NATIONAL GUIDELINES

FOR PROGRAMMATIC MANAGEMENT OF DRUG RESISTANT TUBERCULOSIS



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# Preface

Tuberculosis is one of the most prevalent diseases and serious public health problem in Iraq. Currently 16000 population in Iraq has TB of which 400 cases are diagnosed to have MDR/XDR- TB. The World Health Organization (WHO) has expressed concern over the emergence of the drug resistance TB and is calling for measures to address the problem. Conforming to the WHO objective to control MDR-TB, NTP Iraq is working aggressively to control the spread of MDR-TB. One of the steps taken by NTP Iraq in this process is the preparation of “National Guidelines management of MDR-TB”. The intent is to provide guidance to the Physicians and other health care staff, involved in the management of Drug-Resistance Tuberculosis (DR-TB) in Iraq. Its content is based on the latest views of the WHO guidelines for the management of DR-TB. The Guideline provides practical instructions on management of DR-TB as well as the national policies for DR-TB control in Iraq which need to be followed by health care workers involved in the management of DR-TB.

The National Tuberculosis Control Program in Iraq is pleased to present the first edition of the Drug Resistance Tuberculosis Control Guidelines and would like to wish you every possible success in your efforts to provide the very best for our country and our community.

# 

# Acknowledgement

The preparation of 'MDR Guidelines' was coordinated by Ministry of Health (MOH) Iraq in collaboration with The World Health Organization (WHO), Iraq Office and National Tuberculosis Program (NTP) Iraq with contributions from several experts in the field.

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# Abbreviations

|  |  |
| --- | --- |
| **ACSM** | Advocacy, Communication & Social Mobilization |
| **AFB** | Acid Fast Bacilli |
| **AIDS** | Acquired Immune Deficiency Syndrome |
| **AKJ** | Azad Kashmir Jammu |
| **ART** | Anti-Retroviral Therapy |
| **ARV** | Anti-Retro Virals |
| **ATT** | Anti TB Treatment |
| **BMU** | Basic Management Unit |
| **BSL** | Bio Safety Level |
| **CBC** | Complete Blood Count |
| **CDC** | Centers for Disease Control and Prevention |
| **CHW** | Community Health Worker |
| **CPT** | Co-trimoxazole Preventive Therapy |
| **CB-TBC** | Community-based TB Care |
| **CHBCC** | Community and Hospital Based Care Center |
| **CXR** | Chest X-Ray |
| **DOH** | Department of Health |
| **DOT** | Directly Observed Treatment |
| **DOTS** | Directly Observed Treatment Short course |
| **DR** | Drug Resistance |
| **DRS** | Drug Resistance Surveillance or Survey |
| **DR-TB** | Drug Resistant Tuberculosis |
| **DRTBMU** | Drug Resistant Tuberculosis Management Unit |
| **DST** | Drug Susceptibility Testing |
| **EP** | Extra-pulmonary Tuberculosis |
| **EQA** | External Quality Assurance |
| **ESR** | Erythrocyte Sedimentation Rate |
| **FANA** | Federally Administered Northern Areas |
| **FATA** | Federally Administered Tribal Areas |
| **FDC** | Fixed Dose Drug Combination |
| **FLD** | First-Line Drug |
| **GDF** | Global TB Drug Facility |
| **GLC** | Green Light Committee |
| **GP** | General Practitioner |
| **HBC** | High Burden Country |
| **HEPA** | High Efficiency Particular Air (filter) |
| **HCW** | Health Care Worker |
| **HIV** | Human Immuno-Deficiency Virus |
| **HRD** | Human Resource Development |
| **IC** | Infection Control |
| **ID** | Infectious Disease |

|  |  |
| --- | --- |
| **IDL** | Intermediate District Laboratory |
| **IEC** | Information, Education & Communication |
| **IPT** | Isoniazid Preventive Therapy |
| **ISTC** | International Standards for Tuberculosis Care |
| **KFT** | Kidney Function Test |
| **LFT** | Liver Function Test |
| **LQAS** | Laboratory Quality Assurance Services |
| **MDG** | Millennium Development Goal |
| **MDR** | Multi Drug Resistance |
| **MDR-TB** | MDR Multi-Drug-Resistant Tuberculosis |
| **MOH** | Ministry of Health |
| **MTB** | Mycobacterium Tuberculosis |
| **NGO** | Non Governmental Organization |
| **NRL** | National Reference Laboratory |
| **NTM** | Non Tuberculosis Mycobacterium |
| **NTP** | National Tuberculosis Program |
| **OI** | Opportunistic Infection |
| **PAL** | Practical Approach to Lung Health |
| **PHC** | Primary Health Care |
| **PLWHA** | Patients Living with HIV/AIDS |
| **PPM** | Public–Private or Public–Public Mix |
| **PRL** | Provincial Reference Laboratory |
| **PT** | Pulmonary Tuberculosis |
| **QA** | Quality Assurance |
| **R & R** | Recording and Reporting |
| **SCC** | Short Course Chemotherapy |
| **SLD** | Second-Line Drugs |
| **SNRL** | Supra-National Reference Laboratory |
| **SOP** | Standard Operating Procedure |
| **THE UNION** | International Union Against Tuberculosis and Lung Disease |
| **TSH** | Thyroid Stimulating Hormone |
| **TWG** | Technical Working Group |
| **UNAIDS** | Joint United Nations Program on HIV/AIDS |
| **UNITAID** | United Nations Initiative Against Infectious Diseases |
| **USAID** | United States Agency for International Development |
| **UVGI** | Ultraviolet Germicidal Irradiation |
| **VCT** | Voluntary Counseling and Testing |
| **WHO** | World Health Organization |
| **XDR-TB** | Extensively Drug Resistant Tuberculosis |

|  |  |  |  |
| --- | --- | --- | --- |
| **Anti-Tuberculosis Drugs** | | | |
| Group | Description | Drug | Abbreviation |
| 1 | First-line oral anti-tuberculosis drugs | Isoniazid  Rifampicin  Ethambutol Pyrazinamide  Rifabutin | H  R  E  Z  Rfb |
| 2 | Injectable anti-tuberculosis drugs | Kanamycin  Amikacin  Capreomycin  Streptomycin | Km  Amk  Cm  S |
| 3 | Fluoroquinolones | Levofloxacin  Moxifloxacin  Ofloxacin | Lfx  Mfx  Ofx |
| 4 | Oral bacterio-static second-line ATT drugs | Ethionamide Protionamide Cycloserine  Terizidone  P-aminosalicylic acid | Eth/ETO/ETA Pto  Cs  Trd  PAS |
| 5 | Anti-Tuberculosis drugs with unclear efficacy or role in DR-TB treatment (not recommended by WHO for routine use in DR-TB patients) | Clofazimine  Linezolid  Amoxicillin/ Clavulanate  Thioacetazone Clarithromycin Imipenem | Cfz  Lzd  Amx/Clv  Thz  Clr  Ipm |

|  |  |  |
| --- | --- | --- |
| **ART Drugs** |  |  |
| Class | Name | Abbreviations |
| Non-nucleoside reverse transcriptase inhibitors | Efavirenz  Nevirapine | EFV  NVP |
| Nucleoside reverse transcriptase inhibitors | Zidovudine Lamivudine Stavudine Didanosine Zalcitabine Abacavir  Tenofovir | AZT  3TC  d4t  ddl  ddc  ABC  TDF1 |

# 1. Tuberculosis and Drug-Resistant Tuberculosis

# Trends and Magnitude in Iraq

## 1.1. Geographic and Socio-demographic Features

According to a 2008 estimate, the total population in Iraq is 29,249,432 residing within a total geographical area of 437,072 sq. km, divided into 18 governorates and 122 districts. The average of the annual population growth rate was 3% over the last three decades with approximately 67% of the population living in urban areas.

## 1.2. Health Situation

The status of the health sector in Iraq has suffered major blows due to decades of war and economic sanctions. This resulted in a severe drop in Iraq’s gross domestic product and consequently its public expenditure on health led to decline and deterioration of facilities and shortages of drugs and supplies. Moreover, the ongoing war and poor security situation have exacerbated the situation causing severe damage to the health infrastructure, and resulting in the loss of many health professionals and limited access to basic health services.

## 1.3. Health Care System Structure

The Health care system in Iraq consists of two sectors; public and private.

## 1.4. Heath Care Delivery through the Public Sector

The Ministry of Health is the provider of public health care in Iraq. Where there is a Directorate of Health (DOH) in each of the 17 governorates (2 in Baghdad). The governorates are further divided for administrative purposes into 122 health districts. Each district covers on average between 200,000 – 300,000 people. In addition, the primary health care is provided through PHC centers and hospitals.

## 1.5. PHC Infrastructure

There are 1922 PHC centers and sub-centers across the country. PHC centers provide preventative and basic curative services, along with simple diagnostic investigations. About 50% of the PHC centers are staffed by at least one doctor and are referred to as PHC main centers. The other 50% are staffed by trained health workers (nurses and medical assistants) and are referred to as PHC sub-centers.

### Table1.1.Overview Type and Number of PHC Centers

|  |  |  |
| --- | --- | --- |
| **Type of PHC Centers** | **Number of PHC Centers** | **Summary of Services** |
| PHC Main Centers (Cat A) | 742 | Deliver all the primary health care services |
| PHC Main Centers (Cat B) | 19 | Main building delivers the same services in addition to training activities for the medical, paramedical staff of health facilities, medical institutions and medical schools students. |
| PHC Main Centers(Cat C) | 145 | Primary health care centers with a delivery room and emergency  unit |
| Total Main Centers | 906 |  |
| PHC Sub-centers (Cat D) | 1020 | These sub-centers deliver simple maternal and child health services, immunization activities and simple curative services |
| Total | 1926 |  |

Source: Ministry of Health, Iraq

## 1.6. Hospitals

The total number of district hospitals is 85, According to a figure by Iraq Health Compass from 2007; there were 204 public hospitals throughout the country with about 20% of them located in Baghdad.

## 1.7. Referral System between Primary and Secondary Care

Practically speaking, there is minimal coordination between the PHC level and the district hospitals apart from communicable disease surveillance, as the referral system only from PHC to the hospital.

## 1.8. Human Resources

Human resources are inadequate in number and unevenly distributed. In addition, there is a high turnover of staff at all levels, which has a negative impact on the continuity of delivery of health care services.

### Table 1.2. Burden of Tuberculosis in Iraq

|  |  |
| --- | --- |
| ESTIMATES | VALUE |
| Global Rank (by estimated number of cases) | 44 |
| Incidence (all cases by 100,000 pop./yr) | 56 |
| Incidence (new TB SS+ cases/100,000 pop./yr) | 25 |
| Prevalence (all cases/100,000 pop.) | 78 |
| TB mortality (all cases/100,000 pop.) | 11 |
| % New cases multidrug-resistant TB | NA |
| % Adults, 15-49 years, of TB cases with HIV+ | NA |

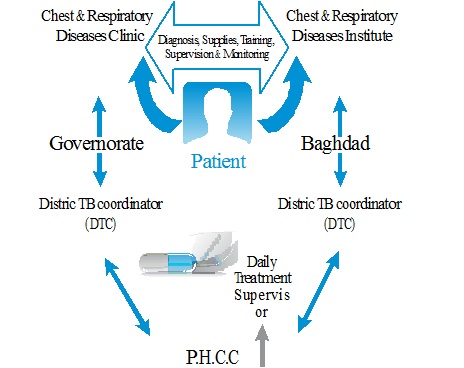
### Table 1.3.Overview of the National Tuberculosis Control Program

|  |  |
| --- | --- |
| Vision | A TB - free country, with elimination of the disease as a public health problem by 2050. |
| Goals | To reduce the country’s burden of TB by 2015, in line with the MDG and Stop TB partnership. |
| Objective | * Ensure access to diagnosis, treatment and cure for each TB patient * Enhance services to ensure high quality DOTS in Iraq * Ensure greater access to TB care for the poor and vulnerable population in Iraq: e.g. poor urban, slum dwellers, prisoners, population in conflict areas and internally displaced population. * Protect vulnerable population from TB, TB/HIV and MDR-TB. |
| Targets | * MDG 6, Target 8: Halt and begin to reverse the incidence of TB by 2015. Epidemiological targets linked to MDGs:1.Maintain detection of 70% of infectious TB cases and cure at least 85% of those cases by 2013 * Reduce the prevalence and deaths due to TB by 50% by 2015 |

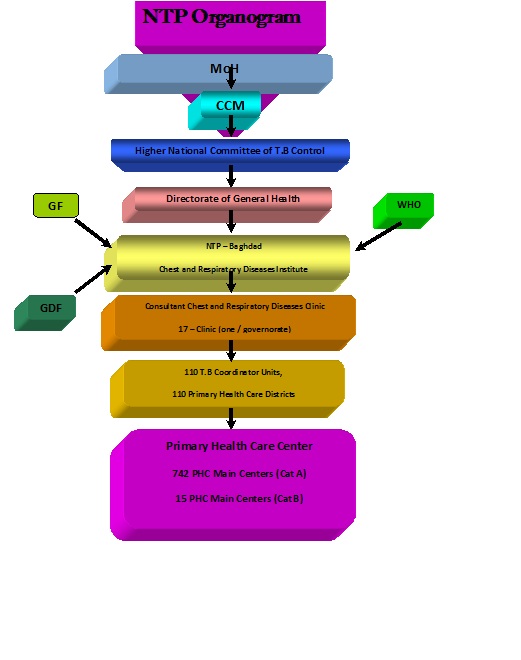
## 1.9. National Tuberculosis Control Program

The MOH has established the National Tuberculosis Control Program (NTP) in 1989 with the technical and financial support of WHO. The mission of the NTP is to reduce the impact of TB as a public health problem in the country. DOTS strategy was introduced in 1998 and by 2000, it was introduced in 15 governorates and population coverage was reported at 100% in the WHO Global TB Report assuming the provision of TB diagnostics and treatment services are available in each governorate (Respiratory and Chest Disease Clinic in each governorate).

### Fig 1.1. DOTS PROGRAMME IMPLEMENTATION PROFILE



### Fig 1.2. Organogram

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## 1.9. Organizational Structure of NTP

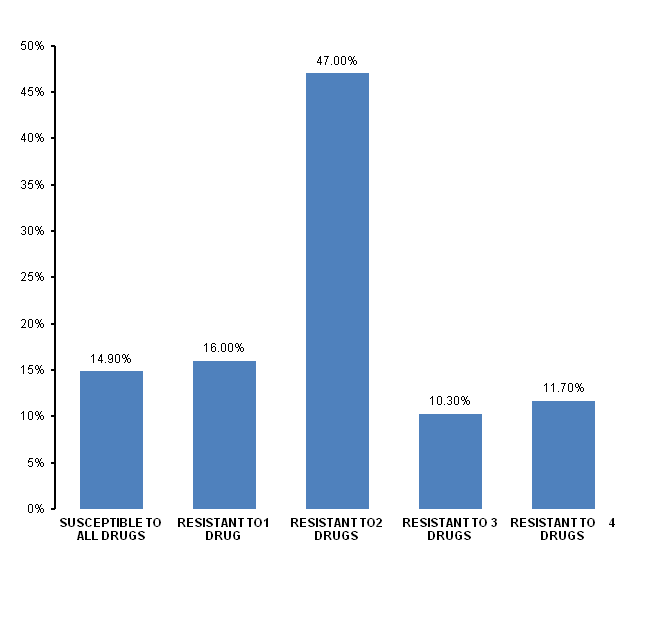
The overall responsibility for TB control rests on the Ministry of Health. The National TB Programme is a technical core for TB control within the MOH, where it is responsible for the formulation of policy and strategy, coordination with partners, planning, implementation and monitoring of control activities. The organizational structure of NTP is based on 3 levels; the National TB Institute (NTI) or respiratory and chest disease institute at the national level in Baghdad and 19 (2 in Baghdad) respiratory and chest disease consultation clinics at the governorate level, and 107 District TB Coordinator units (DTC).

## 1.10. Magnitude of DR-TB Problem in IRAQ

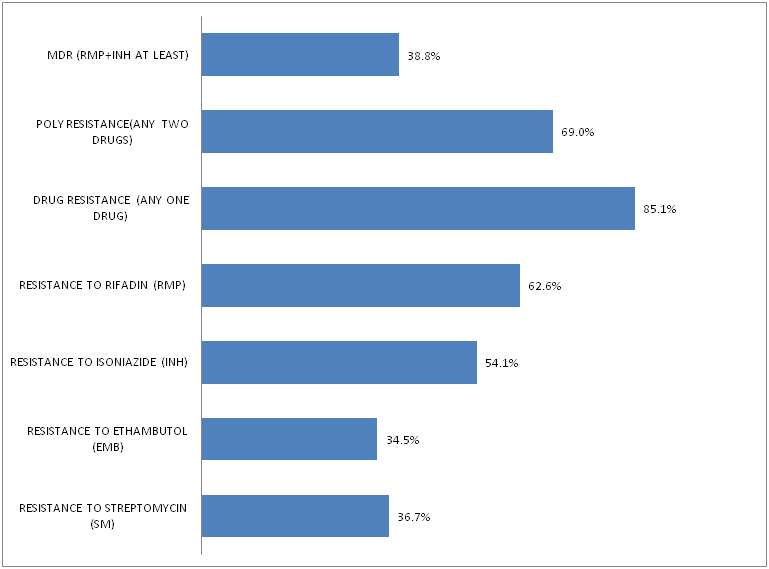
There is currently no survey or surveillance to drug resistant TB and as the result there are no representative data available on anti-TB drug resistance level. The exact magnitude of Multi-drug resistant TB in Iraq is not clear; however similar data in the region indicate that MDR-TB particularly among patients who fail treatment and re-treatment needs further interventions to avoid further spread of resistant strains. Based on the 2010 Global Report on surveillance and response on MDR-TB/XDR-TB, the percentage of MDR-TB among new cases in Iraq is estimated at 2.9%, and among retreatment cases at 35.8% (with confidence interval of 95%). The estimated number of MDR among all incident cases is 820 and among new and relapse cases is 690. The programme assumes treatment of at least 80% of those cases (552/690) by 2015.

In 2006 a cross sectional study was carried out at the National Institution of TB in Iraq, for the determination of drug resistant TB (26). The study found that the prevalence of MDR-TB in Iraq among all TB cases was (1.34 %); the prevalence of any resistance to first-line drug among all TB cases was (2.88%), and number of cases with MDR-TB were 109 which constitutes 38.8% of all positive culture retreatment failure cases. The rate of drug resistance (DR) for at least one drug was (85.1%), and 14.9% of all pulmonary retreatment failure cases were sensitive to all four first-line drugs.

### Fig1.3. Susceptibility and resistance rates in cases studied in Iraq in 2006

****

### Fig 1.4. Rates of types of resistance in Iraq in 2006 among retreatment failure cases



|  |  |  |
| --- | --- | --- |
| MONORESISTANCE Among New Patients Among Retreated Patients | | |
| Isoniazid INH | % | 54.1% |
| Rifampicin R | % | 62.6% |
| Ethambutol E | % | 34.5% |
| Streptomycin S | % | 36.7% |
| MULTIPLE DRUG RESISTANCE |  |  |
|  |  |
| INH + R | % | 38.8% |
| INH + R + E | % | % |
| INH + R + S | % | % |
| INH + R + E + S | % | % |

## 1.11. The Prospect of Drug-Resistant Tuberculosis Management in IRAQ

The management of DR-TB should be fully integrated into the NTP. The challenge involved in this integration should not be underestimated. However, the complexity of the process should not deter programmes from taking the necessary steps to provide all DR-TB patients with universal access to treatment. Since many of the patients with DR-TB are being treated in the private sector, integration can be facilitated through PPM approaches. The most important consideration is the political will to deliver rational treatment to patients with DR-TB as a part of a sound NTP. Following confirmation of political will, a needs assessment should be carried out which will facilitate the design and implementation of a plan to meet the identified gaps, in terms of both infrastructure and functioning of the health care system. Once the infrastructure is in place and the key functions such as a quality-assured TB laboratory are operating, a stepwise integration of activities to control DR-TB can proceed within the NTP. This means that those districts or administrative areas where the integration is more likely to succeed should be prioritized.

## 1.12. How Resistance Develops and Different Resistance Patterns and Types

The management of DR-TB should be fully integrated into the NTP. The challenge involved in this integration should not be underestimated. However, the complexity of the process should not deter programmes from taking the necessary steps to provide all DR-TB patients with universal access to treatment. Since many of the patients with DR-TB are being treated in the private sector, integration can be facilitated through PPM approaches.

The most important consideration is the political will to deliver rational treatment to patients with DR-TB as a part of a sound NTP. Following confirmation of political will, a need of assessment should be carried out which will facilitate the design and implementation of a plan to meet the identified gaps, in terms of both infrastructure and functioning of the health care system. Once the infrastructure is in place and the key functions such as a quality-assured TB laboratory are operating, a stepwise integration of activities to control DR-TB can proceed within the NTP. This means that those districts or administrative areas where the integration is more likely to succeed should be prioritized.

1. **HEALTH-CARE PROVIDERS**

* Inadequate regimens
* Poorly organized or funded TB control programs
* Inappropriate, absence or noncompliance with guidelines
* Poor training
* Lack of proper monitoring and evaluation.

1. **DRUGS**

* Poor quality
* Stock-outs or delivery disruptions
* In-appropriate dosage
* Poor storage conditions

1. **PATIENTS**

* Inadequate drug intake (patient incompliance)
* Poor adherence
* Lack of information, and poor health education
* Poor management of adverse effects
* Socio-economic barriers
* Malabsorption
* Lack of transportation and treatment support

# 2. Definitions

## 2.1. Drug-Resistant TB and Diagnostic Category IV

### Drug Resistant TB

Four different categories of drug resistance (DR) to Mycobacterium tuberculosis (MTB) have been established:

* **Mono-resistance:** resistance to one anti-tuberculosis drug.
* **Poly-resistance:** resistance to more than one first line anti-tuberculosis drug other than both Isoniazid and Rifampicin.
* **Multidrug-resistance:** resistance to both Isoniazid and Rifampicin with or without resistance to any other drug
* **Extensive drug-resistance:** resistance to any Fluoroquinolone, and at least one of three injectable second- line drugs (Capreomycin, Kanamycin, or Amikacin) in addition to multidrug-resistance.

DR-TB is typically confirmed through laboratory tests showing that infecting isolates of MTB can grow in vitro in the presence of one or more anti-tuberculosis drugs (culture and drug susceptibility testing).

### Diagnostic Category IV

DOTS treatment is divided into **four** categories (I, II, III and IV). CAT IV includes all patients with:

* Confirmed MDR-TB
* Poly-resistant TB: Some cases of poly-resistant TB will require Category IV treatments. These patients require prolonged treatment (18 months or more) with first-line drugs combined with two or more second-line drugs and should be entered into the Category IV register.
* Primary resistance and acquired resistance: The term “Primary Resistance” means that the patient was infected with already resistant bacilli while “Acquired Resistance” means that the patient was initially infected with sensitive bacilli but developed resistance of any pattern during the course of treatment because of any or a combination of the previously mentioned causes. These drug resistance types cannot be distinguished in most settings for control of drug-resistant TB except If DST is done before the start of the patient’s first anti-tuberculosis treatment, any resistance documented is considered primary resistance. If new resistance is found when DST is later repeated during treatment and genetic testing confirms that it is the same strain, only then, it can be concluded that the strain has acquired resistance.

## 2.2. Case registration based on location of disease, bacteriology and history of previous treatment

The three determinants of case definition are:

* Location of TB disease
* Bacteriology (result of sputum smear and culture)
* History of previous TB treatment

### Location of DR-TB Disease (Pulmonary and Extra pulmonary)

* Pulmonary TB: Tuberculosis involving only the lung parenchyma.
* Extra pulmonary TB: Tuberculosis of organs other than the lungs i.e. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, and meninges. Tuberculous intra-thoracic lymphadenopathy (mediastinal and/or hilar) or Tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of extra pulmonary TB. The definition of an extra pulmonary case with several sites affected depends on the site representing the most severe form of disease. Patients with both pulmonary and extra pulmonary TB should be classified as a case of pulmonary TB.

*Note: In general, recommended treatment regimens for drug-resistant forms of TB are similar regardless of location. The importance of defining site is primarily for recording and reporting purposes.*

### Bacteriology and Sputum Conversion

Bacteriological examinations used in patients with DR-TB include sputum smear microscopy, culture and drug susceptibility testing (DST). Sputum smear microscopy, culture and DST should be done and results should be reported according to international standards of WHO guidelines. These examinations should be done at the beginning of treatment to confirm TB disease by bacteriology and to group patients according to infectiousness.

Sputum conversion in patients with DR-TB is defined as two sets of consecutive negative smears (each set includes 3 consecutive samples collected on 3 separate days) and cultures from samples collected at least 30 days apart. Both bacteriological techniques (smear and culture) should be used to monitor patients throughout therapy. The date of the first set of negative cultures and smears is used as the date of conversion (this date is also used to determine the length of the initial phase of treatment).

### Category IV Patient Registration Group Based on History of Previous Anti- Tuberculosis Treatment

Category IV patients should be assigned to a registration group based on their treatment history which is useful in assessing the risk of MDR-TB. The treatment history should be assessed at the time of collecting the sputum sample which is ultimately used to confirm MDR-TB using culture and DST.

Classification according to history of previous treatment with ATT drugs (mainly to assign the appropriate treatment regimen)

* New: A patient who has received ATT drugs for less than one month or never received anti-tuberculosis treatment. Patients are placed in this group if their sputum was collected for Drug Sensitivity Testing (DST) at the start of a Category I regimen and were then switched to a Category IV regimen because MDR-TB was later confirmed. They should be considered “new” if DST was performed within one month of the start of treatment (even if they have received more than one month of Category I treatment by the time the results of DST are back and are consequentially registered as Category IV).
* Previously treated with first-line drugs only: A patient who has been treated for one month or more for TB with first-line drugs only.
* Previously treated with second-line drugs: A patient who has been treated for one month or more for TB with one or more second-line drugs, with or without first-line drugs.
* Relapse: A patient whose most recent treatment outcome was “cured” or “treatment completed” and is later diagnosed with bacteriologically positive TB by sputum smear microscopy or culture.
* Treatment after Default: A patient who returns for treatment, and bacteriologically positive by sputum smear microscopy or culture, after interruption of treatment for two or more consecutive months.
* Treatment after failure of Category I: A patient who has received Category I treatment for TB yet treatment has failed. Failure is defined as sputum smear positive at five months or later since treatment inception.
* Treatment after failure of Category II: A patient who has received Category II treatment for TB yet treatment has failed. Failure is defined as sputum smear positive at five months or later since treatment inception.
* Transfer In: A patient who has transferred in from another register for treatment of DR-TB to continue Category IV treatment.
* Other: There are several types of patients who may not fit into any of the above categories.

Programs are encouraged to classify these patients into groups that are meaningful according to the local epidemiology of disease. Examples of which may include the following: sputum smear positive patients with unknown previous treatment outcome, sputum smear positive patients who received treatment other than Category I or II, previously treated patients with extra-pulmonary TB, and patients who have received several unsuccessful treatments and were considered incurable by health staff and have lived with active TB disease with little or no adequate treatment for a period of time until Category IV treatment became available.

## 2.3. Definitions of Treatment Outcomes of Category IV Patients

The following are mutually exclusive Category IV outcome definitions that rely on the use of laboratory smear and culture as a monitoring tool.

* Cured: A Category IV patient who has completed treatment according to program protocol and has at least five consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment. If only 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 30 days apart.
* Treatment Completed: A Category IV patient who has completed treatment according to program protocol but does not meet the definition for Cured because of lack of bacteriological results (i.e. fewer than five cultures were performed in the final 12 months of treatment).
* Died: A Category IV patient who dies for any reason during the course of MDR-TB treatment.
* Failed: The outcome will be considered as Failed if two or more of the five cultures recorded in the final 12 months of therapy are positive, or if any one of the final three cultures is positive or if a clinical decision has been made to terminate treatment early because of poor clinical or radiological response or adverse events. (These latter failures can be indicated separately in order to do sub-analysis).
* Defaulted: A Category IV patient whose treatment was interrupted for two or more consecutive months for any non-medically approved reason.
* Transferred out: A Category IV patient who has been transferred to another reporting and recording unit and for whom the treatment outcome is unknown. Patients who have transferred in should have their outcome reported back to the treatment centre from which they were originally registered. The responsibility for reporting their final outcomes belongs to the original treatment center.
* Total: The sum of Cured, Treatment completed, Died, Failed, Defaulted, Still on treatment and Transferred out.

# 3. DR-TB Case Finding Strategy in Iraq

## 3.1. Objective

Strategy of DR-TB case finding can be summarized as accurate and timely diagnosis, through quality-assured culture and DST, aiming at prompt initiation of treatment to prevent further transmission of the disease and guard against acquiring further resistance and progressing to a state of permanent lung damage. For this reason, NTP targets the following high risk groups for drug susceptibility test for the first-line anti-TB drugs:

* Contacts of DR-TB patients who developed the disease.
* Patients who failed CAT I, regimen I of the first Anti-TB drugs. NTP recommends to do culture and susceptibility test for patients who remain positive at the end of the third month.
* Patients who are relapsed or defaulted should undergo drug susceptibility testing for the first-line Anti- TB drugs.
* Chronic patients and those who failed retreatment regimens of the first line Anti-TB drugs.
* Patients who have a history of using Anti-Tuberculosis drugs of poor or unknown quality or those who have been treated in areas with frequent out-stock.
* Patients with co-morbid conditions e.g. malabsorption or rapid-transit diarrhea and HIV patients.
* Health-care workers in MDR-TB clinics, laboratories and wards, who develop active TB.

## 3.2. DST Specimen Collection

It is recommended that two sputum specimens be obtained for culture and that DST is performed with the specimen that produces the best culture. Routinely, DST need not be carried out in duplicate. Procedures for collecting and managing specimens for culture and DST are described in section 4, which also addresses different techniques, limitations, quality assurance requirements and other issues of culture and DST.

Previously treated patients may have had DST done in the past but may no longer reflect the resistance pattern of the strain at the time of enrolment in the DR-TB control programme. At least one sputum sample for smear and culture should always be taken at the time of starting Category IV treatment. In order for a patient to be considered culture and / or sputum smear-positive at the start of Category IV treatment, at least one pre-treatment culture or smear should be positive and the collection date of the sample on which the culture or smear was performed is less than 30 days before or 7 days after the initiation of Category IV treatment.

## 3.3. Case Finding in Pediatric Patients

Pediatric cases require adjustments in diagnostic criteria and indications for treatment. Younger children in particular may not be able to produce sputum specimens on demand. Programmes should not exclude children from treatment solely because sputum specimens are not available. Smear and culture negative children with active TB who are in close contact with patients with DR-TB can be started on Category IV regimens.

## 3.4. Case Finding of Patients with Mono and Poly-Drug Resistance

Mono and Poly-Drug Resistant strains are resistant to anti-tuberculosis drugs but not to both Isoniazid and Rifampicin. Most diagnostic strategies used by DR-TB control programmes will also identify cases of mono and poly-drug resistance, in addition to MDR-TB cases. Patients with mono or poly-drug resistance may require modifications to their SCC regimens or to be moved to Category IV regimens (see Section 5).

## 3.5. Use of Rapid Drug-Resistance Testing

Case-finding strategies can be greatly enhanced with rapid drug-resistance testing, which significantly improves the ability to identify earlier cases of DR-TB that can be isolated and started on treatment. Rifampicin is the most potent Anti-Tuberculosis drug of the first-line regimen, and Rifampicin resistance most commonly occurs with concomitant Isoniazid resistance. A positive rapid test for Rifampicin resistance is a strong indicator that a patient may have MDR-TB, while a negative test makes a final diagnosis of MDR-TB highly unlikely. As soon as a patient is identified as a TB suspect, rapid testing can identify DR-TB quickly and allows patients to be properly separated and placed under treatment while waiting for the remaining DST result.

# 4. Laboratory Aspects

## 4.1. General Considerations

Optimal management of drug-resistant TB requires both mycobacterial and clinical laboratory services. The Iraq mycobacteriology reference laboratory provides direct smear microscopy, culture and confirmation of the species as M. tuberculosis, M. bovis or non tuberculosis mycobacterium, and performs DST for first- line Anti-Tuberculosis drugs excluding Pyrazinamide. The Iraq NRL is the only laboratory in charge of doing DSTs for first-line Anti-Tuberculosis drugs. DST to second-line Anti-Tuberculosis drugs are not yet available in the NRL. Clinical laboratory services, including basic hematology, biochemistry, and serology and urine analysis are required for the proper evaluation and monitoring of patients.

The laboratory network consists of one National Reference Laboratory (NRL) with culture and DST and three laboratories, in Basra, Babel and Najaf, for culture, across Iraq. Samples for DST are properly transported to NRL for testing. Within the laboratory network for TB control all aspects concerning specimen collection and transport are standardized. Smear microscopy uses Ziehl- Neelsen stain and culture is performed with Lowenstein-Jensen medium while DST uses the proportions method (1 % threshold).

For MDR cases, follow up smear microscopy will be done monthly, culture examinations will also be performed monthly during the intensive phase of treatment and bi-monthly during the continuation phase of treatment.

The NTP has established a quality assurance system for smear microscopy with the technical support of the WHO TB lab expert. This entailed the development of a lab manual, training of the staff of the National Reference Laboratory on quality assurance procedures and the development of the necessary forms for double blinded reading of slides. The quality assurance procedures are being implemented on a regular basis.

With the technical assistance of the TB lab expert, the National Reference Laboratory (NRL) acquired the necessary capacity to perform cultures and drug sensitivity tests. The laboratory network is supervised by the National Laboratory Supervisor (who is a member of the NTP central unit), with the assistance of the NRL. External quality assurance of the NRL will be carried out through the Supra National Reference Laboratory in EMRO. NRL is in the process of certification of proficiency test by a Supranational Reference laboratory.

## 4.2. General Definitions for the Laboratory and DST

**The following are definitions of the laboratory aspects discussed in this section:**

* **Critical drug concentration:** The lowest concentration of drug that will inhibit 95% (90% for Pyrazinamide) of wild strains of M. Tuberculosis that have never been exposed to drugs, while at the same time not inhibiting clinical strains of M. Tuberculosis that are considered to be resistant (e.g. from patients who are not responding to therapy).
* **Minimum inhibitory drug concentration:** The lowest concentration of drug that will inhibit growth of the M. tuberculosis isolate in vitro.
* **Reproducibility:** The ability of a test or experiment to be accurately reproduced or replicated under independent conditions. Reproducibility relates to the agreement of test results across different laboratories and laboratory technicians or technologists.
* **Reliability:** The extent to which a test result remains consistent when repeated under identical conditions. Reliability does not imply validity. A reliable test generates a consistent result that may not necessarily be accurate; e.g. clinical efficacy may not be accurately predicted, even if a test is highly reliable.
* **Cross-resistance:** Resistant mutations to one anti-tuberculosis drug may confer resistance to some or all of the members of the drug family and, less commonly, to members of different drug families.

## 4.3. Organization and Development of the Laboratory Network

**National Reference Laboratory (NRL/central lab) Capabilities and Responsibilities:**

* Direct smear examination
* Culture & Sensitivity tests
* Supervision of Intermediate labs
* Quality control of direct smear and culture
* Surveillance of MDR
* Renovation, equipment supply and supply of media & stains to intermediate and peripheral labs
* Research work e.g. evaluation of new methods of TB diagnosis in comparison to traditional methods
* Training of lab doctors & technicians for DSM, culture and bacterial identifications
* Bio-safety measures:

In the NR lab there is a separate space for each− activity:

* 2 rooms for culture & sensitivity
* 1 room for direct smear microscopical examination
* 1 for media preparation
* 1 for decontamination & sterilization

There is also a separate room for administrative purpose as Recording and Registry. There are also 4 safety cabinets with non permeable walls and surface with directional airflow. All the containers, specimens and other wastes are collected in special containers and burnt in an incinerator after decontamination.

Every day the lab personnel check and ensure that the equipment is operating correctly, airflow is properly directed and they wear protective clothing (overalls, masks and gloves).

## 4.4. Quality Assurance System in Lab Network

Quality Assurance of direct smear examination (DSE) done at Governorate labs (G.Labs) and all peripheral labs, is carried out by the lab technicians of the G. labs in the same state under the supervision of NRL.

**System of Quality Assurance works in Two Directions:**

* **From peripheral to central lab**: It depends on blind rechecking of random samples of all slides which are kept in slide boxes in the same order as in the laboratory register (reference WHO guide for EQA and DSM).
* **From central to peripheral lab:** Stained slides with different degree of positivity as well as negative slides are sent to the peripheral labs to be re-examined by the technician and results are sent back to central lab.

During supervisory visits to the peripheral and intermediate labs, Quality Assurance (QA) steps of smearing, staining and examination are evaluated on spot.

### 4.4.1. Supervisory activities of NR lab

All G. Labs (intermediate labs) are visited by the central lab at least once a year (or more if there is a problem). All peripheral labs (117) are visited by the G. lab coordinators every 3 months and their reports are sent to the NRL & NTP.

### 4.4.2. Role of Microbiological Laboratory in DR-TB Management

**Microscopy, culture and identification of M. tuberculosis in DR-TB control program**

* Direct smear examination is done in the peripheral lab, and chest hospital Lab
* Culture of specimens for DST is done only at the NRL
* Susceptibility tests are done only in the national reference lab

The local labs will be involved in direct smear examination. In addition, clinical laboratory services, including basic hematology, biochemistry, serology and urine analysis, are essential initially to evaluate the patient and also monitor for side effects in their follow up.

## 4.5. Functions and Responsibilities of the Different Levels of Laboratory Services

**Level I**

The peripheral (often district) laboratory performs the following:

* Receipt of specimens
* Preparation and staining of smears
* Ziehl-Neelsen microscopy and recording of results
* Dispatch of results
* Maintenance of laboratory register
* Cleaning and maintenance of equipment
* Management of reagents and laboratory supplies
* Internal quality control

**Level II**

The intermediate (often regional) laboratory performs the following:

* All the functions of a Level I laboratory
* Fluorescence microscopy (optional)
* Digestion and decontamination of specimens
* Culture and identification of M. Tuberculosis
* Training of microscopists
* Support to and supervision of peripheral-level staff with respect to microscopy
* Preparation and distribution of reagents for microscopy in peripheral laboratories
* Quality improvement and proficiency testing of microscopy at peripheral laboratories

**Level III**

The central (often national) laboratory performs the following:

* All the functions of Level I and II laboratories
* DST of M. Tuberculosis isolates
* Identification of mycobacteria other than M. Tuberculosis
* Technical control and repair of services for laboratory equipment
* Updating and dissemination of laboratory manuals, including guidelines on diagnostic methods on care and maintenance of equipment and on quality assurance
* Close collaboration with the central level of the national TB control programme
* Supervision of intermediate laboratories regarding bacteriological methods and their support (particularly training and supervision) to the peripheral laboratories
* Quality assurance of microscopy and culture performed at intermediate laboratories
* Training of intermediate-level laboratory staff
* Organization of Anti-Tuberculosis drug resistance surveillance
* Operational and applied research relating to the laboratory network, coordinated with the requirements and needs of national TB control programme.

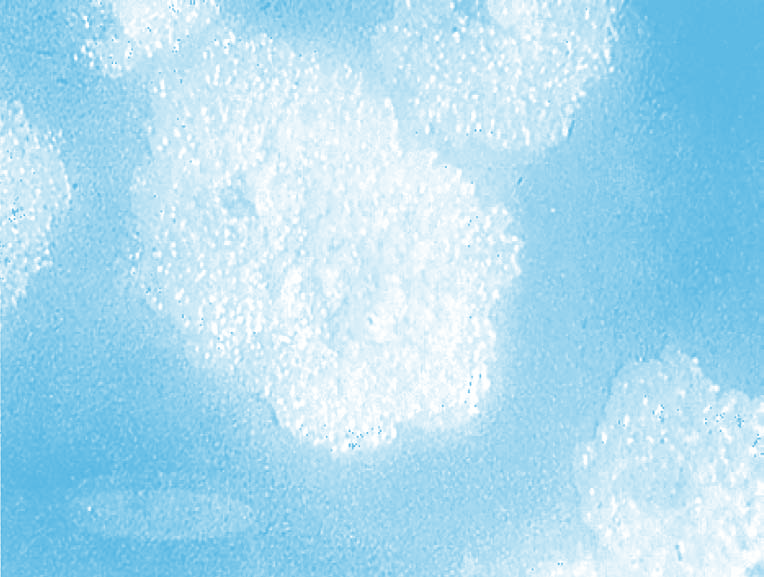
## 4.6. Culture and Drug Susceptibility Testing (DST)

The drugs used for susceptibility testing should never be taken from those used for treatment. They must come from pure compounds that are available only from the manufacturer. For DST, the indirect method is used where at least one sputum specimen is submitted to the laboratory for AFB microscopy (smear) and culture. One of the two cultures can then be used for DST. There are different DST techniques:

* Proportion method
* Absolute concentration
* Resistance ratio
* Broth (or liquid) methods
* Detection of metabolic changes
* Mycobacteriophage-based
* Molecular based technique

### Definition of Resistance

“A decrease in sensitivity to sufficient degree to be reasonably certain that the strain concerned is different from a sample of wild stains of human type that have never come in contact with the drugs”.(Prof. Mitchison)



**Eight week Growth of Mycobacterium tuberculosis on Lowenstein-Jensen Agar**

### 4.6.1. Drug Susceptibility Tests

It is one of the most difficult procedures to perform & to standardize in the Mycobacteriology lab. Proficiency in susceptibility tests demands an understanding of the origin of drug resistance. The variation in stability of drugs subjected to different conditions of filtration, heat or storage. The alteration in the activity of certain drugs when incorporated into different kinds of media

#### 4.6.1.1. Types of drug susceptibility testing

***Direct***

* Sputum Swab Method
* Sputum deposit after processing by Petroff’s

***Indirect***

* MIC or Absolute Concentration Method
* Resistance Ratio Method
* Proportion Susceptibility Testing

**Direct Method** can be applied to only smear positive cases. Sputum swab +1% cetrimide (INH, Rif, and Strep). The inoculum is a digested and decontaminated sputum (or other clinical specimen) in which smear is positive for AFB. The inoculum is truly representative of the bacillary population present in the specimen.

Advantage: Availability of DST results along with the culture results (by 30-42 days).

**Indirect Test** is used for specimens that are smear-negative but culture-positive or when the growth in the control slope of the direct test is inadequate. The inoculums are standardized but at the same time are not truly representative and hence there is a chance of selecting a proportion of susceptible or resistant bacilli from the slope. For this reason, the inoculum is prepared by using a representative sweep of the entire surface of the growth on the slope.

##### 4.6.1.1.1. Proportion Susceptibility Testing Method

This method enables a precise estimation of the proportion of mutants resistant to a given drug. Several 10-fold dilutions of inoculum are planted on to both control (drug-free) and drug-containing media. At least one dilution should yield isolated countable (50 -100) colonies. When these numbers are adjusted by multiplying by the dilution of inoculum used, the total number of viable colonies on the control medium, and the number of mutant colonies resistant to the drug conc. tested may be estimated. The proportion of bacilli resistant to a given drug is then determined by expressing the resistant portion as a percentage of the total population tested.

**The proportion method is currently the method of choice.**

***Proportion Method***

**Bacterial suspension**

Add approx.1 mg moist wt of a representative sample of the bacterial mass visualized as 2/3 loopful of 3 mm internal diameter (24 SWG) into 0.2 ml of sterile (distilled water) D.W.in a 7 ml Bijou bottle containing 10-12 glass beads. Stir for 30 seconds to produce a uniform suspension. Add To this 3.8 ml of sterile D.W. to give a suspension containing approx. 1mg/ ml - (S1). Keep this suspension on the bench for 15-20 min. in order to allow the coarser particles to settle down.

From this suspension 10-fold dilution is made by carefully adding 0.2 ml to 1.8 ml sterile D.W - (S2, 10-1).

Prepare two further serial dilutions 10-2 (S3) and 10-3 (S4) in a similar manner.

Inoculate with one standard loopful (3 mm diameter, 27 SWG) on to drug-free as well as drug-containing LJ slopes.

**Incubation and Reading:**

Incubate the slopes at 3700 C. Read the growth at 28 days and again in 42 days. Record growth as:-

* + + + Confluent growth
* + + More than 100 colonies
* 1-100 cols. The actual number of colonies

When the number of colonies on a given dilution is less than 5, count the number of colonies with the next larger inoculum, or estimate if more than 100.

**Do not estimate to count colonies if the growth is + + +**

##### 4.6.1.1.2. Absolute concentration method

In this method a standardized inoculum grown on drug-free media and media containing graded concentration of the drug (s) is compared. Several concentrations of each drug are tested, and resistance is expressed in terms of the lowest concentration of the drug that inhibits growth, i.e., Minimal inhibitory concentration (MIC). This method is greatly affected by inoculum size and by the viability of the organisms.

##### 4.6.1.1.3. Resistance Ratio Method

This method compares the growth of unknown strains of tubercle bacilli with that of a standard (std.) strain of M.TB (H37RV). Parallel sets of media, containing two-fold dilutions of the drug, are inoculated with a std. inoculum prepared from both the unknown and std. strains of tubercle bacilli. Resistance is expressed as the ratio of the MIC of the test strain to the MIC for the standard strain in the same set. This test is also greatly affected by the inoculum size as well as the viability of the strains. In addition, any variation in the susceptibility of the std. strain also affects the resistance ratio (RR) of the test strain. This, RR method is usually performed for streptomycin. Preparation of the bacterial suspension, inoculation, incubation and reading are identical to that for the MIC method.

#### 4.6.1.2. Direct Sensitivity Tests

The direct test is highly useful for determining the susceptibility of the strain to INH & Rif. The processed sputum deposit is simultaneously inoculated onto one slope each of INH (0.2 mg/ l) & Rif (40 mg/ l) and incubated along with the culture slopes. Examine the drug-containing slopes when growth is obtained on the culture slopes. If the growth seen on the drug containing slopes is similar in grade to that of the drug-free slope, the strain is reported as resistant.

Methods Used in Iraq:

* DST by proportional method on L. J media.
* External quality assurance with Supra-National Reference Lab in Egypt are done yearly through panel testing.

# 5. Treatment Strategies for DR-TB

## 5.1. General Principles

For case finding and selection please refer to **Section 3** of this guideline. Any patient who is diagnosed with DR-TB should fall under the diagnostic category IV and will require specialized treatment termed Category IV Regimen. The patient should be referred to the closest available and convenient treatment site.

### Table 5.1. Classes of Anti-Tuberculosis drugs

**Anti-Tuberculosis drugs are classified into five groups.**

|  |  |
| --- | --- |
| **CLASSES** | **DRUGS WITH ABBREVIATION** |
| **Class 1 - First-line oral Anti-Tuberculosis agents** | Isoniazid (H), Rifampicin (R), Ethambutol (E), Pyrazinamide (Z). |
| **Class 2 - Injectable Anti-Tuberculosis agents (Bactericidal)** | Streptomycin (S), Kanamycin (Km), Amikacin (Am),  Capreomycin (Cm), Viomycin (Vi). |
| **Class 3 - Fluoroquinolone (Bactericidal)** | Ofloxacin (Ofx), Levofloxacin (Lfx), Moxifloxacin (Mfx), Gatifloxacin (Gfx). |
| **Class 4 - Oral bacteriostatic second-line Anti-Tuberculosis agents** | Ethionamide (Eto), Protionamide (Pto), Cycloserine (Cs), Terizidone (Trd), P-aminosalicylic acid (PAS). |
| **Class 5 - Anti-Tuberculosis agents with unclear efficacy (not recommended by WHO for routine use in DR-TB patients)** | Clofazimine (Cfz), Amoxicillin/Clavulanate (Amx/Clv),  Clarithromycin (Clr), Linezolid (Lzd), Thioacetazone (Th), Imipenem/Celestin (Imp/Cln), and high dose Isoniazid. |

## 5.2. Standardized vs. Individualized Treatment Regimen

Access to DST is required in all programmes. Under exceptional circumstances and while building the laboratory capacity to perform DST, selected DR-TB MUs' may use strategies to enroll patients with a very high risk of DR-TB in Category IV regimens, without individual DST2 using a standardized treatment regimen. The two groups that are most likely to be considered for direct enrolment in a Category IV standardized regimen are discussed below.

**Category II failures (chronic TB cases):**

* Patients in whom Category II treatment has failed in sound NTPs often have DR-TB.
* If the quality of DOT is poor or unknown (i.e. if regular ingestion of the medicines during Category II treatment is uncertain).
* Patients may fail Category II treatment for reasons other than DR-TB.

**Close contacts of DR-TB cases that develop active TB disease:**

Close contacts of DR-TB patients who develop active TB disease can be enrolled for treatment with Category IV regimens. (See Section14 for more detail on the management of contacts of DR-TB patients).

**Note: The rate of DR-TB in these groups can vary. These guidelines strongly recommend confirming treatment failure by culture and testing for DR-TB through the use of DST to at least Isoniazid and Rifampicin for all patients who start a Category IV regimen. All programmes should therefore have the capacity for DST of at least Isoniazid and Rifampicin.**

2For example, the results of a representative DRS may identify a group or groups of patients with a very high percentage of DR-TB, which can justify the use of Category IV regimens in all patients in the group.

## 5.3. Available Treatment Strategies

### 5.3.1. Standardized treatment

Designing this treatment regimen depends on representative DRS data. All patients in a patient group or category receive the same regimen.

### 5.3.2. Standardized treatment followed by individualized treatment

Initially, all patients in a certain group receive the same regimen based on DST survey data from representative populations. The regimen is adjusted when DST results become available.

### 5.3.3. Empirical treatment followed by individualized treatment

Each regimen is individually designed on the basis of patient history and then regimen is adjusted when DST results become available.

In Iraq, Standardized treatment regimen will be used for treatment. Treatment regimens might be adjusted according to resistance patterns when DST results are available.

**Advantages of standardized regimens:**

* Based on representative DRS and history of prior use of second line drugs.
* Enable more patients to access care
* Maintain cure rates comparable to those obtained with individualized treatment
* Simplify operational aspects of implementation
* Simplify drug ordering
* Facilitate training
* Decrease likelihood of mismanagement,
* Decrease dependence on highly technical laboratories

## 5.4. Designing a Treatment Regimen

### 5.4.1. General Principles

The following are the basic principles involved in any SLD treatment regimen design:

* 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.
* Regimens should consist of at least four drugs with either certain or almost certain effectiveness. If the evidence about the effectiveness of a certain drug is unclear, the drug can be part of the regimen but it should not be solely depended upon for success. Often, more than four drugs may be started if the susceptibility pattern is unknown, effectiveness is questionable for one or more drugs or if extensive bilateral pulmonary disease is present.
* When possible, Pyrazinamide, Ethambutol and Fluoroquinolones should be given once per day as high peaks attained in once/ day dosing may be more efficacious. Once/day dosing is permitted for other second-line drugs depending on patient tolerance; however Ethionamide, Protionamide, Cycloserine and PAS are given in divided doses during the day to reduce adverse effects.
* The drug dosage should be determined by body weight. A suggested weight-based dosing scheme is shown in Annex #1.
* 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 (for more information on side effects of treatment please refer to Section 6).
* An injectable agent should be used for a minimum of six months and at least four months past culture conversion.
* The minimum length of treatment is 18 months after culture conversion.
* Each dose is given as DOT throughout the treatment, and a treatment card is marked for each observed dose.

### 5.4.2. Recommended Drugs for a Standardized Treatment Regimen

The following drugs may be used:

* Injectable (Kanamycin, Amikacin or Capreomycin) 15- 20 mg/ kg/ day for 6 days/ week (during intensive phase treatment)
* Cycloserine tab 15-20 mg/ kg/ day. Begin with 2 tab/ day and increase gradually according to patient’s weight until maximum 1 g daily in 2 divided doses as tolerated.
* Ethionamide tab 15-20 mg/kg/day. Follow the same recommendation as mentioned above for Cyclocerine.
* Levoflaxacin 7.5 mg-10 mg/ kg. Give 500-1000 mg daily in single dose or 2 divided doses if single dose is not tolerated well.
* Para-Amino-Salicylic Acid (PAS) 150 mg/ kg/ day. This drug may be used in order to provide 4 new drugs if needed. Give 5-7 g granules twice/day.
* Vitamin B6 200 mg daily should be given to every MDR-TB patient
* Add to the above drugs PZA
* Add Ethambutol (if DST shows that the patient is sensitive to Ethambutol)
* All drugs are given daily except the injectable which is given 6 days/week

All drugs are given according to the body wt. dosage listed in annex I

### 5.4.3. Treatment Strategy Guide Based on the Availability of Culture and DST

### Table 5.2.Drug selection for the treatment of DR-TB

|  |  |
| --- | --- |
| STEP 1  Use any available Group 1 First-Line oral drugs based on DST result | Begin with any first-line drug that DST shows sensitivity. 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  The above plus one of these Group 2 injectable drugs such as Kanamycin, Amikacin or Capreomycin. | Add an injectable drug 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  The above plus one of these Group 3 Fluoroquinolones such as Levofloxacin, Moxifloxacin or 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  Add one or more of Group 4 second-line oral bacteriostatic agents such as P-aminosalicylic acid, Cycloserine (or Terizadone), Ethionamide (or Protionamide) | Add Group 4 drugs until you have at least four drugs likely to be effective. Base choice on treatment history, adverse effects profile, and cost. DST is not standardized for the drugs in this group. |
| STEP 5  Consider the use of these Group 5 drugs of unclear role in DR-TB treatment:  Clofazimine,Linezolid,Amoxacillin/Clavulanate,Thioacetazone,Imipenem/Cilastatin, high-dose Isoniazid or Clarithromycin. | Consider adding Group 5 drugs in consultation with a DR- TB expert if there are no 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. |

#### 5.4.3.1. Duration of Treatment

The recommended duration of treatment is guided by culture conversion. The treatment is divided into Intensive and Continuation phases (see below).

#### 5.5.4.2. Completion of an Inject able Agent (Intensive Phase)

The recommended duration of administration of an injectable drug, during the intensive phase, is guided by culture conversion. The injectable drug should be continued for at least six months with at least four months of injectables followed by 2 consecutive negative cultures with 30 days apart. Intermittent therapy (three times a week) with the injectable drug can be considered when the injectable drug has been used for a prolonged period of time and when toxicity becomes a greater risk.

#### 5.5.4.3. Extra Pulmonary DR-TB and DR-TB Treatment

The treatment strategy does not differ for patients with pulmonary and extra pulmonary DR-TB. If CNS is involved, the following provides some general information: Rifampicin, Isoniazid, Pyrazinamide, Protionamide/ Ethionamide and Cycloserine have good penetration into CNS.Kanamycin, Amikacin and Capreomycin penetrate effectively only in the presence of meningeal inflammation. PAS and Ethambutol have poor or no penetration.

## 5.6. Guidelines for Patient Treatment Enrollment

The NTP acknowledges and supports the following two strategies for patient’s management:

* Ambulatory based strategy. The treatment center will enroll the patient under CAT-IV treatment on an ambulatory basis provided, a strong DOT policy is in place, an infection control policy is well implemented to prevent household transmission of DR-TB to another contact, and a proper mechanism for early recognition/ management of adverse reaction is established which might include admission to an in-patient DR-TB designated treatment site due to severe adverse reactions.
* Hospitalization based strategy. The treatment center will admit the patient into a hospital to begin CAT- IV treatment until such a time when the patient shows evidence of treatment tolerance and no signs or symptoms of adverse reactions. The patient can then be discharged for ambulatory treatment provided that the conditions for DOT are in place.

**Note: MDR-TB management in Iraq:** In Iraq MDR- TB management is only ambulatory with a family member as treatment supporter which may lead to failure of SLDs’

**The following table compares the advantages of a health worker as treatment supporter versus a family member.**

### Table 5.3 Health Worker versus Family member

|  |  |
| --- | --- |
| Health Worker | Family member |
| Every single dose is given under direct observation | Difficult especially if the treatment supporter is wife. |
| Can administer injectable drugs | Cannot administer injectable drugs |
| Can complete all the information on the patient treatment card | Cannot |
| Can identify side effects and adverse reactions early | Cannot |
| Trained with necessary health education | Needs to be trained |
| Can follow up with scheduled tests and visits to the health clinic | Cannot |

**Methods to address the problem**

* MDR drugs to be administered by a health worker who lives in close proximity to the patient and not by a family member.
* Health worker should be provided additional training (if required)
* He/she should be acknowledged by incentives and short periods of rest.
* Any transportation problems the health worker has needs to be immediately addressed.

## 5.7. Diagnostic and Follow up Management

### 5.7.1. Upon arrival to the treatment site the patient should bring the following items

* A referral letter (For further information please see form 9).
* Previous Chest Radiographs (CXR) and any other medical documents from any relevant centers or treatment facilities indicating previous or current treatment.
* An ID card, two contact phone numbers, and complete contact information.
* An official report of the result of sputum culture and DST if available. All cultures and DST must be done in a certified laboratory (EQA).

### 5.7.2. The following work up should be done upon admission

**Initial evaluation of the patient includes the following investigations:**

Complete history and physical exam that includes past medical history, family history, previous treatment (including TB) in detail, previous or current family TB history, detailed history of previous contact with a TB case, incarceration/ travel/ working conditions, and HIV status.

**Baseline chemistry and hematological tests including:**

* CBC, Diff and ESR
* Serum Creatinine, Blood Urea, complete urine analysis(CUE) with estimation of total urine protein content
* Liver functions: Total serum bilirubin, SGPT & SGOT, total serum albumin, total serum protein and A/ G ratio, screening for Hepatitis A, B and C.
* Electrolytes
* Serum Uric Acid
* TSH
* HIV
* Urine test for pregnancy in females
* Direct smear examination
* DST for first and second-line Anti-TB drugs
* Fasting and PP blood sugar.
* Initial chest x-ray
* Audiometry and visual tests

### 5.7.3. The Treatment Regimen is divided into two phases

#### 5.7.3.1. The Intensive Phase

This phase should take place for at least 6 months. During this phase the following drugs may be used:

* Injectable 15- 20 mg/ kg/ day for 6 days/week
* Cycloserine tab 15-20 mg/ kg/ day. Begin with 2 tab/ day and increase gradually according to patient’s weight until maximum 1 g daily in 2 divided doses, as tolerated.
* Ethionamide tab 15-20 mg/ kg/ day. Follow the same recommendation as mentioned above for Cyclocerine.
* Levoflaxacin 7.5mg-10 mg/ kg. Give 500-1000 mg daily in single dose or 2 divided doses if single dose is not tolerated well.
* Para-Amino-Salicylic Acid (PAS) 150 mg/ kg/ day. This drug may be used in order to provide 4 new drugs if needed. Give 5-7 g granules twice/ day.
* Vitamin B6 200 mg daily should be given to every MDR-TB patient.
* Add to the above drugs PZA.
* Add Ethambutol (if DST shows that the patient is sensitive to Ethambutol).
* All drugs are given daily except the injectable ones which are given 6 days/ week
* All drugs are given according to the body wt. dosage listed in annex I.

For case management during the intensive phase treatment the following tests should be done:

**Monthly:**

* Sputum for direct AFB microscopy on 3 consecutive days
* Sputum for AFB culture
* Hgb, and ESR
* Audiometry and visual tests
* PA CXR during the first 3 months

**Every two months:**

* KFT, electrolytes and LFT

**Every 3-6 months:**

* TFT
* CXR

***Direct Observed Treatment (DOT)***

* If the patient is being treated via the ambulatory strategy, the patient must report to the treatment site or the district/ peripheral TB center weekly. Every treatment dose must be given under DOT. If the patient is hospitalized, the patient should remain in the hospital until is stable enough to be discharged.
* The patient can then be discharged to receive ambulatory care provided patient supporter (social worker, family member, volunteer etc.) who is properly trained to administer daily DOT, to give an injectable drug and recognize early signs and symptoms of adverse reactions is available.
* The patient and his DOT supporter can make weekly visits to the nearest TB center for review and replenishment of drugs. A copy of the patient’s category IV treatment card should be forwarded to the local TB center.
* The patient can make monthly visits to a treatment site for the necessary work ups and for monitoring and evaluation by a clinician. A copy of the patient’s category IV treatment card (DR-TB Form 01) should be transferred to the treatment site for review and appropriate updating. When the patient completes at least 6 months of intensive phase treatment, and has two negative cultures of at least 30 days apart after a minimum of 4 months of injectable, the patient can then move to the continuation phase (defined below). If progress for movement is not present, intensive phase treatment should continue until 2 consecutive negative cultures are available and are at least 30 days apart.

#### 5.7.3.2. The Continuation Phase

During this phase, only the injectable drug is discontinued and the patient continues to receive the same oral drugs which have been used at the end of the intensive phase. The local TB center and/or health provider is responsible for:

* Arranging for DOT. The patient could report daily to the center or have a trained volunteer administer DOT under the supervision of the center. A special treatment card should be provided
* Requesting drugs from the treatment site and maintaining their availability and proper storage. A refrigerator should be available at the center to store the drugs which require refrigeration
* Monitoring the patient on a weekly basis for early detection of adverse reactions
* Performing direct smear microscopy on a monthly basis on at least 3 consecutive specimens (collected on 3 separate days)
* Referring the patient to the treatment site every 2 months for CBC, ESR, and TSH, CXR (every 3- 6 months) and sputum culture.

A copy of the patient’s category IV treatment card (DR-TB Form 01) should be used for referring the patient to the treatment site. The continuation phase should last 18 months from the point at which the patient arrived and remained culture negative. For determining when the patient is considered cured or treatment complete please refer to 'Definitions for Treatment Outcomes of Category IV Patients' in Section 2.

### Table 5.4.Monitoring during DR-TB treatment

|  |  |
| --- | --- |
| Sputum smear and culture | Monthly smear and culture during intensive phase then bi-monthly during continuation  phase |
| DST | Initially then done for patient whose culture remains positive for at 4-6 months |
| Weight | Initially then monthly |
| Chest radiograph | Initially then every 3- 6 months |
| Serum Creatinine | Initially then monthly while receiving injectable drugs |
| Electrolytes | Monthly while receiving injectable drugs |
| TSH | Every 6 months if receiving Ethionamide/Prothionamide or PAS and monitor monthly for signs and symptoms of hypothyroidism |
| Liver 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 |
| HIV | Initially and repeat if clinically indicated |
| Pregnancy test | Initially and repeat if indicated |
| Clinical evaluation | Initially then at least monthly until conversion, then every 2-3 months |

## 5.8. DR-TB other than MDR-TB Incubation and Reading

Mono-resistance refers to resistance to a single first-line drug.Poly-resistance refers to resistance to two or more first-line drugs but not to both Isoniazid and Rifampicin.

No definitive randomized or controlled studies are available to determine the best treatment for various patterns of drug resistance, except for Streptomycin resistance. The recommendations in these guidelines are based on evidence from the Pre-Rifampicin era, observational studies, general principles of microbiology and therapeutics in TB, and extrapolations from established evidence and expert opinion. When a decision is made to modify standardized SCC, the most effective regimen should be chosen to maximize the likelihood of cure; effective drugs should not be withheld for later use. If a patient was receiving functionally only Rifampicin and Pyrazinamide in the initial phase (because of resistance to Isoniazid and Ethambutol), resistance to Rifampicin may develop. Thus, it is crucial to consider which functional drugs the patient received between the time of DST specimen collection and the time of the new regimen design (i.e. consider whether resistance has developed to any of the functional drugs).

The DST result that prompts a change in treatment may not accurately reflect the bacterial population at the time it is reported since it reflects the bacterial population at the time the sputum was collected. It is also important to note that a high level of confidence in the laboratory is needed for effective use of the regimens mentioned in this presentation. DST of Ethambutol and Pyrazinamide is not highly reproducible.

### Table 5.5. Suggested Treatment Regimens for Mono- and Poly-Resistance Patterns.

|  |  |  |  |
| --- | --- | --- | --- |
| Pattern of drug  Resistance | Suggested treatment | Duration of treatment | Comments |
| H + S | R, Z &E | 6 -9 | A FQ may strengthen the regimen for patients with extensive disease |
| H and Z | R, E and FQ | 9-12 | A longer duration of treatment should be used to patients with extensive disease |
| H and E | R, Z and FQ | 9-12 | A longer duration of treatment should be used to patients with extensive disease |
| R | H, E, FQ + at least 2 months of Z | 12-18 | An injectable agent may strengthen the regimen for patients with extensive disease |
| R and E (+ S) | H, Z, FQ + an injectable for at least the first 2-3 months | 18 | A longer course (6months) of the injectable drug may strengthen the regimen for patients with extensive disease |
| R and Z (+ S) | H, E, FQ + an injectable for at least the first 2-3 months | 18 | A longer course (6 months) of the injectable drug may strengthen the regimen for patients with extensive disease |
| H, E, Z (+ S) | R, FQ + an oral second line agent,  + an injectable for the first 2-3  months | 18 | A longer course (6 months) of the injectable drug may strengthen the regimen for patients with extensive |

Pattern of Drug Resistance

# 6. Management of Adverse Reactions to DR-TB Drugs

## 6.1. Adverse Reactions to Second-Line Drugs

Second-line drugs for treating DR-TB are generally toxic and very difficult to tolerate. The adverse effects of drugs used in treatment of DR-TB are shown in detail in the following Tables. Close monitoring of patients is necessary to ensure that the adverse effects of these drugs are quickly recognized. Aside from clinical monitoring, basic audiometric screens and simple vestibular function assessments, biochemical monitoring of electrolytes, liver function, renal function, and thyroid function are important. In addition to visual acuity assessments, tests to detect peripheral neuropathy are sometimes needed. If adverse effects are mild, continuation with supportive psychological and pharmacological therapy with minor dosage reduction of the problematic drug is required. If the adverse event is severe or potentially dangerous, such as a significant neurological reaction, then a more intensive management strategy is necessary. The effective management of adverse reactions has been proven possible without sacrificing the clinical efficacy of DR-TB treatment. It is also of importance to note that while depression, anxiety, and psychosis during DR-TB treatment have been found to be quite common, Cycloserine could still be the drug of choice (with dosage modification) for the majority of patients when concurrent psychiatric pharmacotherapy is given. Psychosocial support is also an important component in the management of adverse effects. DOT supporters, both professionals and volunteers, have an important role to play through education, counseling and encouragement of patients with DR-TB.

The following are some interventions that might be helpful in managing DR-TB adverse reactions:

* Pain and Cough Relief
* Paracetamol, Dextropropoxyphene, Codeine and Morphine constitute the analgesic ladder to meet pain control requirements
* Codeine and other cough suppressants to control irritating cough
* Oxygen for alleviating hypoxemia and shortness of breath
* Morphine for relief of intractable terminal dyspnea
* Nutritional Support
* Small and frequent meals for comfort
* Metoclopramide, Prochlorperazine or Promethazine to alleviate nausea and vomiting
* Regular medical visits.

Even with cessation of therapy, regular visits by or to a health-care team, should continue to provide psychological support, necessary infection control measurement and symptomatic treatment such as: antihistamines, antidepressants, anxiolytics, inhaled bronchodilators / corticosteroids and if necessary, hospice or home nursing care.

Palliative care such as supportive measures and end-of life care for DR-TB hospitalization for terminal illness should be provided to those who cannot be cared for at home, or who prefer inpatient management.

Home based care to assist families who wish to keep their diseased members at home. Oral care and prevention of decubitus ulcers and muscle/joint contractures should be indicated for all bedridden patients.

## 6.2. Monitoring of side effects should include the following base line work up

* Full blood count
* In highly risk patients (over 50 years, renal insufficiency, DM, HIV, underweight), creatinine should be evaluated every week or every other week for at least the first month of treatment
* Creatinine clearance may be needed for high risk group patients
* Audiometry or hearing evaluation
* Visual acuity and color vision evaluation
* If serum Potassium is low, check the Magnesium and Calcium levels
* Special attention should be paid for:
* Liver toxicity
* Vestibular and hearing toxicity with injectable drugs
* Psychiatric disorders with Cycloserine
* Allergic reactions
* Hematological changes

## 6.3. Management of side effects (general considerations)

* All Anti-Tuberculosis drugs are associated with side effects
* Adverse effects are not a contraindication to appropriate treatment
* Poorly managed side effects may lead to non-adherence or inappropriate therapy
* Minor side effects are common during initial months of treatment
* Serious reactions are rare but require attention
* Community health workers and DOT enable close surveillance for adverse effects during ambulatory treatment besides, close communication with patient and family members
* Timely diagnosis and early management are crucial
* Exploration of alternative etiologies and contributing factors are important
* Correction of underlying abnormalities
* Changes to MDR-TB regimen are rarely indicated
* Ambulatory management is usually adequate.

### Table6.1. Adverse Reactions to Anti-Tuberculosis Drugs Used for Treatment of DR-TB

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Common** | **Uncommon** | **Rare** |
| Pyrazinamide | Anorexia | Hepatitis | Sideroblastic anaemia |
| Nausea | Vomiting | Gout |
| Flushing | Arthralgia |  |
| Photo-sensitization | Cutaneous reactions |  |
| Ethambutol |  | Retro bulbar neuritis | Hepatitis |
|  | Arthralgia | Cutaneous reactions |
|  |  | Peripheral neuropathy |
| Streptomycin | Cutaneous hypersensitivity | Vertigo | Renal damage |
| Giddiness | Ataxia | Aplastic anemia |
| Numbness | Deafness |  |
| Tinnitus |  |  |
| Thiacetazone | Gastrointestinal reactions | Hepatitis | Agranulocytosis |
| Cutaneous hypersensitivity | Erythema multiforme |  |
| Vertigo | Exfoliative dermatitis |  |
| Conjunctivitis | Haemolytic anaemia |  |
| Amikacin, Kanamycin, Capreomycin | Ototoxicity: hearing damage | Clinical renal failure | Hypokalaemia |
| Vestibular disturbance |  | Hypocalcaemia |
| Nephrotoxicity: deranged renal function tests |  | Hypomagnesaemia |
| Ofloxacin, Ciprofloxacin | Gastrointestinal reactions | Anxiety | Convulsions |
| Insomnia | Dizziness | Haemolysis |
| Thrush | Headache | Tendonitis/tendon rupture |
|  | Tremor | Arthropathy |
|  |  | Colitis |
| Levofloxacin, Moxifloxacin | Similar to those of Ofloxacin or Ciprofloxacin, except less central nervous system dysfunction | | |
| Ethionamide, Prothionamide | Metallic taste | Hepatitis | Convulsions |
| Salivation | Peripheral neuropathy | Mental disturbances |
| Gastrointestinal reactions | Headache | Impotence Menstrual  disturbances |
|  |  | Gynaecomastia |
|  |  | Hypothyroidism |
|  |  | Hypoglycemia |
|  |  | Alopecia |
| Cycloserine | Dizziness | Agitation | Sideroblastic anaemia |
| Headache | Psychosis | Stevens–Johnson syndrome |
| Depression | Convulsions |  |
| Memory loss |  |  |
| Para-aminosalicylic acid | Gastrointestinal reactions | Hepatitis | Hypothyroidism |
|  | Drug fever | Hematological reactions |
|  | Cutaneous reactions | Hypokalaemia |
|  |  | Metabolic acidosis |
|  |  | Sodium overload |
| Clofazimine | Photo-sensitization | Gastrointestinal reactions | Intestinal obstruction |
| Hyperpigmentation | Retinopathy |  |
| Cutaneous reactions |  |  |
| Amoxicillin- Clavulanate | Gastrointestinal reactions | Headache | Hepatitis |
| Cutaneous hypersensitivity | Hematological reactions | Colitis |
|  | Hypersensitivity vasculitis | Stevens–Johnson syndrome  Convulsions |
| Linezolid | Diarrhea | Thrombocytopenia | Colitis |
| Dyspepsia | Aplastic anaemia | Peripheral and optic neuropathies |
| Headache |  |  |

### Table 6.2. Management of Adverse Reactions of DR- TB Drugs

|  |  |  |  |
| --- | --- | --- | --- |
| Adverse Reactions | Suspected Agents | Suggested Management Strategies | Comments |
| Seizures | Cs,H,  Fluoroquinolones | * Suspend suspected agent pending resolution of seizures * Initiate anticonvulsant therapy (e.g. Phenytion,Valproic acid) * Increase pyridoxine to maximum daily dose (200mg / day) * Restart suspected agent or reinitiate suspected agent at lower dose, if essential to the regimen * Discontinue suspected agent if this can be done without compromising the regimen | * Anticonvulsant is generally continued until MDR-TB treatment completed or suspected agent discontinued * History of previous seizure disorder is not a contraindication to the use of agents listed here if patients, seizures are well controlled and/ or patient is receiving anticonvulsant therapy * Patients with history of prior seizures may be at increased risk for development of seizures during DR –TB therapy |
| Peripheral Neuropathy | Cs, Lzd, H, S,Km, Am,Cm, Eto/Pto, Fluoroquinolones | * Increase pyridoxine to maximum daily dose (200mg / day) * Change injectable to Capreomycin if patient has documented susceptibility to Capreomycin * Initiate therapy with tricyclic antidepressant such as Amitriptyline. Non-steroidal anti-inflammatory drugs or * Acetaminophen may help alleviate symptoms * Lower dose of suspected agent, if this can be done without compromising regimen * Discontinue suspected agent if this can be done without compromising regimen | * Patients with co-morbid disease (e.g. diabetes, HIV, alcohol dependence) may be more likely to develop peripheral neuropathy, but these conditions are not contraindications to the use of the agents listed here * 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 | * Document hearing loss and compare with baseline audiometry if available * Change parenteral to oral Capreomycin if patient has documented susceptibility to Capreomycin * Decrease frequency and/or lower dose of suspected agent if this can be done without compromising the regimen (consider administration three times per week) * Discontinue suspected agent if this can be done without compromising the regimen | * Patients with co-morbid disease (e.g. diabetes, HIV, alcohol dependence) may be more likely to develop peripheral neuropathy, but these conditions are not contraindications to the use of the agents listed here * Neuropathy may be irreversible; however, some patients may experience improvement when offending agents are suspended |

### Table6.3. Commonly Used Ancillary Medications

|  |  |
| --- | --- |
| Nausea, vomiting, upset stomach | Metoclopramide Prochlorperazine Promethazine |
| Heartburn, acid indigestion, sour stomach, ulcer | H2-blockers (ranitidine, famotidine, etc.), proton pump inhibitors (Omeprazole, etc.) Avoid antacids because they can decrease absorption of Flouroquinolones |
| Oral candidiasis (non-AIDS patient) | Fluconazole, Clotrimazole lozenges, etc |
| Diarrhea | Loperamide or other anti-diarrheal |
| Depression | Selective serotonin reuptake inhibitors (Fluoxetine, Sertraline), tricyclic antidepressants (Amitriptyline) |
| Prophylaxis of neurological complications of cycloserine | Pyridoxine (vitamin B6) |
| Peripheral neuropathy | Amitriptyline |
| Vestibular symptoms | Meclizine, Dimenhydrinate, Prochlorperazine, Promethazine |
| Musculoskeletal pain, arthralgia, headaches | Ibuprofen, Paracetamol |
| Cutaneous reactions, itching | Hydrocortisone cream, calamine, caladryl lotions |
| Systemic hypersensitivity reactions | Antihistamines (Diphenhydramine, Chlorpheniramine, Dimenhydrinate), corticosteroids (prednisone, Dexamethasone) |
| bronchospasm | Inhaled beta-agonists (Albuterol,etc.), inhaled corticosteroids (Beclomethasone,etc.), oral steroids (Prednisone), injectable steroids (Dexamethasone, Methylprednisolone) |
| Hypothyroidism | Levothyroxine |
| Electrolyte wasting | Potassium and magnesium replacement |
| Severe anxiety | Lorazepam, Diazepam, Clonazepam |
| Insomnia | Dimenhydrinate |
| Psychosis | Haloperidol, Thorazine, Risperidone (consider Benzotropine or Biperidene to prevent extrapyramidal effects) |
| Seizures | Phenytoin, Carbamazepine, Phenobarbital |

# 7. DR-TB Treatment in Special Conditions

## 7.1. Objectives

This section outlines the administration of drug-resistant TB in the following special conditions and situations:

* Pregnancy
* Breastfeeding
* Contraception
* Children
* Diabetes mellitus
* Renal insufficiency
* Liver disorders
* Seizure disorders
* Psychiatric disorders
* Substance dependence

### 7.1.1. Pregnancy

All female patients of childbearing age should be tested for pregnancy when initially diagnosed. Pregnancy is not a contra-indication for treatment of DR-TB although this disease does present great hazards to both the mother and fetus. However, birth control is strongly recommended for all non- pregnant women receiving therapy for DR-TB.Pregnant patients should be carefully evaluated, taking into consideration the gestational age and severity of the DR-TB with careful consideration of the risks and benefits of treatment. Because the major teratogenic effects occur in the first trimester, therapy may be delayed until the second trimester if clinically feasible.

In general, Aminoglycosides should be avoided in treatment regimens for DR-TB among pregnant women as they can be particularly ototoxic to the fetus. Capreomycin may carry the same risk to a lesser extent. Ethionamide can aggravate nausea and vomiting in some pregnant women, and as teratogenic effects have been observed in animal studies, it appears to be safer to add this drug after delivery.

### 7.1.2. Breastfeeding

Women who are breastfeeding and have active drug-resistant TB should receive a full course of anti-tuberculosis treatment. Timely and properly applied chemotherapy is the best way to prevent transmission of tubercle bacilli to her baby through airborne contacts. However, among lactating mothers on treatment, most anti-tuberculosis drugs consequentially found in breast milk are of concentrations fractionally smaller than the therapeutic dose used for an infected infant. Despite this, the effects of such exposure to infants during the full course of DR-TB treatment have yet to be established. Mother and baby ideally should not be completely separated, but if the mother is sputum smear-positive then she should transfer the care of the baby to another family member, until she becomes sputum smear-negative. When the mother and infant are together, this common time should be spent in well-ventilated areas or outdoors. It may be ideal that the mother be offered the option of using a surgical mask or an N-95 respirator until she becomes sputum smear-negative.

### 7.1.3. Contraception

There is no contra-indication for the use of oral contraceptives with the non-Rifampicin containing regimens. Patients who vomit directly after taking an oral contraceptive can be at risk of decreased absorption of the drug which therefore becomes less beneficial. These patients should be advised to take their contraceptives apart from times when they may experience vomiting caused by the anti-tuberculosis treatment. Patients who vomit within the first two hours after ingesting an oral contraceptive should use a barrier method for a month until the contraceptive tablets can be tolerated. For patients with mono or poly-resistant TB and are susceptible to Rifampicin, an alternative to commonly used oral contraceptives should be sought since Rifampicin negatively interacts with such contraceptives resulting in decreased pregnancy prevention. A woman on oral contraception while receiving Rifampicin treatment may choose, following a consultation with her physician, the use of an oral contraceptive pill containing a higher dose of estrogen (at least 50 μg) or the use of another form of contraception.

### 7.1.4. Children

Children with drug-resistant TB generally have primary resistance transmitted from an index case with drug-resistant TB. DST should be used to guide therapy, although children with paucibacillary TB are often culture-negative. Still, every effort should be made to confirm drug-resistant TB bacteriologically by DST to avoid needless exposure to toxic drugs. The treatment of culture-negative children, with clinical evidence of active TB disease or contact with a documented case of drug-resistant TB, should be guided by the results of DST as well as their history of exposure to anti-tuberculosis drugs. Unfortunately there are only a limited number of reported cases documenting the use of second-line drugs in children over extended periods of time. The risks and benefits of each drug should be carefully considered when designing a regimen. Frank discussion with family members is critical, especially at the outset of therapy. No anti-tuberculosis drugs are absolutely contraindicated in children, and the few cases available have reported that children with drug-resistant TB have generally tolerated second-line drugs rather positively. Although Fluoroquinolones have been shown to retard cartilage development in beagle puppies, experience with the use of Fluoroquinolones has not demonstrated similar effects in humans. The benefits of Fluoroquinolones in treating MDR-TB in children outweigh the risks. Ethionamide, PAS, and Cycloserine have been shown both effective and well tolerated among pediatric patients. In general, anti-tuberculosis drugs should be dosed according to body weight (see table below,' Pediatric Dosage of Second-Line Antituberculosis Drugs'). Monthly monitoring of body weight is therefore especially important in pediatric cases and dose adjustments should be made as healthy weight gain occurs. All drugs, including Fluoroquinolones, should be prescribed at maximum recommended dosage whenever possible, except Ethambutol which should be used at 15 mg/kg (not 25 mg/kg as sometimes used in adults with MDR-TB since it is more difficult to monitor for optic neuritis in children). In children who are not initially culture-positive, treatment failure is difficult to assess. Persistent abnormalities on chest radiographs do not necessarily signify a lack of improvement. In children, weight loss, or more commonly failure to gain adequate weight, is of particular concern and often one of the first (or only) concerns.

### Table7.1: Pediatric Dosage of Second-Line Anti-Tuberculosis Drugs

|  |  |  |  |
| --- | --- | --- | --- |
| **Drug Daily Dose ( mg/kg) Frequency Maximum Daily dose** | | | |
| Streptomycin | 20-40 | Once daily | 1 g |
| Kanamycin | 15-30 | Once daily | 1 g |
| Amikacin | 15-22.5 | Once daily | 1 g |
| Capreomycin | 15-30 | Once daily | 1 g |
| Ofloxacin | 15-20 | Twice daily | 800 mg |
| Levofloxacin | 7.5-10 | Once daily | 750 mg |
| Moxifloxacin | 7.5-10 | Once daily | 400 mg |
| Gatifloxacin | 7.5-10 | Once daily | 400 mg |
| Ethionamide | 15-20 | Twice daily | 1 g |
| Protionamide | 15-20 | Twice daily | 1 g |
| Cycloserine | 10-20 | Once or twice daily | 1 g |
| P-aminosalicylic acid | 150 | Twice or three times daily | 12 g |

### 7.1.5. Diabetes Mellitus

Diabetic patients with DR-TB are often at risk for poor outcomes. The presence of diabetes mellitus may amplify the adverse effects of anti-tuberculous drugs, especially renal dysfunction and peripheral neuropathy. Diabetes must be managed closely throughout the treatment of drug-resistant TB. The health-care provider should be in close communication with the physician who manages the patient’s diabetes. Oral hypoglycemic agents are not contraindicated during the treatment of drug-resistant TB but the daily dosage may have to be adjusted to provide a better blood sugar control. The use of Ethionamide or Protionamide may increase the difficulty in controlling the daily Insulin production levels. KFT and electrolytes have to be monitored regularly throughout treatment phase.

### 7.1.6. Renal Insufficiency

Renal insufficiency caused by longstanding TB infection itself or previous use of amino-glycosides is common. Great care should be taken in the administration of second-line drugs in patients with renal insufficiency, and the dose and/or the interval between dosing should be adjusted according to the following table:

### Table 7.2.Adjustment of Anti-tuberculosis Medication in Renal Insufficiency

|  |  |  |
| --- | --- | --- |
|  |  | **With Creatinine Clearance <30 for Patients Receiving**  **Haemodialysis** |
|  |  |
| Isoniazid | No Change | 300 mg once daily, or 900 mg three times/week |
| Rifampicin | No Change | 600 mg once daily, or 600 mg three times/ week |
| Ethambutol | Yes | 15–25 mg/kg/ dose three times/ week (not daily) |
| Pyrazinamide | Yes | 25–35 mg/kg/ dose three times / week (not daily) |
| Ciprofloxacin | Yes | 1000–1500 mg/ dose three times/ week (not daily) |
| Oflaxacin | Yes | 600–800 mg / dose three times / week (not daily) |
| Levofloxacin | Yes | 750–1000 mg / dose three times / week (not daily) |
| Maxifloxacin | No Change | 400 mg once daily |
| Gatifloxacin | Yes | 400 mg / dose three times / week (not daily) |
| Cycloserine | Yes | 250 mg once daily, or 500 mg/dose three times/ week |
| Terizidone | - | Recommendations not available |
| Protionamide | No Change | 250–500 mg/ 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 twice or three times/ week  (not daily) |
| Capreomycin | Yes | 12–15 mg/kg / dose twice or three times / week  (not daily) |
| Amikacin | Yes | 12–15 mg/kg/ dose twice or three times / week  (not daily) |
| Kanamycin | Yes | 12–15 mg/kg/ dose twice or three times/ week  (not daily) |

### 7.1.7. Liver disorders

The first-line drugs Isoniazid, Rifampicin and Pyrazinamide are all associated with hepatotoxicity. Of the three, Rifampicin is least likely to cause hepatocellular damage although it is associated with cholestatic jaundice. On the other hand, Pyrazinamide is the most hepatotoxic of the three first-line drugs. The second-line drugs Ethionamide, Protionamide, and PAS can also be hepatotoxic but to a lesser extent than the first-line drugs. Hepatitis occurs rarely with the Fluoroquinolones. Patients with a liver disease history can receive the usual drug-resistant TB chemotherapy regimens provided there is no clinical evidence of chronic liver disease, hepatitis virus carriage, past history of acute hepatitis, or excessive alcohol consumption. However, hepatotoxic reactions to anti-tuberculosis drugs may be more common in these patients and should be anticipated. In general, patients with chronic liver disease should not receive Pyrazinamide. All other drugs can be used, but under close monitoring of liver enzymes. If significant aggravation or inflammation of the liver occurs (when liver enzymes level is 5 times greater than the average) the drug(s) responsible should be stopped. While rare, a patient with TB may have concurrent acute hepatitis that is unrelated to TB or anti- tuberculosis treatment; in such cases, clinical judgment is necessary to defer anti-tuberculosis treatment until the acute hepatitis has been resolved. When necessary to treat drug-resistant TB during acute hepatitis, the combination of four non-hepatotoxic drugs is the safest option.

### 7.1.8. Seizure Disorders

Some patients requiring treatment for drug-resistant TB may have or are currently experiencing Seizure disorders. The first step when evaluating such patients is to determine whether the disorder is under control and if the patient is taking anti-seizure medication. If the seizures are not under control, initiation or adjustment of anti-seizure medication is imperative prior to the start of drug-resistant TB therapy. The underlying conditions or causes of seizures should also be addressed. Cycloserine should be avoided in patients with active seizure disorders that are not well controlled with medication. However, in cases where Cycloserine is a crucial component of the treatment regimen, the drug should be administered while adjusting relevant anti-seizure medications to achieve greater seizure control. The risks and benefits of providing Cycloserine should be discussed with the patient to reach a mutual decision on its use. Isoniazid and Rifampicin may also interfere with many anti-seizure medications. Drug interactions should always be checked prior to treatment initiation. Seizures that develop during anti-tuberculosis therapy are likely to be the result of an adverse effect of one of the treatment drugs employed.

### 7.1.9. Psychiatric Disorders

It is recommended that psychiatric patients be evaluated by a professional psychiatric health-care worker prior to the start of treatment for drug-resistant TB. The initial evaluation should document any existing psychiatric conditions and establish baselines for comparison if any new psychiatric symptoms develop while during TB treatment. Any psychiatric illness identified prior to or during treatment should be fully addressed. High baseline incidence of depression and anxiety often exists in patients with MDR-TB and is connected with the chronic nature and socioeconomic stressors related to the disease. Psychiatric management with medication or individual/group therapy may be necessary to manage the TB patient’s initial psychiatric condition or adverse psychiatric effects caused by TB treatment. Group therapy has been shown to be very successful in providing MDR-TB patients with supportive environments and may in turn be helpful for patients with or without psychiatric conditions (adequate measures to prevent infection risk should be implemented when group therapy is employed).The use of Cycloserine is not absolutely contraindicated for the psychiatric TB patient. Adverse effects from Cycloserine may be more prevalent in the psychiatric patient, but the potential benefits of this drug outweigh the negative risks associated with these adverse effects. Close monitoring is recommended if Cycloserine is included in the TB treatment regimen of patients with psychiatric disorders. All health-care workers treating drug-resistant TB should work closely with a mental health specialist and have contingency plan in place if psychiatric emergencies take place. Such emergencies may include psychosis, suicidal intentions, or the potential development of a violent confrontation involving the patient and those around him/her.

### 7.1.10. Substance Dependence/Abuse

Patients with substance dependence disorders should be offered treatment for their addictions. Complete abstinence from alcohol or other potential negative dependencies should be strongly encouraged although active consumption of problematic substances is not necessarily a contraindication for TB treatment. However, if TB treatment is repeatedly interrupted because of the patient’s dependence, TB therapy should be suspended until successful measures to ensure adherence have been established. Good DOT provides the patient with contact and support from health-care providers resulting in successful treatment completion even if they are suffering from substance abuse. Cycloserine may result in higher incidence of adverse effects (such as seizure occurrence) among patients dependent on alcohol or other substances. However, if Cycloserine is crucial to the treatment regimen, its use requires close patient observation for adverse effects which should in turn be adequately treated.

## 7.2. Adjunctive Therapies and the Role of Surgery in MDR Management

### 7.2.1. Adjunctive Therapies

**Nutritional Tips**

* DR-TB can be exacerbated by poor nutritional status
* Second-line drugs may also further decrease the appetite, making adequate\* nutrition a greater challenge
* Vitamin B6 (pyridoxine) should also be given to all patients receiving cycloserine to prevent adverse neurological effects
* Minerals (zinc, iron, calcium, etc.) should be administered at a different time from the Fluoroquinolones, as they can interfere with their absorption

**Corticosteroids**

* Corticosteroids are beneficial in cases of severe respiratory insufficiency and CNS involvement
* Prednisone starting dose at approximately 1 mg/ kg, with gradual decrease in the daily dose by 10 mg/week when a longer course is indicated
* Used also in COPD exacerbation, prednisone in a short tapering course over 1–2 weeks, starting at approximately 1 mg/kg and decreasing the dose by 5–10 mg/ day

**Cross-Resistance**

Consideration of cross-resistance is important for selecting the drugs acceptable for treatment of apparent or proven DR tuberculosis. As usual in the treatment of infectious diseases when the combination of several drugs is required, it is ineffective to combine two drugs of the same group or to combine in the prescribed chemotherapy regimen a drug potentially ineffective because of cross-resistance.

***Examples:***

**Thioamides and Thioacetazone**: Ethionamide, in the group of Thioamides, induces complete cross-resistance with Prothionamide. They should be considered as the same drug. Frequently there is also cross resistance between Thioamides and Thioacetazone. Strains naturally resistant to Thioacetazone are usually still susceptible to Ethionamide-Prothionamide and strains resistant to Ethionamide-Prothionamide are usually resistant also to Thioacetazone, in more than 70% of cases.

**Aminoglycosides:** Strains resistant to Streptomycin are susceptible to Kanamycin-Amikacin. Resistance to Kanamycin induces a complete cross-resistance with Amikacin and they should be considered as the same drug. Resistance to Kanamycin-Amikacin induces also resistance to Streptomycin. Strains resistant to Streptomycin, Kanamycin, and Amikacin are still susceptible to Capreomycin.

**Fluoroquinolones:** Ofloxacin, Ciprofloxacin induces complete cross-resistance for all Fluoroquinolones. That is why you should carefully consider the use of Ofloxacin, since some new more active Quinolones (e.g. Levofloxacin) could replace Ofloxacin in the future. There is no cross-resistance with other classes of drugs.

**Cycloserine and Terizidone:** There is complete cross-resistance between these two drugs, so they should be considered as the same drug. There is no cross-resistance with other classes of drugs.

### 7.2.2. Role of Surgery in DR-TB Management

The most common operative procedure in patients with pulmonary DR-TB is resection surgery (taking out part or all of a lung). Large case-series analysis has shown resection surgery to be effective and safe under appropriate surgical conditions. It is considered as an adjunct to chemotherapy and appears to be beneficial for patients when a review panel decision is made and skilled thoracic surgeons and excellent postoperative care are available. It is not indicated in patients with extensive bilateral disease. Resection surgery should be timed to offer the patient the best possible chances of cure with the least morbidity. Thus, the timing of surgery may be earlier in the course of the disease when the patient’s risk of morbidity and mortality is lower, for example, when the disease is localized in one lung or one lung lobe and should not be considered as a last resort. Generally, bacterial infection therapy should be given for at least two months before resection surgery. Even with successful resection, an additional 12–24 months of chemotherapy should be given.

## 7.3. Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis

Specialized surgical facilities should include stringent infection control measures, since infectious substances and aerosols are generated in large quantities during surgery and during mechanical ventilation and postoperative pulmonary hygiene maneuvers. Many programmes will have limited access to surgical interventions. General indications for resection surgery for programmes with limited access to surgery include patients who remain smear-positive, with resistance to a large number of drugs; and localized pulmonary disease. Computerized tomography, pulmonary function testing and quantitative lung perfusion/ ventilation are recommended as part of the preoperative work-up. Programmes with suboptimal surgical facilities and no trained thoracic surgeons should refrain from resection surgery, as the result may be an increase in morbidity or mortality.

# Section 8. HIV infection and DR-TB

## 8.1. Objective

The WHO and Joint United Nations Program on HIV/AIDS (UNAIDS) recommend that all TB patients undergo HIV testing and subsequent data be used for HIV surveillance among TB patients.

## 8.2. Anti-Retroviral Therapy (ART) in DR-TB/HIV Patients.

TB is an indicator disease for ART, irrespective of CD4 cell count. ART is similarly recommended for DR-TB/HIV-infected cases given the elevated mortality in these co-infected patients. ART should not be delayed for fear of excess patient medication. In addition, usual protocols on the prevention of immune- reconstitution syndrome should be followed.

## 8.3. Treatment Follow-Up by a Specialized Team

These teams should be familiar with treatment for both DR-TB and HIV to closely monitor potentially additive adverse effects, provide prophylaxis and treatment of opportunistic infections, and offer general primary care as well as necessary vaccinations and nutritional support. The presentation of DR-TB does not differ from that of drug-susceptible TB in the HIV-infected patient. The diagnosis of TB in HIV-positive people is more complicated and may be confused with other pulmonary or systemic infections since in such cases TB is more likely to be extra-pulmonary or associated with negative sputum smears. Thus, misdiagnoses or delays in diagnosis may occur resulting in higher rates of morbidity and mortality. The use of X-ray and/or culture improves the ability to early diagnose TB in HIV patients and is recommended if such tools are available. All HIV patients with TB should be screened for DR-TB with DST. Rapid diagnostic techniques for DR-TB should be employed when possible since HIV-infected patients with TB receiving little to no adequate anti-tuberculosis treatment for even short periods of time are at high risk of death.

## 8.4. Concomitant Treatment of Drug-Resistant TB and HIV

The recommended treatment of TB, whether drug-susceptible or resistant, is the same for HIV-infected and non-HIV-infected patients except for Thioacetazone which should not be used. However, TB treatment among such patients is much more difficult and adverse events are more common. Deaths during treatment, regardless of the causal disease, are more frequent in HIV-infected patients particularly in the advanced stages of immunodeficiency. The use of ART in HIV-infected patients with TB improves survival and slows progression to AIDS despite the fact that initiation of ART in HIV-infected patients with drug-susceptible or drug-resistant TB is often associated with adverse events that may lead to the interruption of both TB and/or HIV therapy. Information on when and how to design regimens for HIV treatment is available in other WHO publications. Given a large amount of drugs that need to be ingested and the potential of overlying toxicities, the following issues should be considered:

**Potential Drug Interactions in the Treatment of Drug-Resistant TB and HIV**

There are several known interactions among drugs used to treat TB and HIV. Rifamycins (Rifampicin and Rifabutin), while not used in DR-TB treatment, are needed in the treatment of many mono and poly-resistant cases. Rifamycins may lower the levels of protease inhibitors and non-nucleoside reverse transcriptase inhibitors contributing to the development of these drugs’ resistance, and Rifabutin has the least effect of all the Rifamycins. ART drugs increase the level of Rifampicin and thus the risk of toxicity. Other interactions include those between Fluoroquinolones and Didanosine. Non-enteric coated Didanosine contains an aluminum/ magnesium-based antacid that, if given jointly with Fluoroquinolones, may result in decreased Fluoroquinolone absorption and therefore should be given six hours before or two hours after Fluoroquinolone administration. Clarithromycin, a drug that is not routinely recommended for DR-TB by the WHO but used by some programs, is also known to have several interactions with HIV medications**.**

**Potential Drug Toxicity in the Treatment of Drug-Resistant TB and HIV**

HIV patients typically experience high rates of adverse drug reactions to both TB and non-TB medications. Known adverse effects of increased severity in co-infected patients include peripheral neuropathy (Stavudine, Aminoglycosides, Cycloserine, Pyrazinamide), Cutaneous and Hypersensitivity reactions (Thioacetazone), gastrointestinal adverse effects, renal toxicity (injectable drugs), and neuropsychiatric effects (Cycloserine and Efavirenz).

**Monitoring of Drug-Resistant TB and HIV Therapies in Co-infected Patients**

HIV ART medication must be given daily to co-infected patients through DOT. The complexity of ART regimens and treatment of drug-resistant TB demands rigorous monitoring among this particular group of patients, each with its own specific toxicity profiles (some of which may be potentiated by concomitant therapy). Ideally, ART should be initiated and monitored in collaboration with a health- care provider knowledgeable in both drug-resistant TB and HIV. Standard observation procedures for those on ART should be followed. Monitoring of chest X-rays, smears and cultures in the co-infected patient is the same as for HIV-negative DR-TB patients. Patients with HIV-associated DR-TB will usually require extraordinary social support as together these regimens are particularly difficult to tolerate as well as the stigma of both diseases, all of which may result in an elevated risk of mortality.

## 8.5. Special Considerations

The following activities are recommended by the WHO to decrease the dual burden of TB and HIV:

* The establishment of collaboration mechanisms
* Decreasing the burden of TB in people suffering from HIV/AIDS (through intensified TB case finding, introduction of Isoniazid preventive therapy, and ensuring TB infection control in health-care and congregate settings)
* Decreasing the burden of HIV in TB patients (through HIV testing and counseling, HIV prevention methods, Co-trimoxazole prophylaxis, and antiretroviral therapy).

Such activities constitute the backbone of the WHO TB/HIV collaborative strategy, which along with proper DOT, should be established prior to the initiation of TB/HIV collaborative strategies to prevent potential treatment failures and thus increased relevant patient morbidity rates.

DR-TB in HIV-infected patient carries a high risk of mortality, especially when diagnosed late. Furthermore, extra-pulmonary localization has also been identified as an independent poor prognostic factor. Thus, drug susceptibility testing should be performed in cases of active TB in HIV-infected individuals with risk factors for DR-TB, or in areas where high rates of DR-TB have been identified. ART is recommended for MDR-TB/HIV-infected patients given the excessive mortality rates among these subjects. In general, ART should not be delayed for fear of excess patient medication. The usual protocols to ameliorate immune reconstitution inflammatory syndrome should be followed. Known drug interactions in DR-TB/HIV are relatively uncommon. However, one example is the Fluoroquinolone–Didanosine interaction, which results in decreased absorption of the Fluoroquinolone when suitable spacing is not allowed between the administrations of the two drugs. HIV-infected patients usually have a higher rate of adverse drug reactions to both anti-tuberculosis drugs and other concomitant medications.

## 8.6. Summary

Understanding the regional prevalence of HIV, DR-TB, and DR-TB/HIV co-infection is the first step in developing strategies for DR-TB/HIV activities. Patients with drug-resistant TB and HIV require intensive medical care to decrease the high level of mortality. Rigorous infection control measures should also be implemented. All drug-resistant TB and HIV control programs should coordinate collaborative activities described in this section to prevent the occurrence of HIV related DR-TB epidemics.

# 9. Management of Extensively Drug Resistance (XDR) Cases

## 9.1. Definition of XDR-TB

XDR-TB (Extensively Drug Resistant Tuberculosis) is a form of TB identified by its resistance to at least Isoniazid and Rifampicin in addition to any Fluoroquinolone and at least one of the second-line anti-TB injectable drugs (Amikacin Kanamycin or Capreomycin).

## 9.2. Epidemiology

The identification of XDR-TB was first used in 2006 following a joint survey by the WHO and the US Centers for Disease Control and Prevention (CDC). The incidence of this subset of resistant tuberculosis is 2-8% and may be even greater in high TB burden countries where control programs are not yet well established.

## 9.3. Available Drugs to Treat XDR Tuberculosis

Aminoglycosides: Kanamycin & Amikacin (15 mg/Kg. maximum dose 1 Gram/day) are bactericidal. Amikacin is better tolerated and can be given IM & IV.Capreomycin (15 mg/Kg. maximum dose 1 g/day) is bactericidal and very expensive. It is very useful in cases with tubercle bacilli resistant to Streptomycin, Kanamycin and Amikacin

Thioamides: Ethionamide(10-20 mg/kg.maximum 750 mg/day) is bactericidal but causes more GI upset

Cycloserine: (10-20 mg/kg. maximum 1 g/day), it is bacteriostatic with no cross-resistance with other antituberculosis agents

Para-aminosalicylic acid (PAS): (120mg/Kg. maximum dose 12 g/day in divided doses), it is bacteriostatic and need large number of tablets to swallow

Thioacetazone: (4mg/Kg/ 150mg/day), it is a weak bacteriostatic drug with risk of cross-resistance with Ethionamide and additional toxicity when Thioacetazone is used along with Thioamide

Clofazimine :It inhibits mycobacterial growth

Oxazolidinones: Linizolid is bacteriostatic and have shown activity against M. tuberculosis in a murine model. Linezolid has been used sporadically in DR-TB patients. Although all reports are anecdotal, linezolid does seem to have biologic activity as evidenced by sputum culture conversion. Linizolid (600 mg twice daily for adults) is safe for courses of therapy of <28 days, but on long-term use causes reversible hematopoietic suppression, primarily thrombocytopenia and peripheral and optic neuropathy on prolonged use

Macrolides: Second generation macrolides i.e. Clarithromycin, Roxithromycin, and Azithromycin are the most active clinical agents against the MAC (Mycobacterium Avium Complex) but unfortunately it is not effective against M. tuberculosis

Amoxicillin-Clavulanate: It is active against M. tuberculosis in vitro but it penetrates poorly in mammalian tissue that limits its effectiveness in tuberculosis treatment

Pyrazinamide: Some authorities recommend use of Pyrazinamide as the resistance is neither easy to acquire nor to prove by susceptibility testing. Pyrazinamide is bactericidal in an acid medium (bacilli inside macrophages)

Others: Streptomycin and Ethambutol can be used if they are sensitive. When resistance to Streptomycin is confirmed, one of the other Aminoglycosides can be used as a bactericidal agent against actively multiplying organisms.

## 9.4. Principles of Treatment

The patient must know that his or her prescribed regimen is the ultimate chance for recovery from this disease and thus he/ she must exert every effort to tolerate any potential unpleasant side effects that may develop. The following should be implemented:

* All patients with XDR- TB should be admitted for intensive phase treatment.
* The regimen should be tailored according to susceptibility patterns of the relevant disease strain
* The treatment regimen should include a minimum of three drugs but preferably 4-6 drugs if possible
* The treatment should be undertaken in specialized centers under the supervision of XDR-TB specialists. The center should have access to adequate laboratory facilities, isolation arrangements, sufficient drug supplies, and the ability to manage adverse drug reactions

While devising the regimen, the following cross-resistances should be taken into consideration:

1. Ethionamide and Thioacetazone: Cross-resistance exists between Ethionamide and Thioacetazone; strains naturally resistant to Thioacetazone are still usually susceptible to Ethionamide. However, strains resistant to Ethionamide are also resistant to Thioacetazone in over 70% of cases
2. Aminoglycosides: Strains resistant to Streptomycin are susceptible to Kanamycin and Amikacin. Resistance to Kanamycin induces a complete cross-resistance with Amikacin as such should be considered one in the same. Resistance to Kanamycin and Amikacin also induces resistance to Streptomycin. Strains resistant to Streptomycin, Kanamycin, and Amikacin are still susceptible to Capreomycin
3. Fluoroquinolones: There is no cross-resistance with other classes of drugs
4. Cycloserine: There is no cross-resistance with other classes of drugs

The intensive phase should last at least 6 months, provided that the patient has received 4 months of injectable drugs followed by 2 consecutive negative cultures with 30 days apart, followed by a continuation phase of 18 months

All medications should be given under direct observation (DOT) until negative sputum-smears can be produced. The patient must receive personal and psychological support.

# 10. Rational Use of Second Line Drugs

## 10.1. Second-line Anti-TB Drugs Management

The management cycle of drugs comprises six elements: Drug selection, quantitative assessment of drug requirements, and management of procurement, distribution, drug quality assurance and ensuring rational drug use.

### 10.1.1. Selection

According to Iraq GLC application, the following treatment regimens will be used for treatment of MDR- TB patients:

6 months of Kanamycin/ Capreomycin, Pyrazinamide, Levofloxacin, Ethionamide, Cycloserine and PAS and 18 months of Pyrazinamide, Levofloxacin, Ethionamide, Cycloserine and PAS using the following code: 6 Cm(Km)-Z-Lfx-Eto-Cs- PAS /18Z-Lfx- Eth-Cs- PAS. In the absence of DST testing for second line drugs, it is expected that 50% of MDR-TB patients have previous history of using Amikacin or Kanamycin (these patients will receive Capreomycin instead).The treatment regimen will be standardized followed by a slight modification based on the DST result of each patient and the history of using SLD.

### 10.1.2. Quantification

Morbidity based method is recommended and actually used especially for new projects as DR-Tuberculosis in Iraq. In this method, the treatment regimen which is standardized then individualized and the number of patients is considered. The quantities of drugs are calculated accordingly.

### 10.1.3. Procurement

Effective procurement ensures the availability of drugs in right quantities, at the right time, at affordable prices and quality assured standards which is done through GDF and IDA. Lead time for delivery, drug’s shelf-life (18-36 months) and pace of patient enrollment are considered in timely ordering the quantities of needed drugs.

### 10.1.4. Distribution

To preserve quality, drugs should be stored and transported according to good storage practices and recommendations regarding storage temperature and humidity especially that these drugs are thermolabile. Moreover, drugs are used only in specified centers. These precautions should be taken into consideration when ambulatory treatment started.

### 10.1.5. Drug Quality Assurance

Second line drugs supplied from the IDA meet the WHO recommended standards for safety, efficacy and quality.

### 10.1.6. Ensuring Rational Drug Use

Misuse of these drugs may result in loss of susceptibility to these drugs, causing emergence of XDR-TB. For these reasons, the drugs are only available in the centers specified for managing DR-TB cases and personnel trained for that. Second-line drugs, except for quinolones are not available in pharmacies.

# 11. Treatment Continuation and Patient’s Adherence to Therapy

## 11.1. Objective

Patients with DR-TB are more likely to have had problems with non- adherence in the past. Adherence to DR-TB therapy is particularly difficult because of its prolonged treatment regimens with larger number of drugs that have more serious adverse effect profiles; therefore DR-TB patients are at increased risk of non-adherence to treatment.

Treatment adherence is crucial to achieve good results and guard against developing XDR-TB strains. This is achieved through several strategies for the delivery of DR-TB treatment which include:

* Community-based care
* Clinic-based treatment
* Hospitalization
* Very often mixed models are used in MDR care.

Regardless of the mode of the treatment delivery, the management of DR-TB depends on a steady free supply of medicine provided to patients through a reliable network of qualified and trained health providers. DR-TB treatment can be successful, with high overall rates of adherence, when adequate support measures are provided through:

* Awareness and education of patients
* Directly observed therapy (DOT)
* Social and emotional support
* Follow-up of the non-adherent patient.

Early and effective management of adverse drug effects

If possible, the patient will be hospitalized during the first few months of the intensive phase treatment, until such a time when the patient shows evidence of treatment tolerance and no signs or symptoms of adverse reactions. The patient can then be discharged for ambulatory treatment provided that:

* A strong DOT policy is in place
* An infection control policy is well implemented to prevent household transmission of DR-TB to another person
* A proper mechanism for early recognition/management of treatment adverse reaction is established which might include admission to an in-patient DR-TB designated treatment site due to severe adverse reactions.

If the circumstances become difficult to provide hospitalization such as long distances, lack of availability of beds or lack of willingness of the patient to be admitted, then the outpatient treatment will be permitted with a close follow-up of patient from a DOT center close to where he/she is living.

## 11.2. Patient-Centered Approach is considered a Priority for the NTP

It is extremely important to make sure that the patients are adhering to treatment. To this end appropriate brochures and psychosocial counseling should be provided to the patients. In order to ensure a close follow-up of patients, the following information is requested on the treatment card for a better patient identification:

* Complete address of the patient : neighborhood, area or sector, street, house number if applicable, particular surroundings (mosque, shops, administration …)
* Work address for working patients
* Work address of spouse / husband if applicable
* Two phone numbers of the couple in addition to the phone number of the patient

The DOT worker, at the hospital where the patient is hospitalized or in the outpatient department where the patient is receiving treatment, will directly observe each dose of the treatment. If the patient lives far from the hospital or the treatment centers, community service providers will be asked to provide support to these patients. These community health workers and NGOs will receive appropriate training and support to serve as DOT workers. They will visit patients in their homes or work places and they will receive an ongoing supervision by the health professionals. Social support services must be provided to enable patients and their families to adhere to MDR-TB treatment. This includes the provision of incentives which is under discussion within NTP.

Follow up of the patients who might default treatment will be through the same system which is applied to non resistant TB patients. When a patient fails to attend a DOT appointment, the DOT supervisor (health worker or community health worker) will visit the patient’s home within three days of delay to find out the reasons of default and ensure that treatment is resumed promptly and effectively.

## 11.3. Hospitalization

If hospitalization is required, the selected hospital should provide acceptable living conditions, sufficient activities to avoid boredom, adequate food, a heating system in cool areas, fans or cooling systems in hot climates and proper infection control measures as described in section 15.

## 11.4. Disease Education

Patients and their families should receive education about DR-TB, its treatment, potential adverse drug effects and the need for adherence to therapy. Educational interventions should begin at the start of therapy and continue throughout the course of treatment. Education can be provided by physicians, nurses, lay and CHWs and other health-care providers. Materials should be appropriate to the literacy levels of the population and should be culturally sensitive as well.

## 11.5. Directly observed therapy (DOT)

DR-TB treatment might be the last therapeutic option for many patients and continue to present a serious public health consequence. Therefore it is recommended that all patients receiving treatment under DOT either in the community or at the health facilities, DOT should be provided in a way that does not place undue burden on patients and their families such as long transportation, short clinic operation hours and difficulty in accessing services.

## 11.6. Who Can Deliver DOT

The first choice for DOT delivery is to use health-care workers. Otherwise, trained community members can serve as effective DOT workers. With appropriate training and support, they can visit patients in their homes or workplaces. Receiving DOT from a community member is often a convenient alternative to the health centre and can result in excellent treatment adherence. However, community members need more intensive training and ongoing supervision by health professionals. It is generally recommended that the patient’s DOT worker should not be a family member since family relationships are often complicated for the DR-TB patient, and a family observer could be subject to subtle manipulation by the patient, relatives, employer, etc.

## 11.7. Socioeconomic Interventions

Maximal interventions should be given to patients who are facing difficult needs. Programs should benefit from professional social workers who can assess the need for such socioeconomic interventions and monitor their delivery. Socioeconomic interventions include:

* Free health care
* Food parcels for DR-TB patients and their dependents.
* Temporary shelter in a housing facility or in a rented home for DR-TB Patients
* School fees for dependent children
* Transportation fees
* Consultation and assistance in administrative matters related to treatment
* Assistance in defending rights and/or reinforcing the responsibilities
* Providing skills training and livelihood to patients during and after completion of treatment to enable these patients to be integrated into the community upon completion of treatment.

# 12. Management of Patients after MDR-TB Treatment Failure

## 12.1. Assessment of Patients at Risk for Treatment Failure

Patients who do not show signs of improvement after four to six months of treatment are at risk for treatment failure. All patients who show clinical, radiographical or bacteriological evidence of progressive active disease, or reappearance of disease after 4-6 months of treatment, should be considered as being at high risk for treatment failure. The following steps are recommended in such cases:

* The treatment card should be reviewed to confirm that the patient has adhered to treatment
* The treatment regimen should be reviewed while taking the medical history into consideration contacts and all DST reports. If the regimen is deemed inadequate, a new regimen should be designed and the bacteriological data should be reviewed. Often, the smear and culture data are the strongest evidence that a patient is not responding to therapy. One single positive culture in the presence of an otherwise good clinical response can be caused by a laboratory contaminant or error. In this case subsequent cultures that are negative, or in which the number of colonies is decreasing, may help prove that the apparently positive result did not reflect treatment failure. Positive smears with negative cultures may be caused by the presence of dead bacilli and therefore may not indicate treatment failure. Repeated culture- and smear-negative results in a patient with clinical and radiographical deterioration indicate that the patient might have a disease other than MDR-TB
* The health-care worker should confirm that the patient has taken all the prescribed medicines. A non- confrontational interview should be undertaken in the absence of the DOT worker
* A non-confrontational interview of the DOT worker alone should also be carried out. Questions should be asked to rule out the possible manipulation of the DOT worker by the patient. If manipulation is suspected, the DOT worker should be switched to another patient, and the patient with suspected treatment failure should be assigned to a new DOT worker
* Other illnesses that may decrease absorption of medicines (e.g. chronic diarrhea) or may result in immune suppression (e.g. HIV infection) should be excluded
* If surgical resection is feasible, it should be considered
* MDR-TB treatment often consists of a treatment cycle. If no response is seen, reassessment of the regimen and treatment plan and formulation of a new plan of action is necessary. Patients who have persistent positive smears or cultures at month 4-6 but are doing well clinically and radio graphically may not require a regimen change since delayed conversion is always possible. Whenever a regimen change is indicated because of treatment failure, a new regimen is started (with at least four effective drugs) and options for adjunctive treatment – most commonly surgery – can be considered. Adding one or two drugs to a failing regimen should be avoided. Changes in treatment can be made as early as 4–6 months if conversion is not seen and if there is a clinical deterioration.

## 12.2. Indications for Suspending Treatment

It takes 3-4 months to evaluate whether a change in treatment plan has been effective. If the patient continues to deteriorate despite the measures described in the previous section, treatment failure should be considered. There is no single indicator to determine whether a treatment regimen is failing. Although there is no simple definition for treatment failure, but there is a point when it becomes clear that the patient is not going to improve. Signs that might indicate a treatment failure include:

* Persistent positive smears or cultures past month 8–10 of treatment
* Progressive extensive and bilateral lung disease on chest X-ray, with no option for surgery
* High-grade resistance (often XDR-TB), with no option to add two additional agents
* Overall deteriorating clinical condition that usually includes weight loss and respiratory insufficiency.

It is not necessary for all of these signs to be present to identify failure of the treatment regimen. However, a cure is highly unlikely when they are all present.

The epidemiological definition of treatment failure for recording outcomes is often different from that used in the process of suspending therapy in a patient when the therapy is failing. The epidemiological definition is an outcome to account for the patient in a treatment cohort analysis, while the clinical decision to suspend therapy is made after the clinical search for all other options has been exhausted and cure of the patient is considered to be highly unlikely.

## 12.3. Suspending Therapy

Treatment can be considered to have failed and suspension of therapy is recommended in cases where the medical personnel involved are confident that all the drugs have been ingested and there is no possibility of adding other drugs or carrying out surgery. There are two important considerations in suspending therapy or changing it to a supportive care regimen:

* Patient’s quality of life: The drugs used in MDR-TB treatment have significant adverse effects, and continuing them while the treatment is failing may cause additional suffering.
* Public health concern: continuing a treatment that is failing can amplify resistance in the patient’s strain, resulting in highly resistant strains such as XDR-TB that may cause subsequent infection of others.

## 12.4. Approach to Suspending Therapy

The approach to suspending therapy should start with discussions among the clinical 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 prepared for approaching the patient and the family. This process usually requires a number of visits and takes place over several weeks. During this phase, home visits offer an excellent opportunity to talk to the 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.

## 12.5. Supportive Care for Patients in whom all the Possibilities of MDR-TB Treatment have Failed

A number of supportive measures can be used once the therapy has been suspended. It is worth mentioning that the patient should not be abandoned and should be supported through medical visits.

# 13. Management of Contacts of MDR-TB Patients

## 13.1. General Considerations

Close contacts of MDR-TB patients are defined as people living in the same household or spending many hours a day together with the patient in the same indoor living space. The available data indicates that close contacts of MDR-TB patients who develop active TB most commonly have drug-resistant disease. While all contacts of TB require investigation, DR-TB requires the most vigilance. Contact tracing of M/ XDR-TB cases should be given the highest level of alertness and priority because of the high risk of morbidity and mortality among these cases. **NTPs should consider contact investigation of XDR-TB as an emergency situation.**

## 13.2. Management of Symptomatic Adult Contacts of Patients with MDR-TB

All close contacts of MDR-TB cases should be identified through a contact tracing mechanism and evaluated for active TB by a health-care provider. If the contact appears to have active TB disease, culture and DST should be performed. While DST results are still pending, a standardized-empirical regimen based on the resistance pattern of the index case may be started. Symptomatic adult contact yielding no evidence of TB may receive a trial of a broad-spectrum antibiotic which is not active against TB, such as Trimethoprim /sulfamethoxazole.If the contact remains symptomatic, physical examinations, smears and cultures should be performed monthly with repeat chest X-ray as needed.Bronchoscopy and BAL samples for smear and culture should be considered if available.

## 13.3. Symptomatic Pediatric Contacts of Patients with DR-TB

Sputum Smear and Culture should be done for:

* Children who are in close contact with DR-TB patient
* Children who are in contact of a TB patient who died during the treatment phase with suspicion that the disease was DR-TB
* Children with bacteriologically proven TB who are not responding to first line drugs given with direct observation

The diagnosis of TB is more difficult in children than in adults. Symptoms of TB in young children can be nonspecific, e.g. chronic cough or wheeze, failure to thrive and recurrent fevers. Bacteriological confirmation may be difficult to obtain because of the inability of children to generate a sputum sample, as well as the paucibacillary nature of pediatric TB and the increased likelihood of extra pulmonary TB in children. While every effort should be made to establish a bacteriological diagnosis (and obtain DST) in a child with suspected MDR-TB, yet in practice pediatric cases are often not confirmed bacteriologically. Use of scoring systems that have been produced to aid screening and diagnosis of active TB is strongly recommended.

Symptomatic pediatric household contacts should receive:

* An evaluation by a physician, including history and physical examination.
* Tuberculin skin test with purified protein derivative (PPD)
* A chest X-ray examination (computerized tomography is helpful especially in documenting hilar adenopathy, but this is often not available in low resource areas)

Efforts should be made to obtain sputum for smear, culture and DST in a child with suspected DR-TB. Bacteriological confirmation may include more aggressive measures such as induced sputum, gastric aspirate, and lymph node aspirate or other relevant sample, plus culture and DST especially for children who are 5 years old or less.

## 13.4. Chemoprophylaxis of Contacts of MDR-TB Index Cases

The only Chemoprophylaxis regimens that have been studied are based on Isoniazid and, to a lesser extent, Rifampicin. Since by definition MDR-TB is resistant to both of these drugs, it is unlikely that the use of these drugs to treat latent infection caused by an MDR-TB strain will prevent the development of active TB disease.

Contacts of MDR-TB patients in whom latent infection is diagnosed may not be infected with the same strain. Some may have been infected with Isoniazid susceptible strains, particularly in high-burden areas where many different strains of TB may circulate in homes, schools, workplaces, etc. Studies from high- burden TB areas have shown that approximately one-half to two-thirds of household members had the same strain of TB, as evidenced by genetic testing. The degree of strain concordance could be higher among children contacts who are 5 years old or less because they have less exposure to strains circulating outside the household. Close contacts of DR-TB patients should receive careful clinical follow-up for a period of at least two years. If active disease is developed, prompt initiation of treatment with a regimen designed to treat MDR-TB is recommended. On the basis of the currently available evidence, WHO does not recommend the universal use of second-line drugs for Chemoprophylaxis in MDR-TB contacts.

# 14. Infection Control Measures in MDR Management

## 14.1. Priorities of Infection Control

DR-TB is transmitted in the same manner as drug-susceptible TB. Well documented outbreaks of highly drug-resistant strains of TB constitute convincing evidence that DR-TB is transmissible especially among highly vulnerable populations and in institutional settings. Moreover, DR-TB patients may infect more people because of a longer period of smear/ culture positivity and slow response to treatment. Recommendations for infection control measures in DR-TB are essentially the same as of drug-susceptible TB, with only minor differences in emphasis.

## 14.2. Set of Managerial Measures at Facility-level for TB Infection Control

Identify and strengthen local coordinating bodies for TB infection control and develop a facility plan for implementation including human resources as well as policies and procedures, to ensure proper implementation of the controls listed below

* Revise the use of available spaces considering the renovation of existing facilities or construction of new ones to optimize implementation of controls
* Conduct on-site surveillance of TB disease among health workers and assess the facility
* Address advocacy, communication and social mobilization (ACSM) for health workers, patients and visitors
* Monitor and evaluate the set of TB infection control measures.
* Participate in research

TB infection control has three components. By order of importance, these are:

* Administrative controls
* Environmental or Engineering controls
* Personal Respiratory Protection.

The administrative controls are the most effective and least expensive and therefore have highest priority in resource-constrained settings.

#### 14.2.1. Administrative Control Measures

Administrative control measures include:

* Promptly identify people with TB symptoms (triage)
* Isolate infectious patients
* Control the spread of pathogens (cough etiquette and respiratory hygiene)
* Minimize time spent in health-care facilities
* Provide a package of prevention and care interventions for health workers, including HIV prevention, antiretroviral therapy and Isoniazid preventive therapy (IPT) for HIV-positive health workers.

#### 14.2.2. Environmental Control Measures

Environmental control measures include:

* Methods to reduce the concentration of infectious respiratory aerosols (i.e. droplet nuclei) in the air, and methods to control the direction of infectious air. The choice of environmental controls is intimately related to building design, construction, renovation and use, which in turn must be tailored to local climatic and socioeconomic conditions
* Maximize the use of natural ventilation systems
* Use ultraviolet germicidal irradiation (UVGI) fixtures, at least when adequate ventilation cannot be achieved. (UVGI) are used while rooms are occupied and not to sterilize empty rooms
* Mechanical ventilation systems using high efficiency particulate air filtration and HEPA filters.

#### 14.2.3. Personal Respiratory Protection

Personal respirators have different forms, and more expensive than the familiar surgical masks.

Personal respiratory protection measures include:

* Respirators for staff (e.g. N95 respirator). They have tiny pores which block droplet nuclei and an airtight seal around the edge. The respirator must fit tightly on the face, especially around the bridge of the nose. Ideally, respirators should be “fit tested”
* Face masks for patients. They have large pores and lacks airtight seals around the edges but prevent aerosolization.

|  |  |
| --- | --- |
| **Mask**  **A disposable “surgical mask”** | **Respirator**  **N-95** |
| Purpose: To reduce infections transmission by capturing infectious droplet nuclei that the patient releases before they get into air | Purpose: To reduce exposure by filtering infectious droplet nuclei out of the air, before wearers breathe the air into their lungs |
| Who should wear a mask?  Patients with infectious TB and not in isolation room | Who should wear a respirator?  - Staff, visitors to TB isolation rooms  - Performing cough-inducing or aerosol generating  procedures  - Unlikely to be protected by administrative or environmental controls |

## 14.3. Role of Rapid Tests in Infection Control

The use of a rapid test for Rifampicin or other drugs is an excellent method of distinguishing those who may have DR-TB from others. Patients who are identified by rapid tests can be properly isolated immediately (in addition to starting proper empirical regimens).

# 15. Category IV Recording and Reporting System

## 15.1. Aims of the Information System and Performance Indicators

The aims of the information system are two-fold:

* To allow NTP managers at different levels to monitor overall programme performance (such as patients started on treatment and treatment results), to follow trends in the number of cases notified, to plan drug supply, and to provide the basis for programme and policy developments
* To aid clinical providers in management of each patient.

## 15.2. Main Forms/ Registers and Flow of Information

The forms and registers include the following:

1. Category IV Treatment Card (Form DR-TB 01)
2. Category IV Patient’s Identity Card (DR-TB 02)
3. Category IV Patient’s Register (DR-TB 03)
4. Category IV Quarterly Report (DR-TB 04)
5. Category IV Six Month Interim Report (DR-TB 05)
6. Category IV Annual Report (DR-TB 06)
7. MDR ENRS (equivalent to DR-TB 03)

A copy of each of the above mentioned forms is attached to the guidelines (See Annexure).

# ANNEXURES

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Recommended Dosages of Anti-TB Drugs3 | | | | | |
| Medication  (drug abbreviation), (common presentation) | Weight class | | | | >70 kg  (also maximum dose) |
|  |  | <33 kg | 33–50 kg | 51–70 kg |  |
| Group 1: First-line Oral Antituberculosis Drugs | | | | | |
| Isoniazid (H)  (100, 300 mg tablet) | daily | 4–6 mg/kg  or 8–12 mg  3 x wk | 200–300 mg  or 450–600 mg  3 x wk | 300 mg daily  or 600 mg  3 x wk | 300 mg daily  or 600 mg  3 x wk |
| Rifampicin (R)  (150, 300 mg tablet) | daily | 10–20 mg/kg | 450–600 mg | 600 mg | 600 mg |
| Ethambutol (E)  (100, 400 mg tablet) | daily | 25 mg/kg | 800–1200 mg | 1200-1600 mg | 1600– 2000 mg |
| Pyrazinamide (Z) (500mg tablet) | daily | 30-40 mg/kg | 1000–1750 mg | 1750-2000 mg | 2000-2500 mg |
| Group 2: Injectable Antituberculosis Drugs | | | | | |
| Streptomycin (S) | daily | 15–20 mg/kg | 500–750 mg | 1000 mg | 1000 mg (1 g vial) |
| Kanamycin (Km) | daily | 15–20 mg/kg | 500–750 mg | 1000 mg | 1000 mg (1 g vial) |
| Amikacin (Amk) | daily | 15–20 mg/kg | 500–750 mg | 1000 mg | 1000 mg (1 g vial) |
| Capreomycin (Cm) | daily | 15–20 mg/kg | 500–750 mg | 1000 mg | 1000 mg (1 g vial) |
| Group 3: Fluoroquinolones | | | | | |
| Ofloxacin (Ofx)  (200, 300, 400 mg tablet) | daily | 15–20 mg/kg | 800 mg | 800 mg | 800–1000 mg |
| Levofloxacin (Lfx) (200,  500 mg tablet) | daily | 7.5–10 mg/kg | 750 mg | 750 mg | 750–1000 mg |
| Moxifloxacin (Mfx) (400 mg tablet) | daily | 7.5–10 mg/kg | 400 mg | 400 mg | 400 mg |
| Group 4: Oral Bacteriostatic second-line Anti-tuberculosis Drugs | | | | | |
| Ethionamide (Eto) | daily | 15–20 mg/kg | 500 mg | 750 mg | 750–1000 mg  (250 mg tablet) |
| Protionamide (Pto) | daily | 15–20 mg/kg | 500 mg | 750 mg | 750–1000 mg  (250 mg tablet) |
| Cycloserine (Cs) | daily | 15–20 mg/kg | 500 mg | 750 mg | 750–1000 mg  (250 mg capsule) |
| Terizidone (Trd) | daily | 15–20 mg/kg | 600 mg | 600 mg | 900 mg (250 mg) |
| P-aminosalicylic | daily | 150 mg/kg | 8 g | 8 g | 8-12 g acid (PAS) (4 g) sachet) |
| Sodium 60% PAS | daily | 9.2 gms twice | 9.2 gms twice |  |  |
| Thioacetazone (Thz) | daily | Usual dose is 150 mg for adults | | | |

### Group 5 Agents with Unclear Role in DR-TB Treatment

(Not recommended by WHO for routine use in MDR-TB Patients, Optimal doses for DR-TB are not established)

|  |  |
| --- | --- |
| 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 effects may limit this dosing |
| Thioacetazone (Thz) | Usual adult dose is 150 mg |
| Imipenem/cilastatin | Usual adult dose is 500–1000 mg IV every 6 hours (Ipm/Cln) |
| Clarithromycin (Clr) | Usual adult dose is 500 mg twice daily |
| High-dose Isoniazid | 16–20 mg/kg daily  (High-dose H) |

### Adjustment of Anti-TB Medication in Renal Insufficiencya,b

|  |  |  |
| --- | --- | --- |
| Drug | Change in frequency? | Recommended Dosec 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/ week |
| Rifampicin | No change | 600 mg once daily, or 600 mg three times/ week |
| pyrazinamide | Yes | 25–35 mg/kg/ dose three times/ week (not daily) |
| Ethambutol | Yes | 15–25 mg/kg/ dose three times/ week (not daily) |
| Ofloxacin | Yes | 600–800 mg/ dose three times/ week (not daily) |
| Levofloxacin | Yes | 750–1000 mg/ dose three times/ week (not daily) |
| Moxifloxacin | No change | 400 mg once daily |
| cycloserine | Yes | 250 mg once daily, or 500 mg/dose three times/ weekd |
| Terizidone | – | Recommendations not available |
| Protionamide | No change | 250–500 mg/ dose daily |
| Ethionamide | No change | 250–500 mg/ dose daily |
| p-aminosalicylic  acide | No change | 4 g/ dose, twice daily |
| streptomycin | Yes | 12–15 mg/kg/ dose twice or three times/ week (not daily)f |
| Capreomycin | Yes | 12–15 mg/kg/ dose twice or three times/ week (not daily)f |
| Kanamycin | Yes | 12–15 mg/kg/ dose twice or three times/ week (not daily)f |
| Amikacin | Yes | 12–15 mg/kg/ dose twice or three times/ week (not daily)e |

a From Guidelines for the Programmatic management of Drug-resistant Ttuberculosis. Emergency update, 2008. WHO/HTM/ TB/2008.402. (page 85)

b For Group 5 drugs see manufacturers’ recommendations on adjustment in renal insufficiency.

c To take advantage of the concentration-dependent bactericidal effect of many antituberculosis drugs, standard doses are given unless there is intolerance.

d 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).

e Sodium salt formulations of PAS may result in an excessive sodium load and should be avoided in patients with renal insufficiency. Formulations of PAS that do not use the sodium salt can be used without the hazard of sodium retention.

f Caution should be used with the injectable agents in patients with renal function impairment because of the increased risk of

both ototoxicity and nephrotoxicity.

### Pediatric Dosing of Second-line Anti-TB Drugs

|  |  |  |  |
| --- | --- | --- | --- |
| Drug | Daily Dose (mg/kg ) | Frequency | Maximum Daily Dose |
| Streptomycin | 20–40 | Once daily | 1 g |
| Kanamycin | 15–30 | Once daily | 1 g |
| Amikacin | 15–22.5 | Once daily | 1 g |
| Capreomycin | 15–30 | Once daily | 1 g |
| Ofloxacin | 15–20 | Twice daily | 800 mg |
| Levofloxacin | 7.5–10 | Once daily | 750 mg |
| Moxifloxacin | 7.5–10 | Once daily | 400 mg |
| Ethionamide | 15–20 | Twice daily | 1 g |
| Protionamide | 15–20 | Twice daily | 1 g |
| Cycloserine | 10–20 | Once or twice daily | 1 g |
| P-aminosalicylic acid | 150 | Twice or thrice daily | 12 g |

**DR TB-08**

### Request and Reporting Form for TB Culture and Drug Susceptibility Test (DST)

***Patient Identification (ID):***

TB Register Number:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ MDR Register Number:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Patient’s Full Name.:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Age (yrs):\_\_\_\_\_\_\_\_\_\_ Sex:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Ward / Department: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Address: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\*HIV-status: Pos / Neg / Unknown: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

***TB Disease Type and Treatment History***

Site: Pulmonary History: New (never treated before for ≥1 month)

Extra pulmonary (specify):\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Relapse Failure

Previous treatment: Cat.1 Return after default

Cat.2 Chronic TB Cat.4 (second-line drugs) MDR contact

Other \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Uncertain

MDR on treatment

***Origin of Request****:*

Physician Name: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Health Facility: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_District:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Specimen Collecting Date: \_\_\_\_/\_\_\_\_/20\_\_\_\_ Specimen ID Number:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Local Laboratory: Smear Result: 1st \_\_\_\_\_\_\_\_ 2nd \_\_\_\_\_\_\_\_ 3rd \_\_\_\_\_\_\_\_\_\_\_ specimen

Microscopy Technique Used: Hot Ziehl-Neelsen Direct smear

Cold staining Concentrated smear

Fluorescence

***Request for Testing at the Reference Laboratory:***

Reason: Diagnosis Specimen: Sputum

Follow-up at ……. months during treatment Sputum in preservative, type ……………

Follow-up at ……. months after completion of treatment Other (specify):\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Requested Tests: Microscopy (type \_\_\_\_\_\_\_ ) Culture DST (first / second line)

**Person requesting examination**: Name: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Designation:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Contact #: - Mobile No. \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Office No.:-\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

***Reference Laboratory Results****:*

Date Received in the Reference Laboratory \_\_\_\_\_/\_\_\_\_\_\_/20\_\_\_\_\_ Reference Laboratory Specimen ID:\_\_\_\_\_\_\_\_\_\_

**Microscopic Examination**: Reporting Date \_\_\_\_\_/\_\_\_\_\_\_/20\_\_\_\_\_

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| ID # | Neg | 1-9 | 1+ | 2+ | 3+ | Hot Ziehl-Neelsen Cold staining Fluorescence |
|  |  |  |  |  |  | Direct smear Concentrated smear |

**Culture Result**: Reporting Date \_\_\_\_\_/\_\_\_\_\_\_/20\_\_\_\_\_ Will follow

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| ID # | Contaminated | Neg | Non-TB mycobacteria (species) | Mycobacterium tuberculosis complex | | | |
| 1-9 colonies  actual count | 10 – 100 col  1+ | >100 - 200 col  2+ | >200 col  3+ |
|  |  |  |  |  |  |  |  |

**Results of *M. tuberculosis* Drug Susceptibility Testing**: Will follow

Phenotypic method used \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Genetic method used \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ID # \_\_\_\_\_\_\_\_\_\_\_\_ | | | Legend: S = susceptible; R = resistant; C = contaminated; ND = not done | | | | | | | | | | | |
|  | INH | | Rifampicin | | Ethambutol | | Streptomycin | | Pyrazinamide | | Ofloxacin | | Kanamycin | |
| µg/ml |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| result |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

Date: \_\_\_\_\_/\_\_\_\_\_\_/20\_\_\_\_\_ Signature:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

### Annual Report of Treatment Result of Confirmed MDR/XDR-TB

**Patients Starting Category IV Treatment**

**DR-TB 06**

**DR-TB Control Program**

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| --- | --- | --- | --- | --- |
| **Annual Report of Treatment Result of Confirmed MDR/XDR-TB Patients Starting Category IV Treatment**  **(To be filled within 24 to 36 months from last date of treatment)** | | | | |
|  |  | Date Treatment Started in:\_\_\_\_\_\_\_\_\_\_\_\_\_\_Year |  |  |
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| **Patient’s Group** | **Cured** | **Treatment Completed** | **Failed** | **Defaulted** | **Died** | **Transferred**  **Out** | **Still on Treatment** | **Total** |
| New |  |  |  |  |  |  |  |  |
| Previously treated with 1stLine drugs only |  |  |  |  |  |  |  |  |
| Previously treated with both 1.and 2.line drugs |  |  |  |  |  |  |  |  |
| Total |  |  |  |  |  |  |  |  |

**Form #09**

### A REFERRAL LETTER FORMAT TO THE TREATMENT SITE

**Patient’s Name: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Patient’s Full Address: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Referring Physician’s Name/ Address/ Phone Number: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Referring TB Center (if available): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Patient’s TB Number (if available): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Brief Medical History and Reason for referral:**

**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Sputum Culture Result: Date: Positive Negative (please circle the correct answer)**

**DST Result: Resistant to (please circle the correct answer) H R E S**

**Names of previous anti TB drugs and any other drugs used:**

**Name of the Drug Date of Starting Treatment Date of Stopping the Drug**

**Note:**

***Please send all old CXRs with the patient and any other medical records.***

**Date: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Signature: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**……………………………………………………………………………………………..**

**Acknowledgment Note:**

**Name of the Patient:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Name of the Treatment Site:\_\_\_\_\_\_\_\_\_\_**

**Date Patient was Reported to the Treatment Site:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Name and Signature of the Treatment Site Manager: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Form #10**

### REQUEST FOR SECOND LINE DRUGS FROM THE WAREHOUSE

**Date: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**From: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Name of the Officer Requesting the Drugs**: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Number of DR-TB Patients Requesting Drugs for (if applicable):\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

|  |  |  |
| --- | --- | --- |
| **Drug’s Name** | **Dosage** | **Quantity Requested** |
| **Cycloserine** | 250 mg/ cap |  |
| **Ethionamide/Prothionamide** | 250 mg/tab or caps |  |
| **Levofloxacin** | 250mg/tab |  |
| **Levofloxacin** | 500mg/Tab |  |
| **PAS** | 2gm/sachet |  |
| **Kanamycin** | 1 gm/ vial |  |
| **Amikacin** | 500mg/vial |  |
| **Capreomycin** | 1gm/vial |  |
| **Pyrazinamide** | 500mg/tab |  |
| **B6** | 50mg/tab |  |
| **Others** |  |  |
| **Others** |  |  |
| **Others** |  |  |

**Signature of the Registrar requesting the drugs: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

### MDR-ENRS Template

(Please note: to accommodate the excel sheet is presented in sections)

|  |  |  |  |  |  |  |  |
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| **First Name (As Registered in the ID)** | **Father or Middle Name** | **Family or Last Name** | **Patient's National ID number** | **Nationality** | **Age** | **Age Group** | **Gender** |
| **SUGHRA** | **W/O M. HAROON** | **Sandhelo** | 45303-4328361-2 |  | 7 | 5-14 | F |
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| **Present Address** | **Country** | **Province/ Governerate** | **District** | **Ground Phone Number** | **Mobile phone Number** |
|  |  |  |  |  | 0301-2859197 |
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| **Name of Treatment Supporter** | **Address of Treatment Supporter** | **Phone of Treatment Supporter** | **Patient's previous BMU (Previous TB Center)** | **Patient's Old TB Number** | **Date of Reg. of Old TB #** | Previous Tuberculosis FLD Treatment History and Episodes-type (insert only the last type and treatment regimen) | Previous Tuberculosis FLD Treatment History and Episodes-date Started | Previous Tuberculosis FLD Treatment History and Episodes-drug Regimen |
|  |  |  | PVT |  |  | CAT II | MAY 2009 | RHZES |
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| Previous Tuberculosis FLD Treatment History and Episodes-date Stopped | | Previous Tuberculosis FLD Treatment History and Episodes-outcome | **Did the Patient Receive SLD Previously** | **Date Started** | | **Date Stopped** | **What SLD did the Patient Receive Previously?** | | **Outcome of patient's previous treatment with SLD** | | **Medical history** |
| October-09 | | failed | No |  | |  |  | |  | |  |
|  | |  |  |  | |  |  | |  | |  |
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| **Behaviour Status** | CAT IV (DR-TB) Registration Serial No (Serial Number/ Year/ Treatment Site/ District Name) | | | | CAT IV (DR-TB) Registration No-Year | | | CAT IV (DR-TB) Registration No-treatment Site (Gover.) | | CAT IV (DR-TB) Registration No-District | | |
|  | 1 | | | | 2010 | | | Bagh | |  | | |
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| Date of CAT IV (DR-TB) Registration mm/dd/yyyy | **Day** | **MON** | **QRT** | **YEAR** | **Registration Group** | **Site of DR-TB** |
| 5/10/2011 | 10 | 5 | Q2 | 2011 | after F of CAT2 | Pulmonary |
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| **Sub Diagnosis** | **Date HIV Test** | **Result HIV Test** | **Date ART** | **Date CPT** | Duration of Sickness prior to Diagnosis with DR-TB | Date of DR-TB Enrollment in Treatment mm/ dd/ yyyy | **Day** | **MON** |
|  | 2-Jun-10 |  |  |  |  | 6/5/2010 | 5 | 6 |
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| **QRT** | **YEAR** | | **Date Diagnostic Sample taken for Culture and DST** | | **Date of the result of the diagnostic Culture** | **Result of the Diagnostic Culture** | **Date of the Result of the Rapid Testing** | | **Result of the Diagnostic Rapid Testing** | | **Result of DST (Resistance to 1st line Drugs)** | | **Result of DST (Resistance to 2nd Line Drugs)** | | |
| Q2 | 2010 | |  | | 2-Jun-10 | pos |  | | other(please insert a comment and explain) | |  | | FQ | | |
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| **Type of DR-TB Resistance Now** | | **Reasons for Entering DR Register** | | **Treatment Regimen** | | | | **Is the patient under daily DOT** | | **Sputum Result at the Beginning of Treatment SP 0** | | **Culture Result at the Beginning of Treatment CL 0** | | **Date of the Sputum and Culture Taken Date 0** |
| MDR | | DR TB suspected | | 6AM, LFX,ETO,PAS,CS,B6,Z/18 Lfx-ETO-PAS-Cs-B6-Z | | | |  | | pos3 | | Pos | | 5-Jun-10 |
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| **Sp 1** | **CL 1** | **Date 1** | **Sp 2** | **CL 2** | **Date 2** | **Sp 3** | **CL 3** | **Date 3** |
| pos3 | Pos | 17-Jul-10 | pos3 | Pos | 17-Aug-10 | Pos1 | Neg | 16-Sep-10 |
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| **Interim Result** | **Sp 7** | **CL 7** | **Date 7** | **Sp 8** | **CL 8** | **Date 8** | **Sp 9** | **CL 9** |
| Neg SP and CL | 1-9b | Neg | 18-Jan-11 | Neg | Neg | 17-Feb-11 |  |  |
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| **Date 9** | **Sp 10** | **CL 10** | **Date 10** | **Sp 11** | **CL 11** | **Date 11** | **Sp 12** | **CL 12** |
|  | Neg |  | 16-Apr-11 |  |  |  |  |  |
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| **Date 12** | **Sp 13** | **CL 13** | **Date 13** | **Sp 14** | **CL 14** | **Date 14** | **Sp 15** | **CL 15** |
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| **Date 15** | **Sp 16** | **CL 16** | **Date 16** | **Sp 17** | **CL 17** | **Date 17** | **Sp 18** | **CL 18** |
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| **Date 18** | **Sp 19** | **CL 19** | **Date 19** | **Sp 20** | **CL 20** | **Date 20** | **Sp 21** | **CL 21** |
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| **Date 21** | **Sp 22** | **CL 22** | **Date 22** | **Sp 23** | **CL 23** | **Date 23** | **Sp 24** | **CL 24** |
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| **Date 24** | **Sp 25** | **CL 25** | **Date 25** | **Sp 26** | **CL 26** | **Date 26** | **Sp 27** | **CL 27** |
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| **Date 27** | **Sp 28** | **CL 28** | **Date 28** | **Sp 29** | **CL 29** | **Date 29** | **Sp 30** | **CL 30** |
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| **Date 30** | **Sp 31** | **CL 31** | **Date 31** | **Sp 32** | **CL 32** | **Date 32** | **Sp 33** | **CL 33** |
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| **Date 33** | **Sp 34** | **CL 34** | **Date 34** | **Sp 35** | **CL 35** | **Date 35** | **Sp 36** | **CL 36** |
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| **Date 36** | **Major Adverse Reaction** | **Treatment outcome** | **Treatment End Date** | **Comments** |  |  |  |
|  |  | Still under Tx |  |  |  |  |  |
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**National DR-TB Control Program DR-TB 01**

### Category IV Treatment Card

Name (As registered in the CNIC): First\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_/ Middle\_\_\_\_\_\_\_\_\_\_\_\_\_/ Last\_\_\_\_\_\_\_\_\_\_\_\_\_ National ID Number/ Nationality:\_\_\_\_\_\_\_\_\_\_\_\_/\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Date of Birth:\_\_\_\_/\_\_\_\_/\_\_\_\_ Age:\_\_\_\_\_\_ \_\_\_Sex: Male\_\_\_\_/ Female\_\_\_\_\_ Patient’s Address:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Patient’s Phone Number: Land line\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_/ Mobile\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Patient’s Occupation:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Contact Person: Name\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Address\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Phone Number: Land line\_\_\_\_\_\_\_\_\_\_\_\_ / Mobile \_\_\_\_\_\_\_\_\_\_\_\_ Treatment Supporter ( if different from the contact person): Name\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Address\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_Phone Number: Land line\_\_\_\_\_\_\_\_\_\_ /Mobile\_\_\_\_\_\_\_\_\_ Patient’s Previous BMU (previous TB treatment center):\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Old TB Number:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_/Date of Registration of the old TB Number:\_\_\_\_\_\_\_\_\_\_\_\_

**Previous Tuberculosis FLD Treatment History and Episodes**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Type (CAT I, CAT II, Repeat CATII) | Date Treatment Started | Treatment Regimen  (write drugs abbreviations as mentioned below) | Date Treatment Stopped | Outcome |
|  |  |  |  |  |
|  |  |  |  |  |
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**Previous History of Using Second-Line Drug (SLD):**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Did the Patient Use SLD Before? (Yes/No) | Date Treatment Started | Treatment Regimen  (write drugs abbreviations as mentioned below) | Date Treatment Stopped | Outcome |
|  |  |  |  |  |
|  |  |  |  |  |

**Drug Abbreviations**: First Line Drugs (FLD): H=Isoniazid/R=Rifampicin/E=Ethambutol/Z=Pyrazinamide/S=Streptomycin/T=Thiacetazone. > (SLD): **Km**=Kanamycin/**Am**=Amikacin/**Cm**=Capreomycin/**Ofx**=Ofloxacin/**Cfx**=Ciprofloxacin/**Lfx**=Levofloxacin/ **CS**=Cycloserine / **ETO=**Ethionamide / **PTO=**Prothionamide/**PAS**=Para aminosalycilic acid

**Other Previous Medical and Social History**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Name of the Disease | Date Disease was Diagnosed | Treatment Regimen( mention all the drugs and dosage) | Is the Patient Taking Treatment Regularly? Y/N | Outcome ( disease controlled) Yes/No | Smoking History \_\_\_ p/day | Other Remarks |
|  |  |  |  |  |  |  |
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|  |  |  |  |  |  |  |

**Name of person filling this form and Initials:………………………..………………………………………… Page 1 of 7**

**DR-TB Control Program DR-TB 01**

**Category IV Treatment Card Patient Name:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Category IV Registration Number** (Serial Number/ Year/Treatment Site/ District Name):\_\_\_\_\_\_/\_\_\_\_\_\_/\_\_\_\_\_\_\_/\_\_\_\_\_\_ Date of CAT IV Reg. Number: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ **Registration Group** ( Choose only one): New\_\_\_\_/ Relapse\_\_\_\_/ Treatment after default\_\_\_\_\_/ Treatment after failure of CAT I\_\_\_\_\_/ Treatment after failure of CAT II\_\_\_/ > Transfer in\_\_\_\_\_\_/ Other\_\_\_\_\_ **Location of the Disease:** Pulmonary\_\_\_\_/ Extra Pulmonary\_\_\_\_\_/ Subgroup if Extra Pulmonary\_\_\_\_\_\_\_\_\_\_\_\_ / Both (if Pulmonary and Extra Pulmonary)\_\_\_\_\_ \_\_\_\_

**Type of Resistance**: Poly Drug Resistance\_\_\_\_\_\_\_\_/ MDR\_\_\_\_\_\_\_\_\_/ XDR\_\_\_\_\_\_\_\_\_\_ **Initial Weight**:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Review Panel Meetings**

|  |  |  |  |
| --- | --- | --- | --- |
| Date of Meeting | Decision | Next Date | Remarks |
|  |  |  |  |

**HIV Status of the Patient**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| HIV Testing Done: Y/N/Unknown | Date Test Done/ Result | Started on ART: Y/N/ Date | Started on CPT: Y/N / Date | Remarks |
|  | / | / | / |  |

**Close Contact Screening and History**

|  |  |  |  |
| --- | --- | --- | --- |
| Name of the Person/ Relationship to Patient/ Age/ Sex | Previous history of TB: Y/N and outcome (cured, died, etc…) | Present Status: (Asymptomatic/ present symptoms such as cough, fever, malnourishment etc…) | Action/ Remarks |
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Please add another sheet to the form for extra Contact Screening information **Name of person filling this page and initials**…………………………………………………**Page 2 of 7**

**DR-TB Control Program Category IV Treatment Card DR-TB 01**

**Date of Enrollment in DR-TB Treatment:\_\_\_\_/\_\_\_\_/\_\_\_\_\_\_\_ Patient’s Name:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Sputum Smear Microscopy during DR Management**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Month of Treatment | Date Sputum Collected | Sample No. | Result/ Signature | Month of Treatment | Date Sputum Collected | Sample No. | Result/ Signature |
| Diagnostic Specimen |  |  |  | 13 |  |  |  |
| 0 |  |  |  | 14 |  |  |  |
| 1 |  |  |  | 15 |  |  |  |
| 2 |  |  |  | 16 |  |  |  |
| 3 |  |  |  | 17 |  |  |  |
| 4 |  |  |  | 18 |  |  |  |
| 5 |  |  |  | 19 |  |  |  |
| 6 |  |  |  | 20 |  |  |  |
| 7 |  |  |  | 21 |  |  |  |
| 8 |  |  |  | 22 |  |  |  |
| 9 |  |  |  | 23 |  |  |  |
| 10 |  |  |  | 24 |  |  |  |
| 11 |  |  |  | 25 |  |  |  |
| 12 |  |  |  | 26 |  |  |  |

Method for recording smears: (No AFB = 0 / 1-9 AFB per 100HPF = Scanty and report the number of AFB/ 10-99 AFB per 100 HPF = + /1-10 AFB per HPF = ++ / >10 AFB per HPF= +++)

**TB Culture Results during DR Management**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Month of Treatment | Date Sputum Collected | Sample No. | Result/ Signature | Month of Treatment | Date Sputum Collected | Sample No. | Result/ Signature |
| Diagnostic specimen |  |  |  | 13 |  |  |  |
| 0 |  |  |  | 14 |  |  |  |
| 1 |  |  |  | 15 |  |  |  |
| 2 |  |  |  | 16 |  |  |  |
| 3 |  |  |  | 17 |  |  |  |
| 4 |  |  |  | 18 |  |  |  |
| 5 |  |  |  | 19 |  |  |  |
| 6 |  |  |  | 20 |  |  |  |
| 7 |  |  |  | 21 |  |  |  |
| 8 |  |  |  | 22 |  |  |  |
| 9 |  |  |  | 23 |  |  |  |
| 10 |  |  |  | 24 |  |  |  |
| 11 |  |  |  | 25 |  |  |  |
| 12 |  |  |  | 26 |  |  |  |

Method for recording cultures: (No growth = 0 / fewer than 10 colonies = Report the number of colonies / 10-100 colonies = + / More than 100 colonies = ++ / Innumerable or confluent growth = +++)

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**DR-TB Control Program DR-TB 01**

**Category IV Treatment Card Patient’s Name:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Drug Susceptibility Testing (DST) Results**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Date Sputum Collected** | **Date DST Rapid Testing Result** | **Result of the DST Rapid Testing** | **Date of DST Result** | **S** | **H** | **R** | **E** | **Z** | **Km** | **Am** | **Cm** | **Ofx** | **Lfx** | **Eto** | **Cs** | **PAS** | **Other** | **Other** | **Other** |
|  |  | **H:\_\_\_\_/R:\_\_\_\_\_** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
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**Method for recording DST result: (Resistant = R mark in red color/ Sensitive = S/ Contaminated = C / Not done = N/A )**

**Treatment Model: Hospitalized Based\_\_\_\_\_\_/Community Based\_\_\_\_\_\_\_\_ Name and Date of Transfer to DR-TB BMU (DOT Site)\_\_\_\_\_\_\_\_\_\_\_\_\_\_/\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Category IV Treatment Regimen: (Please enter a new row every time a change of dosage or cessation of a drug occurs)**

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Date of Treatment Start or Change** | **H mg/d** | **R**  **mg/d** | **Z mg/d** | **E mg/d** | **Km mg/d** | **Am mg/d** | **Cm mg/d** | **Lfx mg/d** | **Eto mg/d** | **Cs mg/d** | **PAS mg/d** | **B6 mg/d** | **Other** | **Other** | **Other** | **Other** | **Remark** |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
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**Other Laboratory Tests Results**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Month** | **Hgb/ Hct/ WBC/ ESR** | **Urea/ Cr** | **SGOT/ SGPT/ Tot Bili/ Dir Bili** | **Hepatitis Profiles** | **F. Blood Sugar** | **Thyroid Function Tests** | **Pg Test Urine** | **Visual Test Rt: Lt:** | **Audiogram Test** | **CXR** | **Signature** |
| 0 |  |  |  |  |  |  |  |  |  |  |  |
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| 4 |  |  |  |  |  |  |  |  |  |  |  |
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**DR-TB Control Program DR-TB 01**

**Category IV Treatment Card Patient’s Name:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Other Laboratory Tests Results (Continued from the previous page)**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Month** | **Hgb/ Hct/ WBC/ ESR** | **Urea/ Cr** | **SGOT/ SGPT/ Tot Bili/ Dir. Bili** | **Hepatitis Profiles** | **F. Blood Sugar** | **Thyroid Function Tests** | **Pg Test Urine** | **Visual Test Rt: Lt:** | **CXR** | **Signature** |
| 8 |  |  |  |  |  |  |  |  |  |  |
| 9 |  |  |  |  |  |  |  |  |  |  |
| 10 |  |  |  |  |  |  |  |  |  |  |
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| 14 |  |  |  |  |  |  |  |  |  |  |
| 15 |  |  |  |  |  |  |  |  |  |  |
| 16 |  |  |  |  |  |  |  |  |  |  |
| 17 |  |  |  |  |  |  |  |  |  |  |
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| 19 |  |  |  |  |  |  |  |  |  |  |
| 20 |  |  |  |  |  |  |  |  |  |  |
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| 23 |  |  |  |  |  |  |  |  |  |  |
| 24 |  |  |  |  |  |  |  |  |  |  |

**Administration of Drugs (one line per month) (Mark in the box:** √ **= directly observed / – not observed/ 0 drug not taken)**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
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| Month | Wt | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 |
| 1 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
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| 3 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 4 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 5 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 6 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 7 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
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| 9 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 10 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 11 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

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**DR-TB Control Program DR-TB 01**

**Category IV Treatment Card Patient’s Name:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Administration of Drugs: continued (one line per month) (Mark in the box:** √ **= directly observed / – not observed/ 0 drug not taken)**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
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| Month | Wt | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 |
| 12 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 13 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 14 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 15 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 16 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 17 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 18 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 19 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 20 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 21 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 22 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 23 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 24 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

**History of Adverse Reactions during DR Management**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Date** | **Adverse Reaction** | **Degree of Adverse Reaction**  **Mild/ Moderate/ Severe** | **Name of the Drug(s) that is Causing the Adverse Reaction** | **Action Taken** | **Adjustment in Treatment Regimen** |
|  |  |  |  |  |  |
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**Please use an additional table if extra space is required**

**Treatment End Date and Outcome** (please circle only one)**:**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Treatment End Date | Treatment Outcome | | | | | |
| Cure | Complete | Default | Died | Failure | Transfer out |

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**Additional Comments: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

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**National DR-TB Control Program DR-TB 02**

Patient Identity Card **Name of the DR-TB MU\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Name** (As registered in the CNIC): First\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_/ Middle\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_/ Last\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ **National ID (CNIC) Number**:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ **Date of Birth**:\_\_\_\_/\_\_\_\_/\_\_\_\_ **Age**:\_\_\_\_\_\_ \_\_\_**Sex**: Male\_\_\_\_/ Female\_\_\_\_\_ **Patient’s Address**:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ **Patient’s Phone Number**: Land line\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_/Mobile\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ **Contact Person**: Name\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Address\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Phone Number: Land line\_\_\_\_\_\_\_\_\_\_\_\_ / Mobile \_\_\_\_\_\_\_\_\_\_\_\_ Patient’s Previous **BMU** (previous TB treatment center): \_\_\_\_\_\_\_\_\_\_\_\_\_ **Old TB Number**:\_\_\_\_\_\_\_\_\_\_\_\_\_\_/**Date of Registration of the old TB Number**: \_\_\_\_\_\_\_\_\_\_\_

**Category IV Registration Number** (Serial Number/ Year/ Treatment Site/ District Name):\_\_\_\_\_\_/\_\_\_\_\_\_/\_\_\_\_\_\_\_/\_\_\_\_\_\_ **Date of CAT IV Reg. Number**: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ **Registration Group** (Choose only one): New\_\_\_\_/ Relapse\_\_\_\_/ Treatment after default\_\_\_\_\_/ Treatment after failure of CAT I\_\_\_\_\_/ Treatment after failure of CAT II\_\_\_\_/ > Transfer in\_\_\_\_\_\_/ Other\_\_\_\_\_ **Location of the Disease:** Pulmonary\_\_\_\_/ Extra Pulmonary\_\_\_\_\_/ Specific location of Extra Pulmonary\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ / Both (if Pulmonary and Extra Pulmonary) \_\_\_\_\_\_\_\_\_ **Type of Resistance**: Poly-Drug Resistance\_\_\_\_\_\_\_\_/ MDR\_\_\_\_\_\_\_\_\_/ XDR\_\_\_\_\_\_\_\_\_\_ **Initial Weight**: \_\_\_\_\_\_\_\_\_\_\_ **Schedule of Visits to the DR-TB BMU (DOT Site) (Name)\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Schedule of Appointment for Follow-up at Treatment Site**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Current Appointment** | **Next Appointment** | **Current Appointment** | **Next Appointment** | **Current Appointment** | **Next Appointment** |  | **Date** | **Place of Examination** | **Type of Tests (to be filled up by the MDR Practitioner)** | **Remarks** |
|  |  |  |  |  |  |  |  |  |  |
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**Schedule of Appointments to Visit the DOT Site Schedule of Appointments for Follow-up at Treatment Site**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Current Appointment** | **Next Appointment** | **Current Appointment** | **Next Appointment** | **Current Appointment** | **Next Appointment** |  | **Date** | **Place of Examination** | **Type of Tests (to be filled up by the MDR Practitioner)** | **Remarks** |
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Instructions for the patient in the local language:

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |  | Registration Group | | | | | | |
| **Category IV Registration Number** | **Date of Category IV Registration** | **Name (in full)** | **Sex**  **M**  **or**  **F** | **Age\_\_**  **Date of Birth D/ Mo/ Yr** | **Address** | **Old TB Registration Number / and Date** | **Location of Disease**  **(P/ EP)** | New | Relapse | After default | After failure of Category I treatment | After failure of Category II | Transfer In | Other |
| 1 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
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National DR-TB Program DR-TB 03 Patient CAT IV Register

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|  |  |  |  |  |  |  | | | | | | | | | | | |  |  |  |  | **Smear (S) and Culture (C) Results During Treatment : P/N** | | | | | | | | | |
|  |  |  | **Result of Drug Resistance Test**  **R= Resistant S = Susceptible**  **C = Contaminated** | | | | | | | | | | | | | | |  |  |  |  | **Start of Treat-ment**  **Month**  **0** | | **Month**  **1** | | **Month**  **2** | | **Month**  **3** | | **Month**  **4** | |
| **SLD Already Received (Yes/ No)** | **Date Sample Taken for DST** | **Date of Result of DST** | **R** | **H** | **E** | | **Z** | **S** | **Km** | **Cm** | **Am** | **Ofx** | **Lfx** | **Pto/Eto** | **Cs** | **PAS** | **Other** | **Type of Resistance**  **(MDR, XDR, poly-resistant)** | **Treatment Started with MDR-TB: Confirmed/ Suspected** | **Regimen (in drug initials)** | **Date Treatment Started** | **S** | **C** | **S** | **C** | **S** | **C** | **S** | **C** | **S** | **C** |
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| Smear (S) and Culture (C) Results During Treatment | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Month 5** | | **Month 6** | | **Month 7** | | **Month 8** | | **Month 9** | | **Month 12** | | **Month 15** | | **Month 18** | | **Month 21** | | **Month 24** | | **Month 27** | | **Month 30** | | **Month 33** | | **Month 36** | | |
| S | C | S | C | S | C | S | C | S | C | S | C | S | C | S | C | S | C | S | C | S | C | S | C | S | C | S | C |
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| **Result and Date** | | | | | | **TB/HIV Activities** | | | | | **Comments** |
| **Cured** | **Completed** | **Failed** | **Died** | **Defaulted** | **Transferred Out** | **HIV Testing** | | | ART  Y/ N  Start Date | CPT  Y/ N  Start  Date |
| **Testing Done**  **(Y/ N/ Unknown)** | **Date of Test** | **Result** |
|  |  |  |  |  |  |  |  |  |  |  |  |
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|  |  |
| --- | --- |
|  | 0 |
| 1 – 9 AFB per 100 HPF | Scanty (and report number of AFB) |
| 10 – 99 AFB per 100 HPF | + |
| 1 – 10 AFB per HPF | + + |
| > 10 AFB per HPF | + + + |

|  |  |
| --- | --- |
| **Notation Method for Recording Smears** | |
| No AFB | 0 |
| 1 – 9 AFB per 100 HPF | Scanty (and report number of AFB) |
| 10 – 99 AFB per 100 HPF | + |
| 1 – 10 AFB per HPF | + + |
| > 10 AFB per HPF | + + + |

**Notation method for recording cultures**

|  |  |
| --- | --- |
| No growth reported | 0 |
| Fewer than 10 colonies | Report number of colonies |
| 10 -100 colonies | + |
| More than 100 colonies | + + |
| Innumerable or confluent growth | + + + |

**First-line drugs Second-line drug**s

H = Isoniazid Km = Kanamycin

R = Rifampicin Cm = Capreomycin

E = Ethambutol Cfx = Ciprofloxacin

Z = Pyrazinamide Ofx = Ofloxacin

S = Streptomycin Lfx = Levofloxin

T = Thiazetazone Moxi = Moxifloxacin

Gati = Gatifloxacin

Pto = Prothionamide

Eto = Ethionamide

CS = Cycloserine

PAS = p-aminosalycilic acid

**DR-TB Control Program DR-TB 06**

### Quarterly report on MDR/XDR-TB detection and Category IV treatment start

|  |  |
| --- | --- |
| Name of treatment site: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ /District\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  Patients detected during \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ quarter of year \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ | Name of treatment site focal person: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  Date \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ |

**1 - Number of patients detected with MDR/XDR-TB in the lab (by date of result of MDR-TB/XDR-TB in lab register) during the quarter:**

**MDR-TB XDR-TB**

**Optional: separate patients by registration group**

**2 - Number of MDR-TB patients who started Category IV treatment during the quarter**

|  |  |  |  |
| --- | --- | --- | --- |
|  | New case | Previously treated with 1st-line drugs | Previously treated with 2nd-line drugs |
| Confirmed cases |  |  |  |
| Suspected cases |  |  |  |

1st quarter: 1st January - 31 March

2nd quarter: 1er April - 30 June

3rd quarter: 1er July - 30 September Signature

4th quarter: 1er October - 31 December

**DR-TB Control Program DR-TB 05**

### Six Month Interim Outcome Assessment of Confirmed MDR-TB Cases

**(To be filled out 9 months after treatment starts)**

Name of the Treatment Site:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Date Filled In: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Quarter Treatment was Started: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Date of the Report : \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Number**  **Started on Treatment** | | **Bacteriological Results at 6 Months of Treatment** | | | | **No Longer on Treatment** | | | | | |
| Negative  (Smear and culture negative) | Positive  (Smear and/or culture positive) | Unknown | | Died | Defaulted | | Transferred  Out | |
|  |  | |  |  |  | |  |  | |

### GLC –Annual Report

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| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Cohort 20??** | | | | | | | | |
| **Registration Group** | **Cured** | **Treatment Completed** | **Died** | **Failed** | **Defaulted** | **Transferred out** | **Still on Treatment** | **Total** |
| **New** |  |  |  |  |  |  |  |  |
| **Relapse** |  |  |  |  |  |  |  |  |
| **After default** |  |  |  |  |  |  |  |  |
| **After failure of Category I treatment** |  |  |  |  |  |  |  |  |
| **After failure of Category II treatment** |  |  |  |  |  |  |  |  |
| **New extra-pulmonary** |  |  |  |  |  |  |  |  |
| **Other** |  |  |  |  |  |  |  |  |
| Total |  |  |  |  |  |  |  |  |

### Lab Culture & DST Register







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