa) has several advantages, including ease of preparation, low cost, and low contamination rates.

Agar-based culture medium (eg. Middlebrook 7H10 or 7H11) has similar advantages, recovers mycobacteria from a higher fraction of specimens, but requires a CO_2 incubator and
is more expensive.

Broth-based culture methods are increasingly available in low- and middle-income countries. In addition, manual systems have been developed that do not require technologically advanced and expensive instruments. Broth culture media will recover *M. tuberculosis* in up to 25% more patients than conventional solid media, especially in patients with negative or low-positive AFB smears. When used in patients with an increased likelihood of having MDR-TB, more patients will be diagnosed before they become highly infectious, hopefully curtailing transmission to others. These methods include:

- Radiometric, semi-automated BACTEC 460 system (Becton Dickinson);
- Automated BACTEC MGIT 960 system or its manual alternative (Becton Dickinson);
- MicroMGIT system (Mycobacterial Growth Indicator Tube; Becton Dickinson);
- BacT-Alert (Organon Technika).

Irrespective of the culture medium used, a **decontamination process** is necessary prior to inoculation of the media to eliminate other bacteria in sputa. The decontamination process needs to be carefully balanced so as to minimise the destruction of any mycobacteria present.

Growth rates of mycobacteria are highly dependent on the culture media used. Growth is more rapid in liquid culture, with *M. tuberculosis* cultures becoming positive from 10 days to four weeks on average. On LJ solid medium, cultures may become positive only after four to eight weeks. The commercial culture systems are significantly more expensive, but allows for rapid results leading to timeous treatment of patients. Once a positive mycobacterial culture is obtained, the mycobacterial species is identified by morphology, and by biochemical or molecular tests.

Local circumstances, history or regulations often determine the media and method of DST in MDR-TB programs. The biggest disadvantage of solid media is the slow growth rate. Mycobacteria grow much faster in liquid media, but detecting and quantifying growth in suspension is more difficult. In addition, contamination with fungi and other bacteria, which make the results not interpretable, are more common in liquid techniques. The BACTEC 460 radiometric method has many advantages, including the longest history of broth-based systems, technical superiority, speed and sensitivity, robust instrumentation, availability at reduced cost, standardized methodology for testing second-line drugs. The main disadvantage of the BACTEC 460 is reliance on C^{14} and accompanying concerns about waste disposal. Widespread misunderstanding of the hazards of the relatively small amounts of C^{14} has led to cumbersome and expensive regulatory barriers to this technology and most countries that use the BACTEC 460 will incur some expense associated with the disposal of the material in order to follow local environmental regulations. MicroMGIT has the important advantage of not requiring expensive, delicate instrumentation. It has mostly replaced the BACTEC 460 in newer laboratories doing liquid culture.

Huancayo. TB cultures on LJ medium at the Daniel Carrion Hospital

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Mycobacterium tuberculosis on LJ culture, showing characteristically cream, rough, waxy growth

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Timely transport of specimens to the laboratory is critical, as any delays will result in a decrease in the viability of mycobacteria as well as overgrowth by normal flora. Specimens should be kept cool during transportation or refrigerated at 4°C if delays are anticipated.

Specimens can be preserved and in cetyl-pyridinium chloride (CPC). In general specimens can be kept in CPC for 5 to 7 days without significant decease in the recovery of the mycobaceria, and good rates of recovery can be obtained from stored specimens for 20 ± 9 days. CPC is known to kill pathogenic fungi from sputum specimens and has been shown to increase the culture positivity and reduce the contamination rate.

Culture results are reported as positive or negative in automated systems, and quantified on solid medium. Quantification may serve as an indication of disease severity, and reporting of results on solid medium is internationally standardised, as follows:

Number of colonies seen	Result reported
None	Negative
1 – 9 colonies	"Actual number" colonies
10 – 100 colonies	1+
100 – 200 colonies	2+
Innumerable discrete colonies	3+
Confluent growth	4+

Quality of laboratory processing is critically important for effective culture. Delays in specimen transport to the laboratory, excessively harsh decontamination of specimens, poor quality of media, and too high or too low incubation temperatures can adversely affect the culture yield. Cross contamination of bacilli between specimens may lead to false positive results.

Laboratory results should always be correlated with the patient's clinical condition, and investigations repeated if necessary. False negative cultures may result from inadequate specimens, poor laboratory technique, and delayed transport of the specimens to the laboratory. Contamination due to overgrowth of common respiratory bacteria occurs if there is delay in transport of specimens and if the decontamination process in the laboratory is inadequate, compromising the growth and isolation of mycobacteria.

Low-positive culture results (< 10 colonies) are not well correlated with clinical prognosis and should be interpreted with caution, especially if a single culture with low colony-counts is reported. On the other hand, persistent positive cultures or any positive culture in the setting of clinical deterioration of a patient should be regarded as significant.

5.3 IDENTIFICATION OF M. TUBERCULOSIS

In high-TB burden countries, the overwhelming majority of mycobacterial isolates will be *M. tuberculosis.*

The prevalence of non-tuberculous mycobacteria (NTM) varies from country to country and can be more common in HIV patients. Unless the species is confirmed as *M. tuberculosis*, mycobacterial isolates appearing phenotypically resistant to first-line drugs may not be drug-resistant TB at all, but may be due to infection with NTM. Treatment of NTM is entirely different from MDR-TB. At minimum, laboratories supporting MDR-TB programs should be able to conduct niacin and nitrate tests (both positive in the vast majority of *M. tuberculosis* strains) or at least two other methods that follow international guidelines.

5.4 DRUG SUSCEPTIBILITY TESTING

Drug susceptibility testing (DST) is required to make a definitive diagnosis of MDR-TB. DST can be done by several methods and by direct or indirect tests:

QUESTION:
What do you think is the difference between direct and indirect drug susceptibility tests?

ANSWER:
In direct tests, the culture and DST media is inoculated with the processed clinical specimen (usually smear-positive sputum). The specimen is digested, decontaminated, neutralized, and concentrated by high-speed centrifugation. The sediment is diluted and a standard volume is inoculated directly onto solid media slants or agar plates containing critical concentrations of anti-tuberculosis drugs and a control containing no drugs. Direct tests have only been well studied with egg-based and agar-based solid media; therefore, broth methods should not be used for direct testing. Results usually need to be confirmed with the indirect method, especially if the isolate is found to be drug-resistant.

In indirect tests, mycobacteria are cultivated on solid and/or broth media. Several colonies are picked from the solid medium or an aliquot is removed from the broth medium to create a suspension. This suspension (of pure isolate) is standardized according to a specific optical density and used to inoculate the DST medium.

In both direct and indirect tests, susceptibility vs resistance is determined by comparing growth in plain (control) medium without drugs to growth in medium to which specified concentrations of drugs have been added.

Direct and indirect tests are done using a variety of conventional technical methods in agar or egg-based solid medium. A brief description of the various methods is as follows:

Proportion method: Anti-TB drugs are added to the medium in the form of stock solutions made from reference powders or drug-impregnated discs in order to achieve the required critical concentrations. Medium is inoculated with either the sediment of a processed clinical specimen (direct test) or a culture suspension (indirect test). The isolate is resistant if more than 1% of the number of colonies on the control cultures grows on a given drug-containing culture.

Absolute-concentration method: The lowest drug concentration required to inhibit mycobacterial growth is determined by preparing culture media with serial dilutions of each drug. Drug-free and drug-containing media are inoculated with a standardized suspension of the isolate and the cultures monitored for growth. The minimum inhibitory concentration (MIC) is the lowest drug concentration that allows the growth of less than 20 colonies on solid media.

Resistance-ratio method: This method is related to the absolute concentration method, except that the MIC for the patient's strain is compared with the MIC of drug-susceptible control strains. The clinical isolate and controls are grown on drug-free and drug-containing media. The MIC for each strain is determined. The resistance-ratio is calculated as the ratio of the patient strain MIC to the mean control MIC. Strains with a resistance-ratio of 1 and 2 are considered susceptible. Strains with a ratio greater than 2 are considered resistant.

Several rounds of proficiency testing in the SRL network have shown that the above three methods are highly reliable and reproducible for first-line drugs and that the results obtained do not differ according to the method used.

Broth-based methods for drug susceptibility testing include the following:

Bactec 460TB utilizes a broth medium containing ^{14}C-labeled palmitic acid to grow the mycobacteria. If the organism grows in the broth, $^{14}CO_2$ from fatty acid metabolism is released and measured by the instrument. The concentration of $^{14}CO_2$ is proportional to the growth. Drug-containing vials receive a 100-fold higher inoculum than the drug-free control vials for each strain, corresponding to the 1% frequency of resistance considered as clinically significant. The results are interpreted based on the change in growth in the drug-containing vials compared to the control vial without drug. If the daily change in the drug-containing vial exceeds the control growth, the isolate is resistant. If growth in the drug-free control vial is greater, the isolate is susceptible. Resistant strains should be confirmed by the proportion method or by molecular assays.

Bactec kits are available for testing first-line TB drugs, ie. streptomycin, isoniazid, rifampicin, ethambutol and pyrazinamide. Second-line drugs can be tested by adding stock solutions from reference powders of individual anti-tuberculosis drugs to the broth vial; however, the methodology has not been standardized internationally.

Newer broth methods are replacing the radiometric (^{14}C) system in order to avoid the use and disposal of radioactive materials. Most of the newer broth systems are fully automated. The BACTEC MGIT 960 system uses a fluorescence quenching-based oxygen sensor to detect mycobacterial growth. If mycobacteria are growing in the system, they consume oxygen, fluorescence increases and are detected by the system. **The BacT/ALERT** 3D system colorimetrically detects CO_2 production in order to indicate mycobacterial growth. The **ESP Culture System II** detects pressure changes due to gas production or consumption due to mycobacterial growth.

The BacT/ALERT 3D detection system	The MGIT 960 detection system

Novel methods for drug susceptibility testing are currently being evaluated in different research settings. These include measuring **metabolic changes** in mycobacteria by indicator dyes that determine the viability of mycobacteria in the presence of a drug. **Indicator dyes** include Alamar blue, resazurin, and MTT. TK medium and the Griess method are based on colorimetric detection of the nitrate reductase reaction, characteristic of *M. tuberculosis*. **Mycobacteriophage-based methods** such as the luciferase reporter technique have been shown to distinguish drug-resistant from drug-susceptible strains in a 48 hour assay. If bacterial cells are resistant to a drug, they become capable of supporting replication of infecting phage in presence of this drug, and consequently express the phage-encoded luciferase gene. This, in turn, leads to light emission which can be captured and quantitatively measured. Another phage-based assay, commercially marketed as Fast-Plaque RIF, is based on the ability of viable mycobacteria to support the replication of mycobacteriophages. If the clinical isolate is replicating, phage particles are released rapidly. Progeny phage particles are detected by forming zones of lysis on a lawn of a rapidly growing sensor strain.

Molecular methods for DST are based on detection of specific mutations associated with drug resistance. Ideal targets are genes whose mutations account for the vast majority of drug resistance, eg. *rpoB* for rifampicin resistance and *pncA* for pyrazinamide resistance. However, only a few reference laboratories in middle-income countries are routinely using molecular methods to rapidly diagnose drug resistance. The methods require specialized instrumentation and expertise. The main advantage of molecular assays is the rapid turnaround time; disadvantages include the high cost, the low sensitivity for certain drugs, the potential for false-positive results due to cross contamination, and lack of standardization of the assays. There are currently a limited number of commercially available molecular tests, including the InnoGenetics Line Probe Assay (LiPA) for rifampicin resistance, and the Genotype MTRTB (Hain) which includes genetic resistance testing for both isoniazid and rifampicin.

5.5 Limitations of DST

Question:
Is DST a fail-safe way to design treatment regimens for MDR-TB?

Answer:
The intrinsic accuracy of DST (performed under the best circumstances) varies with the drug tested: it is most accurate for rifampicin and isoniazid and less so for streptomycin and ethambutol.

DST testing of second-line drugs is not as simple as DST for the first-line drugs. This is partly because critical drug concentrations defining drug resistance are very close to the minimal inhibitory concentrations (MICs). **Proficiency testing results similar to those obtained for first-line drugs are not available for any of the second-line agents**. Without them, little can be said about the reliability of second-line drug susceptibility testing. Drugs for second-line DST should never come from the medicines used for treatment but must come from pure compounds, only available from the manufacturer.

The clinician must be aware of the limitations of DST and interpret the results with this in mind. DST can be viewed as giving information of the probability of a drug being effective or non-effective. Drugs that test susceptible have more probability of being effective than drugs that test resistant. When discrepant results are seen they must be interpreted with care by an experienced clinician in MDR-TB. Module 4 describes how to clinically interpret DST.

Presently, DST capacity to second-line drugs in not mandatory for MDR-TB programs; however it is highly recommended for programmes in areas of extensive second-line drug use, at least in the form of surveillance to help design regimens. In order to diagnose XDR-TB, DST to second-line injectable agents and a fluoroquinolone is recommended. The reliability and reproducibility

of second-line drugs other than the injectable agents and the fluoroquinolones are considered less. Programs often do not put much weight on DST to second-line drugs in individual regimen design, apart from the injectable agents and fluoroquinolones which are considered relatively reliable and reproducible. The advantages and disadvantages of the different treatment strategies and use of DST results are discussed further in Module 5.

6 The role of laboratory services in MDR-TB programmes

Optimal management of MDR-TB requires both **mycobacterial** and **clinical** laboratory services. At minimum, the mycobacteriology reference laboratory should provide culture, confirmation of the species as *M. tuberculosis*, and testing for susceptibility to isoniazid and rifampicin. Clinical laboratory services are required to properly evaluate and monitor patients, including basic haematology, biochemistry, serology, and urine analysis. A comprehensive, routine system of internal quality control and external quality assurance is mandatory.

In addition to diagnostic services, laboratories have a critical role in **surveillance** of TB drug resistance patterns and trends. The WHO/IUATLD network of Supranational Reference Laboratories (SRLs) provides external quality assurance through validation of drug susceptibility data. Central reference labs supporting MDR-TB programmes should establish formal links with a SRL to help ensure the quality of laboratory services and validate DST results. A list of SRLs and contact details are available on the WHO website (http://www.who.int/drugresistance/tb/labs/en/index.html).

The Supranational Reference Laboratory Network links 150 laboratories
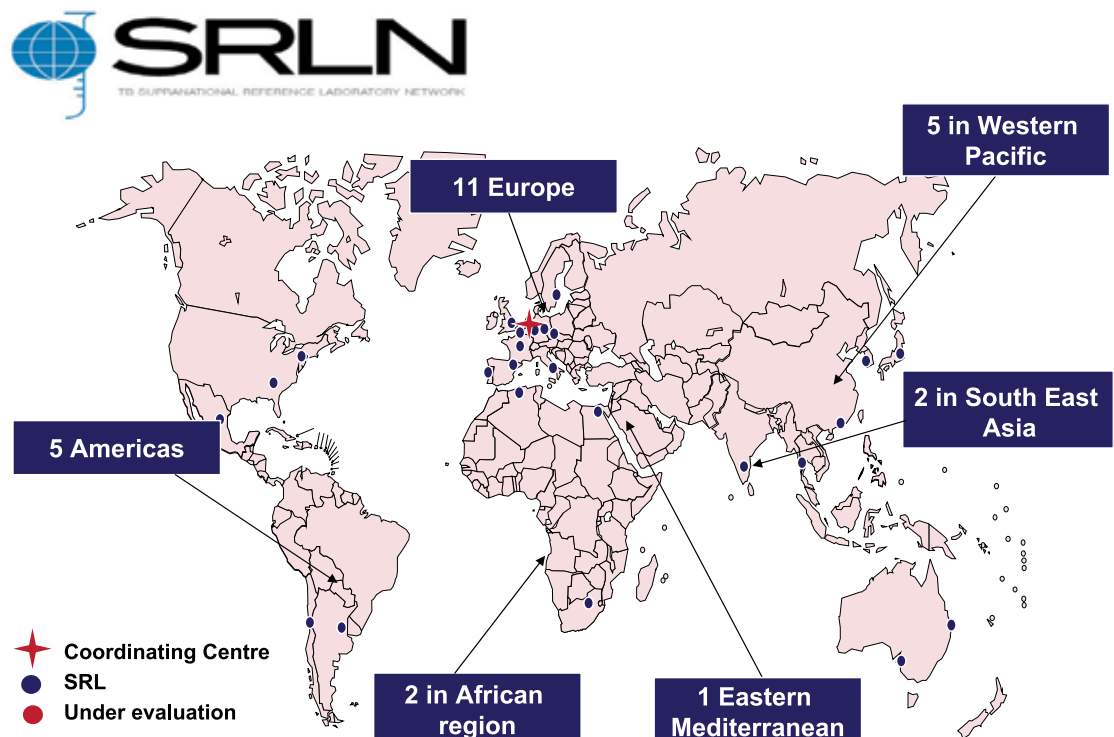
Each MDR-TB programme must have a rapid and reliable system of collecting and moving specimens, cultures, and information from the patient and physician to the laboratory service and the results back again. There should be no financial barrier between the patient and MDR-TB diagnostic services. Ready access to AFB microscopy, culture, and DST at no charge to the patient is an essential element of political commitment to control MDR-TB.

DST for at least isoniazid and rifampicin is needed in any MDR-TB programme. DST for streptomycin and ethambutol is also desirable, but less important than DST to isoniazid and rifampicin. In the initial phase of MDR-TB programme implementation, DST for second-line drugs is best left to SRLs or other reference laboratories with documented capacity, expertise, and proficiency. Once DST for first-line drugs consistently operates at a high level of proficiency, laboratories serving populations and patients with significant prior exposure to second-line drugs may consider extending their services to DST for second-line drugs. However, in areas of high incidence of XDR-TB, it may be warranted to quickly build the local capacity to second-line injectable agents and fluoroquinolones, even at the same time as building capacity for first-line drugs.

In order to ensure accuracy, reliability and reproducibility of laboratory results, a comprehensive quality control/quality assurance (QC/QA) program should be developed in each laboratory. QA/QC procedures should be performed on a regular basis to become an integral part of laboratory operations. QA/QC procedures for smear microscopy, culture and DST are described in detail in selected WHO publications, which are available online:

Laboratory services in tuberculosis control (Part 1, Part 2, Part 3), Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency update 2008 (http://www.who.int/tb/publications/2008/programmatic_guidelines_for_mdrtb/en/index.html).

1. MDR-TB is most highly suspected if:
a) An adherent patient on TB treatment fails to achieve smear or culture conversion
b) A non-adherent patient on TB treatment has an unsatisfactory clinical response
c) A patient is HIV-positive
d) A patient has NTM disease
e) An adherent patient on TB treatment has an unsatisfactory chest x-ray

2. True/False:
( ) Chest x-rays may be normal in patients with active MDR-TB
( ) Chest x-rays showing cavities are conclusive evidence of active MDR-TB
( ) Lung fibrosis always indicate active MDR-TB
( ) Patients with pulmonary MDR-TB may have negative smears
( ) MDR-TB has a different radiographic profile than drug-susceptible TB

3. MDR-TB cultures require prolonged incubation time because:
a) Culture media do not contain adequate nutrients for growth
b) The generation time of mycobacteria is exceptionally long
c) Decontamination procedures destroy mycobacterial DNA
d) Mycobacteria require varying temperatures to grow
e) Tubercle bacilli undergo mutation during growth

4. True/False:
( ) A positive culture confirms the diagnosis of MDR-TB
( ) Cultures are always positive in HIV-infected MDR-TB patients
( ) MDR-TB patients are categorized according to previous TB treatment
( ) Second-line drug susceptibility testing is required to confirm MDR-TB
( ) Negative smears exclude a diagnosis of MDR-TB

5. Drug susceptibility testing is most accurate for:
a) Any first-line anti-tuberculosis drug
b) Ethambutol and streptomycin
c) Any second-line anti-tuberculosis drug
d) Isoniazid and rifampicin
e) Kanamycin

1: a		**ANSWERS**
2: T, F, F, T, F.		
3: b		
4: F, F, T, F, F.		
5: d		

MODULE 5

TREATMENT STRATEGIES FOR MDR-TB

1   LEARNING OBJECTIVES

At the end of this module you should be able to:

- Understand different MDR-TB treatment strategies
- Understand essential MDR-TB treatment principles
- Design MDR-TB treatment strategies (standardized, empiric and individualized)

2 INTRODUCTION

First-line agents are the mainstay of modern treatment for TB, given their long history of use, proven efficacy, good tolerance and low cost. First-line anti-TB drugs are:

QUESTION

Which of the following first-line anti-TB drugs are also used for second-line treatment:

a. Isoniazid,
b. Rifampicin,
c. Pyrazinamide,
d. Ethambutol,
e. Streptomycin.

ANSWER

All five drugs are used as first line anti-TB drugs. Pyrazinamide and Ethambutol are also used for second-line therapy.

Erratic first-line treatment, either through clinical error, programme failure or patient non-adherence and/or default, can result in the emergence of resistance, including MDR.

Treatment of patients with MDR-TB involves second-line, reserve drugs. These are much more expensive, less effective and have more side effects than first-line TB drugs.

3 AVAILABLE MDR-TB DRUGS

According to conventional microbiology the action of antimicrobial agents is often described as bacteriostatic (slowing down growth of bacteria) or bactericidal (killing bacteria). Drugs available for the treatment of MDR-TB are grouped according to efficacy, experience of use, and drug class. These groups are referred to in the following sections and are very useful to help design regimens. The different groups are described in Table 5.1.

Second-line drugs of good quality are required to treat MDR-TB adequately

HELP Design Group

QUESTION
Which of the following anti-TB drugs are given by injection?
a. Streptomycin,
b. Kanamycin,
c. Amikacin,
d. Viomycin,
e. Ethambutol.

ANSWER:
The correct answers are a, b, c and d.
Streptomycin, Kanamycin, Amikacin and Viomycin are given by injection. Ethambutol is given by the oral route.

Table 5.1. Classes of TB agents	
Group	**Drugs (abbreviation)**
GROUP 1: First-line oral anti-TB agents	Isoniazid (H) Rifampicin (R) Ethambutol (E) Pyrazinamide (Z) Rifabutin (Rfb)*
GROUP 2: Injectable anti-TB agents	Streptomycin (S) Kanamycin (Km) Amikacin (Am) Capreomycin (Cm)
GROUP 3: Fluoroquinolones	Ofloxacin (Ofx) Levofloxacin (Lfx) Moxifloxacin (Mfx)
GROUP 4: Oral bacteriostatic second-line anti-TB agents	Ethionamide (Eto) Prothionamide (Pto) Cycloserine (Cs) Terizidone (Trd) Para-aminosalicylic acid (PAS)
GROUP 5: Agents with unclear efficacy or unclear role in MDR-TB treatment (not recommended by WHO for routine use in MDR-TB patients)	Clofazimine (Cfz) Amoxicillin/clavulanate (Amx/Clv) Clarithromycin (Clr) Linazolid (Lzd) Thioazetazone(Thz) Imipenem/cilastatin (Ipm/Cln) High-dose isoniazid (high-dose H)**

* Rifabutin is not on the WHO List of Essential Medicines. It has been added here as it is routinely in patients on protease inhibitors in many settings.
**High-dose H is defined as 16-20 mg/kg per day.

Source: World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency update 2008 (WHO/HTM/TB/2008.402).Geneva, Switzerland: World Health Organization; 2008.

GROUP 1: FIRST LINE ORAL ANTI-TB AGENTS

While isoniazid and rifampicin are not useful in MDR-TB, pyrazinamide and ethambutol are again used in second-line treatment if it is thought their effectiveness can be preserved. Resistance to pyrazinamide is neither easy to acquire nor easy to prove by susceptibility testing. Ethambutol is a valuable bacteriostatic agent for preventing the emergence of resistance to other active drugs. For patients with strains resistant to low concentrations of isoniazid but susceptible to higher concentrations, the use of high-dose isoniazid may have some benefit (when isoniazid is used in this manner it is considered a Group 5 drug, see next page). The newer rifamycins, such as rifabutin, should be considered ineffective if results of DST show resistance to rifampicin.

GROUP 2: INJECTABLE ANTI-TB AGENTS

All patients should receive a Group 2 injectable agent if susceptibility is documented or suspected. Kanamycin and amikacin are aminoglycosides and either is usually the first choice of an injectable agent, given the high rates of streptomycin resistance in DR-TB patients. In addition, both these agents are low cost, have less otoxicity than streptomycin, and have been used extensively for the treatment of DR-TB throughout the world. Amikacin and kanamycin are considered to be very similar and have a high frequency of cross-resistance. If an isolate is resistant to both streptomycin and kanamycin, or if DRS date show high rates of resistance to amikacin and kanamycin, then capreomycin should be used. Viomycin is very similar to capreomycin and these agents also share a high frequency of cross-resistance. Capreomycin and viomycin are cyclic polypeptides that differ structurally from kanamycin and amikacin and exhibit no uniform cross-resistance with the aminoglycosides.

GROUP 3: FLUOROQUINOLONES

All patients should receive a Group 3 medication if the strain is susceptible or if the agent is thought to have efficacy. Ciprofloxacin is no longer recommended to treat drug-susceptible or drug-resistant TB. Currently, the most potent available fluoroquinolones in descending order based on in vitro activity and animal studies are: moxifloxacin > levofloxacin > ofloxacin. While ofloxacin is commonly used because of cost, the higher generation fluoroquinolones, moxifloxacin and levofloxacin, are more effective and have similar adverse effect profiles. Furthermore, the higher generation fluoroquinolones may have some efficacy against ofloxacin-resistant strains. Although gatifloxacin is similar to moxifloxacin in efficacy against TB, serious cases of hypoglycemia, hyperglycemia, and new onset diabetes have been associated with gatifloxacin and it has been removed from the markets of many countries. For this reason it is not placed in the table above or any of the tables of this course and WHO Guidelines recommend avoiding the use of gatifloxacin in the treatment of DR-TB. If gatifloxacin is used, the patient should undergo close monitoring and follow-up.

In summary, moxifloxacin or levofloxacin are the fluoroquinolones of choice. In resource-constrained areas, ofloxacin is an acceptable choice for ofloxacin-susceptible DR-TB. A higher generation fluoroquinolone is recommended for treatment of XDR-TB even if lower generations are testing resistant (see Module 6), although there is inadequate evidence on whether this is an effective strategy. Because the data on long term use of fluoroquinolones are limited, vigilance in monitoring is recommended (see Module 8).

GROUP 4: ORAL BACTERIOSTATIC SECOND-LINE AGENTS

Ethionamide and prothionamide are from the same family of drugs thiomides, with bacteriostatic activity against *M. tuberculosis*. The pharmacokinetics of the two preparations are very similar, but prothionamide may be better tolerated. They induce complete cross-resistance and should therefore be regarded as the same drug.

Terizidone is a combination of two molecules of cycloserine and they should therefore be regarded as the same drug. Terizidone and cycloserine are bacteriostatic at the usual dosage. Both drugs have a high incidence of side effects, but anecdotal evidence seems to suggest that terizidone is better tolerated. Both drugs have significant central nervous system toxicity (cycloserine moreso than terizidone) and can precipitate focal or grand mal seizures with high serum concentrations. Psychotic disturbances and

suicidal thoughts have been reported even in patients with appropriate serum concentrations. Pyridoxine (150mg) should be given together with terizidone or cycloserine to prevent neurological toxicity. Both are valuable companion drugs to prevent resistance to other second-line drugs, since they do not share cross-resistance with other active TB drugs.

Para-aminosalicylic acid (PAS) is a bacteriostatic agent, valuable for preventing resistance to other drugs. It is bulky and unpleasant to take because of gastrointestinal discomfort; however, enteric-coated formulas are better tolerated. A new formulation in granules (PASER®) is now available which is better absorbed than the enteric coated tablets, but has to be taken with fruit juice as it needs an acid pH to facilitate absorption.

GROUP 5: AGENTS OF UNCLEAR EFFICACY

Group 5 medications (sometimes referred to as 'third-line drugs') that have been used for the treatment of MDR-TB include thioacetazone, clofazimine, amoxicillin-clavulanate, macrolides (clarithromycin and azithromycin), linezolid and imipenem/cilastatin. While thioacetazone is a drug with known efficacy against TB, it is placed in Group 5 because its role in MDR-TB treatment is not well-established. Thioacetazone has cross-resistance with some of the other anti-tuberculosis agents (see text below) and overall is a weak bacteriostatic drug. Thioacetazone is not recommended in HIV-positive individuals given the serious risk of adverse reaction that can result in Stevens-Johnson Syndrome and even death. Clofazamine, an antileprosy drug, has in vitro activity against *M. tuberculosis* but clinical efficacy has not 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. Linezolid has not been subjected to rigorous studies, has a high incidence of side effects and is expensive. Imipenem/cilastatin is an injectable agent, is expensive and is of unproven efficacy.

None of the Group 5 drugs are recommended for routine use in MDR-TB treatment. They are, however, used as experimental options as a last report in patients failing conventional MDR-TB therapy or in patients with documented XDR-TB.

QUESTION
Which of the following statements are correct?
a. Pyrazinamide and Ethambutol are First and Second line Medications.
b. Ethambutol is a valuable bacteriostatic agent for preventing the emergence of resistance to other active drugs.
c. Strains resistant to streptomycin are usually resistant to kanamycin and amikacin.
d. Pyridoxine (150mg) should be given together with terizidone or cycloserine to prevent neurological toxicity.
e. Para-aminosalicylic acid (PAS) is a bactericidal agent.

ANSWER:
The correct answers are a, b, and d.
Strains resistant to streptomycin are usually susceptible to kanamycin and amikacin.
Para-aminosalicylic acid (PAS) is a bacteriostatic agent, valuable for preventing resistance to other drugs.

Table 5.2. Known Cross-Resistance Between Anti-TB Drugs

- All rifamycins have high levels of cross-resistance.
- Fluoroquinolonesare believed to have variable cross-resistance between each other, with in vitro data showing that some later-generation fluoroquinolones remain susceptible when earlier-generation fluoroquinolones are resistant. In these cases, it is unknown if the later-generation fluoroquinolones remain effective clinically.
- Amikacin and kanamycin have very high cross-resistance. Capreomycin and viomycin have high cross-resistance. Other aminoglycosides and polypeptides have low cross-resistance.
- Protionamide and ethionamide have 100% cross-resistance.
- Ethionamide can have cross-resistance to isoniazid if the inhA mutation is present.
- Thioacetazone cross-resistance to isoniazid, ethionamide and PAS has been reported but is generally considered to be low.

(Source: World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency update 2008 (WHO/HTM/TB/2008.402). Geneva, Switzerland: World Health Organization; 2008.)

The anti-TB drug thioacetazone causes serious, sometimes fatal, side effects in many HIV-positive patients and is not recommended

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Novel therapies currently under investigation include 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.

4 Standard codes for drugs and regimens

Standard codes are used for MDR-TB treatment regimens. Each anti-TB drug has an abbreviation as shown in Table 5.1.

An MDR-TB regimen consists of two phases; the first while the Injectable agent (IA) is used and the second after it has been stopped. The number shown before each phase stands for phase duration in months, and is the minimum amount of time that stage should last. The number in subscript (eg.$_3$) is the number of drug doses per week. If there is no number in subscript, treatment is daily (or six times a week). An alternative drug(s) appears as a letter(s) in brackets. The drugs in the higher groups are written first, followed by others in descending order.

5   TREATMENT STRATEGIES

Each country should design an appropriate MDR-TB treatment strategy based on available drug resistance surveillance data and the frequency of anti-TB drug use in the country. MDR-TB programmes should be familiar with the prevalence of drug resistance in new TB patients as well as in different groups of retreatment patients. It is essential to determine which second-line drugs have been used and to what extent, as those that have been rarely used are likely to be effective in MDR-TB regimens while those that have been used extensively have a high probability of being ineffective.

Table 5.3. Treatment strategies for MDR-TB	
STANDARDIZED TREATMENT	No DST done or DST only done to confirm MDR-TB. All patients in a patient group or category receive the same regimen
EMPIRIC TREATMENT	No DST done or DST only done to confirm MDR-TB. Each Standardized regimen is individually designed, based on patient history of drug use
INDIVIDUALIZED TREATMENT	Regimen is designed for individual patients based on DST and patient history
STANDARDIZED TREATMENT followed by INDIVIDUALIZED TREATMENT	Initially all patients in a certain group receive the same regimen and it is then adjusted individually when DST results become available
EMPIRIC TREATMENT followed by INDIVIDUALIZED TREATMENT	Each regimen is individually designed based on patient history and then adjusted when DST results become available

6   Choosing between different treatment strategies

Standardized and individualized treatment regimens each have different advantages and disadvantages; however, no direct comparisons have ever been made in controlled trials.

Standardized regimens based on past treatment history and drug resistance surveillance data could lead to more patients having access to MDR-TB care. Other advantages include:

- Simpler implementation;
- Simpler drug ordering;
- Easier training;
- Less chance of mismanagement;
- Less need for highly technical laboratories.

Fully standardized regimens for the treatment of MDR-TB have been shown to be highly effective in countries where the drugs used in the regimen have not been used extensively and where resistance levels to second-line anti-TB drugs are consequently low. Standardized regimens are, however, less effective when second-line anti-TB drugs have been used extensively and where resistance levels are high.

Individualized regimens avoid placing patients on drugs to which the strain is resistant. Individualized regimens also have major advantages in settings with high rates of resistance to second-line drugs, where it may be impossible to find a standardized regimen that is appropriate to all MDR-TB patients. However, individualized regimens put high demands on human, financial and technical resources.

A combination of standardized and individualized treatment can be used as a strategy, depending on the availability of human, financial and laboratory resources. The choice of an appropriate treatment strategy should be made at country or regional level by the TB control programme and physicians treating MDR-TB patients should comply with this strategy at all times.

1. The most potent drug available for MDR-TB treatment is found among:
a) Fluoroquinolones
b) Aminoglycosides
c) Rifamycins
d) Thioamides
e) Macrolides

2. True/False:
( ) Cross-resistance between streptomycin and kanamycin is very low
( ) Cross-resistance between kanamycin and amikacin is very high
( ) Strains resistant to ethionamide are susceptible to protionamide
( ) Strains resistant to cycloserine are resistant to terizidone
( ) Strains resistant to ciprofloxacin are susceptible to ofloxacin

3. Stevens-Johnson syndrome in HIV-positive patients is associated with:
a) Terizidone
b) Kanamycin
c) Ethionamide
d) Thioacetazone
e) Ofloxacin

4. True/False:
( ) MDR-TB treatment strategies depend on local epidemiology
( ) Standardized regimens are most useful when drug resistance is low
( ) An injectable agent should always be used in MDR-TB regimens
( ) Empiric regimens are based on 2nd-line drug susceptibility testing
( ) MDR-TB regimens should contain at least four effective drugs

ANSWERS

1: b
2: T, T, F, T, F.
3: d
4: T, T, T,F ,T.

MODULE 6

Designing MDR-TB treatment regimens

At the end of this module you should be able to:

- Design MDR-TB treatment regimens (standardized, empiric and individualized)
- Determine correct drug dosage and administration

2   INTRODUCTION

The design of regimens to treat patients with MDR-TB poses several challenges, complicated by a limited choice of second-line agents, with greater toxicity and less efficacy. As with drug-susceptible TB, the use of **multiple drugs** is imperative to prevent the development of additional resistance. Consideration of **cross-resistance** is also important when designing treatment regimens for MDR-TB.

MDR-TB treatment requires multiple drugs in the correct combination

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3   DESIGNING TREATMENT REGIMENS

3.1   BASIC PRINCIPLES

QUESTION:
Note the basic principles which you think should apply in the design of a treatment regimen for MDR-TB?

ANSWER:
The following basic principles apply to any regimen design:
- Treatment regimens should be based on the history of drugs taken by the patient.
- Drugs commonly used in the country and prevalence of resistance to first-line and second-line drugs should be taken into consideration when designing a regimen.
- Treatment regimens should consist of at least four drugs with either certain or highly likely effectiveness. If the evidence is unclear for any particular drug, the drug may be included but should not be depended on for success. Often, more than four drugs may be started if the susceptibility pattern is unknown, effectiveness is questionable for an agent(s), or if extensive, bilateral pulmonary disease is present.
- Drugs are administered at least six days a week. Pyrazinamide, ethambutol and fluoroquinolones should preferably be given once a day as the high peaks attained in once a day dosing may be more efficacious. Once a day dosing is also recommended for other second-line drugs; however, Eto, CS, Trd and PAS are often given in split doses during the day to facilitate patient tolerance.

- Drug dosage should be determined by patient weight, as outlined in Table 6.2.
- An injectable agent (an aminoglycoside or capreomycin) is used for a minimum of six months and at least four months past culture conversion.
- The minimum length of treatment is 18 months past culture conversion.
- Each dose should be given under directly observed therapy (DOT) throughout treatment.
- DST, when available from a reliable laboratory, can be used to guide therapy. It should, however, be noted that DST does not predict with 100% certainty the effectiveness or ineffectiveness of a drug. In particular, the reliability and clinical value of DST for ethambutol, and groups 4 and 5 second-line anti-tuberculosis drugs have to date not been fully established.
- Pyrazinamide may be used for the entire treatment period if the strain is thought to be susceptible. Many MDR-TB patients have chronically inflamed lungs which theoretically produce the acidic environment in which pyrazinamide is active.
- Treatment of adverse drug effects should be immediate and adequate in order to minimize the risk of treatment interruptions and prevent increased morbidity and mortality due to serious adverse effects (see Module 8).
- Early MDR-TB detection and prompt initiation of treatment are important factors in determining successful outcomes.

3.2 Drug selection and regimen design

Table 6.1. describes the steps for building a regimen designed for the treatment of MDR-TB.

TB Treatment and drug management at the Pharmacy. Lifecare Knights hospital in Germaiston, South Africa

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Table 6.1. How to build a treatment regimen for MDR-TB		
STEP 1	Use any available **Group 1: First-line oral agents** pyrazinamide ethambutol	Begin with any first-line agents that have certain, or almost certain, efficacy. If a first-line agent has a high likelihood of resistance, do not use it. (For example, most Category IV regimens used in treatment failures of Category II do not include ethambutol because it is likely to be resistant based on treatment history.)
STEP 2	Plus one of these **Group 2: Injectable agents** kanamycin (or amikacin) capreomycin streptomycin	Add an injectable agent based on DST and treatment history. Avoid streptomycin, even if DST suggests susceptibility, because of high rates of resistance with DR-TB strains and higher incidence of ototoxicity.
STEP 3	Plus one of these **Group 3: Fluoroquinolones** levofloxacin moxifloxacin ofloxacin	Add a fluoroquinolone based on DST and treatment history. In cases where resistance to ofloxacin or XDR-TB is suspected, use a higher-generation fluoroquinolone, but do not rely upon it as one of the four core drugs.
STEP 4	Pick one or more of **Group 4: Second-line oral bacteriostatic agents** p-aminosalicylic acid cycloserine (or terizidone) ethionamide (or protionamide)	Add Group 4 drugs until you have at least four drugs likely to be effective. Base choice on treatment history, adverse effect profile and cost. DST is not standardized for the drugs in this group.
STEP 5	Consider use of these **Group 5: Drugs of unclear role in DR-TB treatment** clofazimine linezolid amoxicillin/clavulanate thioacetazone** imipenem/cilastatin high-dose isoniazid clarithromycin	Consider adding Group 5 drugs in consultation with an MDR-TB expert if there are not four drugs that are likely to be effective from Groups 1–4. If drugs are needed from this group, it is recommended to add at least two. DST is not standardized for the drugs in this group.

*Adapted from Drug-resistant tuberculosis: a survival guide for clinicians. San Francisco, Francis J. Curry National Tuberculosis Center and California Department of Health Services, 2004.
**Thioacetazone is contraindicated in HIV-infected individuals because of the serious risk of life-threatening adverse reaction.

For additional information on the five different groups of anti-TB drugs see Module 5.

Table 6.2. Weight-based dosing of drugs for adults				
Medication (abbreviation), (common presentation)	Weight range			
	< 33kg	33 – 50kg	51 – 70kg	> 70kg (also maximum dose)
Group 1: First-line oral agents				
Isoniazid (H) (100, 300 mg)	4-6 mg/kg daily or 8-12 mg 3x/week	200-300 mg daily or 450-600 mg 3x/week	300 mg daily or 600 mg 3x/week	300 mg daily or 600 mg/kg 3x/week
Rifampicin (R) (150, 300 mg)	10-20 mg/kg daily	450-600 mg	600 mg	600 mg
Pyrazinamide (Z) (500 mg)	30-40 mg/kg/day	1000-1750 mg	1750-2000 mg	2000-2500 mg
Ethambutol (E) (100, 400 mg)	25 mg/kg/day	800-1200 mg	1200-1600 mg	1600-2000 mg
Group 2: Injectable agents				
Streptomycin (S) (1 g vial)	15-20 mg/kg/day	500-750 mg	1000 mg	1000 mg
Kanamycin (Km) (1 g vial)	15-20 mg/kg/day	500-750 mg	1000 mg	1000 mg
Amikacin (Am) (1 g vial)	15-20 mg/kg/day	500-750 mg	1000 mg	1000 mg
Capreomycin (Cm) (1 g vial)	15-20 mg/kg/day	500-750 mg	1000 mg	1000 mg
Group 3: Fluoroquinolones				
Ofloxacin (Ofx) (200, 300, 400 mg)	15-20 mg/kg daily	800 mg	800 mg	800 - 1000 mg
Levofloxacin (Lfx) (250, 500 mg)	7.5-10 mg/kg daily	750 mg	750 mg	750-1000 mg
Moxifloxacin (Mfx) (400 mg)	7.5-10 mg/kg daily	400 mg	400 mg	400 mg
Group 4: Oral bacteriostatic agents				
Ethionamide (Eto) (250 mg)	15-20mg/kg/day	500 mg	750 mg	750-1000 mg
Prothionamide (Pto) (250 mg)	15-20mg/kg/day	500 mg	750 mg	750-1000 mg
Cycloserine (Cs) (250 mg)	15-20mg/kg/day	500 mg	750 mg	750-1000 mg
Terizidone (Trd) (300 mg)	15-20mg/kg/day	600 mg	600 mg	900 mg
P-aminosalicylic acid (PAS) (4g sachets)	150 mg/kg/day	8000 mg	8000 mg	8000-12000 mg
Sodium PAS	Dosing can vary with manufacture and preparation; check dose recommended by manufacturer.			
Group 5: Agents with unclear efficacy (not recommended by WHO for routine use in MDR-TB treatment). Optimal doses for DR-TB are not established.				

(Source: World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency update 2008 (WHO/HTM/TB/2008.402). Geneva, Switzerland: World Health Organization; 2008).

Clofazimine (Cfz)	Usual adult dose is 100 mg to 300 mg daily. Some clinicians begin at 300 mg daily and decrease to 100 mg after 4 to 6 weeks.
Linezolid (Lzd)	Usual adult dose is 600 mg twice daily. Most reduce the dose to 600 mg once a day after 4 to 6 weeks to decrease adverse effects.
Amoxicillin/ Clavulanate (Amx/Clv)	Dosages for DR-TB not well defined. Normal adult dose 875/125 mg twice a day or 500/125 mg three times a day. Dosages of 1000/250 have been used but adverse sideeffects may limit this dosing.
Thioacetazone (Thz)	Usual adult dose is 150 mg
Imipenem/cilastatin (Ipm/Cln)	Usual adult dose is 500–1000 mg IV every 6 hours.
Clarithromycin (Clr)	Usual adult dose is 500 mg twice daily
High-dose isoniazid (High-dose H)	16–20 mg/kg daily

Detailed information on each drug is available in the WHO Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency update 2008 (http://www.who.int/entity/tb/publications/2008/programmatic_guidelines_for_mdrtb/en/index.html).

3.3 STANDARDIZED TREATMENT REGIMENS

Physicians treating MDR-TB patients should consult their country's TB control programme for the most appropriate standardized regimen to be used.

Representative data on drug resistance from specific groups of patients is an essential requirement upon which the standardized regimen is based. Usually, patients are divided into defined groups according to their past treatment history. A standardized regimen is designed for each group according to drug resistance survey data for the different groups. Resistance survey data to second-line anti-tuberculosis drugs in these groups is also recommended and helps in the regimen design.

A standardized treatment strategy still needs DST capacity for both surveillance (to identify high risk groups) and as a screening tool (to minimize the number of patients who get falsely classified as having probable MDR-TB). A standardized regimen that will adequately treat the vast majority of patients with four effective drugs often necessitates the use of five or six drugs to cover all possible resistance patterns. Usually, an injectable agent and a fluoroquinolone constitute the core of the regimen.

3.4 EMPIRIC TREATMENT REGIMENS

Empiric regimens are commonly used in specific groups of patients while DST is pending. Empiric regimens can be standardized (ie. all patients from a certain group get the same regimen until DST results return) or individualized for each patient based on the patient's treatment history and contact history.

Empiric regimens are strongly recommended since most DST methods have a turnaround time of several weeks. Empiric regimens are useful to avoid clinical deterioration of patients and prevent transmission to secondary cases; however, in settings where rapid DST methods are available it may be more appropriate to wait for the results to ensure appropriate treatment. In addition, in highly chronic cases that have been treated multiple times with second-line drugs, waiting for DST results may be prudent if the turnaround time is a few weeks, as long as the patient is clinically stable and appropriate infection control measures are in place. If turnaround time is several months, an empiric regimen may be wiser while waiting DST, even if the patient is stable.

QUESTION:
Which information would you use to design an individualised treatment regimen for a patient with MDR-TB?

ANSWER:
With individualized treatment the resistance pattern of the infecting strain of the individual patient is used, in addition to the patient's treatment history and the prevailing resistance patterns in the community. The method of building the regimen is described in Table 6.1. and examples of suggested regimens on specific drug resistance patterns is provide in Table 6.3.

Table 6.3. Individual regimen design based on DST for first-line drugs		
Drug resistance	Suggested regimen (daily unless otherwise stated)	Comments
HR	Z-E-IA-Fq-(+/- one or two Group 4 agents)	One Group 4 agent is sufficient if E and Z susceptibility is well-ascertained. Two Group 4 agents should be used in extensive disease, or if the DST result is questionable (ie. reported susceptibility to E or Z despite a history of these agents being used in a failing regimen).
HR HRS	Z-E-IA-Fq-(+ two or more group 4 agents)	Only use the first-line agents to which the strain is susceptible. Use alternative IA if S resistance present. More than two Group 4 agents should be used in extensive disease or if resistance to E and Z is present or suspected. Group 5 agents can be considered if an adequate regimen of 4 drugs cannot be formed based on DST.
HRE	Z-IA-Fq-(+ two or more group 4 agents)	Only use the first-line agents to which the strain is susceptible. Use S as IA. More than two Group 4 agents should be used in extensive disease. Group 5 agents can be considered if an adequate regimen of 4 drugs cannot be formed based on DST.
HRSE	Z-IA-Fq-(+ two or more group 4 agents)	Only use the first-line agents to which the strain is susceptible. Use alternative IA. More than two Group 4 agents should be used in extensive disease. Group 5 agents can be considered if an adequate regimen of 4 drugs cannot be formed based on DST.
HRZE	Z-E-IA-Fq-(+ two or more group 4 agents)	Use alternative IA. More than three Group 4 agents should be used in extensive disease. Group 5 agents can be considered if an adequate regimen of 4 drugs cannot be formed based on DST.

(Adapted from: World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis (WHO/HTM/TB/2006.361). Geneva, Switzerland: World Health Organization, 2006).

Every effort should be made to supplement the patient's memory with objective records from previous health care providers. **A detailed clinical history** can help suggest which drugs are likely to be ineffective. The probability of acquired drug resistance increases with the duration of time that the drug has been administered. In particular, evidence of clinical or bacteriological treatment failure (positive smears or cultures) during a period of regular drug administration is highly suggestive of drug resistance. If a patient used a drug for over a month with persistent positive smears or cultures, probable resistance should be considered, even if DST is reported as susceptible.

DST results should **complement** rather than invalidate other sources of data about the likely effectiveness of a specific drug. For example, if a history of prior anti-tuberculosis drug use suggests that a drug is likely to be ineffective due to resistance, this drug should not be relied on as one of the four core drugs in the regimen, even if the strain is susceptible in the laboratory. Alternatively, if the strain is resistant to a drug in the laboratory, but the patient has never taken it and resistance to it is extremely uncommon in the community, this may be a case of a laboratory error or a result of the limited specificity of DST of some second-line drugs.

Another important pitfall is that due to the turnaround time necessary for DST, the patient may have already received months of a standard or empiric treatment regimen by the time DST results become available from the laboratory. The possibility of further acquired resistance during this time must be considered. If there is a high probability of acquired resistance to a drug after the culture for DST was collected, this drug should not be counted as one of the four drugs in the core regimen.

3.6 Duration of injectable agent use

The recommended duration of administration of the injectable agent (or the intensive phase), is guided by smear and culture conversion. The current recommendation is that the injectable agent should be continued for at **least six months.**

It is further recommended that culture results, chest x-ray findings and the patient's clinical status be taken into account in deciding whether or not to continue an injectable agent for longer, particularly in the case of patients for whom the susceptibility pattern is unknown, effectiveness is questionable for an agent(s), or extensive or bilateral pulmonary disease is present.

Intermittent therapy with the injectable agent (three times a week after an initial period of two to three months of daily therapy) can also be considered in patients who have been on the injectable for a prolonged period of time and when toxicity becomes a greater risk to the patient. If the patient was on an empiric regimen with five or six drugs, drugs other than the injectable can be considered for suspension once the DST results are available and the patient continues with at least three of the most potent agents.

An injectable agent should be used for at least six months

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3.7 Duration of treatment

The recommended duration of treatment is guided by culture conversion (See Module 11). Treatment should be continued for **at least 18 months after culture conversion.** Extension for up to 24 months may be indicated in chronic cases with extensive pulmonary damage.

4 Designing a programme treatment strategy

Treatment strategies for programmes may vary depending on access to DST, rates of DR-TB, HIV prevalence, technical capacity and financial resources. Despite the variability, there are uniform recommendations for programme treatment strategies that the WHO Green Light Committee (GLC) has developed. Table 6.4. is a treatment strategy guide for programmes. It is based on different situations in resource-constrained areas with limited access to DST and what strategy the GLC has generally recommended in that situation. The table attempts to cover most situations; however, the TB programme may need to adjust the strategy to meet special circumstances. It assumes that DST of isoniazid, rifampicin, the fluoroquinolones and the injectable agents is fairly reliable. It also assumes DST of other agents is less reliable and that basing individualized treatments on DST of these agents should be avoided. Diagnostic Category IV patients are patients documented (or highly likely) to have MDR-TB; the regimens designed to treat patients with MDR-TB are referred to as Category IV treatments.

1. The GLC was established in June 2000 as a partnership among five categories of participants: governments of resource-limited countries; academic institutions; civil-society organizations; bilateral donors; and WHO. The GLC has successfully negotiated prices of drugs with producers; solicited creation of, and adopted sound policies for, proper management of DR-TB; established strict criteria to review proposals for DR-TB management programmes; assisted countries in developing such proposals and ensured their proper implementation; and, finally, has provided access to quality-assured second-line drugs at concessionary prices to those management programmes considered technically and scientifically sound and not at risk of producing additional drug resistance. For more information about the services and how to contact the Green Light Committee for technical support or apply for access to concessionally-priced, quality-assured second-line antituberculosis drugs, see the GLC web page at: [http://www.who.int/tb/challenges/mdr/greenlightcommittee/en/index.html].

2. The WHO Treatment of tuberculosis: Guidelines for national programmes recommends treatment regimens based on different TB diagnostic categories. The diagnostic categories are: Category I : New smear-positive patients; new smear-negative PTB with extensive parenchymal involvement; severe concomitant HIV disease or severe forms of extra-pulmonary TB. Category II : Previously treated sputum smear-positive PTB: relapse; treatment after interruption; failures. Category III: New smear-negative PTB (other than in Cat I) and less severe forms of extra-pulmonary TB. Category IV: Chronic cases (still sputum-positive after supervised re-treatment) and MDR-TB.

Table 6.4. Recommended strategies for different programmatic situations		
Patient group	**Background susceptibility data[a]**	**Recommended strategy[b]**
New patient with active TB	Resistance uncommon to moderately common (i.e. a country where a low to moderate rate of new cases have MDR-TB)	• Start **Category I treatment** • Perform DST of at least H and R in patients not responsive to Category I[c] • Rapid DST techniques are preferable
	Resistance common (i.e. a country where a high rate of new cases have MDR-TB)	• Perform DST of H and R in all patients before treatment starts • Rapid DST techniques are preferable • Start **Category I** treatment while awaiting DST • Adjust regimen to a Category IV regimen if DST reveals DR-TB
Patient in whom Category I failed	Low percentage of failures of Category I have MDR-TB Second-line drug resistance is rare	• Perform DST of H and R at a minimum in all patients before treatment starts • Rapid DST is preferable • Start **Category II** treatment while awaiting DST • Adjust regimen to a Category IV regimen if DST reveals DR-TB
	High percentage of failures of Category I have MDR-TB Second-line drug resistance is rare	• Perform DST of isoniazid and rifampicin at a minimum in all patient treatment starts s before • Start Category IV treatment: **IA-FQ- two Group 4 agents- +/– Z**
	High percentage of failures of Category I have MDR-TB Second- line drug resistance is common	• Perform DST of H, R, IA, FQ before treatment starts • Start **Category IV treatment: IA-FQ three Group 4 agents- +/– Z** while awaiting DST • Adjust regimen according to DST results if using an individualized approach

Table 6.4. Recommended strategies for different programmatic situations		
Patient group	**Background susceptibility data[a]**	**Recommended strategy[b]**
Patient in whom Category II failed	High percentage of failures of Category II have MDR-TB Second-line drug resistance is rare	• Perform DST of H and R at a minimum in all patients before treatment starts • Start **Category IV treatment: IA-FQ two Group 4 agents- +/– Z** while awaiting DST • Adjust regimen according to DST results if using an individualized approach
	High percentage of failures of Category II have MDR-TB Second-line drug resistance is common	• Perform DST of H, R, IA, FQ before treatment starts • Start **Category IV treatment: IA-FQ three Group 4 agents- +/– Z** while awaiting DST • Adjust regimen according to DST results if using an individualized approach
Patient with history of relapse or patient returning after default	Low to moderate rate of MDR-TB in this group of patients is common	• Perform DST of H and R at a minimum in all patients before treatment starts • Start **Category II treatment** while awaiting DST • Adjust regimen to a Category IV regimen if DST returns DR-TB
Contact of MDR-TB patient now with active TB Cotact resistance pattern known	Close contact with high risk of having the same strain	• Perform rapid diagnosis and DST of H and R at a minimum in all patients before treatment starts • Start **Category IV treatment** based on the DST pattern and treatment history of the contact while awaiting DST • Adjust regimen according to DST results
	Casual contact with low risk of having the same strain	• Perform rapid diagnosis and DST of H and R at a minimum in all patients before treatment starts • Start **Category I treatment** while awaiting DST • Adjust regimen according to DST results
Patient with documented MDR-TB	Documented, or almost certain, susceptibility to a FQ and IA	• Start **Category IV treatment: IA-FQ-two Group 4 agents- +/– Z**
	Documented, or almost certain, susceptibility to a FQ Documented, or almost certain, resistance to an IA	• Start **Category IV treatment: IA-FQ-three Group 4 agents- +/– Z** • Use an IA with documented
	Documented, or almost certain, resistance to a FQ Documented, or almost certain, susceptibility to an IA	• Start **Category IV treatment: IA-FQ three Group 4 agents- +/– Z** • Use a later-generation FQ susceptibility • If the strain is resistant to all IAs, use one for which resistanc rare e is relatively
	Documented, or almost certain, resistance to a FQ and IA	• Start **Category IV treatment** for XDR-TB

Table 6.4. Recommended strategies for different programmatic situations		
Patient group	**Background susceptibility data[a]**	**Recommended strategy[b]**
Patient in whom Category IV failed or Patient with documented MDR-TB and history of extensive second-line drug use	Moderate to high rate of XDR-TB in this group of patients	• Perform DST of IA and FQ (and H and R if not already done) before treatment starts • Start **Category IV treatment** for XDR-TB while awaiting DST
Patient with documented XDR-TB	Documented resistance to H, R, IA, and FQ	• Start Category IV treatment for XDR-TB

a. All strategies in this table assume they will be implemented in resource-constrained areas with limited access to DST. There are no absolute thresholds for low, moderate or high resistance. Programmes are encouraged to consult an expert on which recommended strategies in this table are best indicated based on resistance levels and available resources.
b. Whenever possible, perform DST of injectable agents (IA, aminoglycosides or capreomycin) and a fluoroquinolone (FQ) if MDR-TB is documented.
c. Persistently positive smears at 5 months constitute the definition of Category I failure; however some may wish to consider DST earlier based on overall clinical picture, for example if patient is HIV-positive.

A number of principles in Table 6.3. require explanation. First, DST surveillance data for different groups of patients (new, failures of Category I, failures of Category II, relapse and default, and failures of Category IV) will help greatly in determining rates of MDR-TB and of resistance to other antituberculosis drugs. This is essential for developing appropriate treatment strategies

and for evaluating the impact of control programme interventions. Screening all MDR-TB strains for second-line drug resistance is recommended when capacity and resources are available. Because of the relatively good reliability and reproducibility of DST of aminoglycosides, polypeptides and fluoroquinolones, and since resistance to these drugs defines XDR-TB, DST of these second-line drugs constitutes a priority for surveillance and treatment (see Module 4).

5   EXTRAPULMONARY MDR-TB TREATMENT

Extrapulmonary MDR-TB is treated using the **same strategies** and **duration of time** as pulmonary MDR-TB.

If the patient has symptoms suggestive of central nervous system involvement and is infected with MDR-TB, the regimen should have adequate penetration into the central nervous system. Pyrzinamide, ethionamide, cycloserine and terizidone have good penetration; kanamycin, amikacin and capreomycin only show penetration in the presence of meningeal inflammation; PAS and ethambutol have poor or no penetration.

6   TREATMENT OF XDR-TB

Since it was first described, XDR-TB has been reported on 6 continents in at least 37 countries, constituting up to 10% of all MDR-TB strains. It has proven much more difficult to treat than MDR-TB and is extremely difficult to treat in HIV-positive patients. While reports of HIV positive patients being promptly diagnosed with XDR-TB and placed on an adequate regimen are non-existent to date, reports of cohorts of HIV-negative patients have been shown to have cure rates that exceed 50%. Table 6.5. summarizes the latest expert consensus on how to manage XDR-TB. There are very limited data on different clinical approaches to XDR-TB (See the WHO Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency update 2008 for more information: http://www.who.int/entity/tb/publications/2008/programmatic_guidelines_for_mdrtb/en/index.html).

Table 6.5. Management guidelines for patients with documented, or almost certain, XDR-TB

1. Use any Group 1 agents that may be effective.
2. Use an injectable agent to which the strain is susceptible and consider an extended duration of use (12 months or possibly the whole treatment). If resistant to all injectable agents, it is recommended to use one the patient has never used before.
3. Use a later-generation fluoroquinolone such as moxifloxacin.
4. Use all Group 4 agents that have not been used extensively in a previous regimen or any that are likely to be effective.
5. Use two or more agents from Group 5.
6. Consider high-dose isoniazid treatment if low-level resistance is documented.
7. Consider adjuvant surgery if there is localized disease.
8. Ensure strong infection control measures.
9. Treat HIV (See Module 10).
10. Provide comprehensive monitoring and full adherence support (see Module 11).

Source: World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency update 2008 (WHO/HTM/TB/2008.402). Geneva, Switzerland: World Health Organization; 2008.)

QUESTION:
Summarise the general principles which should be used in the constructing of MDR-TB treatment regimens.

ANSWER:
MDR-TB treatment is a complex health intervention and no one strategy will fit all situations. Physicians must consider the epidemiological, financial, and operational factors when deciding which strategy to use. Table 6.6. provides a quick summary on constructing regimens.

Table 6.6. Summary of general principles for constructing MDR-TB regimens	
Basic principles	**Comments**
1. Use at least 4 drugs expected to be effective. If at least 4 drugs are not expected to be effective, use 5 to 7 drugs depending on the specific drugs and level of uncertainty.	Effectiveness is supported by a number of factors (the more present the more likely the drug will be effective in the patient): • DST results show susceptibility. • No prior history of treatment with the drug. • No known close contacts with resistance to the drug. • Surveillance data show that resistance is rare in similar patients • The drug is not commonly used in the area.
2. Do not use drugs for which cross-resistance exists	• All rifamycins have cross-resistance (rifampicin, rifabutin, rifapentine, rifalazil). • Fluoroquinolones are believed to have high cross-resistance between each other. • Not all aminoglycosides show cross-resistance; in general, only kanamycin and amikacin are fully cross-resistant.
4. Eliminate drugs that are not safe in the patient	• Known severe allergy or unmanageable intolerance. • High risk of severe adverse drug effects such as renal failure, deafness, hepatitis, depression and/or psychosis, • Quality of the drug is unknown.

Table 6.6. Summary of general principles for constructing MDR-TB regimens	
5. Include drugs from Groups 1 to 5 in a hierarchal order based on potency.	• Use any Group 1 (oral first-line drugs) that are likely to be effective. • Use an effective injectable (Group 2). • Use a fluoroquinolone (Group 3). • Use the remaining Group 4 drugs to make a regimen of at least 4 effective drugs. • For regimens with < 4 effective drugs, add second-line drugs most likely to be effective up to 5-7 drugs total. The number of drugs will depend on the degree of uncertainty. • Use Group 5 drugs as needed.
6. Be prepared to prevent, monitor and manage side effects for each of the drugs selected.	• Laboratory services for haematology, biochemistry, serology, audiometry required • Establish a baseline before starting the drug. • Initiate treatment gradually, split daily doses. • Ancillary drugs must be in stock to manage side effects

SELF ASSESSMENT QUESTIONS AND EXERCISES:
DESIGNING MDR-TB TREATMENT REGIMENS

1. True/False:
( ) MDR-TB treatment regimens should be based on the history of drugs taken
( ) MDR-TB regimens should contain at least four effective drugs
( ) All MDR-TB drugs should be given in divided doses
( ) The injectable agent should be used for four months
( ) MDR-TB treatment should be adjusted according to patient weight

2. Drug effectiveness is supported by the following:
a) In vitro drug susceptibility
b) No prior history of use
c) Limited use of the drug in a particular setting
d) Low resistance levels indicated by surveillance
e) All of the above

3. True/False:
( ) There is 100% cross-resistance between lower and higher generation fluoroquinolones
( ) Rifamycins other than rifampicin should be used in MDR-TB treatment
( ) Treatment for extra-pulmonary MDR-TB should be extended
( ) All MDR-TB drugs have good central nervous system penetration
( ) All aminoglycosides have cross-resistance

ANSWERS

1: T,T,F,F, T
2: e
3: F,F,F,F,F

MODULE 7

ANCILLARY MEDICATION AND ADJUVANT THERAPIES

1   LEARNING OBJECTIVES

At the end of this module you should be able to:

- Prescribe appropriate ancillary medication and adjuvant therapy to MDR-TB treatment
- Understand the role of surgery in MDR-TB treatment

2   INTRODUCTION

A number of ancillary medications and adjuvant therapies are used to lessen adverse effects and morbidity, and to improve overall MDR-TB treatment outcomes.

3   ANCILLARY MEDICATIONS AND ADJUVANT THERAPIES

CORTICOSTEROIDS: The adjuvant use of corticosteroids in patients on MDR-TB treatment has been shown not to increase mortality and can help alleviate symptoms associated with severe respiratory insufficiency, central nervous system involvement and laryngeal TB. There is no evidence that one corticosteroid is better than another. Prednisone is commonly used, starting at approximately 1 mg/kg and gradually decreasing the dose by 10mg per week. Stopping the prednisone abruptly can be dangerous in patients dependent on corticosteroids. Corticosteroids may also alleviate symptoms in patients with exacerbation of obstructive pulmonary disease. In these cases, prednisone may be given over one to two weeks, starting at approximately 1 mg/kg and decreasing the dose by 5-10 mg per day.

Patients already using corticosteroids for other conditions should continue their use.

PYRIDOXINE: Pyridoxine is an ancillary medication given with cycloserine and terizidone to prevent neurological toxicity and should be provided daily at a dose of 50 mg for every 250mg of cycloserine used (or for every 300 mg of terizadone used). The maximum dose can be used of 200 mg/day when adverse effects related to cyloserine or terizidone use are experienced.

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

PAIN CONTROL: Chronic painful conditions may be present with TB either as a result of TB (pleurisies) or from past or present adverse effects of drugs (neuropathy, headaches). Headaches are often an adverse effect of MDR-TB treatment. It is important to rule out other causes such as meningitis, migraine and cluster headaches. Codeine with acetaminophen gives relief to moderate pain and also helps control cough. Stronger analgesics should be used as appropriate.

RESPIRATORY INSUFFICIENCY: Oxygen can be used to alleviate shortness of breath. Generally, it 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%. Oxygen is usually started at 2-4L/min via nasal cannula. If more than 5 L/min is needed, the oxygen should be delivered through a mask. Retention of CO_2 can occur in some patients and should be checked when starting oxygen or increasing oxygen delivery. Corticosteroids and morphine also provide significant relief from respiratory insufficiency.

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

NUTRITIONAL SUPPORT: In addition to causing malnutrition, MDR-TB can be exacerbated by poor nutritional status. The second-line anti-tuberculosis medications can also further decrease the appetite, making adequate nutrition a greater challenge. Nutritional support can take the form of providing free staple foods, and whenever possible should include a source of protein.

ANCILLARY MEDICATIONS TO TREAT ADVERSE EFFECTS OF ANTI-TB DRUGS: Ancillary medications to treat adverse effects of anti-TB drugs are discussed in Module 8.

QUESTION

Which of the following statements are correct ?

a. The adjuvant use of corticosteroids in patients on MDR-TB treatment has been shown to increase mortality but can help alleviate symptoms associated with severe respiratory insufficiency, central nervous system involvement and laryngeal TB.

b. Corticosteroids may also alleviate symptoms in patients with exacerbation of obstructive pulmonary disease.

c. Stopping the prednisone abruptly can be dangerous in patients dependent on corticosteroids.

d. Pyridoxine is given as adjuvant therapy with streptomycin to prevent neurological toxicity.

e. If minerals are given they should be administered together with the fluoroquinolones.

ANSWER:

The correct answers are b and c.

• The adjuvant use of corticosteroids in patients on MDR-TB treatment has been shown **not** to increase mortality and can help alleviate symptoms associated with severe respiratory insufficiency, central nervous system involvement and laryngeal TB.

• Pyridoxine is given as adjuvant therapy with **cycloserine and terizidone** to prevent neurological toxicity.

• If minerals are given they should be administered at least **one hour before** or after the fluoroquinolones, as zinc, iron and calcium can interfere with fluoroquinolone absorption.

QUESTION

Which of the following statements are correct about ancillary medications in the management of MDR-TB?

a. Antacids should be avoided because they can decrease absorption of fluoroquinolone.

b. Selective serotonin reuptake inhibitors (fluoxetine, sertraline) should not be used for depression.

c. Ibuprofen, paracetamol or codeine are safe for the treatment of musculoskeletal pain, arthralgia and headaches.

d. Inhaled beta-agonists (albuterol, etc.), inhaled corticosteroids (beclomethasone, etc.), oral steroids (prednisone), and injectable steroids (dextamethasone, methylprednisolone) should be avoided in the treatment of bronchospasm.

e. Tegretol is used for the treatment of Peripheral neuropathy.

ANSWER:

The correct answers are a and c.

• Inhaled beta-agonists (albuterol, etc.), inhaled corticosteroids (beclomethasone, etc.), oral steroids (prednisone), injectable steroids (dextamethasone, methylprednisolone) should be used for bronchospasm.

• Selective serotonin inhibitors as well as tricyclic antidepressants may be used for depression.

• Amitriptyline, and not Tegretol, is used for the treatment of peripheral neuropathy.

4   SURGERY

The treatment of MDR-TB 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. For patients with localised disease, surgery can significantly improve outcomes, provided that skilled thoracic surgery and excellent post-operative care are available.

QUESTION

When would surgery indicated in a patient with MDR-TB ?

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

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

c. 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.

d. At least twelve months of treatment should be given before surgery is considered.

e. After the first failure of MDR-TB treatment.

ANSWER

 The correct answers are a, b and c.

- At least **six** months of treatment should be given before surgery is considered.

QUESTION:

What are the indications for surgery in the treatment of MDR-TB?

ANSWER:

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 profile of drug resistance is so great (extensive or extreme resistance, eg. resistance to more than four drugs) that if relapse did occur it may be difficult to re-establish sputum culture conversion.
- In a patient who has undergone sputum conversion but there is residual cavitation or gross lobe or lung destruction and hence the potential for relapse.

It is ideal to have smear conversion prior to surgery and to perform surgery early in the course of therapy, usually between 2 and 6 months. If conversion is not possible, at least **two months** of treatment should be given before surgery is considered.

The decision to perform surgery and the extent of surgery (lobectomy or pneumonectomy) should preferably be made after anatomical localisation of disease by CT scan. Often the apex of a lower lobe is involved together with a corresponding upper lobe and the former should also be removed. Perfusion scans are useful in establishing how much functioning lung is likely to be removed. Basic spirometry (FEV1 and FVC) is adequate in assessing lung function in the majority of patients. Eligible patients should have a FEV1 > 0.8. If the FEV1 is acceptable, analysis of blood for HCT, arterial blood gases (ABG), electrolytes, urea and creatinine should be performed pre-operatively. EKG is useful for excluding pulmonary hypertension which would contraindicate surgery. A pre-operative EKG should be performed on patients older than 50 years and on patients with diabetes.

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In a patient who has not undergone sputum conversion, surgery should only be performed when there is no further possibility of an adequate chemotherapeutic regimen.

The 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-negative at the time of surgery the treatment should continue for at least 18 months after culture conversion. If the patient was culture-positive, treatment should continue for 18 months past the culture conversion date post-surgery.

The resected
specimen should be
sent for histology,
culture and drug
susceptibility testing

Centers for Disease Control and Prevention

1. Ancillary medications of use in MDR-TB treatment include:
a) Corticosteroids
b) Bronchodilators
c) Pyridoxine
d) Pain relievers
e) All of the above

2. Pyridoxine should be routinely prescribed for all MDR-TB patients on:
a) Kanamycin
b) Ethionamide
c) Cycloserine
d) Ofloxacin
e) Pyrazinamide

3. Surgery in persistantly culture postive patients with MDR-TB should be preceded by at least:
a) Two months of MDR-TB treatment
b) Three months of MDR-TB treatment
c) Four months of MDR-TB treatment
d) Six months of MDR-TB treatment
e) Nine months of MDR-TB treatment

ANSWERS

1: e
2: c
3: a

Module 8   Drug adverse effects

MODULE 8

DRUG ADVERSE EFFECTS

1   LEARNING OBJECTIVES

At the end of this module you should be able to:

- Identify known drug adverse effects of MDR-TB treatment
- Detect drug adverse effects early in patients on MDR-TB treatment
- Manage second-line drug adverse drug effects

2   INTRODUCTION

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

3   MOST COMMON DRUG ADVERSE EFFECTS

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

Since MDR-TB patients receive combination chemotherapy, it is often difficult to determine which drug is the source of the undesired effect as drug-drug interactions may also produce adverse effects. Some adverse effects disappear within a short period after treatment begins, while others tend to manifest later.

QUESTION:
Give the list of the known adverse effects of second-line drugs available for MDR-TB treatment and list the drugs associated with each adverse effect.

ANSWER:
The known side effects to second-line anti-TB drugs include (drugs in bold are more strongly associated with the adverse effect than drugs not in bold):
COMMON ADVERESE EFFECTS
- Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, anorexia, abdominal pain, gastritis (drugs associated: **Eto/Pto, PAS,** H, E, Z)
- Arthralgia (drugs associated: Z, FQs)
- Headache (drugs associated: CS)
- Sleep disturbances (drugs associated: CS)
  LESS COMMON
- Rashes (any drug)
- Jaundice (drugs associated: **S, Km, Cm, Am, Vm**)
- Ototoxicity (drugs associated: **S, Km, Am, Cm, Clr**)
- Peripheral neuropathy (drugs associated: **Cs, Lzd, H,** S, Km, Am, Cm, Vi, Eto/Pto, fluoroquinolones)
- Symptoms of electrolyte wasting, eg.muscle cramping, palpitations (drugs associated: **Cm, Vm,**Km, Am, S)
- Psychiatric symptoms eg.depression, anxiety, psychosis, suicidal ideation (drugs associated: **Cs, H**, FQs, Eto/Pto)
- Renal Failure (drugs associated: **S, Km, Am, Cm, Vm**)
- Hypothyroidism (drugs associated: **PAS, Eto/Pto**)

Cutaneous adverse drug events, ranging from pruritus to rashes, and most severely to toxic epidermal necrolysis, sometimes accompanied by fever, may be caused by several agents. Cutaneous drug adverse events are much more frequent among patients with HIV infection.

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

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

Impaired hearing or impaired balance is virtually always due to the injectable agents. It is often, but not always, dose-dependent. Patients with pre-existing vestibulo-cochlear impairment should be counselled on the potential risks and informed consent obtained before these drugs are used. Patients complaining of hearing loss or impaired balance should be checked to establish that the dosage given is appropriate for weight and age, as toxicity increases with both. Also check that the dose is correct for the renal function of the patient (calculate the creatinine clearance and adjust medications as indicated, see Table 9.3).

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

Impaired vision is most frequent caused by ethambutol. Optic toxicity is not detectable fundoscopically and therefore visual acuity and testing of colour vision are required. In patients with impaired vision other than due to myopia, hyperopia or presbyopia, ethambutol should only be given in consultation with an ophthalmologist, carefully weighing the risks and benefits if drug choices are limited.

Neurological symptoms: A distinction should be made between peripheral and central nervous system toxicity from second-line anti-TB medications. Peripheral neuropathy, presenting as paresthesia such as tingling and numbness, starting at the feet with proximal spread is the usual manifestation. Myalgias, weakness and ataxia may accompany these symptoms. Peripheral neuropathy is usually due to cycloserine and terizidone and occurs more commonly in malnourished or alcohol-dependent patients. Pyridoxine is effective in treating peripheral neuropathy.

Infrequently, toxic psychosis and epileptic convulsions may occur with cycloserine and terizidone. While pyridoxine may be helpful for preventing these cases, once they present, the dose of cycloserine or terizidone often will need to be stopped and restarted at a lower dose. Also, cycloserine and terizidone are renally excreted, so if serious adverse effects present, check a creatinine clearance- a low creatinine clearance may result in high blood levels of these drugs responsible for the adverse effects.

Osteo-articular pain: Arthralgia is a frequent adverse drug event resulting from accumulation of uric acid due to pyrazinamide. Acetyl salicylic acid commonly alleviates the symptoms. Intermittent administration of pyrazinamide will also reduce the effect of uric acid retention. Allopurinol is ineffective.

Electrolyte wasting is a known complication of the injectable drugs, most frequently with capreomycin. It is generally a late effect that manifests after months of treatment, and is reversible once the injectable is suspended. Electrolyte wasting is often occult in the early stages.

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

QUESTION:
How would you monitor drug adverse effects in a patient on MDR-TB treatment?

ANSWER:
Laboratory screening is invaluable for detecting adverse effects that are more occult. Table 8.1. provides recommendations for minimal frequency of essential laboratory screening. More frequent screening may be advisable, particularly for high-risk patients and in patients with HIV disease.
Evaluation of drug adverse effects must be done as follows:
• At baseline;
• At least monthly during the first few months of treatment (preferably until culture conversion);
• At least two-monthly after culture conversion.
Treatment supervisors should enquire about drug adverse effects during every encounter with the patient.

Table 8.1. Laboratory monitoring of drug adverse effects	
Monitoring evaluation	**Frequency**
Evaluation by clinician	At baseline, and then at least monthly until conversion, then every 2-3 months
Screening by DOT worker	At every DOT encounter
Sputum smears and cultures	Monitor smears and cultures monthly throughout treatment. (Note: programmes with limited resources may choose to do smears monthly but cultures only every other month)
Weight	At baseline then monthly
Drug susceptibility	At baseline in programmes doing individualized treatment testing (DST) or in programmes doing standardized treatments that need to confirm MDR-TB. For patients who remain culture-positive, it is not necessary to repeat DST within less than 3 months of treatment
Chest radiograph	At baseline, and then every 6 months
Serum creatinine	At baseline, then monthly if possible while receiving an injectable drug. Every 1–3 weeks in HIV-infected patients, diabetics and other high-risk patients
Serum potassium	Monthly while receiving an injectable agent. Every 1–3 weeks in HIV-infected patients, diabetics and other high-risk patients
Thyroid stimulating hormone (TSH)	Every 6 months if receiving ethionamide/protionamide hormone and/or PAS; and monitor monthly for signs/symptoms of hypothyroidism. TSH is sufficient for screening for hypothyroidism; it is not necessary to measure hormone thyroid levels
Liver serum enzymes	Periodic monitoring (every 1–3 months) in patients receiving pyrazinamide for extended periods or for patients at risk for or with symptoms of hepatitis. For HIV-infected patients, do monthly monitoring

Table 8.1. Laboratory monitoring of drug adverse effects	
Monitoring evaluation	**Frequency**
HIV screening	At baseline, and repeat if clinically indicated
Pregnancy tests	At baseline for women of childbearing age, and repeat if indicated
Haemoglobin and white blood count	If on linezolid monitor weekly at first, then monthly or as needed based on symptoms; there is little clinical experience with prolonged use. For HIV-infected patients on AZT monitor monthly initially and then as needed based on symptoms
Lipase	Indicated for work-up of abdominal pain to rule out pancreatitis in patients on linezolid, D4T, ddI, ddc.
Lactic acidosis	Indicated for work up of lactic acidosis in patients on linezolid or ART.
Serum glucose	If receiving gatifloxacin, monitor glucose frequently (weekly) and educate patient on signs and symptoms of hypoglycaemia and hyperglcycaemia

Serum potassium should be checked at least monthly in all patients receiving capreomycin.

5   MANAGEMENT OF DRUG ADVERSE EFFECTS

Of equal importance to the treatment strategy used is the proper management of drug adverse effects. Second-line anti-tuberculosis drugs have many more adverse effects than first-line anti-tuberculosis drugs; nevertheless, management of adverse effects is possible even in resource-limited settings.

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

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

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

- Management of adverse effects with standardised algorithms: Most adverse effects can be managed with over-the-counter and common prescription drugs. If the adverse effect(s) is mild and not dangerous, continuing the treatment regimen, with the help of ancillary drugs if needed, is the best option. Many adverse effects disappear or diminish with time and patients should be encouraged to tolerate the effects until they subside. Psychosocial support is an important component of management of adverse effects. Published flow diagrams on how to manage adverse effects in MDR-TB are available in The PIH Guide to the Medical Management of Multidrug-resistant Tuberculosis (http://www.pih.org/inforesources/pihguide-mdrtb.html).
- Reduced dosage of suspected drug(s): The adverse effects of a number of second-line anti-tuberculosis drugs are highly dose dependent. If it 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), dosage of each drug can be reduced sequentially until the culprit drug is identified. In this case, when the dosage of a second drug is reduced, the first drug of which the dosage was reduced should be returned to normal dosage. If reduction of dosage of individual drugs does not result in the disappearance of the adverse effects(s), it may be necessary to reduce the dosage of multiple drugs simultaneously. However,

due to the narrow therapeutic margins of second-line drugs, lowering the dose may affect the efficacy as well, so every effort should be made to maintain an adequate dose of the drug according to body weight.

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

Monitoring and management of drug adverse effects may have to be more aggressive in patients with concomitant conditions such as:

- Pregnancy and lactation
- Diabetes mellitus;
- Renal insufficiency;
- Acute or chronic liver disease;
- Thyroid disease;
- Mental illness;
- Drug or alcohol abuse;
- HIV infection;

Management of MDR-TB when these conditions exist are described in Modules 9 and 10.

Drugs used in MDR-TB treatment commonly cause adverse effects which needs to be managed appropriately

Lung Health Image Library

Table 8.2. summarizes the common adverse effects, the likely agents responsible, and suggested management strategies.

Table 8.2. Common drug adverse reactions and management strategies			
Adverse reaction	**Agent***	**Management**	**Comments**
Seizures	**Cs, H,** FQs	1. Suspend suspected agent pending resolution of seizures. 2. Initiate anticonvulsant therapy (eg. phenytoin 3-5 mg/kg/day; valproic acid 750-1250 mg/kg/day; carbamazepine 600-1200 mg/day; phenobarbitol 60-120 mg/kg/day) 3. Increase pyridoxine to maximum daily dose (200 mg daily). 4. Restart suspected agent or reinitiate suspected agent at lower dose, if essential to the regimen. 5. Discontinue suspected agent if this can be done without compromising the regimen.	1. Anticonvulsant generally continued until MDR-TB treatment completed or suspected agent discontinued. 2. History of prior seizure disorder not a contra-indication to the use of agents listed here if patient's seizures are well-controlled and/or patient is receiving anticonvulsant therapy. 3. Patients with history of prior seizures may be at increased risk for development of seizures during MDR-TB therapy.
Peripheral neuropathy	**Cs, Lzd, H,** S, Km, Am, Eto/Pto, Cm, Vi, FQs	1. Increase pyridoxine to maximum daily dose (200 mg per day). 2. Change injectable to capreomycin if patient has document susceptibility to capreomycin. 3. Initiate therapy with tricyclic anti-depressant drugs such as amitriptyline. Non-steroidal anti-inflammatory drugs or acetaminophen may help alleviate symptoms. 4. Lower dose of suspected agent if this can be done without compromising the regimen 5. Discontinue suspected agent if this can be done without compromising regimen.	1. Patients with co-morbid disease (eg. diabetes, HIV, alcoholism) more likely to develop peripheral neuropathy, but these conditions are not contraindications to the use of the agents listed here. 2. Neuropathy may be irreversible; however, some patients may experience improvement when offending agents are suspended.
Hearing loss and vestibular disturbances	**S, Km, Am, Cm,** Clr	1. Document hearing loss and compare with baseline audiometry if available. 2. Change parenteral treatment to capreomycin if patient has documented susceptibility to capreomycin. 3. Decrease frequency and/or lower dose of suspected agent if this can be done without compromising the regimen. 4. Discontinue suspected agent if this can be done without compromising the regimen.	1. Patients with prior exposure to aminoglycosides may have baseline hearing loss. 2. Hearing loss is generally not reversible. 3. The risk of further hearing loss must be weighed against the risks of stopping the injectable in the treatment regimen. 4. While the benefit of hearing aids is minimal to moderate in auditory toxicity, consider a trial use to determine if a patient with hearing loss can benefit from their use.
Psychosis	**Cs, H,** FQs, Eto/Pto	1. Hold suspected agent for short period of time (1-4 weeks) while psychotic symptoms brought under control.2. Initiate anti-psychotic drugs (eg. risperidone 0.5-2 mg PO BID; haloperidol 1-5mg PO IV or IM repeated every hour as needed).3. Lower dose of suspected agent if this can be done without compromising the regimen.4. Discontinue suspected agent if this can be done without compromising the regimen.	1. Some patients will need to continue anti-psychotic treatment throughout MDR-TB therapy.2. 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.3. Psychotic symptoms generally reversible upon MDR-TB treatment completion or discontinuation of offending agent.

| Table 8.2. Common drug adverse reactions and management strategies ||||
Adverse reaction	Agent*	Management	Comments
Depression	**Socioeconomic circumstances, chronic disease, Cs,** FQs, H, Eto/Pto	1. Improve socioeconomic conditions. 2. Institute psychological therapy, ie. group or individual supportive counselling. 3. Initiate anti-depressant drugs (eg. amytriptyline, nortriptyline, fluoxetine, sertraline), but use with caution when history of convulsions. 4. Lower dose of suspected agent if this can be done without compromising the regimen. 5. Discontinue suspected agent if this can be done without compromising the regimen.	1. Importance of socioeconomic conditions should not be underestimated as contributing factor to depression 2. Depression and depressive symptoms may fluctuate during therapy. 3. 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.
Nausea and vomiting	**Eto/Pto,PAS,** H, E, Z	1. Assess for dehydraytion; initiate rehydration if indicated 2. Initiate antiemetic therapy. 3. Lower dose of suspected agent if this can be done without compromising the regimen. 4. Discontinue suspected agent if this can be done without compromising the regimen- rarely necessary.	1. Nausea and vomiting ubiquitous in early weeks of therapy and usually abate with supportive therapy. 2. Electrolytes should be monitored and repleted if vomiting severe. 3. Reversible upon discontinuation of suspected agent. 4. Severe abdominal distress and acute abdomen have been reported with the use of clofazimine. Although these reports are rare, if this effect occurs, clofazimine should be suspended.
Gastritis	**PAS, Eto/Pto**	1. Administer MDR-TB medications with small amount of food. 2. Avoid caffeine, cigarettes. 3. Provide antacids (eg. calcium carbonate, aluminium hydroxide, magnesium-hydroxide) or H2-blockers (eg. cimetidine, ranitidine), proton-pump inhibitors (eg. omeprazole). 4. Hold suspected agent(s) for short periods of time (eg. 1-7 days). 5. Lower dose of suspected agent, if this can be done without compromising the regimen. 6. Discontinue suspected agent, if this can be done without compromising the regimen.	1. Severe gastritis possible, as manifest by hematemesis, melena or hematechezia (but is rare). 2. Dosing of antacids should be carefully timed so as to not interfere with the absorption of MDR-TB drugs (take 2 hours before or 3 hours after antituberculosis medications). 3. Reversible upon discontinuation of suspected agent(s).
Hepatitis	**Z, H, R,** FQs, Eto/Pto, PAS, E	1. Stop all therapy pending resolution of hepatitis. 2. Rule out other potential causes of hepatitis. 3. Consider suspending most likely agent permanently. Reintroduce remaining drugs, one at a time with the most hepatoxic agents first, while monitoring liver function every 1-2 months.	1. History of prior hepatitis should be carefully analyzed to determine most likely causative agent(s); these should be avoided in future regimens. 2. Generally reversible upon discontinuation of suspected agent.

Table 8.2. Common drug adverse reactions and management strategies			
Adverse reaction	**Agent***	**Management**	**Comments**
Nephrotoxicity and renal failure	**S, Km, Am, Cm, Vm**	1. Discontinue suspected agent 2. Consider using capreomycin if an aminoglycide had been the prior injectable in regimen. 3. Consider dosing 2-3 times/week if drug is essential tp the regimen and if the patient can tolerate (close monitoring of creatinine).	1. History of diabetes or renal disease not a contraindication to the use of the agents listed here, although patients with comorbidities may be at increased risk for developing renal failure. 2. Renal impairment may be permanent.
Optic neuritis	**E**, Eto/Pto	1. Stop E. 2. Refer the patient to an ophthalmologist.	1. Usually reverses with cessation of E. 2. Rare case reports of optic neuritis have been attributed to streptomycin.
Arthralgias	**Z**, FQs	1. Initiate therapy with non-steroidal anti-inflammatory drugs. 2. Lower dose of suspected agent if this can be done without compromising the regimen. 3. Discontinue suspected agent if this can be done without compromising the regimen.	1. Symptoms of arthralgia generally diminish over time, even without intervention. 2. Uric acid levels may be elevated in some patients on pyrazinamide but are of little therapeutic relevance and anti-gout therapy (eg. allopurinol, colchicines) is of no proven benefit in these patients.
Electrolyte disturbances (hypokalaemia, hypomagnesaemia)	**Cm, Vm**, Km, Am, S	1. Check potassium. 2. If potassium is low, also check magnesium (and calcium if hypocalcaemia is suspected). 3. Replace electrolytes as needed.	1. Hypokalemia can occur without clinical signs and symptoms and may be life-threatening; consider hospitalization if necessary. 2. Oral potassium replacements can cause significant nausea and vomiting. Oral magnesium may cause diarrhoea. 3. Amiloride 5–10 mg QD or spironolactone 25 mg QD may decrease potassium and magnesium wasting and is useful in refractory cases.

Directly-observed treatment allows health care workers to also check on drug adverse effects

South African Medical Research Council

The management of adverse effects often requires the use of ancillary medications to eliminate or lessen the event. Table 8.3. provides a list of indications and commonly used medications for the management of adverse reactions to second-line anti-tuberculosis drugs.

| Table 8.3. Commonly used ancillary medications ||
Indication	Drug
Nausea, vomiting, upset stomach	Metoclopramide, dimenhydrinate, prochlorperazine, promethazine, bismuth subsalicylate
Heartburn, acid indigestion, sour stomach, ulcer	H2-blockers (ranitidine, cimetidine, famotidine, etc.), proton pump inhibitors (omeprazole, lansoprazole, etc.) Avoid antacids because they can decrease absorption of flouroquinolones
Oral candidiasis (non-AIDS patient)	Fluconazole, clotrimazole lozenges
Diarrhoea	Loperamide
Depression	Selective serotonin reuptake inhibitors (fluoxetine, sertraline), tricyclic antidepressants (amitriptyline)
Severe anxiety	Lorazepam, diazepam, clonazepam
Insomnia	Dimenhydrinate
Psychosis	Haloperidol, thorazine, risperidone (consider benzotropine or biperiden to prevent extrapyramidal side effects)
Seizures	Phenytoin, carbamazepine, valproic acid, phenobarbital
Prophylaxis of neurological complications of cycloserine or terizidone	Pyridoxine (vitamin B6)
Peripheral neuropathy	Amitriptyline
Vestibular symptoms	Meclizine, dimenhydrinate, prochlorperazine, promethazine
Musculoskeletal pain, arthralgia, headaches	Ibuprofen, paracetamol, codeine
Cutaneous reactions, itching	Hydrocortisone cream, calamine, caladryl lotions
Systemic hypersensitivity reactions	Antihistamines (diphenhydramine, chlorpheniramine, dimenhydrinate), corticosteroids (prednisone, dexamethasone)
Bronchospasm	Inhaled beta-agonists (albuterol, etc.), inhaled corticosteroids (beclomethasone, etc.), oral steroids (prednisone), injectable steroids (dextamethasone, methylprednisolone)
Hypothyroidism	Levo-thyroxine
Electrolyte wasting	Potassium and magnesium replacement

(Source: World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency update 2008 (WHO/HTM/TB/2008.402). Geneva, Switzerland: World Health Organization; 2008).

1. The most common drug adverse effect of MDR-TB drugs is:
a) Central nervous system effects
b) Peripheral neuropathy
c) Hearing loss
d) Gastrointestinal effects
e) Hepatitis

2. Serum Creatinine should be measured:
a) Weekly throughout treatment
b) Weekly while on the injectable agent
c) Monthly while on the Injectable agent
d) Every two months throughout treatment
e) Every 6 months thoughout treatment

3. Hypokalaemia (often without clinical symptoms) is most common with:
a) Fluoroquinolones
b) Thioamides
c) Injectable agents
d) Ethambutol
e) Cycloserine/terizidone

ANSWERS

1: d
2: c
3: c

Module 9   Special situations

MODULE 9

SPECIAL SITUATIONS

1   LEARNING OBJECTIVES

At the end of this module you should be able to:

- Manage MDR-TB patients in special situations
- Manage co-morbid conditions in MDR-TB patients
- Manage patients who are failing MDR-TB treatment
- Understand the indications for terminating treatment
- Understand end-of-life supportive measures

2   Introduction

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

3   Oral contraception use

Birth control is strongly recommended for all women receiving MDR-TB treatment because of the potential negative consequences in both mother and foetus of frequent and/or severe adverse drug reactions.

There is **no contraindication to taking oral contraceptives** with MDR-TB regimens; however, 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 MDR-TB treatment.

Patients who experience vomiting directly after taking an oral contraceptive can be at risk for decreased absorption of the latter, resulting in decreased efficacy. Patients should be educated on this possibility and advised to take their contraceptives apart from times when they may experience vomiting due to the anti-tuberculosis treatment. If the patient has vomiting anytime directly after, or within the first two hours after, taking the anti-contraceptive tablet, she should use a barrier method of contraception until she is able to take a full month of the anti-contraceptive tablets without vomiting.

Question
Which of the following statements are correct regarding contraception and pregnancy in the management of MDR-TB?
a. There are serious contraindications to the taking of oral contraceptives with MDR-TB regimens;
b. Alternate measures include the use of medroxy-progesterone (Depo-Provera) intramuscular every 14 weeks;
c. Birth control is strongly recommended for all women receiving MDR-TB treatment;
d. Patients who experience vomiting directly after taking an oral contraceptive can be at risk for decreased absorption of the latter;
e. Pregnancy is a contraindication to the treatment of active MDR-TB.

Answer
The correct answers are: b, c and d.
- Oral contraception is not contra-indicated in patients who are on MDR-TB regime.
- Pregnancy itself is not a contra-indication for the administration of MDR-TB therapy.

4   Pregnancy

Female MDR-TB patients of childbearing age should be tested for pregnancy upon initial evaluation. Pregnancy is not a contraindication to the treatment of active MDR-TB since active, untreated MDR-TB poses great risks to the lives of both the mother and foetus.

Gravid patients should be carefully evaluated, taking into consideration gestational age and MDR-TB severity. The risks and benefits of MDR-TB treatment should be carefully considered. The following recommendations apply:

- Consider delaying MDR-TB treatment until the second trimester: Since the majority of teratogenic effects occur in the first trimester, therapy can be delayed until the second trimester un-

less life-threatening symptoms occur. The decision to postpone treatment should be agreed by both patient and physician. It is primarily based on clinical judgment resulting from the analysis of life-threatening signs/symptoms and severity or aggressiveness of the disease (usually reflected in extent of weight loss and radiographic picture during the previous weeks). A discussion of risks and benefits must address any concerns a patient may have in delaying the start of therapy or in using medicines while pregnant. If the decision is to start therapy, use three or four oral drugs with demonstrated efficacy and then reinforce the regimen with an injectable agent and possibly other drugs immediately postpartum.

- **Avoid injectable agents:** For the most part, aminoglycosides should not be used in the regimens of pregnant patients and can be particularly toxic to the developing foetal ear. Capreomycin may carry the same risk of ototoxicity, but is the injectable of choice if an injectable agent cannot be avoided.

- **Avoid ethionamide:** Ethionamide can increase the risk of nausea and vomiting associated with pregnancy and teratogenic effects have been observed in animal studies. If possible, avoid ethionamide in gravid patients.

Table 9.1. lists the safety during pregnancy of medications used in the treatment of MDR-TB.

Table 9.1. Safety of MDR-TB medications during pregnancy		
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.
Streptomycin Kanamycin Amikacin Capreomycin	D	Avoid use. Documented toxicity to developing foetal 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 Protionamide	C	Avoid use. Teratogenic effects observed in animal studies; significantly worsens nausea associated with pregnancy.
Cycloserine Terizidone	C	Significant experience in gravid patients: animal studies have 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 adverse effect
 D = Unsafe, risk may only be justifiable under certain clinical circumstances.

(Source: Partners In Health. The PIH Guide to Medical Management of Multidrug-Resistant Tuberculosis. Boston, Massachusetts: Partners In Health, Program in Infectious Diseases and Social Change, Harvard Medical School, Division of Social Medicine and Health Inequalities, Brigham and Women's Hospital; 2003).

5   Breastfeeding

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

Nursing infants: In lactating mothers on treatment, most anti-tuberculosis drugs are found in the breast milk in concentrations that would equal only a small fraction compared to a therapeutic dose used in an infant. However, the effects on infants of such exposure during the full course of MDR-TB treatment have not been established. 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.

The mother and baby should not be forced to stay apart. If the mother is smear-positive, she should consider leaving the care of the infant to family members until she is negative. However, she should be always offered the option to use an N-95 respirator (see Module 14) for more information on respirators) until smear-negative and try to spend time with the infant in well ventilated areas, even outdoors.

6   CHILDREN

Children with MDR-TB generally have primary disease transmitted from an adult contact with MDR-TB. Because children often have paucibacillary disease, they are seldom culture-positive. Nevertheless, every effort should be made to bacteriologically confirm MDR-TB in children.

Jaco (middle, at back) with the children of his ward. Jaco is 14 years old and has MDR-TB. He has been at the hospital for 7 months taking his treatment. Brooklyn Chest Hospital, Cape Town.

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In culture-negative children who have clinical evidence of active TB and close contact with documented MDR-TB, the child's treatment should be guided by results of DST and history of TB drug exposure of the contact (also see Modules 4, 5 and 6).

There is limited reported experience on the use of the second-line medications for extended periods in children. Careful consideration of the risks and benefits of each drug should be made. Frank discussion with the patient and family members is critical, especially at the outset of therapy. Given the life-threatening aspects of MDR-TB, **no second-line drugs are absolutely contraindicated in children.**

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

In general, drugs should be dosed according to weight, as outlined in Table 9.2. Monitoring monthly weight is therefore especially important in paediatric cases, with adjustment of drug dosages as the child gains weight. All drugs, including the fluoroquinolones, should be dosed at the higher end of recommended ranges whenever possible, **except ethambutol**. As it is more difficult to monitor optic neuritis in children, ethambutol should be dosed at 15 mg/kg and not the 25 mg/kg dosing sometimes used in adults with MDR-TB.

TB patients wait to see the doctor at the Ibuje Health Centre

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In children who are not culture-positive at the start of MDR-TB treatment, failure is difficult to assess. Persistent abnormalities on chest radiograph do not necessarily signify a lack of improvement. **Failure to gain weight** or weight loss (less common) is of particular concern, and often one of the first (or only) signs of treatment failure. This is a key reason to monitor weight carefully in children.

Anecdotal evidence suggests that **adolescents** are at high risk for poor treatment outcomes, perhaps due to biologic reasons (more advance disease due to late diagnosis) and social factors (more problems with adherence, behaviour, drug use, pregnancy, poor acceptance of illness). Early diagnosis, strong social support, individual and family counselling, and a close relationship with the medical provider may help improve outcomes.

Table 9.2. Paediatric dosing of second-line medications				
Drug	Formulation	Daily dose mg/kg/day	Frequency	Maximum daily dose
Streptomycin	Vials: 37.5, 250, 333, 500 mg/ml	20-40	QD	1g
Kanamycin	Vials: 37.5, 250, 333, 500 mg/ml	15 – 30	QD	1g
Amikacin	Vials: 50, 250 mg/ml	15 – 22.5	QD	1g
Capreomycin	Vials: 1g/ml	15 – 30	QD	1g
Ofloxacin	Tablets: 200, 300, 400 mg	15 – 20	BID	800mg
Levofloxacin	Tablets: 250, 500, 750 mg	7.5 – 10	QD	750mg
Moxifloxacin	Tablets: 400 mg	7.5 – 10	QD	400mg
Ethionamide	Tablets: 250 mg	15 – 20	BID	1g
Prothionamide	Tablets: 250 mg	15 – 20	BID	1g
Cycloserine Terizidone	Capsules: 250 mg	10 – 20	QD or BID	1g
PAS	PASER® 4 g packets	150	BID or TID	12 g

(Source: World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency update 2008 (WHO/HTM/TB/2008.402). Geneva, Switzerland: World Health Organization; 2008).

Practical exercise: Designing a paediatric treatment regimen

A mother on treatment for MDR-TB for 9 months is now smear and culture negative for 6 months. She brings her child to you for evaluation. The child is 14 months old and weighs 6.9 kg. She had BCG at birth, and now presents with 4 months of failure to thrive, poor appetite, and intermittent low grade fever. Purified protein derivative (PPD) skin testing is 16 mm, and chest radiography reveals hilar adenopathy but no infiltrates. There are no other know contacts. The mother was first diagnosed with TB shortly after giving birth to the child and is a patient in whom the WHO category I and II regimens both failed. Her resistance pattern from the start of her MDR-TB treatment is

Resistance to H,R,E,Z,S
Susceptible to Am, Cm, O, Eto
DST to PAS and Cs not done.

QUESTION:
What advice and regimen do you prescribe for the child?

ANSWER:
It should be explained to the mother that the child almost definitely has tuberculosis and most likely MDR-TB. If available, DST should be attempted (see Module 4). While waiting for the DST results, or if the diagnostic procedure is not available, the child should be started on an empiric regimen based on the DST pattern of the mother. The following regimen is indicated:

IA-Fq-Eto(Pto)-Cs   -or-   IA -Fq-PAS-Cs

The injectable agent (IA) can be anything other than streptomycin, in this case Km, Cm, or Am.

Example of dose calculation is given below for the regimen of Km-Of-Pt-Cs to illustrate how dosing is calculated. In short, calculate both the low and high dose for the child's weight, and then choose a convenient dosing between the two numbers (if need be a pharmacist can mix up the exact dosing so one can choose any milligram amount, and dosing is not limited to ¼ or ½ tablets):

Km: (15 mg x 6.9 kg = 103 and 30 mg x 6.9 Kg = 207) pick a dose between the two numbers (choose a dose nearer the high end dosing), eg. **200 mg per day, single dose.**

Ofx: (15 mg x 6.9 kg = 103 and 20 mg x 6.9 kg = 138). A convenient dose is 100 mg/day. This is the full daily dose. Table 9.2. indicates that the daily dose is given BID, so the patient would receive **50 mg (1/4 tablet) in the morning and 50 mg (1/4 tablet) in the evening.**

Pto: (15 mg x 6.9 kg = 103 and 20 mg x 6.9 kg = 138). A convenient dosing is 125 mg/day. This is the full daily dose. Table 9.2. indicates that the daily dose is given BID, so the patient would receive **62.5 mg (1/4 tablet) in the morning and 62.5 mg (1/4 tablet) mg in the evening.**

Cs: (15 mg x 6.9 kg = 103 and 20 mg x 6.9 kg = 138). A convenient dosing is 125 mg/day. This is the full daily dose. Table 9.2. indicates that the daily dose is given BID, so the patient would receive **62.5 mg (1/4 capsule) in the morning and 62.5 mg (1/4 capsule) mg in the evening.**

AS THE CHILD GAINS WEIGHT THE DOSES WILL HAVE TO BE ADJUSTED (CHECK WEIGHT EVERY MONTH)

TB patients at Lifecare Knights hospitl in Germiston

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7 DIABETES

The treatment of MDR-TB in the diabetic will result in poor outcomes if glucose is not well controlled. The responsibility therefore falls on the physician treating the patient for MDR-TB to ensure proper diabetic care. In addition, calculate both the low and high dose for the child's weight, and then choose a convenient dosing between the two numbers. **Oral hypoglycaemic agents are not contraindicated with the treatment of MDR-TB.** Ethionamide and prothionamide may make it more difficult to control levels of insulin.

QUESTION:
What guidelines should be followed in the management of MDR-TB in the diabetic patient?
a. Glucose levels and blood pressure should be well controlled;
b. Goals for capillary blood testing: 140 mg/dl before meals;
c. Blood sugar may be monitored weekly to ensure that targets are being maintained;
d. Hypertensive patients with diabetes should be started on a beta-blocker plus a thiazides diuretic;
e. If the serum creatinine rises, creatinine clearance should be checked and MDR-TB mediations should be adjusted.

ANSWER:
The following answers are correct: a and e.
- The glucose level before meals should be between 80 and 120 mg/dl.
- Blood sugar should be estimated at regular intervals during the day and the dose of insulin calculated accordingly. Once a patient is on a stable dose of insulin, blood sugar may be monitored four times weekly.
- Hypertension in diabetics preferably should be treated with an ACE Inhibitor.

The following guidelines are suggested to assist in the management of the diabetic patient with MDR-TB:
- Medical follow-up: Diabetes must be managed closely throughout treatment.
- Patient education: The basics of a diabetic diet should be communicated to the patients, together with the need for weight control, exercise, and foot care. Patients should be educated on the symptoms of hypo- and hyper-glycaemia.
- Glucose monitoring
  - Goals for capillary blood testing: 80-120 mg/dl before meals; 100-140 mg/dl before bedtime; the range should be higher if patient has a history of hypoglycaemia;
  - Patients may need a period of intensive glucose monitoring until these goals are met;
  - Once a patient is on a stable dose of insulin, blood sugar may be monitored four times weekly to ensure that targets are being maintained;
  - If a patient is on oral anti-diabetic agents, sugar may be monitored twice weekly.
- Regular monitoring
  - Creatinine and potassium should be monitored weekly for the first month and then at least monthly thereafter;
  - If the creatinine rises, creatinine clearance should be checked and MDR-TB mediations should be adjusted according to Table 9.3. Once the dose is adjusted, the creatinine should be checked weekly until it has stabilized;
  - HbA1C every three months if treatment changes or patient is not meeting goals; every six 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
  - Injectable dosing according to Table 9.3.
  - Consider using an ACE inhibitor for patients with albuminuria (>300 mg/24 h).

8   RENAL INSUFFICIENCY

Renal insufficiency due to longstanding tuberculosis infection itself or previous use of aminoglycosides is not uncommon. Great care should be taken in the administration of second-line drugs in the patient with renal insufficiency, and the dose and/or the interval between dosing should be adjusted according to Table 9.3.

Table 9.3. Adjustment of medications in renal insufficiency		
Drug	**Change in frequency?**	**Recommended dose† and frequency for patients with creatinine clearance < 30 ml/min or for patients receiving haemodialysis.**
Isoniazid	No change	300 mg once daily, or 900 mg three times per week
Rifampicin	No change	600 mg once daily, or 600 mg three times per week
Pyrazinamide	Yes	25–35 mg/kg/dose three times per week (not daily)
Ethambutol	Yes	15–25 mg/kg/dose three times per week (not daily)
Ofloxacin	Yes	600-800 mg per dose three times per week (not daily)
Levofloxacin	Yes	750–1000 mg per dose three times per week (not daily)
Moxifloxacin	No change	400 mg once daily
Gatifloxacin	Yes	400 mg per dose three times per week (not daily)
Cycloserine/ Terizidone	Yes	250 mg once daily, or 500 mg/dose three times per week*
Prothionamide	No change	250-500 mg per dose daily
Ethionamide	No change	250–500 mg/dose daily
p-Aminosalicylic acid**	No change	4 g/dose, twice daily
Streptomycin	Yes	12–15 mg/kg/dose two or three times per week (not daily)***
Capreomycin	Yes	12–15 mg/kg/dose two or three times per week (not daily) ***
Kanamycin	Yes	12–15 mg/kg/dose two or three times per week (not daily) ***
Amikacin	Yes	12–15 mg/kg/dose two or three times per week (not daily) **

† To take advantage of the concentration-dependent bactericidal effect of many antituberculosis drugs, standard doses are given unless there is intolerance. For Group 5 drugs see manufacturers' recommendations on adjustments in renal insufficiency.
* 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).
** Sodium salt formulations of PAS may result in an excessive sodium load; these should be avoided. Formulations of PAS that do not use the sodium salt (e.g., Jacobus PASER®) can be used without the hazard of sodium retention.
***Caution should be used with the injectable agents in patients with renal function impairment because of the increased risk of both ototoxicity and nephrotoxicity.

Source: World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency update 2008 (WHO/HTM/TB/2008.402). Geneva, Switzerland: World Health Organization; 2008.)

9   Liver disorders

The first-line drugs isoniazid, rifampicin, and pyrazinamide are all associated with hepatitis. Of the second-line drugs, ethionamide, prothionamide and PAS can also be hepatotoxic, although less so than any of the first-line drugs. Hepatitis is quite rare with the fluoroquinolones, but can occur. In general, **patients with chronic liver disease should not receive pyrazinamide**. All other MDR-TB drugs can be used, however close monitoring of liver enzymes is advised, and if significant worsening of liver inflammation is seen, responsible drugs may need to be stopped.

Patients who are hepatitis virus carriers and those with a past history of acute hepatitis or excessive alcohol consumption can receive MDR-TB treatment provided that there is no clinical evidence of chronic liver disease; however, hepatotoxic reactions may be more common in these patients and should be anticipated.

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

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

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

Women: x   0.85

Normal values for creatinine clearance are:
Men: 97 to 137ml/min
Women: 88 to 128ml/min

Practical exercise: Adjusting the dose of a medication in renal insufficiency:

QUESTION:
A male patient has a serum creatinine = 2.4, age = 59, ideal body weight = 53 kg. What should the dose of kanamycin be?

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

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

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

=   24.8 ml/min

Step 2: Refer to Table 9.3. 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 9.3. 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.

10 SEIZURE DISORDERS

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

Cycloserine and terizidone should be avoided in patients with active seizure disorders that are not well controlled with medicines. However, in cases where there is no option, cycloserine/terizidone may be given and the anti-seizure medications adjusted as needed to control the seizure disorder. The risk and benefits of using cycloserine/terizidone should be considered and the decision on whether to use them be made together with the patient.

When seizures present for the first time on MDR-TB therapy, there is a good chance that they are related to one of the anti-tuberculosis medications. More information regarding specific strategies and protocols to address side-effects is available in Chapter 11 of the WHO Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency update 2008 (http://www.who.int/tb/publications/2008/programmatic_guidelines_for_mdrtb/en/index.html).

Many MDR-TB patients may have comorbid conditions which require specialized management. Huancayo, Perú. TB Patients is hooked up to an IV.

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11 Substance dependency

Patients with substance dependency problems pose a considerable challenge. Addiction treatment should be offered. Although complete abstinence from alcohol or drugs should be strongly encouraged, active **alcohol or drug use is not a contraindication to treatment**. If the treatment is repeatedly interrupted due to the patient's addiction, therapy should be suspended until successful addiction treatment or measures to ensure adherence are established.

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

IV drug user in Casal Ventoso, Lisbon.

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12 Psychiatric patients

It is prudent to have a health care worker with psychiatric training do an evaluation before the start of MDR-TB treatment. The initial evaluation documents any pre-existing psychiatric condition and establishes a baseline for comparison if new psychiatric symptoms develop while the patient is on treatment. Any identified psychiatric illness at the start or during treatment should be fully addressed. There is a high baseline incidence of depression and anxiety in patients with MDR-TB, often connected with the chronicity and socioeconomic stressors related to the disease. If a health care worker with psychiatric training is not available, the treating physician should document any psychiatric conditions the patient may have at the initial evaluation.

Treatment with psychiatric medications, individual counselling, and/or group therapy may be necessary to manage the patient suffering from a psychiatric condition or adverse psychiatric effect due to medications. Group therapy has been very successful in providing a supportive environment for MDR-

TB patients and may be helpful for patients with or without psychiatric conditions (adequate measures to prevent infection risk should be in place for the group therapy).

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

All physicians treating MDR-TB should closely work with a psychiatrist and have an organized system for psychiatric emergencies. Psychiatric emergencies include psychosis, suicidal ideation, and any situation involving the patient being a danger to him/herself or others. Mechanisms to deal with psychiatric emergencies (often inpatient psychiatric hospital admissions) should be available twenty-four hours per day. Proper infection-control measures must be taken for the smear-positive MDR-TB patient who requires hospitalization.

13   MDR-TB TREATMENT FAILURES

When no response to MDR-TB treatment is seen, re-assessment of the regimen and treatment plan, and formulation of a new plan of action is necessary. Changes in treatment may be necessary as early as 4 – 6 months if bacteriological conversion is not seen or if clinically deterioration is evident. **Always try to avoid just adding one or two drugs to an apparently failing regimen;** instead try to redesign the regimen with four effective drugs (see Module 6).

13.1 PATIENTS WITH SUSPECTED MDR-TB TREATMENT FAILURE

Patients that show clinical, radiographic, or bacteriological evidence of persistent active disease or re-appearance of disease after four months of treatment should be evaluated for possible failure. In addition, patients who show rapid clinical deterioration before month 4 should also be evaluated.

QUESTION:
What course of action should be taken for patients with suspected MDR-TB treatment failure?
a. The treatment card should be reviewed to confirm that the patient has been adherent.
b. A non-confrontational patient interview should be undertaken in the presence of the DOT supervisor.
c. A confrontational interview with the DOT supervisor should be done.
d. The DOT supervisor should be switched to another patient and the patient should be assigned a new DOT supervisor.
e. The bacteriological data should be reviewed especially for positive smears.

ANSWER:
The following answers are correct: a and e.
• An interview with the patient should not include the DOT supervisor to ensure frankness of discussion.
• The interview with the supervisor should not be confrontational but rather sensitive and diplomatic.
• DOT supervisors need not be changed if there is no evidence of manipulation by the patient.
• The treatment card and bacteriological data should be reviewed. Positive smears with corresponding negative cultures may reflect dead bacilli, thereby not indicating treatment failure.

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

- **The treatment card should be reviewed** to confirm that the patient has been adherent. The health-care worker should investigate whether the patient has taken all the medicines. A non-confrontational **patient interview** should be undertaken **without the presence of the DOT supervisor.**
- A non-confrontational **interview with the DOT supervisor** should be done **without the presence of the patient**. Questions should be asked to rule out possible manipulation of the DOT supervisor by the patient. If this is suspected, the DOT supervisor should be switched to another patient and the patient should be assigned a new DOT supervisor.
- **The treatment regimen should be reviewed** in relation to medical history, contacts, and all available DST reports. If the regimen is deemed inadequate a new regimen should be designed.
- The **bacteriological data should be reviewed.** Often the smear and culture data provides the strongest evidence that a patient is not responding to therapy. A single positive culture in the presence of otherwise good clinical response is not necessarily indicative of treatment failure, especially if follow-up cultures are negative or the number of colonies is decreasing. Positive smears with corresponding negative cultures may reflect dead bacilli, thereby not indicating treatment failure. Repeated negative smear and culture results in a patient with clinical and radiographic deterioration may indicate that disease other than MDR-TB is also affecting the patient.
- **Other illnesses** that may decrease absorption of medication (like chronic diarrhoea) or may result in immune-suppression (like HIV) should be excluded.

13.2 Patients with apparent MDR-TB treatment failure

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

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

All of these signs need not necessarily be present to declare failure of the treatment regimen; nevertheless, **cure is highly unlikely when they all exist**. Of note is that the epidemiological definition of treatment failure for recording outcomes given in Module 11 is often different from the process of suspending therapy in a patient when it is failing. The epidemiological definition is an outcome to account for the patient in treatment cohort analysis; the clinical decision to suspend therapy is one made after the search for all other options has been exhausted, and cure of the patient has been determined to be highly unlikely.

13.3 Suspending therapy

QUESTION
Which of the following statements are correct regarding suspension of therapy in a patient with MDR-TB?
a. Suspending therapy should only be considered after all other options for treatment have been explored.
b. If there is no possibility of adding agents (or surgery, where appropriate), the MDR-TB treatment should be considered a failure and suspension of therapy is recommended.
c. When medications used in MDR-TB treatment have considerable side effects, treatment should be discontinued.

Answer:

The correct answers are a, b and e.

• Treatment should be suspended if there is no evidence of improvement and side-effects are becoming intolerable.

• The emergence of "super" resistant strains is a real danger and can be transmitted to other patients.

Suspending therapy should only be considered **after all other options for treatment have been explored**. Suspending therapy in a patient who has failed MDR-TB treatment is a delicate situation and difficult for family members and caretakers, but it is especially difficult for the patient as treatment is often viewed as his/her only hope. Strong support, care, and sympathy to the situation must be rendered to the patient and family.

If the medical personnel are confident that all medications have been ingested and that there is no possibility of adding agents (or surgery, where appropriate), the MDR-TB treatment should be considered a failure and suspension of therapy is recommended.

There are **two important reasons for suspending therapy** or changing it to palliative (supportive) care:

• The **patient's quality of life** - the medications used in MDR-TB treatment have considerable side effects, and continuing them while the treatment is failing may cause additional suffering;

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

Suspending therapy should start with discussions between the treating team, including all physicians, nurses, and DOT workers involved in the patient's care. Once the clinical team decides that treatment should be suspended, a clear plan should be determined for approaching the family and patient. Usually this process takes a number of visits and occurs over several weeks. Home visits during the process offer an excellent opportunity to talk with family members and the patient in a familiar environment. It is not recommended to suspend therapy before the patient understands and accepts the reasons to do so, and agrees with the supportive care offered.

13.4 Palliative/supportive care

Question:

Which of the following statements regarding palliative care offered to a patient if MDR-TB therapy is suspended is correct ?

a. Paracetamol or codeine with paracetamol gives relief to moderate pain.

b. Morphine is not indicated even with severe pain.

c. Relief of respiratory insufficiency oxygen can be used to alleviate shortness of breath.

d. Once MDR-TB therapy stops, regular visits by the treating physician and support team may be discontinued.

e. Oral care, prevention of bedsores, bathing and prevention of muscle contractures are indicated in all patients.

A number of palliative measures can be implemented once MDR-TB therapy is suspended. Supportive measures are described in great detail in the WHO guidebook on Palliative care : symptom management and end-of-life care (http://whqlibdoc.who.int/hq/2004/WHO_CDS_IMAI_2004.4.pdf), part of the Integrated management of adolescent and adult illness: interim guidelines for first-level facility workers four-volume series and summarized in Table 9.4.

Table 9.4. End-of-life supportive measures

- **Pain control.** Paracetamol or codeine with paracetamol gives relief to moderate pain. Codeine also helps control cough. If possible, stronger analgesics, including morphine, should be used when appropriate.

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

- **Nutritional support.** Often small and frequent meals are best for a terminally ill person. Intake will reduce as the patient gets sicker and during end-of-life care. Treat all nausea and vomiting or any other conditions that interfere with nutritional support.

- **Regular medical visits.** Once MDR-TB therapy stops, regular visits by the treating physician and support team should not be discontinued. Depression and anxiety, if present, should be addressed.

- **Continuation of ancillary medicines.** All necessary ancillary medications should be continued as needed.

- **Hospitalization, hospice care or nursing home care**. Having a family member die at home can be quite difficult. Hospice care should be offered to families who want to keep the patient at home and inpatient end of life care should be available to those for whom home care is not available.

- **Preventive measures.** Oral care, prevention of bedsores, bathing and prevention of muscle contractures are indicated in all patients. Regular scheduled movement of the bedridden patient is very important.

- **Infection control measures.** The patient who is taken off of MDR-TB treatment because of failure often remains infectious for long periods of time. Infection control measures should be continued (see Module 14).

Source: World Health Organization. Palliative Care: Symptom Management and End-of-Life Care(WHO/CDS/IMA/2004.4). Geneva, Switzerland: World Health Organization; 2004.

1. MDR-TB in children:
a) Cannot be treated at all as the second-line drugs are contraindicated
b) Are treated in the same way as adult MDR-TB, with certain exceptions
c) Are treated in exactly the same way as adult MDR-TB
d) Can only be prevented through chemoprophylaxis
e) Are treated with different second-line drugs

2. Patients with chronic liver disease should not receive:
a) Ofloxacin
b) Ethionamide
c) Pyrazinamide
d) Kanamycin
e) Ethambutol

3. True/False:
( ) MDR-TB treatment is contraindicated in pregnancy
( ) MDR-TB treatment is contraindicated in children
( ) MDR-TB is a contraindication for breast-feeding
( ) Diabetes is a contraindication for MDR-TB treatment
( ) Renal insufficiency is a contraindication for MDR-TB treatment

4. The MDR-TB agents contraindicated in pregnancy is:
a) Fluoroquinolones
b) Aminoglycosides
c) First-line TB drugs
d) Thioamides
e) None of the above

5. Drug administration should be changed in renal failure for:
a) Ofloxacin
b) Cycloserine
c) Ethambutol
d) Kanamycin
e) All of the above

ANSWERS

1: b
2: c
3: F,F,F,F,F
4: b
5: e

MODULE 10

MDR-TB and HIV

1   Learning Objectives

At the end of this module you should be able to:

- Understand diagnostic and clinical guidelines for HIV-associated MDR-TB
- Understand drug interactions and additive toxicities in dual treatment
- Prescribe appropriate antiretroviral regimens for MDR-TB patients
- Conduct adequate patient monitoring
- Prescribe appropriate adjuvant therapies

2   Introduction

HIV co-infection is a significant challenge for the prevention, diagnosis, and treatment of MDR-TB. The local epidemiological prevalence of HIV, MDR-TB and MDR/HIV co-infection is important in guiding strategies for HIV and MDR-TB treatment. **HIV counselling and testing are now considered to be the standard of care** for TB (including MDR-TB) patients, and MDR-TB programmes are also encouraged to conduct MDR-TB surveillance in HIV-positive TB patients.

Ghana. TB workers at one of their regular meetings.

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3   Clinical presentation of HIV-related MDR-TB

MDR-TB presents with the same signs and symptoms as drug-susceptible TB in a patient infected with HIV.

The clinical presentation of HIV-associated MDR-TB (as well as drug-susceptible TB) is influenced by the degree of underlying immunodeficiency. In the earlier stages of HIV disease, the pathology of MDR-TB is similar to that seen in patients without HIV infection, ie. pulmonary MDR-TB is most frequent and is often sputum smear-positive. As immunodeficiency progresses, extra-pulmonary presentation of MDR-TB becomes more common. Clinical features may furthermore be affected by the existence of concurrent infections like septicaemia, multiple respiratory pathogens, digestive infections, etc.

4   Diagnosis of HIV-related MDR-TB

Question:
What are the diagnostic guidelines for HIV-related MDR-TB?

Answer:
The diagnosis of MDR-TB in HIV-positive persons is more difficult and may be confused with other pulmonary or systemic infections. Increasingly, the presentation is extra-pulmonary. This can result in misdiagnosis or delayed diagnosis, which may lead to higher morbidity and mortality. The use of culture greatly improves the diagnosis of TB in HIV patients and is now recom-

mended as the standard of care. In areas where epidemiological data has indicated MDR-TB to be a problem in HIV positive patients, **all HIV patients with signs and symptoms of TB should be screened for MDR-TB**. If available, rapid diagnostic techniques for MDR-TB should be employed since HIV patients on inadequate treatment for even short periods of time are at high risk of death.

Protocols for diagnosis of MDR-TB in HIV follow the same principles as for HIV-negative patients. Sputum investigations (culture and DST) should always be done, even if extra-pulmonary MDR-TB is suspected. Common sites of HIV-related extra-pulmonary MDR-TB are the pleura, the lymph nodes and the pericardium. Blood cultures for tubercle bacilli sometimes yield positive results.

5   MDR-TB treatment

MDR-TB treatment is the same for HIV-positive and HIV-negative patients, with the **exception of thioacetazone, which should not be used in the HIV-positive patient.** However, MDR-TB treatment is much more difficult and adverse events much more common in HIV-positive patients. Deaths during treatment, partly due to MDR-TB and partly due to other HIV-related diseases, are more frequent in dually-infected patients, particularly in the advanced stages of immunodeficiency.

Patients already on antiretroviral treatment (see below) when MDR-TB is diagnosed should immediately be started on appropriate MDR-TB treatment.

6   Antiretroviral treatment

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

- Timing of initiation of antiretroviral treatment (ART) in MDR-TB patients;
- Drug-drug interactions;
- Overlapping toxicities;
- Adherence to complicated treatment regimens;
- Clinical management of co-infected patients.

The appropriate time to initiate ART in MDR-TB patients is not known and depends on a careful calculation of risks and benefit.

Rapid development of new antiretroviral drugs requires that clinicians keep up with continuous updates of information to guide their management of patients. As ART guidelines are constantly reviewed, physicians are encouraged to keep regular up to date with international and country-specific policies and treatment guidelines.

Ghana. TB patient in the clinic.

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6.1 Goals of antiretroviral therapy

The primary goal of antiretroviral therapy is to decrease HIV-related morbidity and mortality:
- The patient should experience fewer HIV-related illnesses;
- The patient's CD4 count should rise and remain above the baseline count;
- The patient's viral load should become undetectable (< 400 copies/ml) and remain undetectable on ART.

6.2 Timing of initiation of ART in adult MDR-TB patients

QUESTION:
When should ART be initiated in adults with MDR-TB?

ANSWER:
International guidelines refer to clinical staging and CD4 count as criteria to initiate ART in drug-susceptible TB patients (see WHO TB/HIV: A clinical manual online for more in-depth information: http://whqlibdoc.who.int/publications/2004/9241546344.pdf) however, optimal time for initiating ART in MDR-TB patients is not defined, although simultaneous initiation of both treatments is discouraged.

Reasons to start ART early
- The need to decrease high HIV/AIDS associated morbidity and mortality.
- Antiretroviral therapy in HIV co-infected MDR-TB patients has been associated with improved survival and decreased acceleration to AIDS.

Reasons to delay initiating ART
- Overlapping side effects from ART and MDR-TB drugs;
- Complex drug-drug interactions;
- Occurrence of immune reconstitution syndrome;
- Difficulties associated with adherence to a high number of drugs.

Initiation of ART in HIV-co-infected patients is associated with adverse events that may lead to the interruption of both MDR-TB and/or HIV therapy. Deferred initiation of ART may help the clinician to identify the potential cause of drug adverse effects without neglecting the possibility of concurrent illness.

WHO criteria for clinical staging and CD4 count for consideration of ART in drug susceptible TB patients are as follows:
- WHO Clinical Stage 4, irrespective of CD4 count
- WHO Stage 3 and CD4 < 350/mm3
- WHO Stage 1 or 2 and CD4 < 200/mm3

There is consensus that **MDR-TB treatment should be started first** in co-infected cases and that ART initiation should follow according to the patient's clinical condition and CD4 levels (see Figure 10.1.).
In countries with a high HIV burden it is often recommended that ART be started in the first few months of MDR-TB treatment in patients with low CD4 counts (provided that the MDR-TB treatment is tolerated), and that ART be deferred in MDR-TB patients with relatively high CD4 counts until the patient is clinically stable and tolerating the MDR-TB regimen.

ART should be initiated and monitored in conjunction with a health care specialist knowledgeable in both MDR-TB and HIV.

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

• **Patient develops MDR-TB while on ART**

Antiretroviral therapy should be continued throughout MDR-TB treatment, with a change to efavirenz recommended for patients on nevirapine wherever possible, as there is a danger of increased hepatotoxicity. If this is not possible (eg. intolerance to efavirenz or significant risk of becoming pregnant), nevirapine may be continued in selected cases, with monthly ALT monitoring. In addition, there are significant overlapping toxicities with increased risk of neuropathy with the concomitant use of stavudine (D4T) and cycloserine/terizadone. While their use together is not contraindicated, most practitioners try to avoid using these drugs together. Zidovudine (AZT) is often substituted for D4T.

Discuss these cases with an HIV expert.

• **Patient presents with MDR-TB before commencing ART**

It is recommended to start MDR-TB treatment before commencing ART in order to avoid immune reconstitution inflammatory syndrome (IRIS – see below for more discussion). The optimal timing for the introduction of ART in patients beginning MDR-TB treatment is unknown. Figure 10.1., based on other available WHO publications, provides recommendations for initiating ART in relationship to starting therapy for DR-TB.

Table 10.1. Timing of ART in the ART-naïve patient starting anti-tuberculosis therapy for DR-TB in adults		
CD4 CELL COUNT	**ART RECOMMENDATIONS**	**TIMING OF ART IN RELATION TO START OF DR-TB TREATMENT**
CD4<200 cells/mm^3	Recommend ART	At two weeks or as soon as DR-TB treatment is tolerated
CD4 between 200 and 350 cells/mm^3	Recommend ART	After eight weeks[a]
CD4>350 cells/mm^3	Defer ART[b]	Re-evaluate patient monthly for consideration of ART start. CD4 testing is recommended every three months during DR-TB treatment
Not Available	Recommend ART[c]	Between two and eight weeks

a. Clinical evaluation may prompt earlier initiation of ART
b. ART should be started if other non-TB stage 3 or 4 events are present
c. This recognizes that some patients may be prematurely placed on life-long ART.

Source: World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency update 2008 (WHO/HTM/TB/2008.402). Geneva, Switzerland: World Health Organization; 2008.

Figure 10.1. FLOWCHART - Treatment of adult patients with concomitant MDR-TB

MDR-TB develops while on ART	MDR-TB is present before starting ART

MDR-TB develops while on ART

Continue ARV therapy throughout MDR-TB treatment
Patients on first-line therapy containing nevirapine should generally be swapped to efavirenz. In addition, consider swapping stavudine for zidovodine to avoid neuropathy.

Recommended first-line ART therapy:
1. Zidovudine 300mg every 12 hours
+
2. Lamivudine 150mg every 12 hours
+
3. Efavirenz 600mg at night

MDR-TB is present before starting ART

CD4+ count > 350/mm³ (and no other HIV-related symptoms):
Start MDR-TB treatment. Assess the need for ART after every 3 months while on MDR-TB therapy, using CD4 and clinical criteria

CD4+ count between 200 and 350/mm³:
Delay ARVs until after 8 weeks of MDR-TB therapy.
Then start first line therapy as outlined below.

CD4+ count of < 200/ mm³ or other serious HIV illness: introduce ART as soon as the patient is stabilized on MDR-TB therapy and as soon as two weeks after MDR-TB treatment is tolerated.

Recommended First-line ART therapy:
1. Zidovudine 300mg every 12 hours
+
2. Lamivudine 150mg every 12 hours
+
3. Efavirenz 600mg at night

Remember:
Patients on MDR-TB medication and ARVs are taking a large number of tablets - Do pre-emptive counselling to improve adherence

6.3 CONCOMITANT MDR-TB IN CHILDREN WITH HIV INFECTION

While children with MDR-TB and HIV are a challenge to manage given frequent dose adjustments based on changing weights and due to not being able to use some ART medications in the very young, children generally have good tolerance to both MDR-TB and HIV medications when compared to adults.

ART should never be denied in eligible children. Start MDR-TB therapy before commencing ART. The optimal timing of when to start ART in children who have commenced MDR-TB therapy has not been determined. The classification of immunosuppression in HIV infected children under five years of age is best assessed by percentage of CD4 cells of all T-lymphocytes (all CD3 positive cells) rather than by absolute CD4 count. Table 10.2. summarizes a reasonable approach of when to start ART therapy in relation to the start of MDR-TB treatment. The table uses the CD4% in addition to the absoluteCD4 number. **Some experts start all children with MDR-TB disease and HIV infecion on ART between two and eight weeks after MDR-TB treatment is tolerated regardless of CD4 percentage or absolute CD4 count.**

Table 10.2. Timing of ART in the ART-naïve patient starting anti-tuberculosis therapy for DR-TB in children		
Age of Child	**CD4 cell count or percentage**	**Timing of ART in relation to start of MDR-TB treatment**
<12 months	CD4 < 25% or < 1500 cells/mm3	Start ART therapy between two and eight weeks after MDR-TB treatment is tolerated
12 – 36 months	CD4 < 20% or < 750 cells/mm3	
36 – 60 months	CD4 < 15% or < 350 cells/mm3	
0-60 months	Not available	

The choice of first-line ART regimen in children on treatment for MDR-TB is zidovudine-lamivudine-efavirenz. However,

- Efavirenz cannot be used in children less than 3 years old or with a weight of less than 10 kilograms;
- If the child has failed a nevirapine vertical transmission programme, lopinovir/ritonovir should be used as the third drug (i.e. not efavirenz or nivirapine);
- AZT is preferred over D4T because the increased risk of neuropathy with the concomitant use of cycloserine or terizadone.

HIV-infected patients need increased monitoring for adverse effects, which is described in Module 8, Table 8.1.

7   PROPHYLAXIS OF OPPORTUNISTIC INFECTIONS

QUESTION:
What is the role of Cotrimoxazole in the prophylaxis of opportunistic infections in HIV patients with MDR-TB?

ANSWER:
Cotrimoxazole is highly effective in preventing:
- Pneumocystis carinii pneumonia;
- Toxoplasmosis;
- Pneumococcus;
- Salmonella;
- Nocardia;
- Malaria.

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

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. This will allow differentiation between side effects from MDR-TB drugs and cotrimoxazole.

Dosage of cotrimoxazole prophylaxis in adults: 960 mg (two tablets single strength) or trimethoprim 5mg/kg plus sulphamethoxazole 25mg/kg.

Dosage of cotrimoxazole prophylaxis in children: See Table 10.3.

| Table 10.3. Cotrimoxazole prophylaxis schedule for children ||
Body weight	Cotrimoxazole 40/200 mg/5ml
< 5 kg 5 to 9.9 kg 10 to14.9 kg 15 to 21.9 kg > 22 kg	2.5 ml 5 ml 7.5 ml 10 ml or 1 tab 80/400 mg 15 ml or 1 ½ tab 80/400 mg

Source: Foundation for Professional Development. Management of Tuberculosis. Pretoria, South Africa: Foundation for Professional Development; 2004

Patients on cotrimoxazole prophylaxis as well as antiretroviral drugs should continue the cotrimixazole until they show two consecutive CD4 counts above 350.

Patients with known hypersensitivity to cotrimoxazole could be given dapsone instead.

8   Immune reconstitution syndrome

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

Patients with advanced HIV disease, particularly those with a CD4 count < 50 cells/mm³ may become ill with an immune reconstitution illness during the first few weeks of ART, with symptoms of persistent fever, sweats, loss of weight, cough, shortness of breath, worsening pulmonary infiltrates, and decreasing visual acuity (to name but a few). Immune reconstitution syndrome is common in its mild to moderate forms in patients with TB started on ART (seen in up to one third of patients in some studies); however, it is relatively rare in its severe forms.

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

Opportunistic infections may present in atypical ways during the phase of immune reconstitution. Patients need to be referred to an experienced HIV clinician for advice regarding investigation and management.

Management includes **high doses of corticosteroids** to contain symptoms: prednisolone or methylprednisolone 1 mg/kg for one to two weeks, gradually reduced thereafter. It is not unusual to prolong the use of steroids or to restart if symptoms re-occur.

Clinicians need to be cautious and attentive to the development of complications due to prolonged use of steroids (e.g. *Cytomegalovirus* infections).

Non-steroidal agents tend to not be helpful except in mild forms of immune reconstitution.

9   Patient monitoring

The MDR-TB patient with HIV infection poses a great challenge and requires intensive monitoring of drug interactions and additive toxicities. The complexity of ARV and MDR-TB regimens, each with its

own toxicity profiles (which may be potentiated during concomitant therapy) demands even more rigorous monitoring in co-infected patients. In addition, other opportunistic infections have to be prevented, monitored and treated.

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

Module 11 describes the monitoring requirements for MDR-TB treatment. Monitoring of chest x-rays, smears and cultures in the HIV-positive MDR-TB patient is the same as for HIV-negative MDR-TB patients. If the patient shows signs of treatment failure, the same evaluation as described in Module 11 is warranted.

In patients receiving ART, CD4 counts should be measured at the time of diagnosis and every six months thereafter. **A significant decrease in CD4 count is a decrease from baseline of 30% or more.**

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

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

A TB patient who is infected with HIV has lost over half his body weight in the later stages of the disease

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10 MANAGEMENT OF DRUG ADVERSE EFFECTS

The complexity of antiretroviral regimens and second-line TB treatment, each with its own toxicity profiles and some of which may be potentiated by concomitant therapy, demands rigorous clinical monitoring. Module 8, Table 8.1. describes the monitoring requirements while on MDR-TB therapy and indicates where any extra monitoring is required for patients co-infected with HIV and/or on ART.

Two particular common overlapping toxicities are hepatotoxicity and peripheral neuropathy, and are discussed below in some detail. Table 8.2. of Module 8 lists all known potential overlying and additive toxicities.

Hepatotoxicity is a common and potentially serious adverse event. It is defined as

- A serum level of AST or ALT of more than **three** times the upper limit **with** accompanying symptoms, or
- A serum level of AST or ALT greater than **five** times the upper limit **without** accompanying symptoms.

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

Peripheral neuropathy may be caused by nucleoside analogues (ddI, d4T, ddc) and additive toxicity of ethionamide, cycloserine/terizidone and pyrazinamide when associated with stavudine and/or didanosine has been demonstrated. Pyridoxine at a dose of 50 mg for every 250 mg of cycloserine (every 300 mg of terizadone) daily should be used in all HIV-infected patients receiving cycloserine/terizidone.

1. Cotrimoxazole prophylaxis should be given to:
a) HIV-infected children
b) HIV-infected adults with TB infection
c) HIV-infected adults with TB disease
d) All of the above
e) None of the above

2. True/False:
( ) Immune reconstitution syndrome is more frequent in early stage HIV disease
( ) Immune reconstitution syndrome is related to specific ARV drugs
( ) Immune reconstitution syndrome usually occurs after 6 months of treatment
( ) Immune reconstitution syndrome requires a change in ART regimen
( ) Immune reconstitution syndrome requires a change in MDR-TB treatment

3. True/False:
( ) Immune reconstitution syndrome does not occur in MDR-TB patients
( ) Absorption of quinolones is affected by antacids
( ) Patients on HAART should not receive MDR-TB treatment
( ) Cotrimoxazole is contraindicated in MDR-TB patients
( ) ART should always be started together with MDR-TB treatment

4. An appropriate ARV regimen for MDR-TB patients contains:
a) Nevirapine, stavudine, lamiduvine
b) Stavudine, lamiduvine, efavirenz
c) Nevirapine, efavirenz, stavudine
d) Stavudine, lamiduvine, ritonavir
e) None of the above

5. The MDR-TB drug contraindicated in HIV is:

a) Ofloxacin
b) Kanamycin
c) Thioacetazone
d) Cycloserine/Terizidone
e) Ethionamide

ANSWERS

1: d
2: F,F,F,F,F.
3: F,F,F,F,F.
4: b
5: c

Module 11 Monitoring and outcome evaluation of MDR-TB patients

MODULE 11

Monitoring and outcome evaluation of MDR-TB patients

1   Learning Objectives

At the end of this module you should be able to:

- Understand the need for patient counselling and education
- Understand the need for directly-observed treatment in MDR-TB
- Monitor patients according to MDR-TB standards of care
- Manage treatment interruption and default
- Define MDR-TB treatment outcomes

2 Introduction

Having MDR-TB can be an emotionally devastating experience for patients and their families, while stigma attached to the disease may interfere with adherence to therapy. In addition, the long duration of MDR-TB therapy, combined with drug adverse effects, may contribute to depression, anxiety and further jeopardize treatment adherence.

Monitoring and evaluation of treatment is therefore essential. The classic symptoms of MDR-TB generally improve within the first few months of treatment. However, early resolution of symptoms is not an indication of cure, and recurrence of symptoms after sputum conversion may be the first sign of treatment failure. Laboratory evidence of improvement is therefore required, together with regular clinical assessment of patient progress. Standardized definitions to define treatment outcome are required and these are based on bacteriological culture.

3 Patient education and counseling

Question

What are the challenges to be faced by the care-givers in the management of MDR-TB?
a. Managing the stigma of the disease on the patient and the family.
b. How to cope with adverse drug effects.
c. Managing depression.
d. Managing anxiety.
e. Enthusiasm for prolonged observation and follow-up.

Answers:

All of the above answers are correct
- The various factors mentioned are all of importance to the conscientious care-giver as well as to the patient who faces a prolonged program of treatment, unpleasant side-effects and possible early death.
- The care-giver should be enthusiastic about his/her work and regard it as a responsible task.
- The patent should be educated within the limits of his/her understanding and comprehension.

Patients with MDR-TB face the prospect of lengthy and often unpleasant treatment as well as the real possibility of premature death. Therefore, education, counselling and emotional support are particularly important, much as in any other chronic life-threatening illness. Proper early counselling will also help to ensure good adherence to the treatment regimen and increase the likelihood of a successful outcome.

Patients and their families should receive education about MDR-TB, the treatment, potential adverse drug effects, and the need for adherence with therapy. Patients should sign a written informed consent form prior to starting MDR-TB treatment. Educational interventions should commence at the start of therapy and continue throughout the course of treatment. Education can be provided by physicians, nurses, lay and community health workers and other health care providers. Materials should be appropriate to the literacy levels of the population and should also be culturally sensitive.

Once the patient is on treatment, further support is required to maintain adherence and to help to identify social and emotional problems early so that they may be addressed before jeopardising the treatment programme.

4   TREATMENT ADHERENCE

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

MDR-TB treatment can be successful with high overall rates of adherence when adequate support measures are implemented. These measures include enablers and incentives for delivery of directly observed therapy (DOT) and for adherence to treatment such as nutritional supplementation, emotional support, patient, family and peer's education on MDR-TB treatment, and early and effective management of adverse drug reactions.

4.1   DIRECTLY-OBSERVED TREATMENT (DOT)

QUESTION
Which of the following statements concerning DOT in the management of MDR-TB is correct ?
a. Receiving adequate and complete treatment may be the last chance of survival the patient has.
b. The responsibility of DOT can be transferred to a family member.
c. Responsible community members, after due training, can act as substitute health care workers.
d. Distance and logistics are seldom a problem for patents with MDR-TB.

ANSWER
The following answers are correct: a) and c).
• Family members are subject to manipulation, lack of concern, inadequate responsibility and should never be given the task of observing DOT.
• Health care workers, even a lay person, may be a satisfactory alternative to a certified nurse if a nurse is not available provided that adequate instructions and training have been given to such a person.
• Distance and logistics can be an important factor in the continued monitoring of patients.

Because MDR-TB patients often have only one last chance for cure and there is a serious public health consequence if a patient with MDR-TB fails therapy, it is recommended that all MDR-TB patients receive their treatment under DOT, either in the community, at health facilities or within the hospital setting.

DOT should be provided in such a way that it does not introduce undue burdens to patients and their families. Long distances and difficulties accessing services may all contribute to decreased efficacy of DOT.

The first choice for providing DOT is to use health care workers when possible. When human or financial resources do not permit the use of health care workers, trained community members can serve as effective DOT workers. With appropriate training and support they can visit patients in their homes or work places. However, community members need intensive training, ongoing supervision by health professionals, and support to deliver DOT for MDR-TB.

A family member should not deliver DOT. Family dynamics are often complicated for the MDR-TB patient, and a family member could be subject to subtle manipulation by the patient and/or relatives.

HELP Design Group

4.2 Maintaining confidentiality

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

4.3 Social and emotional support

The provision of emotional support to patients may improve chances of adhering with therapy. This support may be provided formally in the form of support groups or one-on-one counselling with trained providers. Informal support can also be provided by physicians, nurses, DOT workers and family members. Most MDR-TB programmes use a multidisciplinary team consisting of a social worker, nurse, health educators, companions, and doctors.

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5   Management of treatment interruption and default

QUESTION

Which of the following statements are applicable to "treatment default" in MDR-TB?
a. Treatment default is equal to failed treatment and possibly a fatal event.
b. No treatment for a period of one month constitutes failed treatment.
c. The patient needs to be visited at home on the same day to obtain a reason for the default.
d. The situation should be addressed in a sympathetic, friendly, and non-judgmental manner.
e. Patient education should be limited to the initiation of treatment.

ANSWER:

The correct answers are a,c and d.
- A patient is regarded as having defaulted from MDR-TB treatment if treatment has been missed for a consecutive period of two months.
- Patient education should be repeated as often as deemed appropiate.

A patient is regarded as having defaulted from MDR-TB treatment if treatment has been missed for a consecutive period of two months. Every effort must be made to rapidly recall MDR-TB patients who interrupt and to persuade them to resume treatment.

When a patient fails to attend an appointment, a system should be in place that allows prompt patient follow-up. Most commonly this involves a DOT worker visiting the patient's home the same day to find out why the patient has defaulted and to ensure that treatment is resumed promptly and effectively.

The situation should be addressed in a sympathetic, friendly, and non-judgmental manner. Every effort should be made to listen to reasons for why the patient missed a dose(s) and to work with patient and family to ensure treatment continuation.

6   PATIENT FOLLOW-UP AFTER TREATMENT COMPLETION

Patients who complete a full course of MDR-TB treatment should be followed up at six-monthly intervals for a total duration of 24 months. They should be questioned about signs and symptoms of TB and two sputum specimens collected at each interval if symptoms are present. Active follow-up of patients failing appointments is essential and knowledge about each patient during the follow-up phase must be secured.

7   MDR-TB DOCUMENTATION

MDR-TB standards of care require extensive documentation for patients to ensure that all relevant data are collected. Many countries have standardized forms (see Module 12) and physicians treating MDR-TB patients should ensure that patient records contain all required data, including:

- MDR-TB reference number;
- Patient informed consent;
- Demographics;
- Patient classification;
- MDR treatment details;
- HIV status ;
- Chest radiography;
- Dates and results of monthly sputum smear investigations;
- Dates and results of monthly culture investigations;
- Dates and results of DST;
- Monthly body weight;
- Clinical details (concomitant conditions);
- Detailed adherence record, including the number of directly-observed doses of each drug and the number of treatment doses missed for each drug;
- Monitoring laboratory data including creatinine, potassium, liver function tests, and thyroid tests;
- Drug adverse effects, including serious drug adverse events;
- Patient referral forms;
- Clinic treatment cards and adherence monitoring reports;
- Treatment outcomes.

Doctors and nurses at a TB hospital in Kampala receive a visit from a representative from the health department from the Kampala City Council to verify the record keeping and facilities.

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8   Bacteriological investigations

8.1   Intervals of testing

Conversion of sputum smears and cultures are the most important indicator of patient improvement. Smear microscopy and bacteriological culture are therefore used to monitor patient progress throughout treatment and should be performed monthly prior to culture conversion and at least every second month thereafter. Microscopy is useful as a robust indicator of patient progress; however, it cannot distinguish viable organisms from those that are nonviable (see Module 4). Culture is therefore necessary to monitor treatment progress.

8.2   Definition of conversion

QUESTION:
Which of the following statements regarding "conversion" in MDR-TB are correct?
a. "Culture conversion" is defined as two consecutive negative cultures, taken at least 30 days apart.
b. "Smear conversion" is defined as two consecutive negative smears, taken at least 30 days apart.
c. "Smear conversion" is two consecutive negative results taken at least 2 months apart.
d. Microscopy as a means of conversion is as reliable as the results of culture.
e. One culture conversion is proof of cure.

ANSWER:
The correct answers are a and b.
- Smear conversion is defined as two consecutive negative smears, taken at least 30 days apart.
- Microscopy is not as reliable as culture conversion.
- Sputum should be examined at monthly intervals.
- One culture conversion is not equivalent to cure. A significant proportion of patients may initially convert and later revert to being culture positive.

Two separate indicators of conversion are usually calculated, ie. smear conversion and culture conversion. Both indicators require the smear or culture to be positive at the beginning of treatment.

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

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

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

Sputum conversion is slower when using second-line anti-tuberculosis drugs.

Culture results showing a few colonies should not be automatically regarded as negative when treating MDR-TB, nor should a single positive culture preceded by multiple negative cultures be regarded as treatment failure.

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

9 Radiology

Chest radiographs should be taken at least every six months, whenever the patient's clinical condition worsens, or whenever surgical intervention is being considered. The chest radiograph may be unchanged or show only slight improvement; therefore, no changes in treatment should be made on the basis of a chest x-ray alone.

Dr Praveen examines a chest x-ray of one of his TB patients at the MCD Chest Clinic in Patparganj in East Delhi.

Lung Health Image Library

10 Treatment outcome definitions for MDR-TB programmes

Question:
Which of the following situations may be regarded as a cure in MDR-TB ?
a. Negative sputum smears on two occasions 30 days apart.
b. Bacterial culture yielding no growth on two separate occasions 30 days apart.
c. An MDR-TB patient who has completed treatment according to country protocol and has been consistently culture-negative (with at least two results) in the final twelve months of treatment.

Answer:
None of the above situations could be regarded as a cure.
An MDR-TB patient who has completed treatment according to country protocol and has been consistently culture-negative (with at least five results) in the final twelve months of treatment is regarded as cured.

MDR-TB programmes use mutually exclusive MDR-TB outcome definitions that rely on the use of bacteriological culture as a monitoring tool.

Cure: An MDR-TB patient who has completed treatment according to country protocol and has been consistently culture-negative (with at least five results) in the final twelve months of treatment. If one positive culture is reported during that time and there is no concomitant clinical evidence of deterioration, a patient may still be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative cultures, taken at least thirty days apart.

Treatment completed: An MDR-TB patient who has completed treatment according to country protocol but does not meet the definition for cure due to lack of bacteriologic results (ie. fewer than five cultures were performed in the final twelve months of therapy).

Death: An MDR-TB patient who dies for any reason during the course of MDR-TB treatment.

Treatment default: An MDR-TB patient whose MDR-TB treatment was interrupted for two or more consecutive months for any reason.

Treatment failure: Treatment is considered to have failed if two or more of the five cultures recorded in the final twelve months are positive, or if any one of the final three cultures is positive. Treatment is also considered to have failed if a clinical decision has been made to terminate therapy early due to poor response or adverse events. These latter failures can be indicated separately in order to do sub-analysis.

Transfer out: An MDR-TB patient who has been transferred to another reporting and recording unit and for whom the treatment outcome is unknown.

11   COHORT ANALYSIS OF TREATMENT OUTCOME

All patients that are identified with MDR-TB should be entered into a registry. The registry is described in more detail in Module 12, but must clearly identify MDR-TB patients from those with other forms of drug resistance or from patients with suspected, but not confirmed MDR-TB.

An MDR-TB cohort is defined as a group of patients registered with MDR-TB during a specified time period (eg. one year). The date of the diagnostic DST result (that defined MDR) and the data that MDR-TB treatment was started should also be entered in the registry (see Module 3) but it is the date on which the patient is registered that determines to which cohort the patient belongs.

Cohort analysis should be performed on all registered MDR-TB patients. MDR-TB programmes are encouraged to provide treatment for all diagnosed MDR-TB patients. If any MDR-TB patients are left untreated, the reasons for exclusion should be explicitly delineated. Some examples of reasons for exclusion from treatment include:

- Died before treatment initiated;
- Patient unwilling to be treated;
- Drug supply shortage;
- Limited health facility access;
- Clinical reasons (eg. extenuating medical circumstances where the risk of treatment out weighs not treating);
- Social reasons.

Cohort analysis of treatment outcomes should be performed on all patients who receive MDR-TB treatment, regardless of treatment duration. They should be stratified by the case registration groups. Further sub-analysis of cohorts (e.g. according to HIV status, history of previous second-line drug use, DST pattern, regimen utilized, etc) may also be useful.

The recommended time frame for MDR-TB treatment cohort analyses reflects the long duration of MDR-TB treatment regimens. An initial analysis should be done 24 months after the last patient enrolment date of the cohort. Final analysis should be performed 36 months after the last patient enrolment date in the cohort.

All patients should be assigned the first outcome they experience for MDR-TB recording and reporting purposes. However, it is recommended that any subsequent outcomes also be recorded, e.g. death after default or cure after default.

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

Patients should be followed for two years after the initial outcome is assigned to allow detection of relapse.

Electronic MDR-TB Register in South Africa

South African Medical Research Council

1. Default from MDR-TB treatment is defined as:
a) Two consecutive months of treatment interruption
b) Two consecutive weeks of treatment interruption
c) Sporadic interruption during the intensive phase
d) Sporadic interruption during the continuation phase
e) Three consecutive months of treatment interruption

2. Cure of MDR-TB is defined as:
a) A minimum of five negative cultures in the last 12 months
b) A negative culture at the end of treatment
c) Culture conversion having been achieved and treatment completed
d) Three consecutive negative cultures
e) Negative cultures at the end of the intensive phase

3. Treatment failure in MDR-TB is defined as:
a) One or more positive cultures in the last 12 months of treatment
b) A positive culture among the last three cultures during treatment
c) Persistent culture positivity
d) A clinical decision to end treatment due to patient non-response
e) All of the above

ANSWERS

1:   a
2:   a
3:   e

Module 12   Recording and reporting

MODULE 12
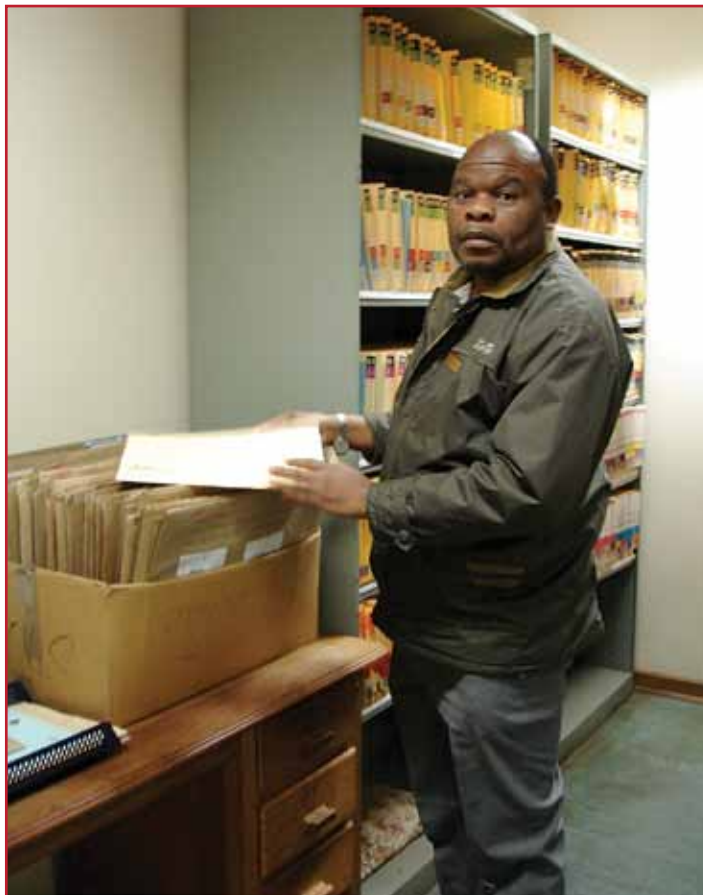
RECORDING AND REPORTING

1 LEARNING OBJECTIVES

At the end of this module you should be able to:

- Understand the rationale for standardized information systems
- Understand the scope of recording and reporting systems
- Understand the core data required for MDR-TB

2 INTRODUCTION

The information system for MDR-TB is an extension of the DOTS information system (see Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency update 2008 for more information: http://www.who.int/entity/tb/publications/2008/programmatic_guidelines_for_mdrtb/en/index.html) and defines the minimum instruments and variables necessary to implement and monitor MDR-TB programmes effectively. This information system does not include the detailed information that physicians may find necessary to manage individual patients, which depends on the local MDR-TB requirements and policies. In addition, forms may have to be modified according to the local setting and physicians are encouraged to consult their individual country policies for MDR-TB recording and reporting.

3 MDR-TB FORMS/REGISTERS AND FLOW OF INFORMATION

The following describes the core set forms that should exist in a MDR-TB programme to enable proper patient diagnosis, monitoring, and care, in addition to the reporting of outcomes.

3.1 TREATMENT CARD

QUESTION:
What is the role of the "Treatment card" in the MDR-TB treatment programme?

ANSWER:
The electronic copy of WHO Category IV Form 1 is available online: http://www.who.int/entity/tb/publications/2008/programmatic_guidelines_for_mdrtb/en/index.html.
This card is a key instrument for health staff administrating drugs daily to the patient. The treatment card should be completed when a patient is started on MDR-TB treatment and should be updated daily. The card is the source to complete and periodically update the MDR-TB register. When or if the patient moves (or example from a specialised hospital to his/her province/district of origin for follow-up) the card, or a copy of the card, must follow the patient. A copy of this card may be used as notification form and also to record final outcome of treatment.
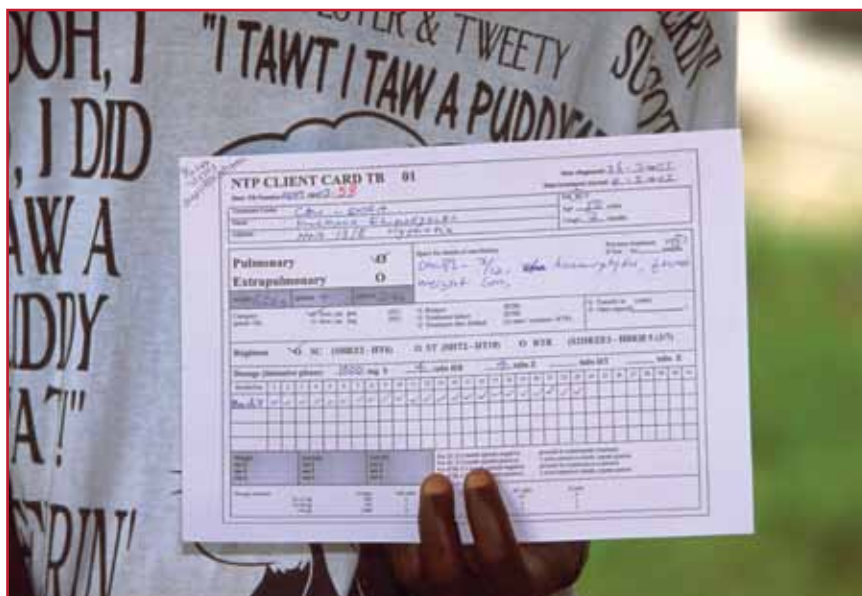
A TB patient shows his TB treatment card

Lung Health Image Library

The card contains the following sections:

- **Basic demographic information:** Name, gender, age, address, etc.
- **MDR-TB registry number:** This is a **unique** patient identification number. If there is another patient record number, like a hospital record number, social insurance number, or previous TB registration number those can be added to the form in addition to the unique MDR-TB registry number.
- **Registration group of patient according to previous treatment:** There are eight possible groups. The group "Other" can be used when the patient is a failure from a non-conventional treatment or when none of the other groups correctly describe the situation. Definitions of the different registration groups are given in Module 3.
- **Treatment history:** Number refers to whether it was first treatment episode, second episode etc. Specific drugs can be placed in the block according to the standard code for MDR-TB regimens described in Module 6.
- **Consilium Meeting section:** WHO guidelines promote the idea of periodic meetings with the group of caregivers involved with MDR-TB patients. This section provides a space to record any major changes decided by the group of caregivers.
- **HIV Testing Information:** This section is filled in for all patients. If tested for HIV include date of testing and results. If HIV-infected, indicate whether patient is on ART and/or cotrimoxizole prophylactic therapy.
- **HIV flow sheet.** This section is only filled in for HIV-infected patients.
- **Regimen:** The initial MDR-TB regimen is recorded on the treatment card, as well as any changes. One line is used for each date on which a drug (or drugs) is changed.
- **Record of daily observed administration of drugs:** One line per month is used, which makes it easy to assess adherence. Some programs may want to design treatment cards with a more detailed system where a box is ticked off for each drug daily, since there may be irregularity in administration of drugs caused by stock-outs, side effects etc.
- **DST:** The date and results of any DST are recorded on the treatment card.
- **Smear and culture:** Periodic monitoring of smear and culture is required as described in Module 11. These should be recorded on the treatment card.
- **Weight, laboratory and X-ray monitoring:** These items can be recorded on the treatment card in the monthly drug administration section in the last column.
- **Outcome of treatment:** At the end of treatment the outcome should be recorded on the treatment card according to the outcome definitions described in Module 11.

3.2 MDR-TB Register

QUESTION:
What is the role of the MDR-TB Register in a national TB programme?

ANSWER:
The electronic copy of WHO Category IV form 2 is available online (http://www.who.int/entity/tb/publications/2008/programmatic_guidelines_for_mdrtb/en/index.html).
WHO guidelines promote a system where the national TB programme maintains two registers:
One register enters all TB patients who start WHO first-line treatment regimens. This first register is the same register that already exists in most DOTS programs.
The second register records all patients that receive MDR-TB regimens. This register is a key instrument to follow the progress of MDR-TB patients and allows quick assessment of the implementation of the MDR-TB programme, facilitating quarterly reporting and analysis of case finding and treatment outcome.

MDR-TB recording
and reporting

Lung Health Image Library

The national TB control programme should define where the MDR-TB registers are located. If the first months of MDR-TB treatment is centralised to one treatment unit (usually hospitalized, sometimes ambulatory), this unit should keep the MDR-TB register. If part or all of MDR-TB treatment is taking place at the provincial or district levels, and the number of cases in the province/district is considerable, there should be a provincial/district MDR-TB register.

The MDR-TB register is filled in based on information in the treatment card, and should be updated daily as new patients are registered. Smear and culture information as well as final outcome can be filled in once a month.

The person responsible for the register should enter the patient into the MDR-TB register as soon as the patient is known to be an MDR-TB case or qualifies to enter treatment by the MDR-TB programme protocol. This moment will define the **date of MDR-TB registration.** Patients should be entered consecutively by their date of registration. There should be a clear separation (extra line) when a new quarter is started.

All patients in whom an MDR-TB regimen is indicated should be entered in the MDR-TB register, even if they are not starting MDR-TB treatment. The following is recorded in the MDR-TB registry:

- **MDR-TB registry number:** This is a unique patient identification number for patients that enter MDR-TB treatment.
- **Date registered.**
- **Name, sex, date of birth, address.**
- **District TB register number.**
- **Site of disease:** Pulmonary vs. extra-pulmonary.
- **Registration Category:** Described in Module 3.
- **Second-line drugs already received:** Yes or no.
- **DST:** Date and results. Patients may have had more than one DST. The diagnostic DST (which resulted in the patient being registered as a MDR-TB patient) is entered. Full DST history is recorded on the treatment card. Follow-up DST results are not recorded in the register.
- **MDR-TB regimen:** The date and the initial regimen is recorded.
- **Smear and culture monitoring results:** Date and result.
- **HIV status:** Testing results, cotrimoxazole prophylactic therapy and ART treatment information.
- **Final outcomes:** See Module 4 for definitions.
- **Comments.** This section is reserved for any additional information.

3.3 Request for sputum examination

The electronic copy of WHO Category IV Form 3 is available online (http://www.who.int/tb/publications/2008/programmatic_guidelines_for_mdrtb/en/index.html).

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

3.4 Laboratory registers

The electronic copy of WHO Category IV Forms 4 is available online (http://www.who.int/tb/publications/2008/programmatic_guidelines_for_mdrtb/en/index.html).

Laboratories should have a registers from smear microscopy and a separate register for culture and DST. MDR-TB Form 4 is the laboratory register used to record culture and DST. The culture and DST register should be compared with the MDR-TB register regularly to ensure that all MDR-TB cases are entered in the MDR-TB register.

3.5 Quarterly report of MDR-TB case finding

The electronic copy of WHO Category IV Form 5 is available online (http://www.who.int/tb/publications/2008/programmatic_guidelines_for_mdrtb/en/index.html).

This report is used to assess the number of MDR-TB cases detected (distribution and trends) and the number of MDR-TB cases who start treatment. The report should be made quarterly.

The quarterly report includes:
- The number of patients with date of result showing MDR-TB during the relevant quarter, taken from the Laboratory Register (Form 04).
- The number of MDR-TB patients started on Category IV treatment during the quarter, taken from the Category IV Register (Form 02).

If relevant, the number of XDR-TB cases registered (after cross-checking DST results with type of resistance) and the number of XDR-TB cases started on XDR-TB treatment should be added.

Since there may be a considerable delay between Category IV registration and the start of Category IV treatment, the patients who start treatment during the quarter may not be the same as the ones detected with MDR-TB. The information gives however an approximate indication of treatment coverage.

3.6 Preliminary 6-month interim outcome assessment form

The electronic copy of WHO Category IV Form 6 is available online (http://www.who.int/tb/publications/2008/programmatic_guidelines_for_mdrtb/en/index.html)

Each defined cohort should have an interim or preliminary outcome report. This report is based on the MDR-TB treatment register and the form is completed nine months after the closing day of the cohort. Since reporting at the end of treatment is very late (after two or even three years), interim results are desirable for all cohorts.

3.7 Annual report of treatment outcome of MDR-TB cases

The electronic copy of WHO Category IV Form 7 is available online (http://www.who.int/tb/publications/2008/programmatic_guidelines_for_mdrtb/en/index.html).

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

Since treatment is of long duration, the results will reflect the management of treatment during a prolonged period in the past. In order to assess quicker changes in default, failure, deaths etc., optional forms for preliminary outcomes are also available. These forms are much easier to fill in if the MDR-TB treatment register is computerized.

3.8 Patient identity card

This is an optional form and an example is not available on the WHO website. Once a patient is diagnosed with MDR-TB, a patient identity card can be filled out at the same time that the treatment card is filled out, and kept by the patient. The card contains the following:

- Demographic details (name, age, sex);
- MDR-TB register number;
- Essential treatment information (start date, regimen);
- Health centre where the patient will receive treatment;
- Dates of appointments.

4 Computerized systems

All the forms can be handwritten. However, an electronic version entering the data from the MDR-TB treatment card into a MDR-TB register is highly desirable since it improves the quality of the information and facilitates data analysis. Forms 5 - 7 can then easily be generated from the computerized register.
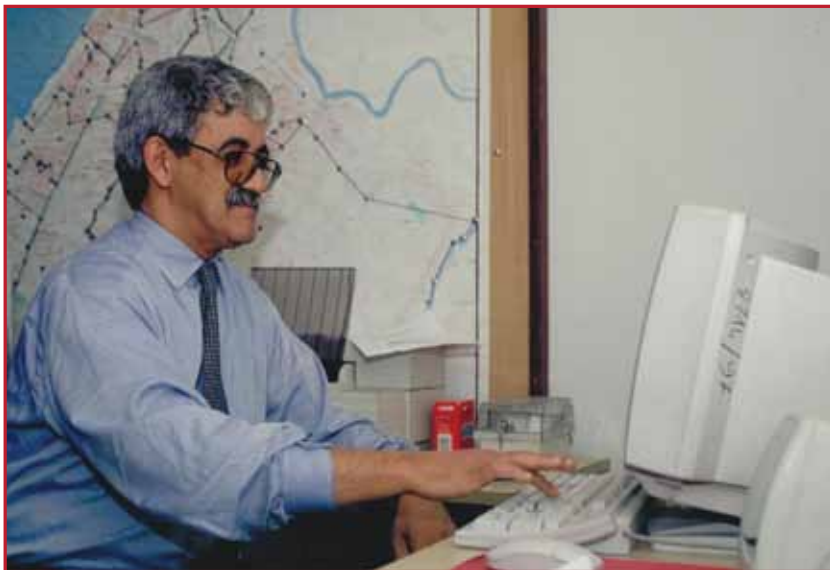
Centers for Disease Control and Prevention

SELF ASSESSMENT QUESTIONS AND EXERCISES: RECORDING AND REPORTING

1. The treatment card used in the management of MDR-TB contains amongst others the following information (choose one):
a) Basic demographic information
b) MDR-TB registry number
c) Treatment history
d) The date and results of any DST
e) All of the above

2. The following information is amongst the recorded information in the MDR-TB registry:
a) Date registered
b) Second-line drugs already received: (Yes or no)
c) Marital status
d) Number of dependants
e) Smear and culture monitoring results

3. Once a patient is diagnosed with MDR-TB, a patient identity card should be filled out at the same time that the treatment card is filled out, and kept by the treatment officer. True of false?

ANSWERS

1: e
2: a, b and e
3: F

Module 13   MDR-TB contacts

MODULE 13

MDR-TB CONTACTS

1   LEARNING OBJECTIVES

At the end of this module you should be able to:

- Identifying high-risk contacts
- Manage adult and paediatric contacts of MDR-TB patients
- Manage HIV-positive contacts of MDR-TB patients

2   INTRODUCTION

The opportunity to halt the spread of MDR-TB in communities and to treat MDR-TB in a timely fashion is often lost because contacts of MDR-TB patients are not investigated.

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

3   EVALUATING THE RISK OF MDR-TB IN CONTACTS

QUESTION:
Which of the following would you consider to be added risk factors for contacting MDR-TB from another patient?
a. Infectiousness of the source of contact.
b. Closeness of the contact of the patient with the patient with MDR-TB.
c. Duration of contact.
d. Intensity of the contact.
e. Socio-economic status of the index patient.

ANSWER:
The corrects answers are a,b,c and d.
MDR-TB patients who cough and have smear-positive sputum are substantially more infectious than those do not cough or who have smear-negative sputum.
Persons who share air space with an MDR-TB patient for a prolonged time (eg. a household member, hospital room mate, prisons) are at higher risk for infection than those with a brief exposure.

Factors which should be considered in the management of contacts of MDR-TB patients include:

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

Contacts that have had exposure to a patient with MDR-TB 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:

- Infectiousness of the MDR-TB source case
- Closeness and intensity of the exposure
- Likelihood of exposure to persons with drug-susceptible TB.

3.1   INFECTIOUSNESS OF THE SOURCE CASE

MDR-TB patients who cough and have smear-positive sputum are substantially more infectious than those do not cough or who have smear-negative sputum.

3.2 Closeness and intensity of MDR-TB exposure

Persons who share air space with an MDR-TB patient for a prolonged time (e.g. a household member, hospital room mate) are at higher risk for infection than those with a brief exposure.

Exposure in a small, enclosed, poorly ventilated space is more likely to result in transmission than exposure in a large, well-ventilated space.

Exposure during cough-inducing procedures (e.g. sputum induction, bronchoscopy) may greatly enhance transmission.

3.3 Contact history

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

Persons with **recently acquired** *M. tuberculosis* infection are at relatively high risk of developing active disease: in immuno-competent persons, the risk of developing TB is highest within the **first two years** following infection, after which this risk declines markedly. In general, 5%-10% of infected immuno-competent persons will develop active disease within the first two years.

Child contacts of MDR-TB patients (especially those under two years of age) are at increased risk.

The most potent factor that increases the probability that a person infected with MDR-TB will develop active disease is impaired immunity, such as that seen in HIV infection. It should be remembered, however, that there are many other medical causes of impaired immunity:

- Malnutrition;
- Congenital syndromes;
- Certain haematological diseases;
- Endocrine diseases;
- Renal disease;
- Diabetes mellitus.

In addition, patients who are receiving immunosuppressive drugs (steroids, anti-cancer chemotherapy) or radiation therapy may also be at increased risk.

Voluntary HIV counselling and testing or point-of-care HIV testing should be offered to all contacts under investigation for TB, particularly in countries/subpopulations with a high HIV prevalence.

4   Vaccination

The ability to prevent MDR-TB through vaccination would have a profound effect on the global epidemiology of MDR-TB; however, the only vaccine currently available is BCG, derived from an attenuated strain of *M. tuberculosis* and first used in 1921. Randomized placebo-controlled trials and retrospective case-control and cohort studies have demonstrated a wide variation in vaccine efficacy, ranging from 0% to 80% depending on geographical region.

Countries have different policies for BCG vaccination and physicians treating MDR-TB patients should comply with their respective TB control program policies. BCG vaccination of adults is not recommended.

Advances in molecular genetics have resulted in the characterisation of the genomic sequence of *M. tuberculosis* and identification of nearly four thousand genes associated with activity of the organism, making it possible to generate a huge array of potential TB vaccines. Three types of vaccines are currently under investigation, ie:

- Live, attenuated vaccines (largely derived from BCG);
- Subunit vaccines (mycobacterial polypeptides, lipid and carbohydrate antigens combined with adjuvants);
- Naked DNA vaccines eliciting protective antigenicity.

A major barrier to vaccine development, however, arises from insufficient knowledge on the roles of specific T-cell subsets, lymphokines, cytokines, and antibodies to *M. tuberculosis* in conferring and serving as surrogate markers of protection. Currently, the only test available to determine protective immunity is assessment of the response to a virulent challenge in experimental animal models and it not clear to what extent vaccine efficacy in animal models relates to activity in humans.

Intradermal BCG vaccination
HELP Design Group

QUESTION

Which of the following measures may be useful in the management of asymptomatic contacts of MDR-TB patients?

a. The use of second-line drugs as a preventative measure.
b. Pyrazinamide and high-dose ethambutol; pyrazinamide and fluoroquinolones.
c. Adopt a 'watchful waiting' approach.
d. Isoniazid preventive therapy.

ANSWER

- WHO does not recommend universal use of second-line drugs for preventive therapy in MDR-TB contacts.
- 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, and therefore are not indicated for asymptomatic contacts.
- Asymptomatic contacts of smear-negative MDR-TB patients should be managed according to the standard recommendations for contacts of drug-susceptible TB patients (URL to WHO Guidelines for TB Preventive Therapy).

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5 MANAGEMENT OF ASYMPTOMATIC CONTACTS OF MDR-TB PATIENTS

The WHO does not recommend universal use of second-line drugs for preventive therapy in MDR-TB contacts. To date, 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. A 'watchful waiting' approach is therefore more appropriate, particularly in high TB burden settings where many different tubercle strains (most often drug-susceptible) are circulating. Given the real possibility that contacts may have been infected by drug-susceptible strains, it is acceptable practice to manage asymptomatic contacts of MDR-TB patients in the same way as contacts of drug-susceptible TB patients, ie. with isoniazid preventive therapy.

Asymptomatic contacts of smear-negative MDR-TB patients should be managed according to the standard recommendations for contacts of drug-susceptible TB patients (see the WHO Tuberculosis infection-control in the era of expanding HIV care and treatment, addendum to Guidelines for the prevention of tuberculosis in health care facilities in resource-limited settings: http://whqlibdoc.who.int/hq/1999/WHO_TB_99.269.pdf).

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

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 preventive (drug-susceptible) treatment depends on clinical history, examination and investigation.

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

Contacts who are HIV-positive should be followed up monthly for at least three months and encouraged to report symptoms and signs as soon as they become evident.

6   Management of symptomatic contacts of MDR-TB patients

6.1   Adult contacts

All symptomatic close contacts of MDR-TB cases should be examined immediately. If the contact appears to have active tuberculosis disease, culture and DST should be performed. If DST is not available, or while awaiting DST results, an empiric regimen based on either the resistance pattern of the index case or the most common resistance pattern in the community may be started.

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

6.2   Pediatric contacts

QUESTION
What are the clinical symptoms and signs suggestive of MDR-TB in children?
a. Children who have had no confirmed contact with a confirmed MDR-TB case.
b. Children who are contacts of patients who died of tuberculosis while on treatment and there are reasons to suspect it was MDR-TB.
c. Children with bacteriologically proven TB that are not responding to first-line drugs given under direct observation.
d. Symptoms of TB in young children can be non-specific, eg. chronic cough or wheeze, failure to thrive and recurrent fevers.
e. Children who consistently gain weight.

MDR-TB should be suspected in the following situations:

- Children who are contacts of a confirmed MDR-TB case.
- Children who are contacts of patients who died of tuberculosis while on treatment and there are reasons to suspect it was MDR-TB (contact of another MDR-TB case, poor adherence to treatment or had received more than two courses of TB treatment).
- Children with bacteriologically proven TB that are not responding to first-line drugs given under direct observation.

The diagnosis of TB is more difficult in children than in adults. Symptoms of TB in young children can be non-specific, eg. chronic cough or wheeze, failure to thrive and recurrent fevers. Bacteriologic confirmation may be difficult to obtain due to the inability of children to produce sputum, the pauci-bacillary nature of paediatric TB, and the increased likelihood of extra-pulmonary TB in children. While every effort should be made to establish a bacteriologic diagnosis by DST in a child with suspected MDR-TB, paediatric cases are often not bacteriologically confirmed.

Five children in Nuru

Lung Health Image Library

Symptomatic paediatric household contacts of MDR-TB patients should receive:

- A medical evaluation, including history and physical examination;
- Skin testing with tuberculin purified protein derivative (PPD);
- A chest X-ray (computerized tomography is helpful, especially in documenting hilar adenopathy but often not available in low resource areas);

- Culture and DST: If the child is very young or cannot expectorate sputum, sputum induction with chest percussion or gastric aspiration should be performed. (Note: gastric aspiration should only be undertaken where culture facilities are available due to the low yield from microscopy and the distress involved to the child).
- Use of the scoring systems have been produced to aid screening and diagnosis of active TB are strongly recommended (See WHO Guidance for national tuberculosis programmes on the management of tuberculosis in children for more detailed information: http://whqlibdoc.who.int/hq/2006/WHO_HTM_TB_2006.371_eng.pdf).

If the tuberculin PPD skin test is >5 mm but a symptomatic child has a negative chest radiography and gastric aspirate or sputum culture, s/he can be treated with a broad spectrum antibiotic that is not active against tuberculosis, such as trimethoprim/sulfamethoxazole. The child should be followed closely, with monthly evaluations that include culture on samples from induce sputum or gastric aspirates and chest X-rays, until three months of negative cultures or resolution of the symptoms occurs. If the patient's clinical condition is highly suggestive of tuberculosis or progressively worsens, empiric therapy designed according to the DST pattern of the strain from the index case based on common DST patterns of resistance in the community may be started.

Self Assessment Questions and Exercises: MDR-TB Contacts

1. True/False:
( ) Smear-negative adult MDR-TB cases cannot infect children
( ) Household contacts are particularly important for MDR-TB in young children
( ) Children with MDR-TB make a significant contribution to MDR-TB epidemiology
( ) Children with MDR-TB is usually infectious
( ) Indoor exposure is a significant risk factor for MDR-TB in children

2. A child with HIV-infection presents with symptoms of MDR-TB. You should:
a) Prescribe MDR-TB treatment
b) Prescribe MDR-TB preventive therapy
c) Assess patient for the need of ARV treatment
d) First prescribe a course of broad-spectrum antibiotics and assess response
e) Choice "a" and "c".
f) Choice "c" and "d"

3. Child contacts of MDR-TB patients should receive:
a) Full MDR-TB treatment
b) Preventive therapy for drug-susceptible TB
c) Preventive therapy for MDR-TB
d) BCG vaccination
e) Presumptive MDR-TB treatment

ANSWERS

1: F, T, T, F, T
2: f
3: b

MODULE 14
INFECTION CONTROL

1   LEARNING OBJECTIVES

At the end of this module you should be able to:

- Describe measures for reducing MDR-TB transmission in health care settings
- Identify priorities for infection control
- Describe available infection control measures and evidence for efficacy
- Understand the role of surgical masks and respirators in respiratory protection

2 INTRODUCTION

MDR-TB is transmitted in the same way as drug susceptible TB, ie. through the **airborne route.** Well-documented outbreaks of nosocomial (acquired in hospital) MDR-TB epidemics provide convincing evidence that MDR-TB is highly transmissible, especially among vulnerable populations and in institutional settings. Moreover, because MDR-TB patients may respond to treatment slowly and remain sputum smear-positive longer, they may infect more contacts over time than drug-susceptible TB patients.

The majority of guidelines developed to address the prevention of transmission of MDR-TB have been introduced in the developed world and are prohibitively expensive. Many of the factors responsible for MDR-TB transmission may be remedied by simple and often inexpensive infection control measures. The control measures likely to have the greatest impact on reducing transmission (e.g. rapid diagnosis and triage of infectious MDR-TB patients) can be implemented with minimal additional financial resources.

3 THE PRIORITIES OF INFECTION CONTROL

Acquisition of MDR-TB implies longer, more arduous, complicated, and possibly unsuccessful treatment. No proven preventive treatment is available. The seriousness of MDR-TB does not much alter available infection control strategies, but by raising the stakes, it does demand that every physician/ program attempting to treat MDR-TB also undertake a systematic review of current practices to prevent transmission of MDR-TB to patients and staff.

Recommendations for infection control to prevent MDR-TB are essentially the same as those to prevent the spread of drug susceptible TB, with only minor differences in emphasis (http://whqlibdoc. who.int/hq/1999/WHO_TB_99.269.pdf). This module will briefly review those recommendations with a focus on MDR-TB. The above mentioned prevention guidelines are currently being supplemented by recommendations for regions with high HIV-prevalence (Tuberculosis Infection-Control in the Era of Expanding HIV Care and Treatment, Geneva, World Health Organization, 2007).

Over a third of all fatalities among HIV-positive people include patients with TB. If TB is not treated properly, drug-resistant TB can spread quickly among other HIV-positive individuals, health workers and hospital visitors

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

- Administrative (managerial);
- Environmental;
- Personal respiratory protection.

Administrative controls are the most important since environmental controls and personal respiratory protection will not work in the absence of solid administrative control measures.

Each level operates at a different point in the transmission process:

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

4 ADMINISTRATIVE CONTROLS

QUESTION:
How can administrative measures in health care facilities be used to prevent the spread of MDR-TB in those facilities?

ANSWER:
The first and most important level of infection control is the use of **reduce the exposure** of HCWs and patients to *M. tuberculosis*. Important administrative measures include:

- Early diagnosis of potentially infectious MDR-TB patients.
- Prompt separation or isolation of infectious MDR-TB patients.
- Prompt initiation of appropriate MDR-TB treatment.

The most important aspect of administrative control measures is the **physical separation of patients known to have or suspected of having MDR-TB** (especially smear-positive cases) from other patients, especially those who are immunocompromised.

Ideally, patients with MDR-TB should be treated in isolated (or at least separated) wards. If no facilities exist and it is necessary to manage MDR-TB cases in a general hospital setting, special measures are needed: Because of prolonged infectiousness and the consequent increased risk of nosocomial transmission, patients suspected of having MDR-TB should, whenever possible, be placed in a separate area or building in the facility, preferably in well-ventilated rooms where the possibility of contact with other patients is minimal. If this is not feasible and there are large numbers of patients suspected of having MDR-TB, then a dedicated MDR-TB ward or area of a ward should be established.

Patients who are seriously ill at diagnosis or develop MDR-TB complications may require prolonged hospitalisation, and many countries hospitalise MDR-TB patients for the first several months of treatment. These patients are often admitted to specialized MDR-TB wards. Paradoxically, the risk to HCWs may be lower in such facilities than in general hospitals since the diagnosis has been made at or prior to admission and many of the patients rapidly become non-infectious once placed on adequate MDR-TB therapy.

Known or suspected HIV-positive **patients should be kept separate from MDR-TB patients** at all times. Such patients have a particularly high risk of contracting MDR-TB and in many countries, explosive outbreaks of MDR-TB have occurred on wards containing HIV-infected patients.

Immunocompromised HCWs should be given opportunities to work in areas with a lower risk of exposure to *M. tuberculosis*. MDR-TB should be strongly considered as part of a differential diagnosis for immunocompromised HCWs with respiratory complaints in close contact with confirmed MDR-TB patients. Immunocompromised HCWs suspected of having MDR-TB should be promptly evaluated and treated, preferably on an outpatient basis. They should be removed from work until infectiousness is ruled out or until they have become smear-negative.

Patients' willingness to remain in isolation/separation may be facilitated by keeping them occupied through various activities such as the provision of television, books/magazines, billiards, crafts, etc. It should be remembered that the difficulties in enforcing isolation can be reduced by ensuring timely diagnosis and prompt treatment.

In hospital settings and for drug susceptible TB, isolation may be stopped after a patient has had **three negative smears** (at least one must be on an early-morning specimen) taken on three separate days, and shows maintained clinical improvement, including resolution of cough. While some facilities use the same criteria for patients with MDR-TB; however, many experts are more cautious about returning MDR-TB patients back to their homes, schools, work sites and congregate settings. The reasons for this are the more dire consequences of MDR-TB and the fact that there are not good prophylactic regimens for the treatment of latent TB infection due to MDR-TB. Patients with smear-negative, culture-positive sputum on treatment certainly can still transmit MDR-TB. The WHO guidelines consider patients with MDR-TB to be contagious until their sputa are culture-negative and forbids travel in public airplanes or other public transportation until their sputa are culture negative. Many institutions will not stop isolation until the patient is proven culture-negative.

Infectious patients with XDR-TB, whether infected with HIV or not, should not be placed on open wards (even if the ward is designated for patients on MDR-TB treatment). Given the high mortality associated with XDR-TB, isolation until the patient is not longer infectious is recommended.

Community-based ambulatory MDR-TB treatment can reduce the risk of transmission to patients and health care workers. Although most transmission is likely to have occurred before the diagnosis and start of MDR-TB treatment, ambulatory patients should be advised to avoid contact with the general public, practice home isolation, and especially avoid contact with susceptible persons, such as young children or HIV-infected individuals. Other important administrative measures that should be in place in facilities treating MDR-TB patients include:

- Assessment of the risk of transmission in the facility;
- Development of an infection control (IC) plan that details in writing the measures that should be taken in a given facility;
- Adequate training of HCWs to implement the plan.

The appointment of a director of infection control for the institution, and an infection control committee representing key departments of the facility, are strongly recommended. The initial task of the committee is the formulation of a comprehensive infection control plan for the institution, including a program for the education of all staff on infection control policies and procedures.
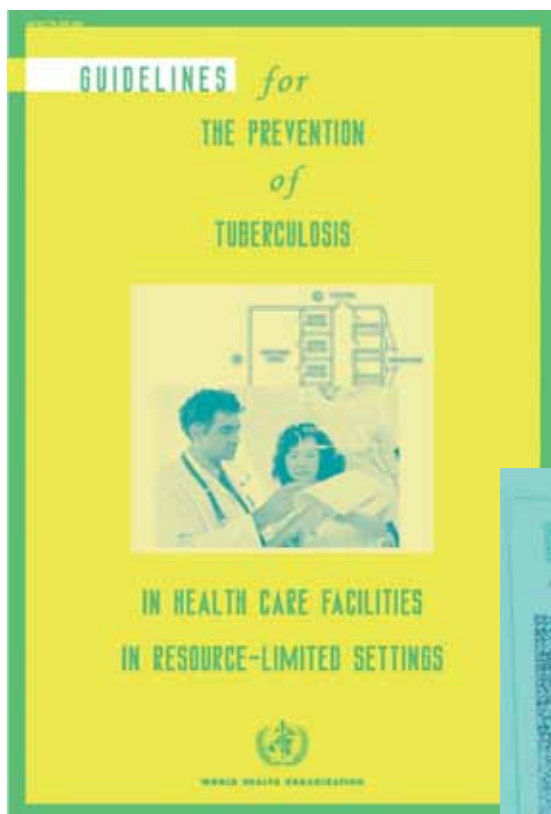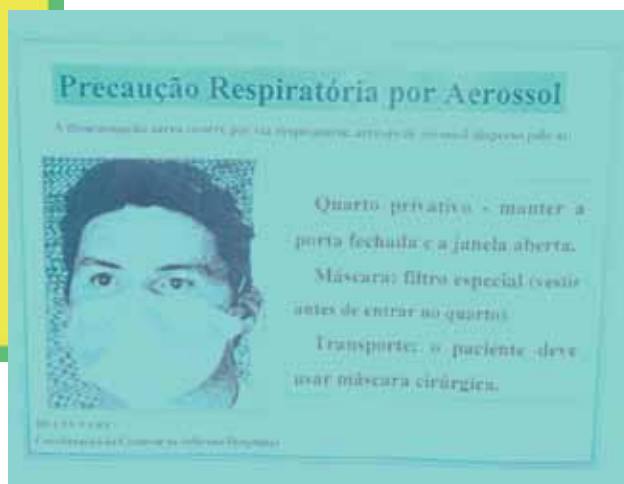
International guidelines should be used when drawing up institutional infection control plans

Appropriate signage is an administrative measure used to identify high risk areas

World Health Organization

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5   ENVIRONMENTAL CONTROLS

5.1 GENERAL CONSIDERATIONS

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

A variety of environmental controls can be used to reduce the number of aerosolised infectious particles in the work environment. Although some environmental controls do not require a large expenditure of resources, most are expensive and technically complex. Implementation of these control measures should be guided by the assessment of risk as well as available resources.

The administrative control measure of physically separating suspected or known infectious MDR-TB patients from others is an essential first step prior to the implementation of environmental control measures. This can be achieved by placing infectious patients in a separate room, ward, or building. Most environmental control measures are easier to implement and maintain if their use can be limited to part, rather than all, of a large facility.

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The best way of reducing high concentrations of infectious particles in the work environment is through ventilation, ie. the movement of air to ensure dilution and air exchange. Ventilation may be achieved as follows:

- Using air currents generated from outdoor winds;
- By convection using indoor sources of heat;
- By mechanical fans that pull air in a directional manner;
- By various types of mechanical ventilation.

Ideally, fresh air is constantly pulled through a room and safely exhausted to the outside, such that the air is changed several times every hour (Figure 14.1.).

Figure 14.1.
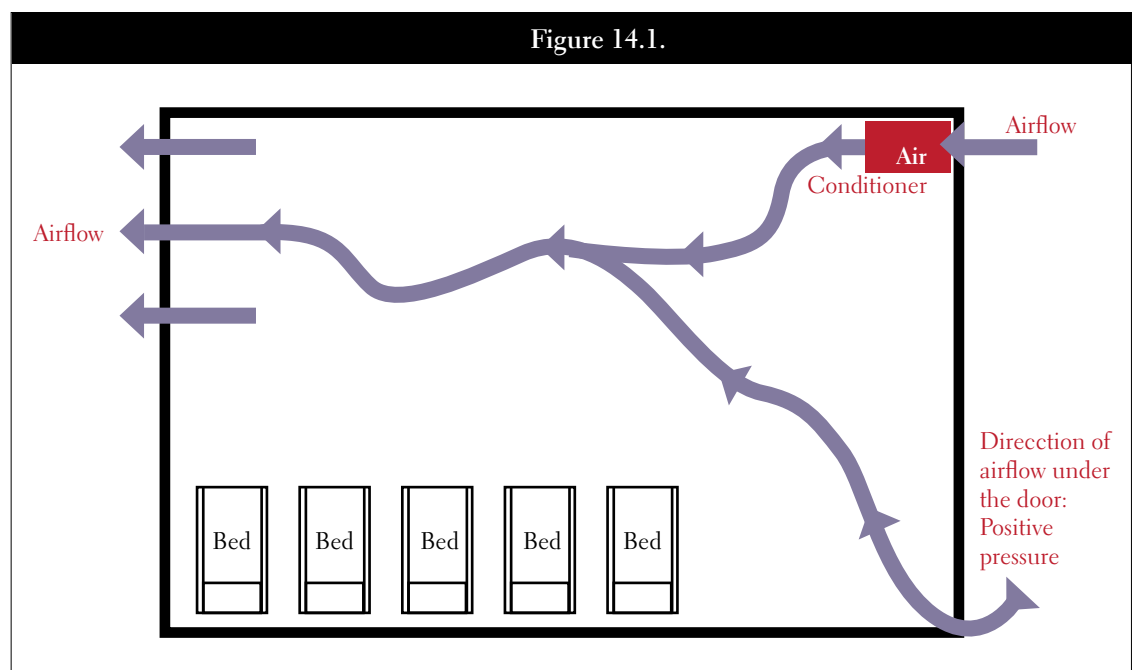
Where the establishment of adequate ventilation is not feasible for climatic or other reasons, alternative means of reducing the concentration of infectious particles include the use of ultraviolet germicidal irradiation (UVGI) to kill infectious organisms or air filtration methods to remove infectious particles. However, these latter methods are of limited effectiveness unless combined with methods to mix and move the air.

Environmental control measures may include:

- **Open windows** that maximise natural ventilation and dilute the air (the simplest and least expensive technique).
- **Overhead fans,** which are already present in many settings, and may be used to further enhance natural ventilation in settings where windows can remain open.
- **Exhaust fans** that provide directional air flow in areas where open windows and overhead fans are not sufficient. Directional air flow refers to the introduction of a 'clean' air stream into the space occupied by the infectious patient to dilute the concentration of airborne tubercle bacilli and thereby reduce the risk of transmission. These fans, which are usually placed in windows, are designed to move air containing infectious particles to the outside and replace it with air coming from "clean" parts of the facility or from the outside.
- **Exhaust ventilation systems** that provide at least six air changes per hour and prevent contaminated air from escaping into 'clean' parts of the facility may be considered where risk is deemed extremely high and the financial means exist. The most common way in which such ventilation can be established is through the use of negative pressure ventilation, in which a room is kept at negative pressure relative to the surrounding area and air is drawn into the room from the corridor and exhausted directly outside.
- Adjunctive measures such as the use of high efficiency particulate air (HEPA) filters or ultraviolet germicidal irradiation (UVGI) may be helpful but should not be relied upon as substitutes for the environmental controls mentioned above. Their usefulness is limited unless air movement is adequate to ensure contact of infectious particles with these devices, and it is difficult to assess their effectiveness in field use.
- HEPA filters should be replaced only by properly trained staff. A very high risk exists if untrained staff try to change HEPA filters

5.2 Natural ventilation

Natural ventilation was the only form of environmental infection control for TB until relatively recently.

Natural ventilation can be used in medical wards or other sites in health facilities in temperate or tropical climates where windows can be left open. Natural ventilation can occur when a room or ward is of open construction with free low of ambient air through open windows (in one side and out the other).

Maximizing natural ventilation patterns for the hospital, clinic, ward or room may be the simplest and least costly approach to achieving better ventilation. Various strategies may be employed:

- Waiting areas, examination rooms, and wards should be 'opened' to the environment (eg. established in covered open areas or in areas with open windows). Additionally, windows may be installed that would allow for more ventilation. Windows should be placed to the open environment and not to other wards.
- Ceiling fans may be used to facilitate air mixing and movement. Since diluting and exchanging rather than just mixing the air is the objective, ceiling fans should be used in conjunction with open windows.
- Because of the increased risk of creating more highly concentrated infectious aerosols during coughing, sputum collection should be done in a well-ventilated area, preferably outdoors and well away from other persons. Care should be taken to assess these areas to assure that there is good air movement since some areas immediately adjacent to buildings or on porches or verandas may have poor air movement.

In many situations, it is not possible to establish cross-ventilation. Closed rooms that contain air with aerosolised infectious particles present a particular risk. A room with an open window at one end provides air exchange near the window; however, little air is exchanged a short distance from the window. In such settings, having another window in the room open or keeping a door open may improve air exchange, but having open windows and doors does not guarantee good dilution ventilation.

A common problem in settings that rely on natural ventilation is that patients or staff close the windows during cooler weather or at night. There is likely to be variability of air flow patterns due to varying weather patterns or to the presence of other structures blocking air currents. Where natural ventilation is used, air movement can be easily assessed using smoke tubes or similar measures. If inadequate additional mechanical or other measures may be needed, especially in areas where risk of transmission is high.

Managua. "Ventilation and sunshine are very important in the house."

ES MUY IMPORTANTE LA VENTILACION Y LA ENTRADA DE SOL EN LA CASA.

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5.2.1 Mechanical ventilation

Mechanical ventilation should be used in situations **where natural ventilation does not produce adequate airflow** to reduce the concentration of infectious droplet nuclei. Mechanical ventilation is especially recommended in areas in which there may be high concentrations of infectious aerosols, such as:

- Wards or rooms containing large numbers of infectious MDR-TB patients;
- Bronchoscopy suites;
- Sputum induction areas;
- Laboratories handling concentrated sputum specimens and cultures;
- Autopsy or mortuary rooms.

If mechanical ventilation is used, it is important to use equipment with sufficient power to facilitate air entry into, and exhaust from, the room or area. In other words, if no air is allowed to enter the area, then it will be impossible to exhaust air. It is also important to attempt to direct air movement so that infectious particles produced by coughing patients are exhausted away from others.

Directional air flow from a 'clean' area, across the HCW, across the patient, and to the outside should be maintained. The area where air is entering should be located away from the air intake to avoid 'short-circuiting' whereby newly exhausted contaminated air is drawn back into the room through the air intake. It should be noted, however, that if patients are highly mobile, the potential benefit of directional airflow will not be realised.

The simplest form of mechanical ventilation is **exhaust fans**, which are generally placed in windows and move air from inside a room to the outdoors. If exhaust fans are used, it is important to ensure that airflow is adequate, and also that air flows across the room (not in and out the same window or vent). This can be monitored through the use of smoke tubes or other devices designed to assess direction of airflow.

Window fans that move air from inside the room to the outdoors are the least expensive and most feasible method of providing mechanical ventilation. In most circumstances, they can serve to effectively dilute air containing infectious particles. They may also be more acceptable to staff and patients than keeping windows consistently open, although they too may decrease the temperature of the room.

Mechanical ventilation is not without its limitations:

- Ventilation rates in rooms may vary depending on whether doors or windows are open or closed as well as the situation in other rooms on the same ventilation system.
- Systems may not function properly as a result of poor maintenance, electrical power failures, or poorly planned renovations.
- Poorly designed or maintained mechanical ventilation systems may provide false reassurance to health care workers. In addition, they can also be a source of indoor air quality problems that may affect the health of HCWs and patients.

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5.2.2 *Monitoring of ventilation and ventilation systems*

Ventilation systems should be evaluated regularly to determine that they are functioning properly. The simplest evaluation includes the use of visible smoke (eg. using 'smoke tubes') to monitor proper airflow direction. More sophisticated tests utilising a flow velometer or tracer gas analyses also can be used to determine airflow rates and calculate the number of air exchanges per hour. Evaluations should be conducted periodically and documented in a maintenance record.

Many countries have their own ventilation standards, which should consider those published by ASHRAE, the American Society of Heating Refrigeration and Air Conditioning Engineers (http://www.ashrae.org/)

5.2.3 *Ultraviolet germicidal irradiation (UVGI)*

Laboratory studies show that *M. tuberculosis* is killed if the organisms are exposed to UVGI sufficiently. For this reason, UVGI has been recommended by some as an inexpensive environmental control measure. For it to be effective, however, contaminated air must come in contact with the light rays, which may be a major problem in areas where air circulation is poor, and its effectiveness may be limited in areas where the humidity is high or in dusty areas. Furthermore, skin and eye reactions may occur in HCWs and patients from overexposure if the UVGI is not installed and maintained properly. A final major limitation to the use of UVGI is the inability to assess its effectiveness in the field, especially given the various types of available products, positions in rooms, and variability of room air mixing in various settings.

If UVGI is installed a regular program of maintenance is essential. Responsibility should be assigned to ensure that the lamps are dusted periodically and changed at regular intervals. It is also important to periodically assess airflow to ensure that air flow patterns maximise *M. tuberculosis* UVGI killing. The quality of UVGI lamps is very important. Usually a good one will last 5 000 to 10 000 hours (7 - 14 months). After that, the irradiance drops off rapidly. Ideally, irradiance should be measured with a radiometer. In addition, care must be taken to minimize risk to HCWs and patients who, if inadequately protected, may complain of skin and eye irritation. Maximum permissible exposure times for selected effective irradiance levels are available (refer to the Centers for Disease Control and Prevention website for more information: htttp://www.cdc.gov/).

Upper room UVGI is intended to be used while rooms are occupied, not to sterilize empty rooms, as is commonly done in some parts of the world. It is much more important to decontaminate air while the infectious source and other occupants are present, and upper room UVGI is designed to do that without significant radiation risks.

A growing number of manufacturers of fixtures designed for upper room use now exist in low-income countries and can provide products at lower cost. However, there are currently no standards and the buyer still needs to obtain advice from someone knowledgeable on the subject.

In addition to UVGI designed for upper room use, germicidal UV is sometimes used in ventilation ducts or in fan-driven air sterilizing devices mounted on ceilings or walls, or portable units that can be moved from room to room. Their efficacy is limited by the number of air changes they can produce, especially in large spaces.

Laboratories that process specimens that may be MDR-TB especially need strict environmental controls. These aspects are addressed in other documents.

6   PERSONAL RESPIRATORY PROTECTION

Because neither administrative nor engineering controls can provide complete protection, the third line of defence against nosocomial TB transmission is the use of personal respirators, which contain special filter material that protects the wearer from inhaling airborne hazards such as *M. tuberculosis* and are designed to fit tightly to the face to prevent leakage between the face and the edge of the mask.

Although respirators may serve as valuable components of infection control measures, they are **not** a substitute for appropriate administrative and engineering controls.

Respirators are most appropriately used for short-term protection against high-risk exposures, such as during sputum induction procedures, bronchoscopies, and autopsies.

The use of respirators is also appropriate when there is very close contact with an infectious MDR-TB patient, e.g. while giving a bed-bath to a patient or drawing blood samples. It is **not** reasonable to expect HCWs to wear respirators for long-term exposures, eg. for an entire shift on a hospital ward.

6.1 SURGICAL MASKS

QUESTION:
What is the value of surgical face masks to minimise the spread of MDR-TB?

ANSWER

There are important differences between a face mask and a respirator. Face masks, such as surgical masks (cloth or paper):

• are meant to prevent the spread of micro organisms from the wearer (eg. surgeon, MDR-TB patient, etc.) to others by capturing the large wet particles near the source (mouth)

• do not provide adequate protection to the wearer (eg. HCW, patient, family member) from inhaling infectious droplet nuclei in the air. Masks usually have limited filtration capacity and are loosely fitted over the mouth and nose, allowing free entrance of aerosolised *M. tuberculosis*.

Although not the highest priority intervention, disposable/cloth masks can be used to reduce aerosols generated from potentially infectious MDR-TB patients. Disposable or surgical masks should therefore be considered for suspect and known infectious MDR-TB patients leaving the ward for medically essential procedures or other reasons. However, because surgical masks may also serve to identify MDR-TB patients, the risk of stigma also needs to be considered. Cloth surgical masks can be washed and reused.

It is important to remember that **a surgical mask does not adequately protect HCWs** or other wearers from inhalation of air contaminated with *M. tuberculosis* and should not be used for this purpose.

Personal protective equipment
Respirators   vs.   Masks

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6.2 Respirators

Respirators are a type of mask that covers the mouth and nose. Unlike surgical masks, they contain special filter material and are designed to fit tightly to the face to prevent leakage between the face and the edge of the mask. Respirators are designed to filter very small particles, including airborne *M. tuberculosis*. Disposable particulate respirators come in many different shapes, including a cup, a duckbill, and a rigid shell supporting the filter. Some may contain one-way valves that facilitate exhalation of air by the wearer. Disposable particulate respirators, eg. N95 respirators, are the simplest and recommended devices to be used.

For a respirator to be effective there must be a tight seal between the mask and the wearer's face. If the respirator does not fit correctly, infectious particles will likely follow the path of least resistance, ie. through gaps between the respirator and the wearer's face rather than through the filter material. Any leak between the face and the mask is a potential entry point for infectious droplet nuclei. Ideally, respirators should be "fit tested" to individual wearers. In addition to choosing the proper model for each worker, this process serves to educate workers on how to properly put on their respirator to minimize face-seal leakage. Persons with beards cannot be properly fitted with a personal respirator.

Since disposable respirators are relatively costly, it may be reasonable to request that HCWs re-use them. Unfortunately, the exact amount of time that they can be re-used is unknown and must be guided by both inspection and common sense. They should be discarded when they become soiled, wet, or appear to lose their structural integrity, such that a tight seal can no longer be maintained between the edge of the mask and the wearer's face. The main factors responsible for their deterioration are humidity, dirt, and crushing. The durability of these devices varies among designs and products, and the extent of use. There is often a trade-off between durability and cost. If respirators are to be re-used, they should be stored in a clean, dry location. One method is to fold a light towel around the respirator (being careful not to crush the respirator). Plastic bags should never be used since they retain humidity.

7   SPECIAL AREAS AND PROCEDURES

QUESTION:
Make a list of high-risk areas for MDR-TB transmission in health care facilities.

ANSWER:
- Radiology
- Waiting areas
- Sputum collection and cough-inducing procedures
- Surgical and autopsy suites
- Intensive care areas

7.1 RADIOLOGY

Radiology departments often provide services to a variety of patients, many of whom may be particularly susceptible to infection with *M. tuberculosis* (eg. young children or HIV-infected patients). Therefore, radiology departments should attempt to:

- schedule inpatient chest radiographs on infectious and suspect MDR-TB patients for non-busy times such as the end of the afternoon;
- provide suspect MDR-TB patients (not documented to be smear negative) as well as all known MDR-TB patients with a surgical mask to wear; alternatively provide tissues or cloth to cough into and instruct on coughing etiquette;
- provide expedited priority service to potentially infectious MDR-TB patients to minimize the length of time spent in the department;
- restrict access to the radiology suite during operating hours to patients and essential personnel only (eg. post signs, enforce the policy);
- use the room with the best ventilation for taking images of potentially infectious MDR-TB patients.

7.2 WAITING AREAS

In many health care facilities in high burden countries, hundreds of patients are waiting to be seen every day. Hallways and waiting areas are often crowded with patients, their families, and HCWs, leading to long queues that forming outside of various departments (e.g. radiology, pharmacy, outpatient, etc.). HCWs should take responsibility to reduce the risk of nosocomial MDR-TB transmission in such settings, either by fast-tracking known MDR-TB patients or by using a numbering system whereby patients are given numbers in the order of arrival and then are asked to wait outside or in a better-ventilated area until their number is called.

7.3 Sputum collection and cough-inducing procedures

Cough-inducing procedures (eg. sputum induction or bronchoscopy) should be done only when absolutely necessary on patients who may have MDR-TB.

Sputum induction should only be done if the patient is unable to produce an adequate specimen without induction; likewise bronchoscopy should be used as a last resort after other less risky diagnostic measures have been taken.

Similarly, spirometry should not be performed on suspect or known infectious MDR-TB patients. When performed, such procedures should be done in rooms where adequate environmental control measures are in place and respiratory protective measures can be enforced.

7.4 Surgical and autopsy suites

Surgery and autopsy suites are often poorly ventilated and may pose considerable risk of infection to HCWs if procedures are performed on MDR-TB patients. In general, surgery on potentially infectious MDR-TB patients should only be performed in the presence of a life-threatening situation. Surgery for MDR-TB patients should ideally be performed when the patient has become smear-negative or when the burden of organisms has been substantially reduced. Personal respiratory protection should be used by all personnel working in the operating room or autopsy suite when procedures are performed on suspected or known MDR-TB patients.

7.5 Intensive care areas

Intensive care areas (high-care) may also be high-risk areas especially when potentially infectious MDR-TB patients are intubated. Both intubation and suctioning can create aerosols. In addition, intensive care units are often small and poorly ventilated. Therefore, if possible, intubation of potentially infectious MDR-TB patients should be avoided. Ventilation in intensive care areas needs special attention and personal respiratory protection should be used by all staff when any procedure is performed on suspected or confirmed MDR-TB patients.

1. The order of priority for infection control strategies is:
a) Personal respiratory protection, environmental controls, administrative
b) Environmental controls, personal respiratory protection, administrative
c) Administrative, environmental controls, personal respiratory protection
d) Administrative, personal respiratory protection, environmental controls
e) Personal respiratory protection, administrative, environmental controls

2. Natural ventilation can be improved by:
a) Ceiling fans in closed environments
b) Free flow of ambient air through open windows
c) Extraction fans in closed environments
d) Directional air flow in closed environments
e) Adequate sunshine through windows

3. True/False:
( ) Personal respiratory protection measures will reduce MDR-TB transmission in the absence of administrative controls
( ) Surgical masks reduce transmission of MDR-TB by the wearer
( ) Aerosolised *M. tuberculosis* can still penetrate personal respirators
( ) Personal respirators must be discarded after single use
( ) Personal respirators must be worn continuously

ANSWERS

1: c
2: b
3: F, T, F, F, F.

Module 15   Tuberculosis and MDR-TB in prisons

MODULE 15
Tuberculosis and MDR-TB in prisons

1   **Learning Objectives**

At the end of this module you should be able to:

- Why prison settings are specifically difficult for TB detection and management
- Why prisoners can be particularly difficult patients
- How different resistant strains of TB are produced or enhanced in prisons
- About the added difficulties in treating MDR-TB in prisoners
- How and why TB-HIV complicate TB and MDR-TB treatment in prisons even further

The specific features of the prison environment and of the prisoner population require specific approaches to implementation of TB management [1,2]. This is all the more important with the advent and dissemination of resistant forms of *Mycobacterium tuberculosis* and specifically MDR-TB. Prisons are sometimes considered to be "ideal" for the treatment of tuberculosis. Unfortunately, certain specific difficulties inherent to the custodial setting, and the fact that prisoners are very different from a "normal" patient population, make TB management in prisons quite more complex than most health professionals expect [3]. Prisons are a central focal point for the pooling of both normal and resistant strains of the TB bacillus. This chapter will deal with the many pitfalls encountered when dealing with TB in prisons. The difficulties inherent to TB management are magnified when treatment of MDR-TB is to be implemented. Finally, with HIV very fast developing as another major plague in the prisons, the equation becomes even more complicated, and the consequences of mismanagement more dire.

Apart from the Public Health Issue – prisons as reservoirs of TB and MDR-TB – which cannot be ignored by Health Authorities, there is also another essentially humane issue at stake.

Contracting tuberculosis is not part of a prisoner's sentence. In the prisons of the developing world, in countries with high rates of TB, contracting MDR-TB in a prison can amount to a death sentence if treatment is not available[4].

The situations and "pitfalls" described in the following pages are based on experience from TB programmes in prisons on four continents, and do not relate to any one specific continent. It must also be underlined that obviously not all prisons present the specific problems related in this chapter, and not all prisoners systematically try to deceive the system. Many prisoners are quite happy to cooperate with the medical staff and their treatment does not entail the serious concerns raised here. Unfortunately, there are however many instances where prisoners do try to trick or take advantage of the system, and often influence others into doing so. It is to inform medical staff who have never worked in a prison environment of these pitfalls that this chapter has been written. It has been said that it may sometimes be better to do nothing at all, rather than run an inefficient TB programme which can lead to the forming of resistant strains of *Mycobacterium tuberculosis*. With the advent of MDR TB programmes, it becomes essential to know how to avoid any situations in the prisons that can thwart the proper management of the programme.

Tuberculosis is today a major health issue in prisons all around the world. The prevalence of the disease in prisons is higher, sometimes much higher, than in the general population. This reality is exacerbated in those countries with already a high prevalence of TB outside prisons. In such countries, the prevalence of TB can be 40, 50 and up to 80 times higher than outside. In the past decade or so, resistant forms of *Mycobacterium tuberculosis*, and particularly MDR-TB, have appeared in prisons and become a major concern. Mortality due to TB has thus increased. There is also now the major concern of having contagious prisoners, with resistant bacilli, forming an additional health hazard for prisoners and staff alike.

In many countries, and until most recently, prisons are often not taken into consideration in national health strategies. A mere 10-15 years ago, national health statistics hardly ever considered prisoner populations or prisoner health issues. Prisons around the world are still mostly under Ministries of the Interior or Justice. Links with the Health Ministry are still the exception. Furthermore, Health Ministries have little knowledge about (and often no influence on) the health situations of the country's prisoner population[5].

2.2. Not just about prisoners

This is more than just a major oversight. Health in prisons is not just about prisoners. Prisons are small communities in themselves, which have custodial staff as well as health staff coming in and out every day. Visitors enter and leave prisons after close contact with the prisoners on a regular basis, several times a week or even more often. Any health problem concerning the prisoner population will inevitably affect those groups of people in close contact with the prisoners. Sooner or later, these health problems inside the prisons will spill out into the outside community.

Politicians, State Authorities and even Health officials often seem oblivious of the potential hazards for health in prisons. They sometimes seem to consider the prisons as if they were populated, not with fellow human beings, who sooner or later will for the most part reintegrate society, but as if they were inhabited by aliens from another planet, whose health is of no concern to the general population.

Question:

In your opinion, why do public authorities, and even health authorities, neglect health in prisons?
a. The health issues in prisons rarely are an issue for the general population.
b. Prisoners do not mix with people in the outside community, therefore their health does not affect them.
c. Health authorities often do not know what conditions in prisons are like.
d. Politicians often do not care about prisoners.
e. Prisoners are not regarded as proper members of society.

Answer:

c, d and e all can be true – sometimes all three are true.
If you answered a or b: Health issues in prisons certainly do affect the general community. Prisons are closed communities, but certainly not hermetically so. Apart from custodial staff and visitors, many other people from the outside go in and out of prisons, such as lawyers, delivery personnel, sanitary technicians and repairmen, just as examples. Contacts with the prisoners may not be as close for all these groups, but if an infectious disease is present amongst the prisoner population, it will spread via these populations that span the gap between the prisons and the community.
In Latin America, they are called "poblaciones puente", or "bridge populations", an expression

that well illustrates this. As mentioned, prisoners, at least the vast majority of them, are eventually released from prison. If those with TB have not been detected, or if they have not received proper treatment, they will spread TB outside into their families and the community.

It is certainly true in many countries, and specifically in high-TB burden countries, that health officials in the Ministry of Health, often have no clear idea as to what the real situation in their prisons is like. There has been a move in the past decade to engage Health Ministries in prison health, and even to have Health in Prisons come directly under the Health Ministry. This topic is far too vast to discuss here, but suffice to say that the issue of TB has certainly been one of the main issues pushing Health Ministries to become involved with the prisons.

d and e These answers may be considered -rightly so- as "politically incorrect" statements. Unfortunately they reflect realities on the ground in many countries. Political authorities need to be convinced that prisons are indeed members of the overall community, temporarily confined inside the prisons, but who, for the immense majority of them will sooner or later rejoin the outside world. Even if only for protection of the Public Health, the authorities must include the prisons in their overall health policies. Finally, from a purely Human Rights point of view, prisoners lose their liberty when they are sentenced to prison, but not their right to receive adequate health care while in custody. As noted before, contracting tuberculosis is not part of a prisoner's sentence.

2.3. TB: PARTICULARLY DIFFICULT TO MANAGE IN PRISON SETTINGS.

The menace of MDR-TB today magnifies the already ominous TB situation in very many of the world's prisons. Resistant tuberculosis does not just "happen" -it is a man-made problem. The same laxity, neglect, lack of motivation, sometimes even corruption that leads to treatment failures in the management of "normal" TB can and will have disastrous effects if the same shortcomings apply now to the way treatment of MDR-TB is managed in the prisons. If medical staff working in the prisons are not aware of the many pitfalls and difficulties they have to tackle, that otherwise lead to the selection of resistant strains of TB, and to MDR-TB, these same deficiencies could ultimately lead to the development of strains of the bacillus that are practically incurable.

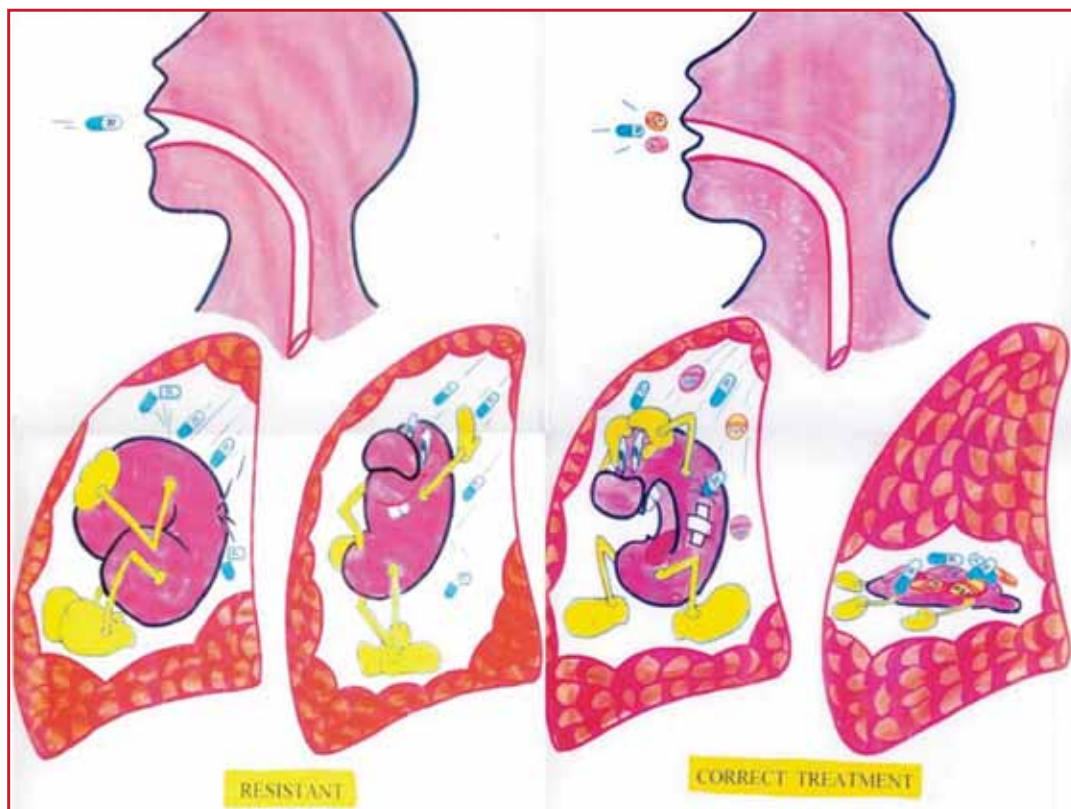Prisons are an active pool and reservoir of TB that needs specific attention and management[6].

> *"The only way to control TB anywhere, is to control it everywhere."*
> Professor Lee Reichman

Trying to "cure TB" in a country without at the same time "curing the prisons" is like treating a patient for an infection without incising and draining his purulent abscess.

In the picture on the next page ("Resistant"), the abstract "patient" is receiving only one medicine (marked R = rifampicin). The cartoon TB bacillus is shown bracing himself against this **mono**therapy, and becoming resistant. In the picture on the right ("Correct Treatment"), the same patient is taking three different medicines (R = rifampicin; INH = isoniazid and PZA = pyrazinamide) and the TB bacillus has furthermore received an injection (shown by the "bandaid patch" on his body). The bacillus is overwhelmed, and you can see he has been defeated.

This poster, in large A3 format, is widely distributed in the prisons and prison medical care centres in the Republic of Georgia, and has also been used in prisons in many other countries.

2.4. General comment.

Not more should be read into the cartoon than is meant. The intent is to show prisoners that treatment of TB needs to combine several drugs including **oral treatment** (in the cartoon: three different tablets: RIF, INH and PZA) and an **injectable** (STR). This treatment regime was actually in use in a prison TB programme in a high-TB burden country in recent years.

Such a graphic explanation has shown to be much more explicit to prisoners than a brochure with merely text and charts that prisoners are not attracted to reading.

In many countries, such basic education on TB is given to prisoners. The main messages are about hygienic conditions (for example encouraging prisoners to ventilate their cells as much as they can, and of course according to climatic conditions; to avoid coughing without adequately covering their mouths) and also telling them to consult the medical services if they have symptoms that could be related to TB.

The posters here explain that TB treatment is only efficient with **several drugs**. In many prisons in high-TB burden developing countries, prisoners are put on a standardized eight-month treatment scheme which already includes Streptomycin in the first two months of the initial phase: e.g.: 2HREZS/1HREZ/5H3R3. (In this cartoon, PZA replaced ETH.) Field experience has shown that there is already a (relatively) high rate of TB drug-resistance in the general population, and as one cannot be sure prisoners truthfully state whether they are really "new" cases or not, this 8-month scheme is used for all prisoners diagnosed as having pulmonary TB[7,8,9].

In other words, in these prisons, **all** prisoners are considered as most probably having been in contact with anti-TB drugs. This is because Drug Sensitivity Testing is not available. With the advent of MDR-TB treatment, DST should become the standard for all incoming patients in prisons - at least in those parts of the world with high-MDR-TB burden.

3. Prisons are bad for tuberculosis

3.1. Prisons and TB

Prisons of course differ from country to country and the living conditions therein depend on the economic development of the state on the whole. The same holds true for the quality of the medical services they have. This being said, however, even states with adequate resources often do not invest in prison health and neglect the public health issues that flourish inside them. Prisons can be extremely unhealthy places. Prison health services, and particularly in countries with high prevalence rates of TB, are often inadequate. These factors can have disastrous effects on the development and dissemination of contagious diseases such as tuberculosis.

Prisons are not mere receptacles packing together large populations who may or may not be ill, in this case, with tuberculosis. Prisons are dynamic structures, and the factors that make TB hard to manage, and MDR-TB all the more so are many.

- prisons receive tuberculosis;
- prisons concentrate tuberculosis;
- prisons disseminate tuberculosis;
- prisons make tuberculosis worse;
- prisons export tuberculosis.

QUESTION:
In your view, do prisoners receive cases of resistant tuberculosis, including MDR-TB, or is MDR-TB produced inside the prisons?

ANSWER:
In some high-TB burden countries, such as the states of the former USSR, high resistance levels have been found in the general population, but even higher ones, up to 50 times higher, in prisons. On-going studies show that, on the one hand, prisoners with resistant bacilli certainly do enter the prisons, but, on the other hand, all the conditions for creating drug-resistance are also found in the prisons. See following pages for additional comments.

Specific studies are on-going in high-TB burden countries to determine what proportion of prisoners enter the prisons with resistant strains of *Mycobacterium tuberculosis*, and what proportion develop resistance because they receive standardized first-line treatment not taking into account their resistance patterns. These studies on such "amplification of resistance" are being carried out in several countries, all high-TB burden, of the former Soviet Union.

3.2. Prisons receive tuberculosis

Prisoners do not represent a mere cross-section of outside society. Prisoners are overwhelmingly male, in the age range between 15 - 45, and come predominantly from poorly educated and socio-economically deprived sectors of the general population. Offenders often belong to minority or migrant groups. Many live on the margins of society. When they enter prison, it is with a higher risk of ill health than found in the general population. These are often people who with little education, and for a variety of reasons, do not take care of their health. Often living outside in unwholesome settings, they are much more likely to already suffer from many debilitating diseases. Additional health problems such as drug

addiction, and of course alcoholism - rampant in many prisons - can add to a deteriorated state of health.

Tuberculosis is a disease of poverty. Prisoners constitute a high risk groups for tuberculosis, and although impossible to quantify, as relevant entry health statistics are lacking in most countries, many prisoners already bring tuberculosis into prisons.

QUESTION:
Is it usual to have visitors visit prisoners inside the prison in such close direct contact?

ANSWER:
In many developed countries, such a "close contact" visit inside a prison would be inconceivable. However in many other countries, including high-TB burden countries, visitors indeed do enter the cells, and sometimes even the TB wards! All the more reason to ensure TB screening on entry and prompt treatment for all prisoners with contagious TB!

Prisoners should be taught basic hygienic measures. For example, never coughing without covering their mouths and noses. They should be told not to spit on the floor, and instead use recipients for that purpose.

Families should not be allowed to enter wards where there are TB patients who are contagious, unless there is some system effectively protecting them against contagion. Where visits with TB patients in the second phase of treatment are allowed, patients should know about the elementary measures mentioned above. In some countries prisoners – or their family members, or both – may receive masks as a first precautionary measure.

illustration
courtesy ICRC Azerbaijan

3.3. PRISONS CONCENTRATE TUBERCULOSIS

Prisons in developing countries and high-TB burden countries are often overcrowded. Filled way beyond their official "capacity", the overcrowded prisons facilitate the spread of tuberculosis infection. Very often, bad ventilation accompanies overcrowding. This adds to the risk of contagion of the airborne disease. Prisoners are put into cells very often without even a cursory health check. Thus they are often pooled together in unhealthy settings.[10,11]
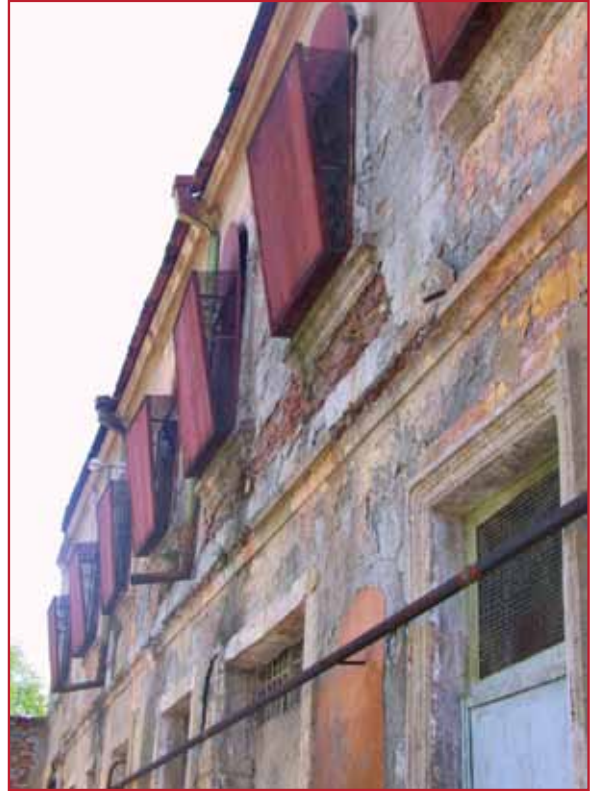
Overcrowding in a prison cell
This may seem to be an extreme case, but such overcrowding is not rare in many countries, some of them high-TB burden countries. Even in less crowded premises, the fact that prisoners are locked up in close proximity for long stretches of time,enhances contagion.

3.4. Prisons disseminate tuberculosis

Closeness and intensity of exposure have been already mentioned as a major risk factor for contagion. International prison rules only require prisoners spend one hour outside their cells (although in balmy climates they may get more). Prisoners thus often spend 23 hours a day in these crowded conditions. Other prisoners, many of them who may already not be in the best of health, can thus contract tuberculosis. Apart from contagion due to proximity and prolonged contact, prisoners often have impaired immunity due to many physical factors, such as concomitant disease, a harsh and unhealthy living environment, and malnutrition. Psychological factors also adversely affect the immune system, such as persistently high levels of stress due to the ever-present uncertainties of prison life, to what is often a very violent environment and the constant nervous tensions of shaky family relationships. All these factors make prisoners more vulnerable to catching and developing tuberculosis disease.

3.5. Prisons make tuberculosis worse

Medical services in prisons are often not as good as those for the general population, sometimes dramatically so. Screening on entry, although often required by law, is many times haphazard or simply not done. Case finding for tuberculosis amongst the prisoner population is at best merely passive. In many prisons, prisoners have difficulties having access to health care. This may be due to various causes. Sometimes prisoner gangs interfere with access from rival groups. Other times prisoners have to pay a "fee" - to guards or other staff - so as to have access, and many may not be able to afford it. Restrictions of access to health care may be further compounded by a health service with staff that are not very motivated, due to poor salaries or lack of any training about tuberculosis.

QUESTION:
Entry screening is essential in prisons, for health problems in general, but particularly for TB. It is done in many prisons. Why is entry screening often not sufficient?
a. Entry screening may not be sufficient because it relies on sufficient number of trained medical staff at all times, which is often not the case in precisely high-TB burden countries.
b. Entry screening may not be sufficient because prisons often offer unhealthy conditions that weaken prisoners' immune systems, allowing TB infection to develop into TB disease.
c. Entry screening may not be sufficient because many prisoners are also at high risk for HIV, or may contract HIV inside the prison, thereby allowing latent TB to manifest itself.

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all three answers are arguably possible, as the situation in the prisons will differ form country to country.

COMMENTS :
TB shouldn't be the menace it is in prisons. However, even in countries with low-TB burden, and with adequately financed prison medical services, the arrival of prisoners from other, high-TB burden, countries is making TB management difficult. The problems are of course much more serious when lack of funds or lack of political will to tackle health issues in prisons are the main problems.

a. Entry screening is often a mandatory requirement (sometimes even by law) in Prison Systems. However, in many countries, often precisely those with high-TB burdens, lack of organization, lack of adequate budgets for prison health, lack of trained staff, or a **combination of all three** result in entry screening being less than optimum. Sometimes it is simply erratic, for example not done at all on weekends, when no trained staff is present, and with no enforceable system for having weekend entries called up for screening later in the week.

b. The combination of unhealthy living conditions, often overcrowded, with bad ventilation, and the many sources of psychological stress in the prison combine over time to weaken prisoners' immune systems. HIV infection will obviously make all this even worse. Therefore, even if entry screening is done on each and every prisoner entering the system, these other health issues need to be addressed, otherwise latent TB infections will inevitably be reactivated, and (contagious) pulmonary TB will spread into the prisoner population.

c. Contracting air-borne TB in prisons is different from contracting HIV, which depends on risky behaviour. TB and HIV both reinforce each other, making management of TB – and hence MDR-TB – much more difficult. Entry screening for HIV is a subject in itself, and cannot be dealt with here. It implies not only public health issues, but also questions of confidentiality and trust. Clinical interviews will often not suffice to detect some of the prisoners who are at risk for being HIV positive. (Nor will testing, because of the "window period". Testing in prisons, on an anonymous basis, has been done in some prisons so as to establish a "base-line" of HIV prevalence. Testing arguably may give prisoners and staff alike a false sense of security as well.) The main point here is that prisoners should be considered as a **population at high-risk** for both TB and HIV: TB screening (entry, passive and active) should therefore be all the more vigilant inside prisons. This is discussed further on.

LATE CASE DETECTION

All these issues may result in late, sometimes very late, diagnosis of the disease among prisoners. In the meantime, symptomatic prisoners spread their bacilli to fellow inmates. Prisoners also may be diagnosed too late in their disease to be cured. Poorly trained health staff may deliver inadequate treatment. Poor treatment may result in failure to cure patients, but still keep them alive, thus prolonging infectiousness, and therefore dangerous to peers and staff alike[10].

Prisoners often do not adhere to prescribed treatments. They may be taking "self-prescribed" erratic treatment or improper doses of drugs. Worse still, prisoners sometimes prefer to resort to "**self-medication**", taking drugs brought in from "black markets" by families or complacent guards. These inadequately and haphazardly treated prisoners may develop **resistant forms of tuberculosis** which they can then spread among their fellow inmates.

In prisons, **passive screening** for tuberculosis (i.e. medical staff simply waiting for prisoners with TB symptoms to "show up" at the medical consultation) may not be sufficient. Prison medical staff (doctors, but also nurses and other para-medical staff) should all be trained to identify TB symptoms. The medical staff should, as far as possible, go into the prison itself, and not just stay in the medical rooms, and be on

the lookout for prisoners with symptoms that could indicate they have (contagious) pulmonary TB. In prisons in high-TB burden countries it may be necessary to carry out **active case finding** for TB. This may involve different procedures, applied in different ways in different prisons. Questionnaires filled out by prisoners **together with the medical staff** may help to detect cases. In other places, Mass Miniature Radiography (**MMR**) may be used to screen every prisoner, thus avoiding the "trap" sometimes encountered in prisons, of guards or other staff demanding a "fee" for access to health care. Prisoners with pathological images on their MMR should of course then be further assessed, clinically and by the taking of sputum for examining by the laboratory.

In **all** cases, sputum microscopy should be the bottom line for diagnosis of contagious pulmonary TB. In the overcrowded and unhealthy prison environment, it is these cases which have high priority for treatment, as they can transmit the disease further to their peers. Chest X-Rays will of course be part of the work up as needed, but in many high-TB burden countries may be not feasible for economic reasons.

In high-TB burden countries, prisoners with pulmonary TB symptoms may already have some form of resistant TB, or even MDR TB. The criteria for Drug Sensitivity Testing (**DST**) on entry will have to be determined together with the NTP, and according to the capacities - in trained staff and lab facilities - of the prison system. If these criteria are met, and financing is available, entry DST should be done for all prisoners in high-TB burden countries.

3.6. Prisons export tuberculosis

Tuberculosis bacilli may not only infect fellow prisoners but also, as has been said, prison staff and families visiting prisoners. When released, those prisoners not diagnosed as having TB, or who have been insufficiently or inadequately treated, may further infect their families and the general community. In many countries, including high-TB burden countries, there is still no proper coordination between **prisons** and the outside **NTP** to ensure continuity of TB treatments started inside the prisons. If resistant strains of TB have developed in the prison, including MDR-TB, these strains will also disseminate into the general community unless there is proper follow-up.

In remand (under trial) prisons, detainees may be incarcerated (also in often unsavory and overcrowded conditions) just long enough to contract the disease, but not long enough to be effectively treated (even if proper treatment is available). Prison health systems are sometimes reluctant to start treatment of what they see as a chronic disease, when detainees may well be released within a short time. This also applies to sentenced prisoner who are diagnosed as having TB shortly before their release date. prisons may be reluctant to initiate treatment, knowing there is no proper follow-up outside.

It is imperative for NTPs to coordinate their work with the prison health systems, to provide them training, and to supervise not only their work, but also the way they collect and interpret data from the prison TB programme.

Uncured TB patient leaving prison

illustration: courtesy ICRC Azerbaijan

The characteristics of tuberculosis make it a disease more difficult to treat in any setting, but prisons are like small factories which receive TB, and – in the absence of an adequately functioning health service – can churn out not only more TB disease, but also MDR-TB.

4. TUBERCULOSIS IS BAD FOR PRISONS

Some of the characteristics of prisons that have a negative impact on TB management have already been mentioned. There are other factors inherent to the disease itself, which make TB a particularly difficult disease to treat in the prison environment. All these factors are clearly exacerbated, and have even graver consequences, if MDR-TB is present.

TB is bad for prisons because the specific treatment of the disease entails certain conditions and considerations that prisons either do not have, or that do not fit in with the realities of prison life. The issue of patient compliance is a major factor here, which prisoners very often have no intention of obeying.

Several types of problems make for these "pitfalls" in the management of TB and MDR-TB:

- Problems related to prisons as a closed and coercive environment
- Problems related to the prisoners themselves
- Specific medical problems encountered
- Social problems regarding health in prisons and allocation of resources

QUESTION:
If one lives in a wealthy industrialized country, why should one worry about TB emergence and treatment in the prisons of developing countries?

ANSWER:
TB had indeed all but "disappeared" in the Western world. However, it has re-emerged with a vengeance in the last decade of the 20th century. In Eastern Europe, TB treatment became erratic and disorganized for a variety of both political and economic reasons in the early nineties, accompanying increasingly dysfunctional health systems in the region. As always a disease of poverty, TB increased significantly in the prisons as well.

In Russia, for example, at the turn of the century it was determined that there were around one million prisoners in the country, and that some ten percent of them suffered from active pulmonary TB. Of those 100 000 patients, a high number (15-20 000? perhaps more) of them will have resistant strains of the TB bacillus, including MDR-TB [10,11]. The actual number is impossible to measure at the present time because of inadequate case-finding and lack of laboratory confirmation of drug sensitivities.

Furthermore, with the advent of HIV, TB is increasing, as it is the major complication of the HIV epidemic. In some countries HIV is rampant, (e.g. Sub Saharan Africa), in other regions (countries of the former Soviet Union) HIV is increasing, in some places slowly, elsewhere very rapidly. For all these reasons, the TB and MDR-TB epidemics are increasing worldwide, and prisons are an important breeding ground for both. Prisoners eventually leave prison, and can and do migrate across borders. The vast number of persons (and former prisoners) moving across borders, looking for work, or for whatever reason, increase the risk of spreading TB and MDR TB.

The treatment of tuberculosis, and a fortiori MDR-TB, implies several requirements that are absolutely necessary to ensure adequate and complete treatment. The prison setting, with its first and highest priority being "security" and the keeping locked up its prisoner population, has many requirements of its own that clash with TB management.

4.1.1. Entry screening

As has been mentioned, prisons often have no efficient health screening of prisoners on entry. While prisoners are being assessed for TB disease, and all the more so when they initiate treatment for infectious TB, they should be in a separate environment where they cannot infect fellow inmates. It would seem that having separate compartments is not a problem in prisons. It must be remembered, though, that prisons are often grossly overcrowded. That, and also inadequate organization of resources, make it often impossible to isolate infectious prisoners during the first month (or sometimes the entire first phase) of treatment. Thus prisoners identified as having TB may still disseminate bacilli amongst fellow prisoners.

Even if separate premises can be allotted to infectious cases, in many prisons, this will often not be enforceable. Countries with high rates of TB are most often those with severe difficulties in maintaining their prison systems. Staff salaries are low. Often guards will allow prisoners to circulate, even in normally "off limits" infectious wards, for a fee of even for a few cigarettes in the worst cases. This underlines the need to identify TB suspects as early as possible and administer treatment as soon as possible to all infectious cases.

4.1.2. Timely diagnosis

Timely diagnosis is thus a major factor in proper management of TB, all the more in the case of MDR-TB. The importance of the laboratory has been mentioned in previous chapters. The need for precise and reliable sputum microscopy and culture results, necessary for TB management, becomes imperative when the issue is MDR-TB. In prisons, quality control for laboratory work should of course be coordinated through the NTP. There should be no question of any outside influence in getting and registering lab results. In some countries, however, field experience has shown that lab technicians and even lab physicians can be coerced into "changing" sputum results, or even DST results, so as to get a specific prisoner onto a TB programme he normally would not warrant entering. This possibility must be kept in the back of the mind so as to ensure strict reliability of all-important lab results for a fruitful programme[13].

Another problem that arises in prisons is **self-medication** by prisoners with drugs brought (or "smuggled") in by their families. Because of delays in getting attention, or inadequate medical services, prisoners may get such erratic treatment from well-meaning families. This is a recipe for creating resistant TB. Timely diagnosis, monitoring and treatment should help eliminate this problem.

4.1.3. Interruptions of treatment.

TB treatment, and all the more so MDR-TB treatment, requires continuity of treatment and supervision. Prisons are notorious for interruptions of treatment. Medication regimes should be adjusted according to antecedents and previous monitoring of the patient's reaction to the drugs taken, and the clinical evolution. In prisons, such continuity is often not possible. Prison regulations often require prisoners to be transferred without warning (so as to avoid any planning of escapes) from one prison to another. Medical staff, even if attentive to this problem, often have either no say or are simply not informed before the prisoner is taken away. This of course leads to interruptions of treatment. Interruptions may take place at any phase of treatment. Often, and this particularly in high-TB burden countries, only selected prisons provide adequate treatment for TB. Transfer to another prison may mean interruption of treatment, or, worse, erratic treatment. In prison systems very often medical files do not follow such transfers.

Even in prisons where TB is treated according to DOTS and with NTP involvement and supervision, prisoners may be transferred either for judicial reasons (for remand detainees: necessities of the on-going inquest or for the needs of the actual trial) or for disciplinary reasons (prisoners sent to a different prison with a harsher regime for having violated the rules). Sometimes it is just prison policy to transfer prisoners from one prison to another as part of security measures, and there may even be transfers without any clear reason evoked at all.

Medical staff should try to ensure that prisoners receiving TB medication stay in the same place for the duration of the treatment. If this is not possible, they should try to ensure continuity of treatment, and have the medical file follow the prisoner to where he goes next.

Commitment to ensuring completion of treatment should imply special considerations for prisoners transferred between prisons. A TB control programme is less complicated when TB patient starts and completes treatment at the same prison. Prison authorities should ensure that a prisoner treated for TB completes at least the initial phase of treatment without transfer between prisons. When a tuberculosis patient in the second (continuation) phase of treatment is transferred to another prison, completion of treatment in the other prison should be guaranteed. These principles apply even more so in a programme treating prisoners with MDR-TB.[10,11]

4.1.4. Punishment cells

Interruptions of treatment can and do occur even within the same prison. Prisoners who transgress prison rules – and many do – are sent to punishment cells. Field experience has shown that medical treatments are often suspended during the time spent in punishment. (This is not necessarily "isolation", as punishment cells are also notoriously overcrowded in many prisons.) Prison authorities should ensure that TB treatment is administered as required even in punishment cells.

It should in addition be noted that when a prisoner's treatment for TB is interrupted, self-medication may further complicate the issue, as prisoners often have access to an internal "black market" of drugs. Self-medication taken may of course not only be inadequate, but may imply low quality or expired drugs. These interruptions of and erratic treatment is a recipe for selecting drug-resistant bacilli. When initiation of MDR-TB treatment is planned, these "loopholes" in the system have to be envisaged. Strict controls should be enforced to ensure no drugs enter the prison system unless fully authorized and controlled by the medical service.

4.1.5. Finding contacts

Prisons may not have an adequate system for case-finding of TB contacts. Medical services are often understaffed, and there is no system for tracking down specific prisoners and making them come to consultation. When there is no adequate control system of prisoner movements within the prison – a not unusual situation in many developing countries, with sometimes mammoth prisoner populations – it may well be impossible for medical staff to track down a specific patient (contact or actually under treatment) if for whatever reason the prisoner in question has no desire to come forward. This has to be taken into account when MDR-TB is the issue, as it becomes even more important to trace all contacts of identified MDR patients.

4.1.6. Prisoner hierarchies

Another issue that often plagues TB programmes in prisons, mainly but not only in developing countries, is the existence of "internal hierarchies" which may to some extent resemble "caste systems". Some prisoners may refuse to be mingled with other prisoners, that they seen as "underdogs". Medical staff may thus find it impossible to segregate patients according to medical criteria, without taking into account these impossible-to-avoid separations. A "Boss" TB patient may thus end up being alone in a cell, while other "lower hierarchy" TB patients may be crowded into a similar sized cell.

Separate cells in a prison Hospital: a prisoner "Boss" may not "agree" to be mixed in with other prisoners. "Low caste" prisoners (here "underdogs") must also be put in cells by themselves. Medical staff are often not in a position to enforce separation based merely on medical grounds, as the custodial staff will "respect" the internal hierarchy to maintain peace and quiet in the prison.

4.1.7. Transfers out – or defaulters?

Prisoners are released after finishing their sentences. If they are on TB treatment this means they need to be followed up at an outside facility, preferably under NTP surveillance. This often does not happen for prisoners. On the one hand, it is often the high-TB burden countries that have the least means for ensuring such follow-up. On the other hand, prisoners released often have given false names and addresses, or have no real home address. They are most often destitute and simply cannot afford to pay for transportation to go and receive treatment or medical supervision. Released prisoners are therefore very often "defaulters" rather than "transfers out" as they have no follow-up of their treatment outside. Merely interrupting treatment (particularly in the second phase) may be less harmful than taking drugs on and off. According to availability and the prisoner's finances, some prisoners may decide to continue "treatment" on their own, with the predictable consequences. In countries where some TB drugs are freely available on the market, and patients have enough money to buy them, this may again be a recipe for creating resistant strains of TB bacilli.

Various control mechanisms and incentives have been introduced to try to get all prisoners released to report for follow-up of treatment at adequate NTP supervised centres. This issue, however, is still a major preoccupation in many countries.

4.2. Problems related to the prisoners themselves

Prisoners are not like patients medical staff are used to handling in the outside world. This is due mainly to the very harsh and violent world inside prisons, which hardens minds and reverses priorities. Education about TB, for example, a key element in any TB programme, may have little or no impact on many prisoners, no matter how well it is delivered. Prisoners have their own priorities, such as their families, often in need of financial support. Violence in prisons is rampant, and such issues as drug debts or gambling debts are taken very seriously, as not to do so can be dangerous. In the poorest countries, just survival inside what has been called the "prison jungle" takes priority over everything else.

In these circumstances, lecturing prisoners about the need for continuity and non-interruption of treatment, for what amounts to "public health" reasons, will most often fall on deaf ears. Of course education should not be abandoned. Whenever possible, posters and flyers informing prisoners about TB and MDR-TB should use illustrations depicting familiar "prison situations", rather than outside ones that may not have any meaning for prisoners.

4.2.1. Drug hoarding

Many prisoners are **notorious** for not taking their prescribed medicines, once the first weeks have passed, and they feel better. They may want to "save" them for a variety of reasons. Medicines and particularly medicines with a reputation for being "strong", such as Rifampicin, have a "market value" inside prisons. (In some countries guards have been known to be eager to get Rifampicin tablets to cure VD. Prisoners may decide thus to not swallow certain tablets so as to sell them, or otherwise use them as "currency". For paying drug debts for example. Others may want to hoard the tablets so as to pay back gambling debts they have contracted in prison. Or they may want to smuggle TB drugs out for their family, not realizing that this is the worse possible thing they could do. Some may simply want to have drugs – which always have a "cash value" in prisons – saved up for " a rainy day".

When prisoners want to hide tablets and "hoard" them, they devise various tactics to escape cursory observation. Sleight of hand may fool health staff who are not knowledgeable about such practices. pris-

oners also use the old trick of creating a minor disturbance, thereby having plenty of leisure to hide or pass on the desired tablets, while pretending to have swallowed them.

Medical staff who supervise TB treatment need to be aware of this, and at all times attentive. Field experience has shown that it is best to have two health staff to ensure compliance. In addition, this may mean, for the most unruly prisoners, observing them very carefully, and introducing extra precautions such as directly inspecting the mouth, after the tablet is (supposedly) swallowed. Making the patient talk, after swallowing a glass of water with the tablets is another way to control actual compliance.

Tablets which combine two or more drugs reduce the number of tablets to supervise. Combination tablets would seem to be less attractive to many prisoners than single drug ones for reasons that are not clear.

In a different scenario, prisoners may decide to stop treatment for other reasons. It may be that prisoners stop their treatment because it is fraught with secondary effects. Rather than openly declare themselves defaulters, they may simply throw away the tablets.

Whatever the reason, it is imperative that TB treatments be administered by **D.O.T.** – directly observed treatment. In prisons, strict and individual monitoring of drug intake is absolutely necessary. Compliance never should be taken for granted in a prison environment.

> *Directly observed tablet swallowing is a must in prisons.*

It has been mentioned elsewhere in this course that "watching a patient swallow tablets, in a way that is sensitive and supportive" is a necessary component of TB treatment. In prisons, such supervision needs to be sensitively but **convincingly** enforced, its efficiency being the priority. Not all prisoners will try to deceive the medical staff, but some will and if the staff is not attentive to this, many will succeed.

If taking the full treatment regime is already imperative for "normal" tuberculosis, this becomes even more critical when treatment of MDR-TB is the issue. The argument that prisoners who are dying will be more disciplined, and will take their medicines may be true for many MDR patients. However, the realities of prison life create situations where this is all but certain. Even an MDR prisoner, accustomed to enduring violence and peer coercion, may choose to sell his "new" (second-line) drugs for any of the reasons already mentioned.

Finally, many prisoners suffering from MDR-TB, may already have undergone several bouts of (first-line) DOTS treatment, and have suffered from secondary effects of the different drugs. Prisoners have a much higher rate of liver problems, including hepatitis B and C, than the general population. They may therefore find it much more difficult to accept new and possibly more severe secondary effects from a much longer bout of second-line drugs, and may try to avoid taking them.

> *In prisons more than outside, inadequate supervision of treatment can lead*
> *to erratic drug treatment, facilitating the development of drug-resistant bacilli.*

4.2.2. "Sputum cheating"

There is another pitfall regarding TB management, occurring in prisons, which has been recorded on all continents. It can be called "sputum cheating". This term refers to practices intended to substitute someone else's (generally AFB positive) sputum for one's own. Sputum cheating can be done to "get on" to a TB programme, even if a prisoner does not has TB. Much more often, it is practiced by patients who are finishing their treatment, and who want to "stay on" the programme at all costs.

To understand this phenomenon it must be understood that prisons in developing countries, with high-TB burdens, often are prisons that have bad living conditions, in some cases extremely bad ones. In such prisons, the attraction of the prison hospital setting – and specifically the TB programme – al-

though it may objectively be bleak compared to "normal" standards, may be quite strong. Conditions in the prison hospital may be seen as "lavish", as prisoners on TB treatment get better food than other prisoners. TB patients are also not required to work. Security is often lax in prison hospitals. Living conditions are better, and patients get "free drugs". Finally, once the first phase of treatment is over, family visits may be an additional "luxury".

For all these reasons, prisoners on TB treatment - whether or not they actually comply with the treatment - may desperately want to stay in the hospital after the end of their treatment. To this end, such prisoners try to "fake" their sputum control results. They obtain "positive" sputum from a prison newcomer, with AFB positive sputum, and try to give that "positive sputum" for the control test instead of their own (most probably negative) sputum. If "sputum cheating" is not detected, the prisoner will stay on and continue getting the perceived advantages in the hospital ward, instead of being sent back to his original prison.

An adequate diet is essential for TB treatment. TB programmes should include high-energy foods and extra protein. A proper food ration is not only nutritious but also makes it easier for patients to sallow their many tablets. In prisons, food rations are often inadequate and food preparation can be quite unsatisfactory. Prisoners around the world complain, rightly or wrongly, about the food in prison. Food sometimes acquires almost a "mythical" importance. Stealing food inside a prison can lead to severe reprisals between prisoners, even death. It is thus easy to comprehend why the "attraction" of hospital food can be one of the factors "tempting" some prisoners to try to "stay on" in the TB programme.

Obviously the decision to declare a patient cured (or not) never depends solely on a laboratory test, but also on the clinical development of the case. However, in prisons, medical supervision is less rigorous than in a civilian hospital, and thus "faked" laboratory tests can wrongly influence the clinical decision. These "sputum cheaters" use a variety of deceptions to fake their results. The oldest trick is of course to send the newcomer to deliver the sputum instead of the prisoner reaching the end of treatment. Although this may seem a fairly obvious ruse to detect, prisons are often very disorganized, and wily prisoners take advantage of changes of staff to try to "cheat". This is solved by having, for example, photographs of each prisoner in the medical files.

Another common way of trying to cheat the system is coming in with someone else's (positive) sputum in the mouth, under the tongue, and delivering it into the goblet as one's own. This can be easily thwarted by having prisoners wash not only their hands (another hiding place) but also having them rinse their mouths thoroughly before giving sputum.

Some prisoners "cheat" on their sputum test to "GET IN" to a TB programme, giving "positive" sputum from someone else – whereas they do not have TB – because the TB programme is seen as advantageous. Others – who have been cured, "cheat" on their sputum test by giving someone else's "positive" sputum, so as to "STAY ON" in the programme, for the same.

ANSWER:
These are examples of how prisoners have tried to "cheat" on their sputum takes. The examples are taken from TB programmes in countries of Latin America, of the former Soviet Union, Europe and Asia. (These are just some examples: prisoners can be very ingenious!)

a. Hiding "positive" sputum, from a prisoner just having arrived in hospital, known to be AFB positive, inside their mouths, and faking as convincingly as possible the "coughing" process.
b. Hiding "positive" sputum inside their hands, or between index and middle finger clenched onto the hand.
c. Trying to smuggle in a small syringe containing "positive" sputum, and by sleight of hand injecting it into the sputum cup.
d. Hiding "positive" sputum inside the hollowed out filter of a cigarette, which is "innocently" smoked (the sputum being "puffed out" of the filter) before the sputum take (and after having been made to rinse out the mouth).
e. One prisoner with a hollow tooth used it to hide "positive" sputum. It was quite easy to stop up the hollow tooth with the tongue so the mouth rinse would be ineffective. He was caught by a very attentive nurse directly observing the sputum take.
f. "Dry positive sputum" can even be a source of internal trade inside the prison! (In some prisons it can be a minor "industry"). Dry sputum is concealed under the nails and deftly put into the cup. Of course dry sputum can often clump up and is detected by the laboratory.

4.2.3. TB - Health Education in Prisons

Prison administrations should understand that they are responsible for ensuring environmental control and that they have to protect the health of their medical and security staff. Very often prison administrations consider that the management of TB is purely a medical issue and rely completely on their medical staff.

Guards play a crucial role in detecting and referring prisoners to medical services and need to understand that the best way to protect themselves is to help prisoners with TB symptoms obtain early diagnosis and treatment. Guards also must be aware about the dangers of self-medication and not let in non-prescribed TB drugs.

When prisoners first enter the prison system, they often cannot be bothered with health information. They are stressed, want to see their lawyer, have family issues and arguably have many other worries. Providing information on TB has to be an integral part of the medical procedures already in place, such as medical screenings (but not necessarily on entry). It is crucial that medical staff provide correct information to prisoners on TB, and give clear explanations in simple language on early signs and symptoms of the disease. Information on diagnostic and treatment services available in the prison needs to be given and explained. Prisoners should also receive a simple leaflet explaining basic facts about TB and health services available.

Posters with key information on TB transmission, "coughing and spitting hygiene", importance of ventilation and sunlight and early signs and symptoms of disease should be placed in key communal areas. Information material can be developed and produced with the aid of "outside" NGOs for example, thus providing outside credibility on medical issues. Innovative ways of providing information can be developed: theatrical sketches, videos, all preferably in a participatory way. Prisoners with drawing skills can

be encouraged to mke illustrations for brochures, posters and health education materials. Developing peer education for prisoners is not easy. Due to internal hierarchy systems, not all prisoners are respected by the others. In some contexts, prisoners who behave well and help provide such health peer education material may even receive "credit" for early release consideration.

The pitfalls of any Health Education Programme is that the information therein can be misused by some of the prisoners. Some may use it to "simulate" TB symptoms for referral to a TB treatment facility, or to "stay on" (after treatment) in a TB prison hospital. These facilities, as has been said, often may have better living conditions than their usual prison. TB information for prisoners should not provide detailed information on treatment, medicines and dosages used, as in some countries, prisoners may try to obtain drugs, through family visits or by paying off the guards, for self-medication.

As has been stated, many prisoners are experts at "cheating" and fooling prison staff. It becomes a "sport" to develop new ways to "cheat the system". Health education should therefore also be very explicit about the dangers of not taking full treatment, "sputum cheating", and erratic treatments.

In the past, one had only to deal with drug-sensitive TB strains. Today poly and multi drug resistant strains are increasing everywhere. This complicates treatment and the overall management of TB in prisons. Prisoners need to understand why they suddenly have to be accommodated and kept apart from their fellow inmates. An example of themes that need to be explained in simple terms:

- The difference between the first and second phases of the treatment.
- What if sputum examination results are negative, but the prisoner is still ill?
- End of treatment: information on follow up and healthy life style.
- Information for families and visitors of TB patients concerning contagion, and the dangers of self-medication.

4.2.4. Importance of the laboratory

Laboratory tests are crucial in the evaluation of TB programmes. It is readily appreciated how "sputum cheating" can make cohort analysis difficult and erroneous. Regarding MDR-TB, very obviously lab tests alone never replace clinical decisions, and extra rigor in supervision should prevent this type of trickery. However, the very real and widespread phenomenon of "sputum cheating" in prisons should recall to all health staff that prisoners can and should be expected to "bend the rules". Vigilance is therefore imperative at all times and for all procedures.

"Sputum cheating" itself should be less of an issue for MDR-TB patients, as even in the worst prisons it is hard to imagine prisoners wanting to remain on an MDR ward, which is seen as something of a "death row", but vigilance is recommended at all times so as to guarantee accuracy of the results obtained.

4.2.5. Sputum collecting "cubicle" inside a prison.

Sputum collection in prisons should ideally always be taken outdoors. This may be impossible in cold climates, but there should at least be a well-ventilated area for the procedure, or a closed cubicle as the one shown above. Prison medical staff need to be constantly told about the need to take individual respiratory precautions so as to avoid getting infected. Prison staff are notorious for misusing respiratory protection. Many of them either refuse to use anything at all, particularly (!) in high-TB burden situations, alleging they have been in contact with such patients for years. Others use surgical paper masks which provide inefficient pro-

Note the cubicle opens toward the exterior by a window, but is closed towards the corridor. This sputum can be taken safely, without having prisoners go outside in very cold weather.

tection. Inversely, when correct respirators are used, medical staff often wear them in settings where they are irrelevant, such as outdoors in the courtyard.

As has been said, direct microscopy cannot distinguish between drug susceptible and drug resistant forms of the TB bacillus, nor between "viable" and "non-viable" bacilli., There are also different species of Mycobacteria that cannot be distinguished by a simple Ziehl-Neelsen. The Smegmatis strain of Mycobacteria has been known to be substituted for *M. Tuberculosis*, with the same aim of "cheating" the laboratory.

To summarize, in many prisons around the world, strict precautions have had to be implemented to avoid "sputum cheating", such as strict identity control, and making the patient wash hands and rinse out mouth before giving any sputum. Directly observed taking of sputum, preferably by two nurses; and not allowing the prisoner to smoke a cigarette before producing a sputum sample.

masks used for sputum taking

*Experience has shown that many prisoners who have been cured try to "stay on" in the TB programme, so as to receive the benefits of better food and lodgings. This has even resulted in prison "**trafficking**" of "fresh" or "dry" positive sputum, which has become a **clandestine trade** in some prisons. For these reasons, it is essential that all health staff working in prison TB programmes know about these various practices.*

DOT is absolutely necessary in Prisons

4.2.6. Other issues: side effects of medical treatment

Side effects of the drugs used in TB treatment have to be clearly explained to prisoners under treatment. This is obviously even more important in treating MDR TB with a combination of first and second line drugs.

Prisoners may be discouraged from these side effects and refuse to continue their treatment. Medical staff should explain to them, in terms they understand, the different reactions they will have, and how to best cope with them. Prisoners should understand the need to resume treatment with the drugs they had to stop, as part of the treatment. Medical staff should not assume that cursory explanations given just once will necessarily work on patients who are often difficult, and often have a tendency to mistrust all staff they see as "working for the prison system".

The TB posters below, made specifically for prisoners explain in pictures how side effects come and go, and the necessity to resume and complete the treatment regimens.

4.2.7. Side effects of treatment

These must be duly explained to the patient, in simple language they can understand. It is essential that the medical staff be trained in this sense, otherwise prisoners will simply stop taking their medicines – and not necessarily inform the staff about this.

Side effects like rashes do occur, but they go away, and treatment should be resumed. It is most important that prisoners are informed about these different side-effects.

illustration courtesy ICRC Azerbaijan

Monitoring and management of drug side effects is essential for proper adherence to treatment. Unruly patients are more likely to be found among prisoners who are disillusioned or even cynical about their treatment, and who often have little in life to look forward to. As mentioned above, education on the public health effects of erratic treatment is often seen as irrelevant by prisoners, in the light of their much more immediate prison-related worries.

If the terms of "primary" and "acquired" resistance have been abandoned, and substituted by the notions of "new" TB patients and "previously treated patients", in prisons this difference may be very difficult to determine. This is particularly true in high-TB burden countries. It is often impossible to determine who is new and who is not. Prisoners come into the prison system most often without any medical records. They may give a false answer according to what they perceive at that moment in time to be in their "best interests". This means that a prisoner may ascertain he is a "new" patient, but this is not necessarily true. In some TB programmes in these countries, everyone is considered as having had some form of TB treatment.

The old sense of "acquired" resistance can have a particularly sinister meaning in high-TB burden countries. The administration of a standard short-course first-line regime of treatment to a patient who is already mono or bi-resistant (even without necessarily being MDR) can lead to amplification of resistance. This has been documented in TB programmes in prisons of the countries of the former Soviet Union, and is a serious on-going concern[15].

For these reasons, MDR-TB testing may indeed be warranted in even supposedly "new" cases among prisoners in those countries with high rates of TB and MDR-TB.

Some medical complications are much more common among prisoners than in the general community. Concomitant conditions such as liver disease are rampant in prisons, particularly with the high number of Intra Venous Drug Users (IVDUs) and with the high rates of hepatitis (particularly B and C) found in prisoner populations. Drug and alcohol abuse is also widespread among prisoners.

- The very conditions that lead to high TB rates in prisons may also lead to development of drug resistant TB and MDR-TB.
- Incoming prisoners may also bring in drug-resistance with them, especially if they have been in prison before or in settings with poorly supervised civilian programs. This is a major problem, for example, in many countries of the former Soviet Union.
- Specific medical challenges posed by the treatment of MDR-TB in prisons:
  - extremely long duration of therapy (24 months!);
  - worse side effects with second-line drugs;
  - a much more challenging monitoring schedule;
  - need for Drug Sensitivity Testing – which is more difficult for second-line drugs;
  - need for even closer links to the civilian programmes.[2,9,11]

4.3.1. HIV

The additional burden of HIV on TB and MDR-TB is extensively described in previous chapters. The HIV / AIDS situation in prisons varies greatly from country to country. IVDU may be a major factor in some, and practically inexistent in others. Sexual practices of "men having sex with other men" (MSM) are often taboo, illegal, severely sanctioned in prisons or a combination of the three in many countries. In others, on the contrary, there may be syringe and needle exchange programmes and distribution of condoms. The daily conditions of prison life may promote the transmission of HIV infection[14]. Prison conditions therefore can promote tuberculosis transmission directly and indirectly through facilitating HIV transmission. A high prevalence of HIV will complicate TB management and particularly MDR-TB treatment.[17]

Sources of HIV in prisons:

- **Intra venous drug use**
- **Men having Sex with Men**
- **Tattooing**

In prisons as well as outside, all HIV positive prisoners with signs and symptoms of tuberculosis, should be screened for TB and possible MDR-TB.

Prisoners symptomatic for respiratory disease, but with consistently negative sputum for TB, could be HIV positive, and should be considered for HIV counselling and testing. In a different light, such prisoners could also be suffering from a different pulmonary disease. Paradoxically, such symptomatic, sputum negative prisoners are often put on (first-line) TB treatment without a clear diagnosis of TB! They should instead be given a trial treatment with a broad spectrum antibiotic that is not active against TB, so as not to squander TB drugs.

The many more extra-pulmonary cases of TB in prisons with the advent of HIV are sometimes difficult to fully document in prisons that have insufficient funds and equipment for a full hospital work-up. This sometimes leads to the inadequate prescription of TB drugs. Or inversely it may lead to misdiagnosis of extra-pulmonary TB.

Any recommendations about the specificities of the prison setting regarding MDR-TB treatment together with Anti Retro Viral (ARV) treatment would be premature, as these "dual" treatments are not yet widespread in high-TB burden countries. ARV treatment in prisons is still an exception in most prison systems where TB and MDR-TB are highly prevalent. However, the many precautions that have been recommended regarding TB and MDR-TB treatment, so as to ensure reliability of results and adherence to full-treatment, are equally relevant – and perhaps even more so – regarding HIV.

With certain treatment regimes, even short interruptions of HIV treatment can lead to resistant strains of HIV. Many prisoners, as has been stated, can be unruly and undisciplined patients, ready to "trick the system" for any perceived personal benefit. This same attitude could have disastrous effects with HIV treatments taken nonchalantly. The recommendation here is to carefully consider all factors, and particularly the presence of reliable, fully trained and competent medical staff, knowledgeable about prisons and prisoners, before attempting to combine MDR-TB and HIV treatments in prisons. The already often major difficulties with adherence to high numbers of tablets for TB (let alone MDR-TB!) treatment will be exacerbated by the addition of ARV therapy. Furthermore, side effects of treatment for HIV, added to those from the anti-TB drugs can be a serious problem, and need careful and competent management. Unfortunately, prison medical staff in many countries receive little or no training on these issues.

There should certainly be a careful calculation of risks and benefits before initiating appropriate ARV therapy in prisons.

4.4. Social problems concerning health in prisons and allocation of resources

Prisons are often on the very bottom of the list for government funding, if indeed they are even on the list. As mentioned before, prisons are very often seen not as priorities for health, but as additional burdens that no one, and often least of all the Health Ministry, wants responsibility for.

In the case of TB and MDR-TB, political commitment is obviously the number one priority, and thus funding should be forthcoming. NTPs, previously excluded from, or uninterested in, prisons for many years, are finally realizing that they simply **cannot** neglect the prisons if they are serious about tackling TB. Treating MDR-TB in the general population without treating the reservoir of MDR patients in the prisons is no longer considered effective or ethical.

5. IN CONCLUSION:

The pitfalls of TB management in prisons, are many. It is essential that prison health staff know about them, so as to ensure adequate treatment of the disease and prevent the development of drug-resistant TB bacilli.[16] These pitfalls apply even more to an MDR-TB context in prisons. Experience has shown that TB specialists who have never worked in prisons simply do not realize the many specific difficulties involved. It is for this reason that this chapter specifically on prisons has been written.

The basic DOTS strategy and the additional components for dealing with MDR-TB have to be agreed upon by all parties before beginning to treat MDR-TB in prisons. Political will and commitment are as necessary for prisons as for the outside world – perhaps even more so. The required training and supervision of medical staff, and the rigorous monitoring of all aspects of MDR-TB treatment and case management are particularly challenging in the prison context. In a programme for the treatment of MDR-TB, there is no place for erratic treatments and irregular compliance due to a malfunctioning prison medical system, or to lack of knowledge by medical staff of the many pitfalls.

Close coordination with the civilian NTP, with targeted social support, should help to ensure that all prisoners having left prison before completion of treatment, receive proper guidance so as to complete treatment and post-treatment supervision once outside. This is true for TB in general, but **all the more important with the advent of resistant forms of Tb and with MDR-TB.**
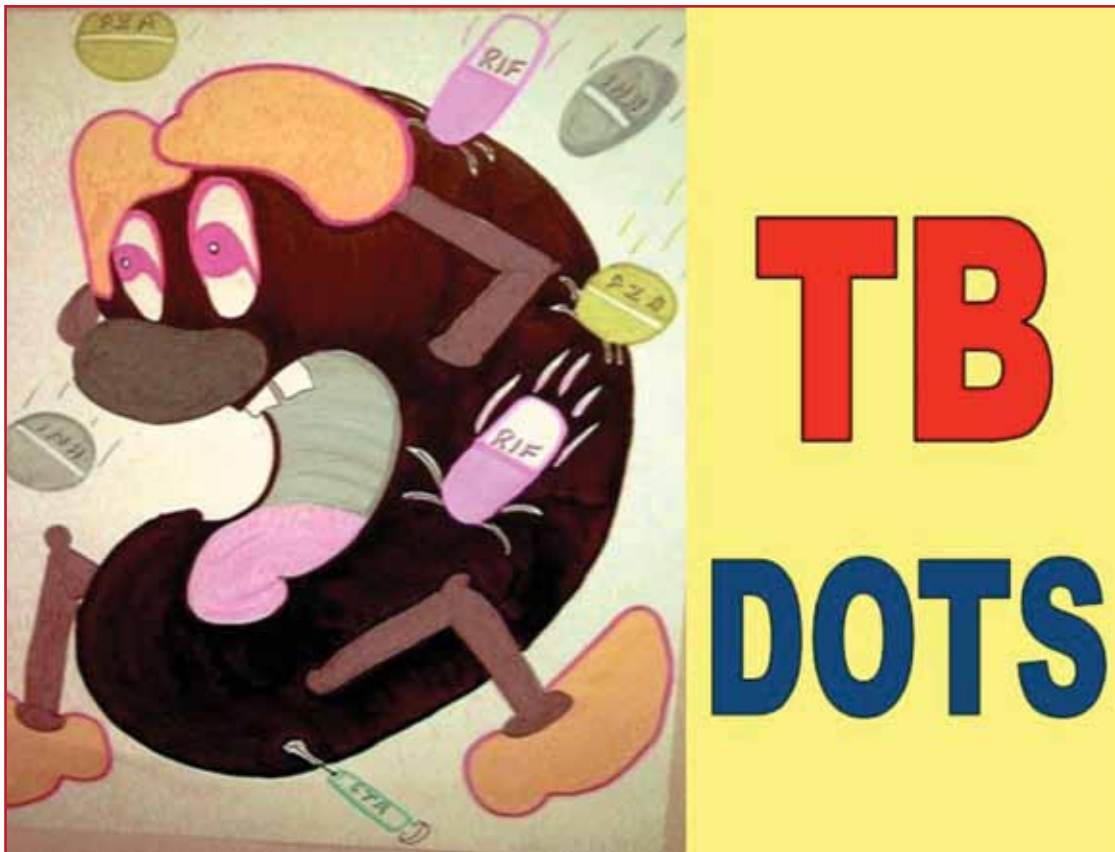
Self Assessment Questions and Exercises:
Tuberculosis and MDR-TB in prisons

1. Taking into account what you have learned, which of the following statements are most probably true regarding TB in prisons ?

a) Prisoners are at high risk for many diseases. TB prevalence in a prison is higher than outside.
b) A TB epidemic can develop in prisons because they are often very overcrowded.
c) Prisoners can avoid catching TB to a certain extent by staying outside in the courtyard as long as possible.
d) Prisons can reduce the risk for TB by having adequate ventilation, with large windows.
e) Prisoners entering a prison suspected of having TB should be isolated.
f) Prisoners under TB treatment should not be allowed to see their families, to avoid contagion.

2. Prisons obviously have a custodial role. However, in many countries they serve to keep the socially deprived, the marginalized, the problematic social groups of society, "away from society". To say these social groups are "dumped" there in some countries would not be politically correct, but would sadly be close to reality. This is all the more worrisome in high-TB burden countries. In which ways does this influence the prevalence of TB in prisons?

a) Prisoners come from those marginal groups which do not care about their health, or have no knowledge about health issues, or who cannot care because they have no economic means to do so.
b) Illicit drug use is a major problem outside, and it is not surprising that it creates health problems inside prisons. This leads to HIV transmission and worsens the TB situation in the prison.
c) Overcrowding is due to the rise in criminality, and may negatively influence prisoners' health, but this can't be helped other than by building new prisons.
d) Prisoners are too demanding – if they follow their prescribed treatment for TB there shouldn't be any problems, and certainly MDR TB would not develop if there was more discipline.

3. Timely diagnosis of TB is particularly important for prisoners because:
a) They can then be put in isolation until it is possible to treat them.
b) Prisoners with pulmonary TB will be contagious for others in an often overcrowded setting, making contagion easier.
c) Prisoners with active pulmonary TB may try to "sell" their sputum to prisoners who do not have TB, who want to try to get medical attention.
d) If prisoners with pulmonary TB are not treated by the prison medical service, they cannot get any other treatment.

4. A prisoner sent to the punishment cell for misbehaviour is no longer receiving his TB treatment (first phase). What action should the prison medical staff take?
a) Insist the patient be immediately brought back to the hospital ward where he was, so as to continue correct treatment.
b) Give the treatment to the punishment sector guards, with explanations of what to take and when, so they can give the treatment to the prisoner.
c) Request permission from the prison Director to have the punished prisoner personally receive the medicines he needs to take for the duration of his punishment. He has been told how to take them already by the medical staff.
d) Have someone from the medical service go to the punishment cell daily to deliver the drugs to the guard responsible, who will give them to the prisoner.
e) Any of the above could be applicable
f) None of the above.

5. Should patients with resistant forms of TB, and particularly MDR TB be treated while in prison, if one is not sure that they can complete the (much longer) treatment once outside? Isn't there a chance they will leave prison (finish their sentence, or benefit from an amnesty) before they complete their treatment?

2:

a) This statement is unfortunately often true, in developing countries as well as in developed countries! The positive side is that prison may be a unique occasion to teach prisoners about vital health issues, such as TB and also HIV / AIDS! Obviously some may not care to learn, and will always try to cheat the system. However, many are willing to learn and will profit from any health education they can get.

b) Absolutely true. Different countries have different drug problems. Intra venous drug use (IVDU) is the major risk for HIV. In some countries, drugs are also used, but smoked rather than injected. This can also increase sexually transmitted diseases and HIV among them, as prisoners who are "high" can forget about sexual transmission. They forget to use the condoms they would normally use, and have unprotected sexual contacts. This issue of sexual contacts in prison is a vast topic, and cannot be dealt with extensively here. What is clear is that these contacts are certainly not exclusively "between homosexuals", as many prison authorities believe or would have us believe. Sexual contacts in prisons are about power, and are usually a taboo subject ..

c) Overcrowding is responsible for transmission of TB, but building prisons does not solve the problem. Experience has shown that most often, the new prison is simply filled up with additional prisoners, and not used to manage the overcrowding. To diminish transmission of TB, it is necessary to tackle the problem from all angles. Getting the NTP to work actively together with the prison health staff is the most important one. Higher authorities should be influenced to do all they can to take measures to diminish the overcrowding, such as speeding up judicial procedures, and introducing alternative punishments instead of prison sentences.

d) Prisoners certainly can be demanding, and there is no room for being naïve about demands that may be unreasonable. As has been noted, prisoners are not supposed to catch TB – or worse, MDR TB – as part of their prison sentence. Adequate treatment should therefore be provided to any and all prisoners with TB, and all measures taken to decrease the risk of catching TB in prison. This being said, sometimes prisoners are not compliant or do not cooperate with the medical staff in taking their treatment as they should. This issue is taken up in the following chapter.

3:

Correct answers are b and c.

Comments if you answered a or d:

a) Prisoners identified as having pulmonary TB can be placed in a separated ward to receive the first weeks (or the full first phase) of treatment. This does not imply isolation as in solitary confinement. Prisoners needing treatment should get it as soon as possible to diminish the risk of contagion to other persons. Because treatment involves supervision and other measures as well, including a special nutritious diet, prisoners under treatment are often kept apart from the others so as to avoid problems such as bartering of food, and also to better supervise all aspects of the treatment.

d) Unfortunately, prisoners can and sometimes do get drugs from other sources. They may get them from their well-meaning families during visits. Self-medication is of course not allowed, but can occur undetected in prisons. It can lead to interruptions of the proper treatment administered by the medical service, and of course to the creating of resistant strains of *Mycobacterium tuberculosis*.

4:

Correct answer is d. Is the only possible solution.

a) In most prisons this will be unrealistic. Prison discipline will vary from prison to prison and obviously from country to country. While there is of course a strong argument for not interrupting a prisoner's TB treatment, the medical staff will usually never be in a position to cut short a prisoner's punishment. Nor should they be. If medical staff are seen by prisoners as having influence in disciplinary matters, some prisoners will may try to abuse the system and get themselves out of punishments by putting pressure on them.

b) As a matter of principle, guards should not administer medical treatment to prisoners – this should only be done by medical staff. Furthermore, field experience has shown that in many developing countries, many of them with high-TB burdens, prison guards, habitually poorly paid and often not very motivated, may not administer the drugs at all, or may give them only in exchange for payment of some kind. This type of situation is to be avoided at all costs. As a final point, such a "solution" as this one would leave the patient without any medical supervision.

c) In prisons even more so than elsewhere, TB treatment must be directly observed. There should be no question of a prisoner receiving the drugs, even if he does "know how to take them". First of all, prison rules most often prohibit prisoners from having drugs in their possession. (Among other issues, there is always the possibility that a prisoner will try a suicide attempt – real or not – and take all the pills at once.) Second, TB treatment cannot and should not be left up to the patient him/herself.

d) This could be a possible solution in some countries, particularly where there are sufficient medical or para-medical staff – and few prisoners. It is however not practical in most countries where TB is a real problem. Even if there are not many such cases of TB patients getting sent for punishment, it may not be practical to have someone from the staff go every day – and according to the scheme used, even several times a day – to the punishment quarters. Thus, there will be a serious problem if a TB patient, particularly in the first phase of treatment, is sent to spend a time in the punishment cell.

This issue should be discussed beforehand, between the medical service and the Director of the prison. Perhaps there is a way that a prisoner under treatment can be given a "suspended" punishment – that he will do cell time after he has finished treatment. If this is impossible, some arrangement can perhaps be made to **facilitate** as much as possible for someone from the medical staff to administer the treatment directly. This means that the medical staff have access to the punishment cells without the hassle and security restraints that usually hinder movements to those sectors. It is essential that the Direction of the prison know **why** TB treatment needs to be continued. Interruption of treatment is not an option and certainly not part of the punishment.

Interruptions of treatments also happen when prisoners are transferred from one prison to another, for judicial reasons, and sometimes also for disciplinary reasons. (A prisoner in a "light regime" prison who contravenes the prison rules may, for example, be sent to a high-security or a strict-regime prison.) If a TB patient is so transferred to a different prison, which does not have the medical facilities for administering and monitoring adequate treatment, this will make the patient a defaulter. This is detrimental for his treatment. In many developing countries, some of them with high-TB burdens, all prisons do not have adequately trained medical staff, and many are not equipped for proper TB treatment.

5:

There is indeed no easy answer here, and it will of course depend on what the National TB Programme has implemented in the country. This being said, there are several considerations that relate directly to the prison setting.

Prisoners with MDR TB (if indeed they have been identified as such) are usually kept in cells or wards separated from other prisoners. Some countries will not have second-line treatment; others will still be in initial the process of implementing the strategies as recommended by WHO for treating MDR TB. For prisoners, the main issue is to treat the source of resistant strains of *Mycobacterium tuberculosis*. We know that watertight segregation of contagious patients in prisons may not be possible, particularly in those very countries where there are most prisoners with MDR TB. Thus there is a need to treat them as soon as possible, so as to eliminate the source of MDR TB infection. The best strategy has to be determined together with the NTP.

In a situation where there is treatment for MDR TB in prisons, and a prisoner with MDR TB finishes his or her sentence before the end of treatment, all arrangements should be made so that the treatment can be continued outside. This should preferably be within NTP approved settings. There is no clear one-size-fits-all solution for getting ex-prisoners to comply with such external treatment and monitoring. Incentives, such as a warm meal, at the NTP may be an option – but there may be no budget for that. Reimbursement of transport money may also help. It has even been suggested to try to get hold of ex-prisoners at the Police Stations or other such places where they have to show up on a regular basis as part of their release arrangement or parole.

Whatever the strategy chosen, it should be taken into account that the only way to stop further dissemination of MDR TB is to cure those prisoners who have it. The risk that a small number may indeed "default" and never show up for the rest of the treatment may be a risk that has to be taken. Not giving them treatment because they will leave the prison before finishing the full scheme cannot be an option. They will leave the prison anyway, and if not treated will **surely** disseminate MDR TB. All this is of course for the NTP and the Prison Medical Service to determine. It may well be the case that some ex-prisoners default on their follow-up treatment, going back to their respective villages. They will however disseminate less resistant bacilli than they ever did within the prison, with its overcrowding and poorly ventilated cells.

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