FEDERAL REPUBLIC OF NIGERIA

FEDERAL MINISTRY OF HEALTH

DEPARTMENT OF PUBLIC HEALTH

NATIONAL TUBERCULOSIS AND LEPROSY CONTROL PROGRAMME

GUIDELINES FOR PROGRAMMATIC AND CLINICAL MANAGEMENT OF DRUG RESISTANT TUBERCULOSIS IN NIGERIA

2015

FOREWORD

Tuberculosis (TB) is a serious public health problem in Nigeria, with a prevalence of 323 per 100,000 people (National TB Prevalence Survey Report, 2012). Nigeria ranks third among the 22 TB High Burden Countries (HBCs) in the world (WHO: Estimated epidemiological burden of TB, 2014), with an estimated 564,460 new cases of TB occurring annually. Nigeria adopted and commenced the implementation of the Directly Observed Treatment Short-course (DOTS) strategy in 1993 and as at the end of 2013, the case notification rate and treatment success rate for TB was put at 17% and 86% respectively with a co-infection rate of 23%.

Apart from other factors especially HIV/AIDS pandemic, the emergence of drug resistant TB (DR-TB) presents an additional challenge to TB control in Nigeria. The 2012 National DR-TB Prevalence Survey Report revealed a DR-TB prevalence of 2.9% among new cases of TB and 14.3% among previously treated cases giving a crude prevalence rate of 4.8% across all treatment categories. The report also found a 4.4% Rifampicin-Resistant (RR-TB) rate among new adult PTB cases and 24.9% among re-treatment adult TB cases respectively.

The NTBLCP is currently intensifying its effort in providing quality diagnostic and treatment services across the country by continuous establishment of both diagnostic and treatment centres for the programmatic management of DR-TB cases and has moved further to compliment this effort with the adoption of community based DR-TB management which entails that patient get treatment at the community level.

This guideline for Programmatic and Clinical Management of Drug Resistant Tuberculosis has been reviewed to capture international best practices in the management of DR-TB and to reflect current WHO terminologies and DR-TB management plans. It is intended for use by all health care providers involved in the task of managing DR-TB patients in Nigeria. It is developed in line with World Health Organization (WHO) recommendation that DR-TB be managed on the principles of the DOTS strategy, using second-line anti-TB drugs, directly observed treatment and standardized recording and reporting to accommodate the need for complex outcome definitions. This document has a strong clinical focus in order to ensure adequate standards of health care for DR-TB patients in keeping with the international Standard for TB Care.

DOTS-Plus is an evolving strategy and has been adapted in Nigeria through evidence-based information and recommendations. Similarly, background information on the development of DR-TB strategies for prevention and control, and the management of health care workers risks has also been provided to strengthen the public health approach to the problem of DR-TB in Nigeria.

Finally, it is my belief that this document will help to provide the platform for the successful management and hence control of DR-TB in Nigeria. I encourage all health care providers and stakeholders who implement TB activities in Nigeria to familiarize themselves with the content of this policy document and ensure that it guides their operations at all times.

Dr. Khaliru Alhassan.
Honourable Minister of Health,
Federal Ministry of Health,
Abuja, Nigeria.

ACKNOWLEDGEMENTS

The Review of this guideline was done by a core team of 23 people. This review was necessary at this point in time to bring in the World Health Organization (WHO) new definitions of terms in line with global best practices. This document is meant to serve as a quick point of reference for General Health Care Workers (GHCWs) in the MDR-TB treatment centres and also in the communities where MDR-TB patients are managed.

I want to appreciate the Coordinator of the NTBLCP and his team members that have sat several times to make this review possible and the implementing partners who supported the team and more importantly the GFATM that ensured that there was enough funding for the meetings to review the guideline. I also want to thank the group of experts who participated and contributed by giving useful advice on how best the review of this Guideline should be done.

I want to graciously and specifically acknowledge the role of Staff from the following organizations: WHO, IHVN, GLRA, TLMN, DFB, FHI360, NIMR, USAID, KNCV and some staff of the MDR-TB treatment centres in Nigeria for their immeasurable contribution to this document. Most of these staff their names are already mentioned in the list of contributors.

I want to acknowledge the role of the M&E unit of NTBLCP for their major contribution to facilitate the review of the recording and reporting tools for MDR-TB which are attached as annexes to this document.

Dr. Bridgette Okoequale
HOD, Department of Public Health.

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CONTRIBUTORS

Dr.J.O. Obasanya
Dr. Gabriel Akang
Dr. Sam O. Ogiri
Dr. Oni Idigbe
Dr. Ayodele O. Awe
Dr. Emmanuel Meribole
Dr. J.N. Chukwu
Dr. (Mrs.) C. Onubogu
Dr. Dan Onwujekwe
Dr. Lovett Lawson
Dr. Enang Oyama
Dr. Omoniyi Amos
Dr. Gidado Mustapha
Dr. Osman Eltayeb
Dr. Micheal Odo
Dr. Babawale Victor
Mrs.Abiola Tubi
Dr.Saswata Dutt
Dr. Bowale Abimbola
Dr. Datonye Alasia
Dr. Tesfaye Basore
Pharm Ekpeno Akpanowo
Dr. Kuye Joseph
Dr Alayo Sopekan
Mrs Jumoke Adebari

ACRONYMS

ACSM	Advocacy, Communication and Social Mobilization
ADR	Adverse Drug Reaction
AFB	Acid Fast Bacilli
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Therapy
BSC	Biosafety Cabinets
CET	Consilium of Experts Team
CNS	Central Nervous System
CPT	Cotrimoxazole Preventive Therapy
CSF	Cerebrospinal Fluid
DOT	Direct Observation of Treatment
DOTS	Directly Observed Treatment Short-course
DR-TB	Drug Resistant Tuberculosis
DST	Drug Susceptibility Testing
ECG	Electrocardiogram
EQA	External Quality Assessment
FMOH	Federal Ministry of Health
GFATM	Global Fund to Fight AIDS, TB and Malaria
GHCW	General Health Care Worker
GLC	Green Light Committee
GLP	Good Laboratory Practice
HBCs	High Burden Countries for Tuberculosis
HIV	Human Immuno-deficiency virus
HMIS	Health Management Information System
IRIS	Immune Reconstitution Inflammatory Syndrome
LGAs	Local Government Areas
LPA	Line Probe Assay
LTFU	Lost to Follow Up
MDGs	Millennium Development Goals
Mtb	Mycobacterium Tuberculosis
MDR-TB	Multi-Drug Resistant Tuberculosis
NAFDAC	National Agency for Food and Drugs Administration and Control
NRA	Nitrate Reductase Assay
NRL	National Reference Laboratory
NTBLCP	National Tuberculosis and Leprosy Control Programme
NTM	Non-tuberculosis Mycobacterium
PHC	Primary Health Care
PLHIV	People Living with HIV
PMDT	Programmatic Management of Drug Resistant Tuberculosis
PSM	Procurement and Supply Management
RR-TB	Rifampicin Resistant Tuberculosis
SCC	Short Course Chemotherapy
SME	Supervision, Monitoring and Evaluation
SNRL	Supra National Reference Laboratory
SOP	Standard Operating Procedures
SRL	Supra-National Reference Laboratory
STBLCO	State TB & Leprosy Control Officer
TB	Tuberculosis
TB/HIV	Tuberculosis and Human Immuno-deficiency Virus Co-infection

TBIC	TB Infection Control
ULN	Upper Limit of Normal
WHO	World Health Organization
XDR-TB	Extensively Drug-Resistant Tuberculosis

1. DRUG RESISTANT TUBERCULOSIS CONTROL IN NIGERIA

1.1 Introduction

The emergence of resistance to drugs used to treat tuberculosis (TB), and particularly Drug Resistant TB (DR-TB) has become a significant public health problem in a number of countries and an obstacle to effective global TB control.

1.1.1 The rationale

The rationale for putting in place a mechanism for the control of DR-TB is based on the following:

- All those affected will have access to life-saving treatment with quality-assured second-line anti-TB drugs.
- Implementation of DR-TB control is consistent with the Stop TB Initiative launched in 2005 by the World Health Organization (WHO) and the Stop TB Partnership. This strategy recognizes the need to provide care to all patients affected by TB, whether the disease is caused by drug-susceptible or drug-resistant bacilli, and the need to avoid jeopardizing TB control efforts where drug-resistant TB is highly prevalent.

Based on the aforementioned rationale, DR-TB control activities in the country has been integrated into the national TB control plan to ensure effective and efficient implementation.

1.1.2 Global burden of DR-TB

The WHO Stop TB Department estimates the number of incident cases (including new and re-treatment cases) occurring worldwide that in 2013, 9.0 million people developed TB and 1.5 million died from the disease; 360,000 of whom were HIV-positive.

Progress in the detection of drug-resistant TB has been facilitated by the use of new rapid diagnostics. Globally, 3.5% of new and 20.5% of previously treated TB cases were estimated to have had MDR-TB in 2013 (which means that an estimated 480,000 people had developed MDR-TB in 2013).Similarly, a total of 97,000 patients were started on MDR-TB treatment in 2013, a three-fold increase compared with 2009. However, 39,000 patients (plus an unknown number detected in previous years) were on waiting lists, and the gap between diagnosis and treatment widened between 2012 and 2013 in several countries.

The most recent treatment outcome data for patients started on MDR-TB treatment in 2011 revealed a global success rate of 48% and on average, an estimated 9.0% of patients with MDR-TB had extensively Drug Resistant TB (XDR-TB).

WHO Global TB Report, 2014

1.1.3 The TB situation in Nigeria

Tuberculosis is a major public health problem in Nigeria with a prevalence of 323 per 100,000 population, and an incidence rate for all forms of TB of 338 per 100,000 population (National TB Prevalence Survey Report, 2014).

A total of 100,401 cases of all form of TB was notified in 2013, out of which 53%, 3%, 1% and 1% were new sputum smear positive, relapse, treatment after failure and treatment after lost to follow-up cases respectively. Similarly, the treatment success rate among new and retreatment cases commenced on treatment in 2012 was 86% and 81% respectively.

1.1.4 Burden of DR-TB in Nigeria

The 2012 National DR-TB Survey reported the prevalence of DR-TB as 2.9% among new TB cases and 14.3% among retreatment cases, and a crude prevalence rate of 4.8%. (Refer to table 1.1 for details)

Table 1.1: Drug resistance patterns among survey respondents

Drug resistance pattern	All cases %	New cases%	Retreatment cases%
MDR –TB	**4.8**	**2.9**	**14.3**
RHZE	3.3		
RHS	12.4		
Rifampicin	3.1	1.4	10.6
Isoniazid	4.8	4.3	5.7
Ethambutol	20	4.9	23.1
Pyrazinamide	9.1	3.7	20.5
Streptomycin	30.6	25.6	41

R=Rifampicin, H=Isoniazid, Z=Pyrazinamide, E=Ethambutol and S=Streptomycin

1.2 The National Tuberculosis and Leprosy Control Programme

The National Tuberculosis and Leprosy Control Programme (NTBLCP) is the body responsible for the control of TB, leprosy and Buruli ulcer in Nigeria. It facilitates policy and human development, tertiary care, resource mobilization and technical support to state programmes. The goal of the NTBLCP in the control of DR-TB is to significantly reduce the burden, socio-economic impact and transmission of DR-TB in Nigeria. Similarly, the state and local government area (LGA) TB and Leprosy (TBL) Control Programme coordinates TB control activities in each state and LGA respectively in line with the overall goal of the NTBLCP. The LGA is the operational level of the programme based on the primary health care (PHC) principle.

1.2.1. Specific objectives of DR-TB control

The two objectives of DR-TB control are:

- To provide access to DR-TB diagnosis to all presumptive DR-TB cases between 2015 and 2020 in line with the national diagnostic algorithm
- To enrol 100% of diagnosed DR-TB patients on appropriate treatment between 2015 and 2020

1.2.2 Strategic interventions for DR-TB

The strategic interventions (SI) established for DR-TB include:

- Strategically expand DR-TB diagnostic sites
- Institute a standardized specimen transport system from the point of collection from presumptive DR-TB cases to DR-TB diagnostic centres for DR-TB diagnosis and treatment follow up
- Increase DR-TB case finding skills among health care providers
- Strengthen the DR-TB surveillance system
- Provide prompt, appropriate treatment & care to all diagnosed DR-TB cases
- Assure adequate supplies of second-line and ancillary drugs and supplies
- Institute appropriate infection control measures to prevent transmission of DR-TB in facilities and the community

1.2.3 Framework for effective DR-TB control in Nigeria

The framework for effective DR-TB control is based on the five essential components of DOTS strategy because the underlying principles are basically the same. DR-TB control in the country will be systematically introduced into the DOTS-based TB control strategy of the NTBLCP.

1.3 Components of DOTS strategy for effective DR-TB control in Nigeria

1.3.1 Sustained political commitment

For effective DR-TB control in Nigeria, strong and sustained political commitment from government is essential. This can be achieved through:

- Continuous support for expansion and strengthening of basic DOTS services, into which DR-TB control will be integrated;
- Embracing and supporting all aspects of the New Stop TB Control Strategy;
- Mobilizing additional financial support for all aspects of TB control from the regular budget and the debt relief funds;
- Inclusion of DR-TB Control in the National TB, Leprosy and BU management and control guideline and updates will be reflected in subsequent editions;
- Establishing a DR-TB technical committee comprising of various partners and experts to provide support and direction in programme planning, implementation, monitoring and evaluation;
- Ensuring that the NTBLCP remains the sole channel through which all first-line anti-TB drugs are imported and distributed in the country; and
- Ensuring the prohibition of over-the-counter sale of all first line anti-TB drugs.

1.3.2 Case finding strategy

The second component of the framework relies on a rational case finding strategy including accurate, timely diagnosis through quality assured rapid molecular testing,

culture and drug susceptibility testing (DST):

- The Government will coordinate support for the expansion and sustenance of network of microscopy services to attain a coverage of at least one microscopy centre per 80,000 population;
- National and sub-national (zonal) reference laboratories will be established and fully equipped to support accurate, reliable and timely diagnosis of DR-TB as well as support surveillance activities;
- TB diagnostic services in the country will be strengthened in collaboration with partners to provide more effective and efficient support to the TB Control Programme;
- The National Programme will ensure regular availability of quality assured reagents and other supplies for culture and DST;
- Appropriate training/re-training will be provided to all relevant staff in the reference laboratories;
- The Government through the NTBLCP will continue to strengthen the Laboratory Quality Assurance System at all levels in the country;
- The National Reference Laboratories (NRL) will be linked to a Supra National Reference Laboratory (SRL) for technical support and external quality assessment; and
- The NTBLCP will ensure the standardization of equipment, reagents and other material as well as a centralized procurement system.

1.3.3 Treatment strategy

To ensure proper case management at all time, the framework recommends the need to develop appropriate treatment strategies which will use second-line anti-TB drugs under proper supervision. This entails that the:

- NTBLCP put in place a drug-resistance surveillance system to determine and monitor the extent and pattern of drug-resistance for first-line and selected second-line drugs;
- Management of identified DR-TB cases be based on a standardized drug regimen with a treatment duration of 20 months;
- DOT approach be used for drug delivery to patients for at least the duration of the intensive phase of treatment;
- Capacity for effective clinical and laboratory monitoring and management of DR-TB cases with special attention to drug side effects be developed;
- Country ensures that at least one in-patient treatment centre per zone (in the states where the sub-national (zonal) reference laboratories are located) be established while the programme strengthens treatment support network for ambulatory cases;
- Programme to continuously organize staff training and re-training to provide appropriate knowledge on how to treat and monitor adverse drug effects when they occur;
- Appropriate infection control measures be developed and implemented at all levels;
- Provision of counselling and appropriate social support be put in place and made available at all times.

1.3.4 Uninterrupted supply of quality-assured second-line anti-TB drugs

The fourth component of the framework focuses on drug supply of second-line drugs, as listed below.

- The programme shall institute an effective and efficient drug logistics and management system;
- The programme shall collaborate with National Agency for Food and Drugs Administration and Control (NAFDAC) for the approval and registration of the second-line anti-TB drugs

(SLDs) to ensure the viability of the drugs; and

- The programme shall collaborate with the Green Light Committee (GLC) for the technical and logistic support in ensuring regular and uninterrupted supply of quality- assured SLDs.

1.3.5 Standardized DR recording and reporting

The final component of the framework supports the development of a standardized DR-TB recording and reporting system:

- The programme shall review the current NTBLCP recording and reporting format to include DR-TB; and
- The programme shall introduce additional DR-TB reporting and recording formats.

1.4 Structure of PMDT control in Nigeria

1.4.1 The PMDT Unit at the central unit of the NTBLCP

The PMDT unit is a thematic section of the central unit of the NTBLCP saddle with the responsibility to coordinate and formulate policy which guides DR-TB management and control in Nigeria. It is headed by a Director Medical and is assisted by other staff who ensure that the goals and objectives of the NTBLCP as it relates to DR-TB prevention and control are met. The unit is responsible to the National Coordinator of the NTBLCP through its head.

1.4.1.1 Responsibilities of the PMDT Unit (NTBLCP)

- Develop national policy, strategy, plan, guidelines and budget for PMDT in consultation with National DR Technical Committee
- In collaboration with the M&E unit of the NTBLCP support the supervision, monitoring and evaluation (SME) of DR-TB activities in Nigeria
- Facilitate the process of reviewing complicated and difficult cases through CET
- Map out the strategies and plan for community involvement in DR-TB control
- In collaboration with the PSM/logistic unit of the central unit of the NTBLCP facilitate effective PSM for DR-TB drugs and commodities
- In collaboration with the M&E unit of the NTBLCP ensure effective DR-TB surveillance through routine reporting
- Facilitate Capacity building for PMDT implementation
- In collaboration with the laboratory unit of the NTBLCP ensure quality assured laboratory services at Zonal and NRLs and linkage to the Supra-national Reference Laboratory

1.4.2 DR-TB Committee and Teams for the support of PMDT in Nigeria

With the gradual involvement of more facilities in the management of DR-TB patients and to complement the effort of the NTBLCP, the NTBLCP and other stakeholders have come up with a technical structure designed to provide support for the management and control of DR-TB in Nigeria. This structure is put in place in form of committee/team to provide technical support at different levels. They include:

1.4.2.1 National DR-TB Technical Review Committee (NDRC)

The National DR-TB Technical Review Ccommittee serves as an advisory body to the NTBLCP (FMoH). This Committee has a clear mandate to steer and work very closely with the NTBLCP to ensure that the goals and objectives of the programme are met. The National DR-TB Technical Review Committee (NDRC) steers the programme, various sub working groups (clinical, laboratory, PSM, ACSM, M&E) ensure policy guidance of all components of PMDT together with all stakeholders.

- **Terms of reference of the National DR-TB Committee**
  - Provide overall strategic direction on DR-TB control in the country
  - Provide technical support to the FMoH in the development of guidelines for DR-TB
  - Provide support in the design and conduct of DR-TB surveillance in the country
  - Provide coordination of all partners supporting DR-TB activities in the country
  - Provide technical assistance in the setting up of TB reference laboratories at the national and zonal levels

1.4.2.2 State DR-TB management team

Each state is to have a State DR-TB management team which will oversee implementation of DR-TB activities within the state and promote effective linkage between the NDRC, DR-TB treatment centres and the DOTS treatment units.

- **Terms of reference of the National DR-TB Committee**
  - Prepare and implement state level DR-TB plans and budgets in consultation with the NTBLCP
  - Coordinate DR-TB activities in the state
  - Manage and distribute drugs and commodity supplies
  - Programme monitoring and supervision
  - Coordinate governmental and non-governmental organization partners working in the DR-TB
  - Compile and present PMDT reports at the National Monitoring and Evaluation Quarterly Meetings

1.4.2.3 The Consilium of Expert Team (CET)

The Consilium of Expert Team is established at each treatment centre to oversee the overall management of DR-TB patients. The team serves as the technical working committee for the treatment centres and meets weekly in the beginning to review the status of patients.

- **Composition of the CET**
  - A committed chest physician or a DR-TB trained Medical Officer
  - A dedicated trained DR-TB nurses
  - A social worker or a trained counsellor

- An administrative assistant
- A pharmacist

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- **The functions of the CET will include**
  - Oversight for all aspects of DR-TB management (with collective responsibility for decisions about any form of treatment
  - Evaluation of the patients
  - Prescribing drugs
  - Follow-up examination of patients
  - Training of other facility staff on DR-TB management
  - Finding solutions for special problems.
  - Problem-solving for special problems

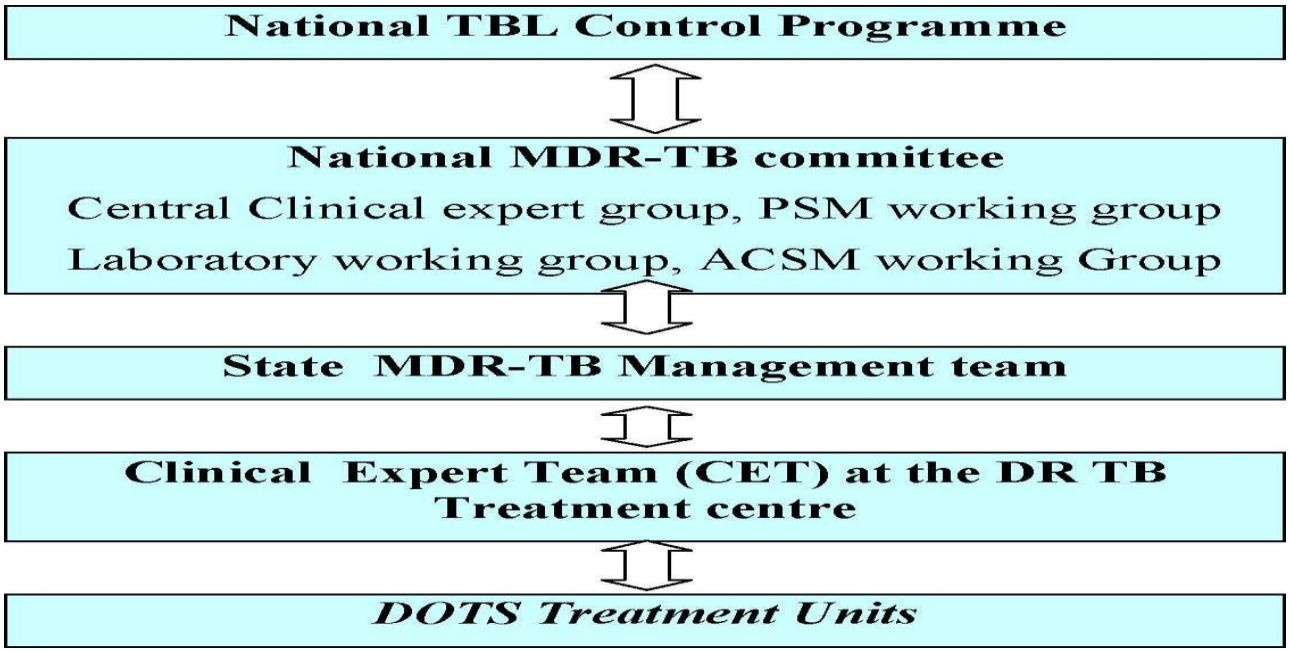
Table 1.2: Roles and responsibilities of other levels and sectors involved in the PMDT

Institution	Roles and Responsibilities
Partners	• Provide technical and financial support
Central clinical expert group	• Review treatment regimens • Review treatment outcome • Assist in formulation treatment policy
PSM working group	• Review and oversee procurement, storage and distribution, inventory from the central down to the point of patient care
Laboratory working group	• Develop policy documents, guidelines, standard operating procedures (SOPs) and manuals • Plan laboratory expansion • Assess of new laboratories • Provide continuing technical assistance • Provide monitoring and supervision
M&E working group	• Develop review and update PMDT recording and reporting tools • Conduct monitoring, supervision and evaluation • Provide technical guide on surveillance for DR-TB
ACSM working group	• Development of ACSM policy guide related to DR-TB • Conduct advocacy, communication and social mobilization
National TB Reference Laboratory	• Perform culture and DST • Assist in maintaining an effective TB surveillance system • Liaise with WHO-accredited supra-national reference laboratory for second-line DST and external quality assessment (EQA) • Assist the NTBLCP in organizing and conducting operational research of TB laboratory issues • Provide training to other culture laboratories • Provide training to peripheral laboratories • Quality assurance of other laboratories • Supervision and monitoring of other laboratories
TB culture laboratories	• Perform culture • Send isolates to reference laboratories for DST • Perform rapid diagnosis (from year 3)

TB and Leprosy Supervisors/State TB and Leprosy Control Officers	• Support and Ensure samples are sent to the laboratory • Liaise with control officer to obtain results and communicate to General Healthcare Workers (GHCW) at the Facility • Support the referral process of the DR-TB patient • Ensure that the drugs are available for the referred patient. • Provides supportive supervision to ensure appropriate documentation, DOTS adherence, patient records are complete and correct, patients are monitored regularly • Retrieval of defaulters
DR-TB Treatment Centres	• Hospitalize patients for whole or part of the intensive phase • Discuss common side effects with the patient and the need to continue treatment even if there are side effects • Educate and counsel the patient on his/her disease and explain the importance of treatment adherence and DOT • Obtain informed consent from the patient • Provide DOT to all DR-TB patients, including injections • Designate a PMDT Medical Officer/Clinician to examine and register patients • Maintain the DR-TB treatment register (this is the responsibility of the PMDT focal person) • In the case of patients who do not match the DR-TB treatment guideline criteria, the state Consilium will consult the national Consilium for recommendations and suggested appropriate treatment • Fill out the treatment card for the patient with treatment details including drugs, duration and dates of case review • Provide relevant training/orientation for State TB & Leprosy Control Officers (STBLCOs) and DOT centre staff • Communicate with respective STBLCOs before discharging patients
Community Volunteer/Treatment Supporter	• Support patient to go to facility for DOT • Support patient to go for routine investigations • Provide DOT to patient where necessary • Ensure adherence to IC standards
DOTS Facility	• Responsible for identifying the presumptive DR-TB cases • Collecting sputum for DR-TB diagnosis from the high risk group and referring for appropriate management. • The DOTS centre may also be responsible for provision of care during the intensive and continuation phase ofDR-TB treatment.

Health workers at PHC and DOTS centres	• Identify presumptive TB, collect and send samples to laboratories • Complete necessary forms • Follow-up with all patients in the PMDT programme and encourage them to take their medicine • Provide continuous health education • Conduct contact investigation • Complete the DR-TB Suspect Register • Liaise with LGA TBLS and Control Officer to send samples to GeneXpert sites • If confirmed as DR-TB patient inform STBLCO • Ensure strict DOT for all periods of treatment • Ensuring regular monitoring of patient • Follow-up with the patient immediately a visit is missed and contact the named treatment supporter if necessary • Document and treat any side effects on the patients hand and treatment card • Refer any patients with significant side effects (as specified by NTBLCP policy and guidelines) to DR-TB treatment centre or designated hospitals in the state • Complete and maintain all appropriate recording and reporting format according to the NTBLCP guidelines

Figure 1.1: Diagrammatic presentation of the PMDT structure in Nigeria

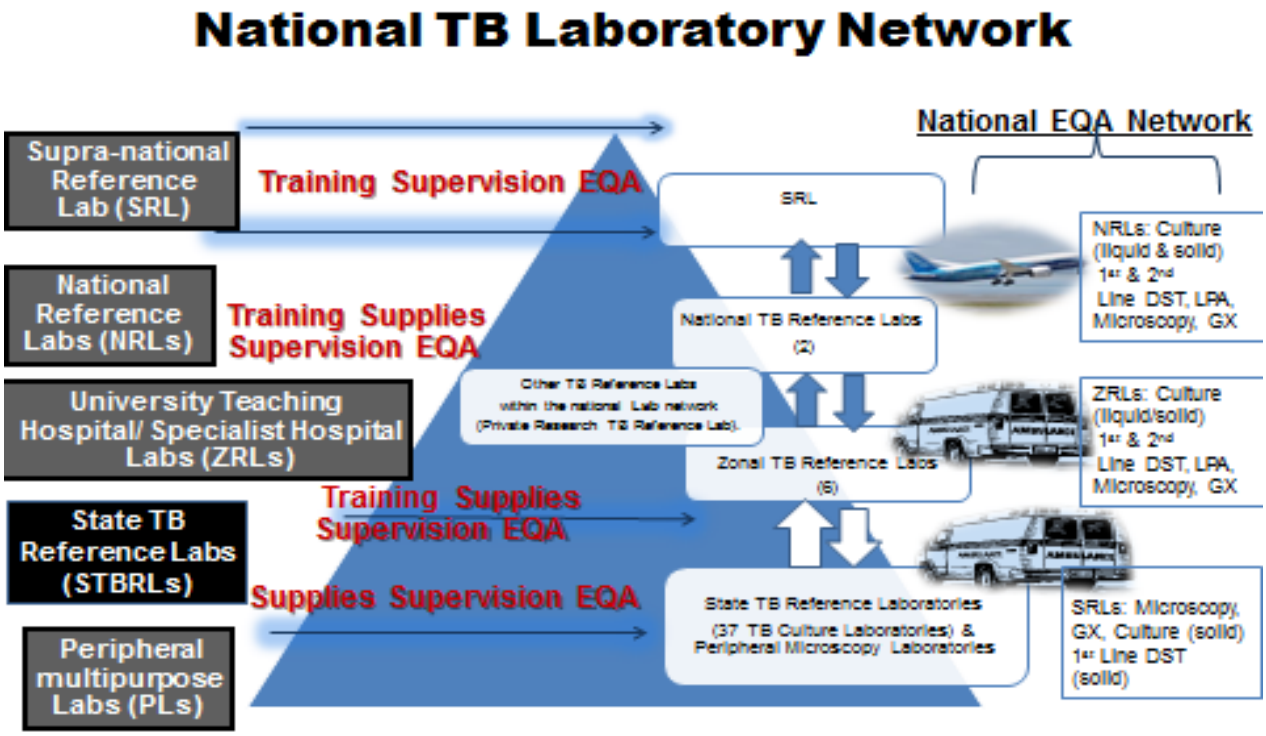


2. ORGANIZATION OF LABORATORY SERVICES

2.1 Functions and responsibilities of the various levels laboratory services of TB

The NTBLCP laboratory network is organized in a pyramidal fashion consisting of four levels within the NTP and is coordinated at the central level by the Laboratory team of the central unit of the NTBLCP. This classification is based on administrative division, geographical location, population coverage and type of activities implemented at various levels. The national TB laboratory network relies on the contribution of labs from across the health system. The functions and responsibilities of the network members are listed in Figure 2.

Figure 2.1: The NTBLCP Laboratory Network



2.1.1 Level 1: Peripheral Laboratory

The peripheral laboratories perform the following technical functions:

- Preparation and staining of smears
- ZN and FM microscopy and recording of results
- GeneXpert
- Internal quality control
- Recording and reporting of test results
- Participation in panel set tests (acid-fast bacilli [AFB] microscopy and GeneXpert)
- Cleaning and Maintenance of equipment
- Serial storage of all slides for blinded slides rechecking EQA programme

The peripheral laboratories perform the following administrative functions:

- Receipt of specimens and review of test results and QC before the release of test reports
- Validation of test results and staff job proficiency
- Maintenance of laboratory register
- Management of reagents and laboratory supplies

2.1.2 Level 2: State Tuberculosis Reference Laboratory

The State Tuberculosis Reference Laboratory (STBRL) will perform all the functions of Level 1(peripheral) laboratories in addition to the following activities:

- Distribution of reagents for microscopy in peripheral laboratories
- Perform solid culture, identification of mycobacterium tuberculosis (Mtb)
- Conventional phenotypic first line DST on solid media using proportional and nitrate reductase assay (NRA) methodology
- Perform TB molecular assays - Line Probe Assay (LPA) and GeneXpert
- Coordination of the EQA panel on the proficiency ofAFB sputumsmear microscopy and GeneXpert
- Participation in panel set tests (culture and DST) from zonal reference laboratories
- Regular maintenance of equipment
- Oversight functions of peripheral laboratories
- Operational research
- Training of Microscopist
- Support supervision of peripheral centres
- Quality improvement and proficiency testing of microscopy at lower laboratories

2.1.3 Level 3: Zonal Reference Laboratory

Zonal Reference Laboratories (ZRLs) perform all the functions of the Level 2laboratories. In addition, ZRLs will perform the following activities:

- Preparation of reagents for smear microscopy
- Distribution of reagents for microscopy in peripheral laboratories
- Perform solid culture, identification of Mtb
- Conventional phenotypic 1st line DST on solid media using proportional and NRA methodology (Operational Research).
- Perform TB molecular assays (LPA and GeneXpert)
- Coordination of the STBRLs on an EQA panel proficiency for AFB sputum smear microscopy, culture, GeneXpert and Line Probe Assay
- Participation in panel set tests (culture and DST) from NRLs and SRL
- Regular maintenance of equipment
- Oversight functions of state laboratories
- Operational Research
- Training of microscopists
- Support to and supervision of peripheral staff with respect to microscopy
- Quality improvement and proficiency testing of microscopy at lower laboratories
- Retrieval of broken equipment from peripheral centres to central point for repairs
- Supportive supervision to STBRLs and monitoring of peripheral staff to ascertain proper

implementation of quality management system

- Coordinate distribution of panel proficiency testing to STBRLs from National Reference Laboratories (NRLs)

2.1.4 Level 4: National Reference Laboratory

NRL perform all the functions of the Level 3(ZRLs), plus:

- Firstand second line drug susceptibility testing of Mtb isolates (using solid and liquid drug susceptibility testing of *M. tuberculosis* isolates)
- Preparation of media for TB culture (LJ medium, NRA, LJ proportion for 1st line DST)
- In country test method validation on new technology e.g. GeneXpert
- Identification of mycobacterium other than Mtb
- Molecular epidemiology studies
- Quality assessments for state and zonal laboratories
- Proficiency testing between the NRL and SNRL
- Operational research
- Technical control of and repair services for laboratory equipment
- Updating and dissemination of manuals on bacteriological methods for diagnosing TB
- Development and dissemination of guidelines on care and maintenance of microscopes and other equipment used in tuberculosis bacteriology
- Development and dissemination of guidelines on TB laboratory supervision and quality assurance
- Collaboration with the central level of the NTBLCP in defining technical specifications for equipment, reagents and other materials used in bacteriological investigations, and in estimating laboratory materials and equipment requirements for the programme budget.
- Training of Level 2 and 3 laboratory staff in bacteriological techniques and support activities, i.e. training, supervision, quality assurance, safety measures and equipment maintenance
- Supervision of Level 2 and 3 laboratories regarding bacteriological methods and their support (particularly training and supervision) to the peripheral laboratories
- Organization of surveillance of primary and acquired mycobacterium drug resistance
- Operational and applied research relating to the laboratory network, coordinated with the requirements and needs of NTBLCP

2.2 Quality assurance

Effective management of DR-TB in the country can only be achieved when high quality and reliable TB laboratory services are in place. To this end, the NTBLCP has recommended that:

i. All medical laboratories which perform TB diagnosis in the country should ensure that all components of their operations, including the work environment, safety measures and quality control, comply with the minimum standards of good Laboratory Practice (GLP).
ii. Written protocols (SOPs) should be developed, displayed and used on a regular basis for all procedures that add to quality assurance in such laboratories.
iii. All existing network of TB laboratories, i.e. TB microscopy centres, State TB laboratories, and the Zonal and National Reference Laboratories, a system of internal quality control (QC), EQA and quality improvement should be effectively implemented.
iv. Other laboratories which may wish to provide TB control services in the country is required to conform to these standards (iii above).
v. Internal quality control and quality improvement measures in all laboratories where smear

microscopy and sputum collection for culture is done should focus on work practices and technical procedures by ensuring that:

- Sputum specimens are properly labelled and accompanied by all relevant and adequately completed forms
- Laboratory registers are correctly filled and slides well marked
- All new batches of stains are tested with known positive and negative slides before use
- Carbol fuchsine and Methylene blue are filtered and labelled properly
- Known positive and negative control slides are included in each staining batch and documented
- Known positive and negative control slides are read first to verify quality of staining and grading
- Biochemical test results for cultures are done using known positive and negative controls
- Distilled and tap water used for culture are checked for presence of acid- fast contaminants
- SOPs are maintained and observed
- Binocular microscopes are used and maintained in good condition
- Stock levels are monitored and documented in the national stock registers

vi. Quality control and improvement measures in these settings will therefore apply on a wider scale than is stated above, and apply in a more rigorous evaluation of laboratory arrangement and administration, equipment selection and installation, collection and transport of specimens, handling of specimens, reagents and media, culture methods and the reporting of results.

vii. SOPs for all processes in the reference laboratories should be developed and displayed at activity points in the laboratories. They will cover culture, identification, susceptibility testing of Mycobacterium strains, and the reporting of results. These SOPs will conform to internationally accepted standards (WHO, Centres for Disease Control and Prevention).

2.3 Laboratory equipment, maintenance and repairs

Written operating procedures, cleaning instructions and dated service records should be displayed near each piece of equipment in the culture laboratories and also kept in a file. Similarly, critical equipment should be monitored from procurement stage to ensure that they meet specifications for what they are required to do, and check regularly to ensure accuracy and precision.

Biological safety cabinets will be subjected to performance tests on installation and re-certified annually thereafter to ensure they meet internationally acceptable standards of safety and performance. These tests include:

- Down flow velocity and volume test (annually)
- Inflow velocity test (annually)
- Airflow smoke patterns tests (daily before use and after certification)
- HEPA filter leak test (annually)
- Cabinet leak test (prior to installation, after relocation, after repairs or filter change)
- Electrical leakage and ground circuit resistance and polarity tests
- Noise level test
- Vibration test

Laboratory scientists in the reference laboratories are expected to also perform daily checks to ensure acceptable rate of airflow of 22.6metre/second for Class 1, and 22.86-30.48metre/second for Class II cabinets. The monitoring activity for biosafety cabinets (BSCs) should be done where all BSCs are located.

Annual certification of BSCs repairs and changing of HEPA filters will be performed by certified

Biomedical Engineers.

2.4 External quality assessment

2.4.1 Supervision to laboratories

In order to ensure improved performers of laboratory staffs at different levels, the NTBLCP has put in place a supervisory system for all laboratories at different levels. These supervisory visits shall be performed quarterly by trained laboratory personnel from the supervising laboratory, to observe laboratory workers' performance under actual working conditions and to assess laboratory equipment, supplies and internal quality control using the standardized (national) checklist.

2.4.2 Blinded re-checking

A statistically determined sample of slides from each laboratory where microscopy is performed will be re-checked quarterly by an external assessor from the supervising State or Zonal Reference Laboratory. A total of 15 slides will be selected per quarter per centre. The Lot Quality Assurance sampling method is adopted in sampling the slides read by the Microscopist (first reader) for EQA at the laboratories in the network.

To avoid bias during blinded re-checking, personnel of the laboratory being assessed shall not be involved in the selection of the slides. The assessor (first controller or second reader) will re-read the slides without knowing the results of the first reader at the microscopy centre, and records his/her results separately. The results of the first reader at the peripheral laboratory are then copied onto the Assessor's Results Form, and compared. If any discrepancies are noted, a third reader is invited to do a blinded re-reading of the discrepant slides, and then makes the final decision on the discrepant slide(s). The slides are re-stained by the second controller or third reader.

2.4.3 Proficiency testing

As part of the EQA system of the NTBLCP, proficiency slides set tests are prepared and distributed from the ZRLs to the peripheral laboratories bi-annually. Each participating laboratories are provided with five stained and five unstained AFB sputum smears. This process is also conducted to ascertain the proficiency level of newly trained TB Microscopist.

Proficiency sets for culture and DST procedures are conducted for the reference laboratories after proper validation of all containment equipment and testing procedures in a newly established TB reference laboratory. The NRLs will arrange with the Supra National Reference Laboratory for the first double blind proficiency test on a panel of mycobacteria species or Mtb strains. The SRL may, at its discretion, arrange for an alternative approach to proficiency testing, if exchange of strains is problematic.

The SRL send panel sets to NRLs and ZRLs annually to test the entire testing procedures and staff proficiencies. The NRLs also arrange for re-checking portion of Mtb isolates during surveys of DR-TB. This will include rechecking all strains found with rifampicin resistance and isoniazid resistance, and those resistant to other first line drugs, as well as 10% fully susceptible strains.

Note

- Resistance in the second line will be sent for rechecking including MDR-TB at the SRL.
- The NRL will perform first line drug susceptibility testing on rifampicin, isoniazid, and pyrazinamide.
- In addition, the NRLs will also perform second line drug testing on MDR-TB isolates.

- The NRL is expected to perform second line DST in a timely manner for patient management.

3. MANAGING PRESUMPTIVE DR-TB CASES

3.1 Introduction

The emergence of resistance to drugs used to treat TB and particularly multi-drug resistant TB (MDR-TB) and XDR-TB poses an obstacle to effective TB control at both national and global levels. Resistance arises from both service and patient-related factors in the management of the disease, ranging from poor, inadequate supervision, poor quality of drugs, inadequate dosing, drug combinations and duration of treatment, poor training of health staff and poor adherence by patients. Therefore, health care providers should consider presumptive Drug Resistant TB in any of the situations outlined in table 3.1.

Table 3.1: Risk factors for presumptive DR-TB

Risk factors for dru- resistant-tb	Comments
Failure of retreatment of reginmens with first line anti-TB drugs (SHREZ) (previously known as chronic TB cases)	Patients who are still sputum smear-positive at the end of a retreatment regimen have perhaps the highest MDR-TB rates in any group often approaching 90% (5).
Exposure to a known drug-resistant TB case	Most studies have shown that close contacts of MDR-TB patients have very high rates of MDR-TB. Management of drug-resistant TB contacts is described in chapter 15.
Failure of new TB regimens (SHREZ)	Patients who, while on treatment, are sputum smear-positive at month five or later during the course are at elevated risk for drug-resistant TB. Not all patients in whom a regimen fails have drug-resistant TB, and the percentage may depend on a number of factors, including whether rifampicin was used in the continuation phase and whether directly observed therapy was used throughout treatment.
Failure of anti-TB treatment in the private sector	Anti-TB regimens from the private sector vary greatly. A detailed history of drugs used is essential. If both isoniazid and rifampicin has been used, the chances of MDR-TB may be high. Sometimes second-line anti-TB drugs may have been used, and this is important information for designing the treatment regimen.
Patients who remain sputum smear- positive at month two or three of a first-line anti-TB drug regimen.	Many programmes may choose to perform culture and DST on patients who remain sputum smear-positive at months two or three. This group of patients is at risk of drug-resistant TB, though rates can vary considerably.
Relapse and return after loss to follow-up, without recent treatment failure	Evidence suggest that most relapse cases and those that return after loss to follow-up (without recent treatment failure) do not have drug-resistant TB. However certain patient histories may point more strongly to possible Drug-Resistant TB. For example- erratic drug use or early relapse.
Exposure in institution that have drug-resistant TB outbreak or a high drug-resistant TB prevalence	In many countries, patients who frequent homeless shelters, prisoners and health care workers in clinics, laboratories and hospitals can have high rates of drug-resistant TB (2,3)
Residence in areas with high drug-resistant TB prevalence	Drug-resistant TB rates in many areas of the world can be high enough to justify routine DST in all new cases.
History of using anti-TB drugs of poor or unknown quality	The percentage of drug-resistant TB caused by use of poor quality drugs is unknown but considered significant. All drugs should comply with acceptable international quality assurance standards.

Treatment in programmes that operate poorly (especially with recent and/or frequent drug stock-outs)j	These are usually with poor drug management and/or distribution systems.
Comorbid conditions associated with malabsorption or rapid-transit diarrhoea	malabsorption may result in selective low serum drug levels and may occur in either HIV-negative or HIV-positive patients.
HIV in some settings	Data from Global project on anti-TB Drug resistance surveillance (2) suggest an association between HIV and MDR-TB in some part of the world, and numerous drug-resistant TB outbreaks have been documented in HIV-positive patients. Data are still limited and specific factors involved in this association may be country specific. Even if HIV is not considered to be a risk factor for drug-resistant TB in a country, it is strongly recommended that all individuals with HIV associated with TB have DST to rule out drug resistant TB and to avoid high rate of mortality due to unrecognized drug-resistant TB in these patients.

3.2 Identifying presumptive DR-TB cases

The diagnosis and treatment of a DR-TB case starts with a proper identification of a presumptive DR- TB case. Therefore it is important for all persons who provide health services to TB patients to be able to identify a presumptive DR-TB case at all times and ensure that this identification is done early to enable prompt diagnosis and appropriate treatment. This is to prevent the disease from spreading to others as well as reducing morbidity and mortality associated with the disease.

To increase surveillance for DR-TB in Nigeria, the NTBLCP has recommended that all health care providers give priority to the following group of persons who present with symptoms of TB in their facilities:

i. Anybody who has come in contact with a confirmed DR-TB patient and who shows symptoms of TB.
ii. Any person whose AFB result is smear positive when smear is repeated at the end of month three (3) of Regimen 1 treatment.
iii. All previously treated Drug Susceptible TB cases:
    a. Relapse
    b. Treatment after failure to Regimen 1
    c. Treatment after loss to follow-up
    d. Other previously treated patients

Similarly, in order to expedite the diagnosis of DR-TB, improve the quality of services provided to patients with TB symptoms and detect early drug resistance to TB, the NTBLCP has also identified a second priority group of patients which include:

i. All persons with smear negative AFB result who still show symptoms of TB after 1 week of administration of broad spectrum antibiotics
ii. All Persons living with HIV (PLHIV) who present with symptoms of TB
iii. All health care staff who present with symptoms of TB
iv. All children who present with symptoms of TB
    a. Relapse
    b. Treatment after failure
    c. Treatment after loss to follow-up
    d. Other previously treated patients

v. All persons with symptoms suggestive of Extra-pulmonary TB in which specimen could be collected for GeneXpert test such as collection of cerebrospinal fluid (CSF) for examination as in TB meningitis.

Note:
Effort is being made to ensure that the current GeneXpert machines and subsequent ones will be able to be used to diagnose TB in presumptive EPTB cases.

Any presumptive DR-TB case identified should be requested to submit 1 sputum specimen for GeneXpert MTB/RIF and managed as outlined in figure 9.1 below.

3.3 Managing a Presumptive DR-TB case

The categories of patients mentioned above require urgent intervention to prevent further damage to their lungs and spread of the disease. Therefore, health care providers should ensure that the following services are provided each time a presumptive DR-TB case is identified to allow for quick and appropriate diagnosis of drug resistance TB;they should:

- Complete the Clinic Register for presumptive TB cases
- Explain the possible outcome and available management options
- Spend time to educate/counsel the patient on infection control
- Liaise with the Local Government TB and Leprosy Supervisors (LGTBLS) prior to specimen collection to discuss logistic for sputum transportation
- Complete the specimen examination request form for TB (GeneXpert test)
- Collect sputum sample (spot) into a standard sputum cup using appropriate SOP
- Collaborate with the LGTBLS to ensure that samples are sent using appropriate transport box
- Ensure that the laboratory focal person in the GeneXpert Laboratory communicate the result to the state in a timely manner.

Table3.2: Procedure for collection and transportation of Sputum specimen to Xpert labs

STEP	ACTION
1.	• Contactthe TBL supervisor prior to collecting specimen for GeneXpert-MTB/RIF for transportation of the sputum sample • Ensure that the request form is correctly filled with all patient information (identifiers)
2.	• Clearly label the side of the sputum cup (not the lid) with patient's name, ID number and date of collection before giving the cup to the patient

3.	• Instruct patient to:
	  • Rinse mouth with clean water
	  • Take 3-4 deep breaths, holding breath for 3-5 seconds after each inhalation
	  • Cough after the last inhalation, emptying the sputum into the sputum cup, with care taken not to contaminate the outside of the cup
	  • Educate patient on cough etiquette and hygiene (TB IC)

4.	• Collect one sputum specimen from the patient using the normal sputum cup • Sputum specimen should be produced in an open, well ventilated space not in the laboratory or offices • Ensure that the sputum cup screw cap is tightly closed • Wipe the outside of the cup with cotton wool soaked in tuberculocidal disinfectant (Phenol, Lysol, bleach).

5.	• Inspect specimen for quality and volume, the recommended volume of sputum specimen *is at least 3 to 5mls*
6.	• Send collected specimen in a sputum collection box e.g. "coolers" to the GeneXpert-MTB/RIF laboratory alongside the completed sputum request form not more than two days after collection

Table 3.3: Procedure for collection and transportation of Sputum specimen to culture labs

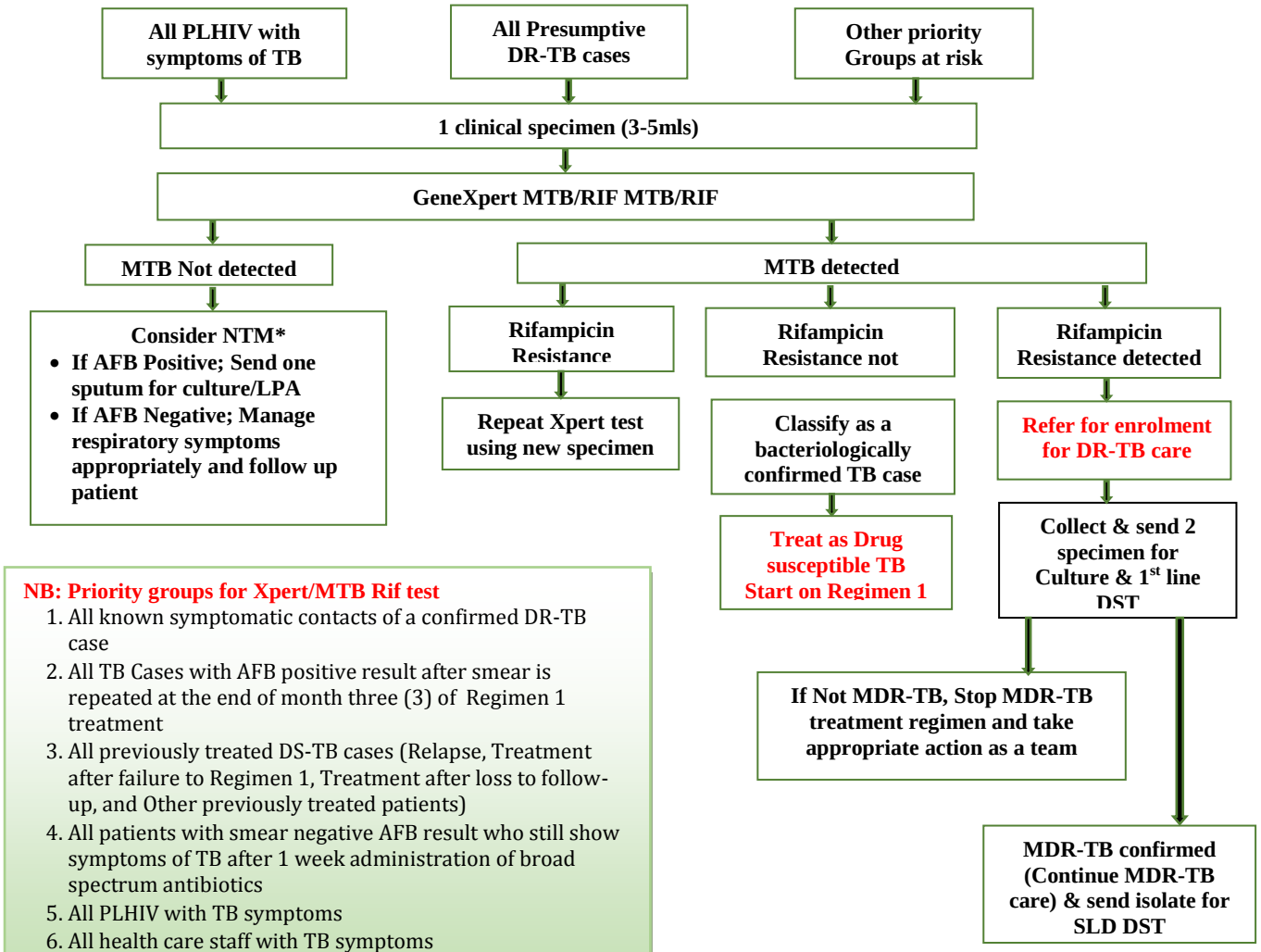
STEP	ACTION
1.	• For sample collection outside the DR-TB Treatment Centre, contact the TBL supervisor prior to collecting specimen for culture and DST for logistics. • Ensure that the request form is correctly filled with all patient information (identifiers)
2.	• Clearly label the sides of the falcon tubes (not the lid) with patient's name, ID number and date of collection before giving out to patients
3.	• Instruct patient to: Rinse mouth with clean water, take 3-4 deep breaths, holding breath for 3-5 seconds after each inhalation and cough after the last inhalation, emptying the sputum into the falcon tube, with care taken not to contaminate the outside of the tube
4	• Collect two spot sputum specimen from each patient at least one hour apart in sterile leak-proof (50ml) falcon tubes • All sputum specimens should be produced in an open and well ventilated space not in the laboratory or offices • Ensure that the falcon tube screw cap is tightly closed • Wipe the outside of the tube with cotton wool soaked in tuberculocidal disinfectant (Phenol, Lysol, bleach)
5	• Inspect specimen for quality and volume, the recommended volume of sputum specimen *is 3-5mls*
6	• Store the specimen at 2-8^{o}C and ship to reach the lab within three days • Package collected specimen for transport to the culture and DST laboratory using SOP on specimen transportation

3.4 DIAGNOSING DR-TB

DR-TB is a laboratory diagnosis. Both sputum smear and culture/DST examinations will be used for the diagnosis and follow-up of DR-TB cases.

The current NTBLCP policy recommends that GeneXpert MTB/RIF remains the initial diagnostic test for those presumed to have DR-TB case or in those who may be susceptible to developing DR-TB especially children and adults with immunosuppression. All persons who have been classified as priority group for Xpert testing should be managed as outlined in the flow chart below.

Figure 3.1: NTBLCP diagnostic algorithm for GeneXpert MTB/RIF test



NB: Priority groups for Xpert/MTB Rif test

1. All known symptomatic contacts of a confirmed DR-TB case
2. All TB Cases with AFB positive result after smear is repeated at the end of month three (3) of Regimen 1 treatment
3. All previously treated DS-TB cases (Relapse, Treatment after failure to Regimen 1, Treatment after loss to follow-up, and Other previously treated patients)
4. All patients with smear negative AFB result who still show symptoms of TB after 1 week administration of broad spectrum antibiotics
5. All PLHIV with TB symptoms
6. All health care staff with TB symptoms
7. All children with TB symptoms
8. Extra-pulmonary TB (Where applicable)

Xpert will not detect MTB in samples of patients with NTM, therefore send specimen for culture or LPA

The biological specimen should be specified e.g. sputum, cerebrospinal fluid (CSF), gastric fluid, lymph node).

Figure 3.2: Algorithm for Culture/DST

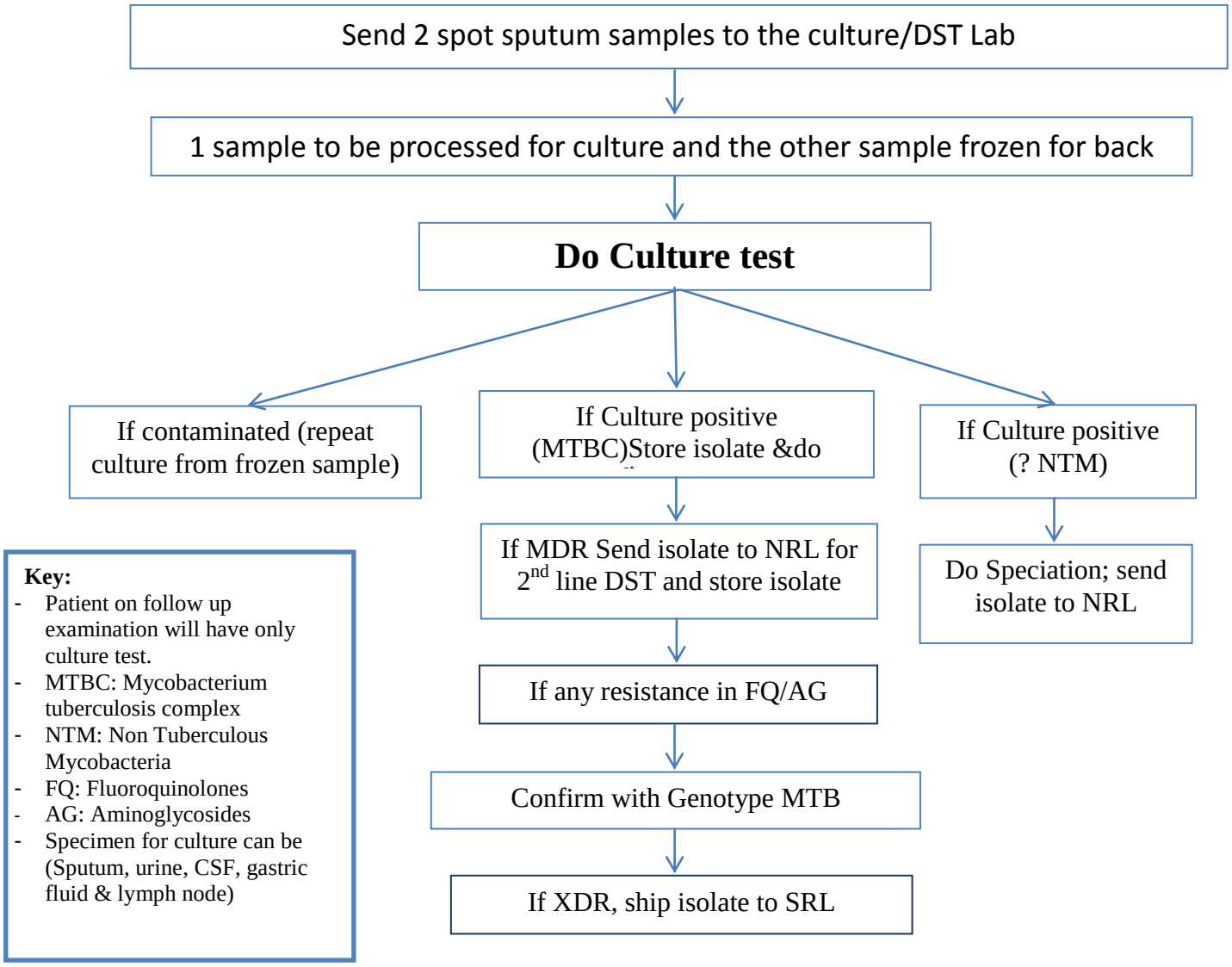


Table 3.1: Pre-enrollment steps for DR-TB treatment

Steps	Actions
1.	• Enter GeneXpert result into the presumptive DR-TB register and inform patient • Inform state DR-TB team about patient • Guide patient and relatives on all available models of treatment and treatment Centres • Educate patient and relatives on the duration of DR-TB treatment and the possible duration of stay at the treatment centre • Refer patient to the agreed treatment centre using appropriate referral form where applicable and include the following investigation results & documents with the referral form such as: GeneXpert/MTB/RIF, culture & DST, AFB microscopy, HIV test, recent chest X-ray, and previous TB treatment card • The state team should facilitate the movement of patient to the treatment centre • Provide patient/relatives the telephone number of the contact person at the treatment centre

2.	• If the patient prefers community based care,
	  • Inform the state team about the patient
	  • Counsel the patient on duration of treatment and side effects
	  • Ensure patient undergoes baseline investigations including SPUTUM FOR CULTURE AND DST BEFORE ANY DRUG IS GIVEN.
	• Establish the date of commencement of treatment with the patient and relative
	• Obtain informed consent from patient before commencement of treatment
	• Identify a health worker who will give injection in the ambulatory phase of treatment
	• Ensure the availability of ancillary medication for management of adverse drug reactions
	• Establish a link with the nearest treatment centre for consultation when needed

4. MANAGING DRUG RESISTANT TUBERCULOSIS CASE

4.1 Defining a Drug Resistant Tuberculosis Case

A patient is considered to be a drug resistant TB case if only there is a laboratory confirmation of resistance to one or more anti- tuberculosis drugs.

Management of a diagnosed DR-TB case begins with proper case definition. This will help to ensure that DR-TB cases are managed in line with the recommendations of the ISTC.

4.2 Classifying a Drug Resistant Tuberculosis Case

To ensure appropriate assigning of treatment to a DR-TB case, it is essential that all diagnosed DR-TB patients are classified properly. Programmatically, a diagnosed DR-TB case may be classified based on previous exposure to anti-TB drugs, drug resistant pattern to clinical isolates, site of the disease and HIV status.

4.2.1Classification of DR-TB case based on previous exposure to anti-TB drugs

1. **Drug resistance among new cases:** Refers to the presence of resistant strains of MTB in a newly diagnosed patient who has never received anti-tuberculosis drugs or has received treatment with them for less than one month.

2. **Drug resistance among previously treated cases:** Refers to resistance found in a patient who has previously received at least one month of anti-tuberculosis therapy.

4.2.1.1 Case Definition for DR-TB cases previously exposed to Anti-TB drugs

1. **New DR-TB Case:** Refers to a diagnosed DR-TB patient who has never had treatment for TB, or who has taken anti-TB drugs for less than 4weeks irrespective of the site of the disease.

2. **Previously treated (Re-treatment) DR-TB Case:**Refer to a diagnosed DR-TB patient who had received 4 weeks or more of anti-TB drugs in the past irrespective of the site of the disease. It is further classified by the outcome of their most recent course of treatment as follows:
    a. **Relapse DR-TB Cases:**Refer to diagnosed DR-TB patients who were previously treated for TB and were declared cured or treatment completed at the end of their most recent treatment episode and are now diagnosed with a recurrent episode of TB. These patients could be true relapses or a new episode of TB caused by reinfection.

    b. **Treatment after failure DR-TB Case:** Refers to a diagnosed DR-TB case who has been previously treated for TB and whose treatment failed at the end of their most recent treatment episode.

    c. **Treatment after loss to follow-up DR-TB Case:** Refers to a diagnosed DR-TB case who was previously treated for TB and was declared lost to follow-up at the end of its most recent treatment episode. (These were previously known as Return after default patients).

d. **Other previously treated DR-TB Case:** Refer to a DR-TB case who was previously treated for TB but with an unknown or undocumented outcome for its most recent treatment episode.

e. **DR-TB TB case with unknown previous TB treatment history:** Refers to a DR-TB case who do not fit into any of the categories listed above.

f. **Transfer in DR-TB Cases:** Refers to a DR-TB case who has been diagnosed and registered for treatment in a facility in one LGA and is transferred to a facility in another LGA to continue treatment. The smear conversion and treatment outcome for this patient must be reported back to the facility that transferred the patient.

4.2.2Classification a DR-TB case based on pattern of drug resistance to anti-TB drugs

TB cases are classified in categories based on drug susceptibility testing (based on bacteriological results) in clinical isolates confirmed to be Mycobacterium tuberculosis: These include:

1. **Mono-resistance DR-TB Case:** Refers to a DR-TB case whose resistance pattern to clinical isolates is to one first-line anti-TB drug only.

2. **Poly-resistance DR-TB Case:** Refers to a DR-TB case whose resistance pattern to clinical isolates is to more than one first-line anti-TB drug, other than both isoniazid and rifampicin.

3. **Multidrug-resistance (MDR):** Refers to a DR-TB case whose resistance pattern to clinical isolates is to at least both isoniazid and rifampicin.

4. **Extensive drug resistance (XDR):** Refers to a DR-TB case whose resistance pattern to clinical isolates is to any Fluoroquinolone, and at least one of three second-line injectable drugs (Capreomycin, Kanamycin and Amikacin), in addition to multidrug resistance.

5. **Rifampicin-resistance (RR-TB):**Refers to a DR-TB case whose resistance pattern to clinical isolates is to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, in the form of mono-resistance, multidrug resistance, poly-drug resistance or extensive drug resistance.

4.2.3Classification of a DR-TB case based on site of disease involvement

Defining the site of disease involvement of a DR-TB case is only important primarily for recording and reporting purposes. This is because the principle of treatment is the same irrespective of the site of disease unlike the treatment in drug susceptible TB cases. Based on site of disease involvement, a DR-TB case could either be pulmonary or extra pulmonary.

1. **Pulmonary DR-TB Case:** Refers to a diagnosed DR-TB case in which the site of maximal involvement is primarily the lung parenchyma.

2. **Extra pulmonary DR-TB Case:** Refers to a diagnosed DR-TB case in which the site of maximal disease involvement are organs other than the lungs, e.g. pleura, lymph nodes (intra-thoracic lymphadenopathy, which could be mediastinal or hilar), genitor-urinary tract, skin, meninges, joint and bones. ***The above means that classification of a DR-TB case should be considered based on the site of maximal disease involvement even if a patient has both pulmonary and extra pulmonary TB.***

4.2.4 Classification based on HIV status

A DR-TB case can also be classified based on the HIV status. This could either be a case with known HIV status (HIV positive or Negative) or unknown HIV status:

1. **HIV-positive DR-TB Case:**Refers to a diagnosed DR-TB case who has a documented HIV-positive result (e.g. there is documented evidence of enrolment in HIV care such as enrolment in the pre-ART register or in the ART register once started on ART) or have a positive HIV result from testing conducted at the time of TB diagnosis.

2. **HIV-negative DR-TB Case:**Refers to a diagnosed DR-TB case who has adocumented HIV negative result from a test conducted at the time of TB diagnosis. HIV- negative DR-TB patients subsequently found to be HIV-positive should be re-classified as HIV-positive DR-TB case.

3. **HIV status unknown DR-TB Case:**Refers to a diagnosed DR-TB case whodo not have a documented HIV test result. Health care providers should everything humanly possible to ensure that all DR-TB cases know their status and if HIV status is subsequently determined the patient should be re-classified as per the HIV test result.

4.3 Registering a diagnosed Drug Resistant Tuberculosis Case in Nigeria

For the purpose of proper case registration and ease of case reporting the NTBLCP has recommended that all cases of DR-TB diagnosed should be given a unique registration number by the LGTBLS of the LGA from which the patient was diagnosed irrespective of where patient will be enrolled for treatment.

To achieve the above, the LGTBLS should give every diagnosed case of DR-TB a DR-TB LGA registration number (consisting of a State code, LGA code, year of registration and serial number) which follows the same numbering system with that of DS-TB with the exception that DR-TB is added before the number.

For example:*A DR-TB case who was diagnosed as the number 10th patient in 2014, in Jemaa LGA (LGA code – 07) of Kaduna State (State code – 18) will be registered as DR-TB 18 07140010 which follows in the order of the State code, LGA code, the last 2 digits of the year of registration and serial number on the DR-TB central Register as at time of registration.*

Consequently, the health/DOTS staff enrolling the patient must ensure that this number is available

as at the time of patient enrolment and this should be subsequently entered into the box already provided on the DR-TB treatment card for patient registration. Similarly, the etb manager unique number (which will be made available by the LGTBLS after the validation of the DR-TB case) should be entered in the appropriate boxes provided on the DR-TB treatment card.
The DST result will determine the following resistance patterns, which will be used as the basis for classification and registration of patients for treatment.

Note: Both sputum smear and culture examinations will be used for the diagnosis and/or follow up of DR-TB cases.

5. MANAGEMENT OF DR-TB IN NIGERIA

Early diagnosis and appropriate treatment is a key component of the NTBLCP strategies to control TB in the country, hence health care workers should ensure that patients are detected early and given appropriate treatment through DOTS. All diagnosed DR-TB cases should be referred to a DR-TB treatment centre using the DR-TB referral form or be commence on ambulatory care in the community.

Appropriate treatment especially through DOT ensures:

- Cure for the patient
- Reduction of transmission of resistant strains of TB bacilli to other persons
- Prevention of further development of resistance

5.1 Treatment delivery models in Nigeria

In order to ensure that DR-TB cases are promptly and appropriately treated, the NTBLCP has adopted a mixed treatment delivery model which include:

1. **Initiation of treatment in a treatment centre which entails that:**
    a. Patients are admitted into the ward to commence the initial part of the intensive phase of treatment.
    b. Ambulatory treatment are provided to patients at the nearest DOT Clinic for the remaining duration of treatment after discharge from the treatment centre.
    c. Specialized clinical services are provided to the patient as at when needed

2. **Initiation of DR-TB treatment in the community which entails that:**
    a. DR-TB patients are commenced on treatment while in their homes through the use of a treatment supporter (Both phases of treatment are provided at the community throughout their treatment period)
    b. Specialized clinical services are provided to the patient as at when needed

A patient on ambulatory care should be considered for admission whenever the following conditions are observed:

- Deteriorating clinical condition
- Frequent treatment interruption (poor adherence)
- Complication such as hemoptysis, signs of renal or hepatic failure.
- Major adverse drug effects

5.1.1 DOTS centres or clinics

These are clinics which are closest to the patients for the purpose of ambulatory treatment in the intensive phase as well as in continuation phase in the community. Treatment should be offered under DOT by well trained, dedicated and motivated health workers. As stated above, the second-line anti-TB drugs will be supplied to the patient on discharge from the treatment centre for not

more than two weeks and the remaining drugs will be sent by the programme to the State TBLCO on patient-named basis. Efforts must be made to provide effective supervision of these DOTS centres by state and LGA TBL teams.

5.1.2 Treatment supporters

A treatment supporter is any individual who performs the following functions:

1. Provides DOT or supports a patient to go to the facility for DOT;
2. Supports patient to go for routine investigations; and
3. Ensures adherence to IC(please refer to Community DR-TB Guidelines).

5.2 Initiating DR-TB Treatment

5.2.1 Classes of anti-TB drugs

The current national DR-TB treatment regimen is designed based on the recognition of five groups of anti-TB drugs as shown in table 5.1 and 5.2. This treatment regimen could either be individualized or standardized based on the resistant pattern and DST result of the clinical isolates in that environment.

Table 5.1: Grouping system of anti-TB drugs

Grouping	Drugs/Codes
Group 1: First-line oral anti-TBdrugs	Isoniazid (H);Rifampicin (R); Ethambutol (E); Pyrazinamide (Z). Rifabutin (Rfb).
Group 2: Injectable anti-TBdrugs	Kanamycin (Km);Amikacin (Am); Capreomycin (Cm);Streptomycin (S)
Group 3: Fluoroquinolones	Levofloxacin (Lfx); Moxifloxacin (Mfx); Gatifloxacin Gfx
Group 4: Oral bacteriostatic second-line anti-TB drugs	Ethionamide (Eto);Prothionamide (Pto); Cycloserine (Cs);Terizidone (Trd); P-aminosalicylic acid (PAS); P-aminosalicylic-Na
Group 5: Anti-TB drugs with uncertain efficacy	Clofazimine (Cfz);Linezolid (Lzd); Amoxicillin/Clavulanate (Amx/Clv); Thiacetazone (Th);Clarithromycin (Clr); Imipenem/Cilastatin (Ipm/Cln), Bedaquiline (Bdq), Delamanid (Dlm); High dose isoniazid (High dose H)

Table 5.2: Drugs used for the treatment of DR-TB

KANAMYCIN	
Drug class	• Aminoglycoside
Activity against TB	• Bactericidal; has strong anti-TB activity

Cross resistance	• Cross-resistance with kanamycin and some data suggesting cross-resistance with Capreomycin
Dose (adult)	• 15-20 mg/kg/day, 7 days per week (maximum dose is 1 gram)
Dose (children)	• 15–30 mg/kg/day (max 1 gram) 7 days per week
Renal failure/dialysis:	• 12–15 mg/kg/dose 2–3 times weekly (not daily)
Route of administration	• Intravenous(IV) or intramuscular (IM) • Intramuscular absorption might be delayed if the same site is used consistently
Oral absorption	• Not absorbed orally; 40–80% of the dose is absorbed intramuscularly
CSF penetration	• Minimal and variable CSF penetration—slightly better with inflamed meninges
Storage	• Store at room temperature
Use in pregnancy	• Generally avoided in pregnancy due to documented congenital deafness
Use with breastfeeding	• Can be used while breastfeeding
Use in renal disease	• Use with caution • Concentrations should be monitored for patients with impaired renal function • Interval adjustment is recommended for renal impairment or dialysis
Use in hepatic disease	• Drug concentrations not affected by hepatic disease (except a larger volume of distribution for alcoholic cirrhotic patients with ascites) • Presumed to be safe in severe liver disease; however, use with caution—some patients with severe liver disease may progress rapidly to hepato-renal syndrome
Diuretic use	• Co-administration of loop diuretics and aminoglycoside antibiotics carries an increased risk of ototoxicity
Adverse reactions	• Nephrotoxicity: 9% may be lower for once-daily use, higher for prolonged use • Ototoxicity: increased with advanced age and prolonged use • Vestibular toxicity • Electrolyte abnormalities, including hypokalemia and hypomagnesaemia
Contraindications	• Pregnancy — relative contraindication (congenital deafness seen with streptomycin and kanamycin use in pregnancy • Hypersensitivity to aminoglycosides • Caution with renal, hepatic, vestibular, or auditory impairment
Monitoring	• Monitor renal function by documenting Creatinine at least monthly (more frequently if renal or hepatic impairment) • Document Creatinine clearance if there is baseline renal impairment or any concerns • Document baseline and monthly audiology exam • Question patient regularly about vestibular complaints and perform serial vestibular exams
Patient instructions	• Patient to contact doctor if he/she has any of these: o Problems with hearing, dizziness, or balance o Rash or swelling of your face o Trouble breathing o Decreased urination o Watery or bloody diarrhoea o Swelling, pain, or redness at IV site o Muscle twitching or weakness

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CAPREOMYCIN	
Drug class	• Cyclic polypeptide
Activity against TB	• Bactericidal; has strong anti-TB activity; inhibits protein synthesis
Cross resistance	• Some data suggesting cross-resistance with Amikacin and kanamycin
Dose (adult)	• Dose (all once daily) 15 mg/kg/day, 7 days per week (maximum dose is generally 1 gram, but a large, muscular person could receive more and should have concentrations monitored)
Dose (children)	• Children: 15–30 mg/kg/day (max 1 gram) 7 days per week.
Preparation	• Capreomycin is available in vials of 1 gm for either IM or IV administration • The contents of the vial should be reconstituted with 2 ml or more of NS or sterile water
Renal failure/dialysis:	• 12–15 mg/kg/dose 2–3 times weekly (not daily)
Route of administration	• IV or IM
Oral absorption	• There is no significant oral absorption • Intramuscular absorption might be delayed if the same site is used consistently.
CSF penetration	• There is a paucity of data regarding Capreomycin penetration of the meninges
Storage	• Reconstituted Capreomycin can be stored in the refrigerator up to 24 hours prior to use • Other data suggest that it may be held for 14 days in the refrigerator or 2 days at room temperature
Use in pregnancy	• Generally avoided in pregnancy due to congenital deafness seen with streptomycin and kanamycin • There are case reports of its safe use in pregnancy (unaffected newborns)
Use with breastfeeding	• Can be used while breastfeeding
Use in renal disease	• Use with caution • Concentrations should be monitored for patients with impaired renal function • Interval adjustment is recommended for renal impairment or dialysis
Use in hepatic disease	• Drug concentrations not affected by hepatic disease (except a larger volume of distribution for alcoholic cirrhotic patients with ascites) • Presumed to be safe in severe liver disease; however, use with caution—some patients with severe liver disease may progress rapidly to hepato-renal syndrome
Adverse reactions	• Nephrotoxicity: 20%–25% including proteinuria, reduced creatinine clearance • Ototoxicity (hearing loss): Occurs more often in elderly persons or those with pre-existing renal impairment • Vestibular toxicity • Local pain with IM injections • Electrolyte abnormalities, including hypokalemia, hypocalemia, and hypomagnesaemia • Liver function test abnormalities when used with other TB drugs
Contraindications	• Hypersensitivity to Capreomycin • Do not use Capreomycin if vestibular side effects resulted from aminoglycoside use • Generally avoided in pregnancy due to congenital deafness seen with streptomycin and kanamycin
Monitoring	• Monitor renal function by documenting Creatinine at least monthly (more frequently if renal or hepatic impairment). • Document Creatinine clearance if there is baseline renal impairment or any concerns

	• Document baseline and monthly audiology exam. • Follow monthly electrolytes, magnesium, and calcium. • Question patient regularly about vestibular complaints and perform serial vestibular exams
Patient instructions	• Patient to contact doctor if he/she has any of these: o Rash o Fever or chills o Bleeding or bruising o Problems with hearing, dizziness, or balance o Bleeding or a lump where the shot is given o Decreased urination o Trouble breathing o Muscle weakness

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LEVOFLOXACIN	
Drug class	• Fluoroquinolone
Activity against TB	• Bactericidal; has strong anti-TB activity • Inhibits DNA gyrase
Cross resistance	• Cross-resistance with other fluoroquinolones
Dose (adult)	• 750 mg once daily
Dose (children)	• 7.5 - 10 mg/kg/ once daily
Renal failure/dialysis:	• 750–1000 mg/dose 3 times weekly (not daily)
Route of administration	• Oral or IV
Oral absorption	• Excellent oral absorption • Should not be administered within 2 hours of ingestion of milk-based products, antacids, or other medications containing divalent cations (iron, magnesium, calcium, zinc, and vitamin)
CSF penetration	• Concentrations are 16–20% of that in the serum
Storage	• Oral forms, undiluted solution, and pre-mixed solutions are stored at room temperature • Once diluted, the solution can be kept at room temperature for 3 days, in the refrigerator for 2 weeks, or frozen for 6 months
Use in pregnancy	• Fluoroquinolones are generally avoided in pregnancy and breastfeeding due to observation of arthropathy in puppy models • However, there are a few case reports of fluoroquinolones being used safely in pregnancy
Use with breastfeeding	• Are generally avoided in breastfeeding due to observation of arthropathy in puppy models
Use in renal disease	• 750-1000mg / dose three times per week (not daily)
Use in hepatic disease	• Drug concentrations not affected by hepatic disease;presumed to be safe in severe liver disease
Adverse reactions	• Nausea and bloating • Headache, dizziness, insomnia, or tremulousness • Rare tendon rupture, arthralgia's (can usually be treated symptomatically) • QTc prolongation
Contraindications	• Fluoroquinolone intolerance, prolonged QTc, pregnancy (relative contraindication)
Patient instructions	Patient to contact doctor if he/she has any of these: • Pain, swelling or tearing of a tendon (such as the back of your ankle, elbow, etc.), or muscle or joint pain

	• Rashes, hives, bruising or blistering, trouble breathing, or tightness in your chest • Diarrhoea • Yellow skin or eyes • Anxiety, confusion, or dizziness

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MOXIFLOXACIN	
Drug class	• Fluoroquinolone
Activity against TB	• Bactericidal; inhibits DNA gyrase
Cross resistance	• Cross-resistance with other fluoroquinolones, but may be more active based on in vitro data
Dose (adult)	Dose (all once daily): 400 mg once daily (PO or IV)
Dose (children)	• Children: 7.5 -10mg/kg once daily
Preparation	• Tablets (400 mg)
Renal failure/dialysis:	• No dose adjustment required
Route of administration	• Oral or IV
Oral absorption	• Good oral absorption (90% bioavailable) • Should not be administered within 2 hours of ingestion of milk-based products, antacids, or other medications containing divalent cations (iron, magnesium, calcium, zinc, vitamins)
CSF penetration	• Good penetration in animal model studies
Storage	• Store oral and IV products at room temperature (do not refrigerate)
Use in pregnancy	• Fluoroquinolones are generally avoided in pregnancy due to observation of arthropathy in puppy models. • However, there are a few case reports of fluoroquinolones being used safely in pregnancy
Use with breastfeeding	• Fluoroquinolones are generally avoided during breastfeeding due to observation of arthropathy in puppy models
Use in renal disease	• Excretion unchanged in the face of renal failure • Excretion unchanged in the face of renal failure
Use in hepatic disease	• Rarely associated with hepatotoxicity; use with caution • No dose adjustment required for mild or moderate liver disease
Adverse reactions	• Nausea and diarrhoea • Headache and dizziness • Rare tendon rupture; arthralgia • Rare hepatotoxicity • QTc prolongation(electrocardiogram [ECG])
Contraindications	• Fluoroquinolone intolerance • Prolonged QTc • Pregnancy (relative contraindication)
Patient instructions	Patient to contact doctor if he/she has any of these: • Pain, swelling or tearing of a tendon (such as the back of your ankle, elbow, etc.) • Muscle or joint pain • Rashes, hives, bruising or blistering • Trouble breathing, or chest tightness • Diarrhoea • Yellow skin or eyes • Anxiety, confusion, or dizziness

CYCLOSERINE	
Drug class	• Analog of D-alanine
Activity against TB	• Bacteriostatic; inhibits cell wall synthesis
Dose (adult)	• 15 mg/kg/day (maximum 1 gram) • Vitamin B6: All patients should receive vitamin B6 while taking cycloserine (50 mg B6 per 250 mg of cycloserine)
Dose (children)	• 10–20 mg/kg/day once or twice daily
Preparation	• 250 mg capsule
Route of administration	• Oral; not available parenterally
Oral absorption	• Modestly decreased by food (best to take on an empty stomach); not significantly affected by antacids and orange juice
CSF penetration	• Concentrations approach those in serum
Storage	• Room temperature in airtight containers
Use in pregnancy	• Not well studied, but no teratogenicity documented.
Use with breastfeeding	• Can be used while breastfeeding (dose the infant with vitamin B6 if breastfed)
Use in renal disease	• 250mg once daily or 500mg per dose three times per week
Use in hepatic disease	• Not associated with hepatotoxicity
Adverse reactions	• Central nervous system (CNS) toxicity, including inability to concentrate and lethargy • More serious CNS side effects, including seizure, depression, psychosis, and suicidal ideation, usually occur at peak concentrations > 35 mcg/ml, but may be seen in the normal therapeutic range • Other side effects include peripheral neuropathy and skin changes; skin problems include lichenoid eruptions and Stevens-Johnson syndrome
Contraindications	• Significant CNS disease, including seizure disorder, psychotic disease, or alcohol abuse
Patient instructions	Patient to contact doctor if he/she has any of these: • Seizures • Shakiness or trouble talking • Depression or thoughts of hurting yourself • Anxiety, confusion, or loss of memory • Personality changes, such as aggressive behaviour • Rash or hives &headache

PROTHIONAMIDE	
Drug class	• Derivative of isonicotinic acid
Activity against TB	• Weakly bactericidal; blocks mycolic acid synthesis
Dose (adult)	• 15–20 mg/kg/day (max dose 1 gm per day)
Dose (children)	• 15–20 mg/kg/day once daily maximum dose 1 gm/day
Preparation	• Coated 250 mg tablet
Renal failure/dialysis	No change
Route of administration	• Oral; not available parenterally
Oral absorption	• Erratic absorption, possibly due to GI disturbances associated with the medication
CSF penetration	• Concentrations approach those in serum
Storage	• Store at room temperature
Use in pregnancy	• Generally avoided during pregnancy due to reports of teratogenicity
Use with breastfeeding	• Little data during breastfeeding—an estimated 20% of a usual therapeutic dose is thought be received

	• Dose the infant with vitamin B6 if breastfed
Use in renal disease	• No precautions are required for renal impairment
Use in hepatic disease	• Can cause hepatotoxicity similar to that of INH—use with caution in liver disease
Adverse reactions	• Gastrointestinal upset and anorexia: Sometimes intolerable (symptoms are moderated by food or taking at bedtime). • Metallic taste • Hepatotoxicity • Endocrine effects: gynaecomastia, hair loss, acne, impotence, menstrual irregularity, and reversible hypothyroidism • Neurotoxicity (patients taking prothionamide should take high doses of vitamin B6) • Side effects may be exaggerated in patients also taking cycloserine
Contraindications	• Sensitivity to prothionamide
Monitoring	• Monitor TSH for evidence of hypothyroidism requiring replacement • Monitor liver function tests
Patient instructions	Patient to contact doctor if he has any of these: • Any problems with eyes: eye pain, blurred vision, colour blindness, or trouble seeing • Numbness, tingling, or pain in your hands or feet • Unusual bruising or bleeding • Personality changes such as depression, confusion, or aggression • Yellowing of your skin or eyes • Dark-coloured urine • Nausea and vomiting • Dizziness • Swollen breasts (in men)

PARA-AMINOSALICYLATE	
Drug class	• Salicylic acid – anti-folate
Activity against TB	• Bacteriostatic
Dose (adult)	• 8–12 grams per day divided 2–3 times per day
Dose (children)	• 150mg/kg/day divided 2–3 times per day
Renal failure/dialysis	• 4g/dose twice daily
Route of administration	• Oral
Oral absorption	• Incomplete absorption—sometimes requires increased doses to achieve therapeutic concentrations
CSF penetration	• Poorly penetrates the meninges (somewhat better with inflammation)
Storage	• For granule (PASER) Packets should be kept in the refrigerator or freezer • For tablet (PAS) should be kept at room temperature
Use in pregnancy	• No known teratogenicity
Use with breastfeeding	• There is little data regarding breastfeeding • No known teratogenicity
Use in renal disease	• Inactive metabolite is cleared by the kidneys
Use in hepatic disease	• Use with caution; 0.5% incidence of hepatotoxicity
Adverse reactions	• Gastrointestinal distress (less with the PASER formulation than with older preparations) • Rare hepatotoxicity and coagulopathy • Reversible hypothyroidism (increased risk with concomitant use of

	prothionamide/ ethionamide)—treat with thyroid replacement
Monitoring	• Monitor TSH, electrolytes, blood counts, and liver function tests
Contraindications	• pregnancy (relative)
Patient instructions	Patient to contact doctor if he/she has any of these: • Skin rash, severe itching, or hives • Severe abdominal pain, nausea, or vomiting • Unusual tiredness or loss of appetite • Black stools or bleeding

LINEZOLID	
Drug class	• Oxazolidinones
Activity against TB	• Has in vitro bactericidal activity • Little clinical experience; inhibits protein synthesis
Dose (adult)	• 600 mg once daily • All patients should receive Vitamin B6 while receiving linezolid
Dose (children)	• Children: 10 mg/kg/dose every 8 hours • All patients should receive vitamin B6 while receiving linezolid
Renal failure/dialysis:	• No dose adjustment required
Route of administration	• Oral or IV
Oral absorption	• Nearly complete oral absorption
Preparation	• Coated tablets: 400 and 600 mg • IV solution: 2 mg/ml: 100, 200, or 300 mg bags • Oral powder for suspension: 100 mg/5 ml 240 ml bottle
CSF penetration	• CSF concentrations are about 1/3 of those in serum in animal models and have been used to treat meningitis in humans
Storage	• Store tablet at room temperature • Reconstituted oral suspension may be stored at room temperature for 21 days • Parenteral preparation should be stored at room temperature (protect from light and do not freeze)
Use in pregnancy	• Not recommended during pregnancy due to limited data
Use with breastfeeding	• Not recommended during breastfeeding due to limited data
Use in renal disease	• No dose adjustment is recommended, but metabolites may accumulate
Use in hepatic disease	• Rarely associated with increased transaminases
Adverse reactions	• Bone marrow suppression (myelosuppression) • Diarrhoea and nausea • Optic neuropathy • Peripheral neuropathy • symptoms of neuropathy: (pain, numbness, tingling or weakness in the extremities) • Lactic acidosis
Contraindications	• Hypersensitivity to oxazolidinones
Monitoring	• Monitor for peripheral neuropathy and optic neuritis • Monitor CBC weekly during the initial period, then monthly, and then as needed based on symptoms
Patient instructions	Patient to contact doctor if he/she has any of these: 1) Pain, numbness, tingling or weakness in the extremities 2) Black, tarry stools or severe diarrhoea 3) Unusual bleeding or bruising

	4) Unusual tiredness or weakness 5) Headache, nausea, or vomiting

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AMOXICILLIN/CLAVULANATE	
Drug class	• Penicillin/beta-lactam inhibitor
Activity against TB	• Early bactericidal activity
Dose (adult)	• Adult (and child >30 kg): 80 mg/kg/day in 2 divided doses
Dose (children)	• Child under 30 kg: 80 mg/kg/day divided twice daily (maximum dose: 3000 mg daily)
Preparation	• For adults: 1000 mg amoxicillin/62.5 mg clavulanate (Augmentin) tablets, 2 tablets twice daily
Route of administration	• Oral
Oral absorption	• Good oral absorption best tolerated and well absorbed when taken at the start of a meal
CSF penetration	• Approximately 5% of the plasma concentration reaches the CSF
Storage	• Store tablets at room temperature • Store suspension in the refrigerator—throw away after 10 days and refill the prescription
Use in pregnancy	• Safe in pregnancy (no known risk)
Use with breastfeeding	• Can be used while breastfeeding
Use in renal disease	• Amoxicillin is renally excreted and the dose should be adjusted for renal failure
Use in hepatic disease	• Clavulanate is cleared by the liver, so care should be used when using in patients with liver failure
Adverse reactions	• Diarrhoea and abdominal discomfort are most common • Nausea, vomiting, and rash are also common • Hypersensitivity
Contraindications	• Penicillin allergy; use with caution with cephalosporin allergies
Patient instructions	Patient to contact doctor if he/she has any of these: 1) Rash or swelling 2) Trouble breathing 3) Severe diarrhoea

CLOFAZIMINE	
Drug class	• Iminophenazine
Activity against TB	• In vitro activity against M. tuberculosis without much in vivo data • Generally reserved for cases with few other options of treatment
Dose (adult)	• 100 to 200 mg daily (oral); a regimen 200mg daily for two months followed by 100mg daily has been used
Dose (children)	• Limited data, but doses of 1 mg/kg/day have been given
Preparation	• 50 and 100 mg capsules
Renal failure/dialysis:	• No adjustment required
Route of administration	• Oral; not available parenterally
Oral absorption	• 70% absorption after an oral dose
CSF penetration	• Limited data are available regarding CNS penetration
Storage	• Room temperature

Use in pregnancy	• Not recommended due to limited data (some reports of normal outcomes, some reports of neonatal deaths)
Use with breastfeeding	• Avoided with breastfeeding due to pigmentation of the infant
Use in renal disease	• No dosage adjustment required
Use in hepatic disease	• Metabolized by the liver; use caution and/or adjust the dose for severe hepatic insufficiency
Adverse reactions	• Pink or red discoloration of skin, conjunctiva, cornea, and body fluids • Gastrointestinal intolerance • Severe abdominal symptoms, bleeding, and bowel obstruction • Photosensitivity • Retinopathy • Dry skin, pruritus and rash
Contraindications	Allergy to Clofazimine
Patient instructions	Patient to contact doctor if he/she has any of these: • Bloody or black stools or diarrhoea • Yellowing of your skin or eyes • Severe nausea, vomiting, abdominal pain, cramps, or burning • Depression or thoughts of hurting yourself

PYRAZINAMIDE	
Drug class	• Synthetic derivative of nicotinamide
Activity against TB	• Bactericidal for semi-dormant M. tuberculosis; mechanism is unclear
Dose (adult)	• 25 mg/kg/day (max dose 2 grams)
Dose (children)	• 30–40 mg/kg/dose
Preparation	• 400 and 500 mg tablet
Renal failure/dialysis:	• 25 mg/kg/dose 3 times per week
Route of administration	• Oral; not available parenterally
Oral absorption	• Well absorbed from the GI tract
CSF penetration	• Concentrations equivalent to serum
Storage	• Store the tablets at room temperature
Use in pregnancy	• No known teratogenicity
Use with breastfeeding	• Can be used while breastfeeding
Use in renal disease	• Cleared by the kidneys; dose 3 times a week and after dialysis
Use in hepatic disease	• Use with caution; pyrazinamide is associated with hepatotoxicity in about 1% of patients. it can be quite severe and worsen off treatment
Adverse reactions	• Gout (hyperuricemia) and arthralgia • Hepatotoxicity • Rash • Photosensitivity • Gastrointestinal upset
Contraindications	• Allergy to pyrazinamide • Severe gout
Monitoring	• Monitor transaminases • Check uric acid if the patient develops arthralgias
Patient instructions	Patient to contact doctor if he/she has any of these: • Skin rash, severe itching, or hives • Pain or swelling in the joints • Yellowing of the skin or eyes or dark urine • Nausea or vomiting

	• Unusual tiredness or loss of appetite

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BEDAQUILINE	
Drug class	• Diarylquinoline
Activity against TB	• Antimycobacterial drug indicated as part of combination therapy in adults (≥18 years) with pulmonary DR-TB • Inhibits mycobacterial ATP (adenosine 5-triphosphate) synthase, an enzyme that is essential for the generation of energy in Mtb
Dose (adult)	• Weeks 1-2: 400 mg (4 tablets of 100 mg) **once daily** • Weeks 3-24: 200 mg (2 tablets of 100 mg) **3 times per week** (with at least 48 hours between doses) for a total dose of 600 mg per week • The total duration of treatment is 24 weeks • Should be taken with food
Dose (children)	• The safety and effectiveness of in children and adolescents less than 18 years of age have not been established
Preparation	• 100 mg tablet
Route of administration	• Oral
Oral absorption	• Administration with food increases oral bioavailability
Storage	• Room temperature
Use in pregnancy	• Pregnancy Category B • There are no adequate and well-controlled studies in pregnant women • Use of Bedaquiline during pregnancy only if clearly needed
Use with breastfeeding	• It is not known whether Bedaquiline and its metabolites are excreted in human milk • Rat studies have shown that the drug is concentrated in breast milk • Because of the potential for adverse reactions in nursing infants, a decision should be made whether to discontinue breast feeding or to discontinue the drug, taking into account the importance of the drug to the mother
Use in renal disease	• Renal excretion of unchanged drug is not substantial (<0.001%) • No dose adjustment is required in patients with mild or moderate renal impairment • In patients with severe renal impairment or end stage renal disease requiring haemodialysis or peritoneal dialysis, Bedaquiline should be used with caution
Use in hepatic disease	• No dose adjustment is necessary in patients with mild or moderate hepatic impairment • Bedaquiline has not been studied in patients with severe hepatic impairment and should be used with caution in these patients only when the benefits outweigh the risks

QT Prolongation	• Bedaquiline prolongs the QT interval
	• An ECG should be obtained before initiation of treatment, and at least 2, 12, and 24 weeks after starting treatment with Bedaquiline
	• The following may increase the risk for QT prolongation when patients are receiving bedaquiline and therefore ECGs should be monitored closely:
	  • Use with other QT prolonging drugs including fluoroquinolones and macrolide antibacterial drugs and the antimycobacterial drug, clofazimine
	  • History of congenital long QT syndrome
	  • History of hypothyroidism and bradyarrhythmias
	  • History of uncompensated heart failure
	  • Serum calcium, magnesium, or potassium levels below the lower limits of normal
	• Discontinue Bedaquiline and all other QT prolonging drugs if the patient develops:
	  • Clinically significant ventricular arrhythmia
	  • A QTcF interval of > 500 ms (confirmed by repeat ECG)

	• Monitor ECGs frequently to confirm that the QTc interval has returned to baseline.
Adverse reactions	• Nausea (38%) • Arthralgia (32.9%) • Headache (27.8%) • Increase transaminases (8.9%) (aspartate aminotransferase increased, alanine aminotransferase increased, hepatic enzyme increased) • Blood amylase increased (2.5%) • Hemoptysis(17.7%) • Chest Pain (11.4%) • Anorexia (8.9%) • Rash (7.6%)
Absolute Contraindications	• Patient refuses to consent • High risk of cardiac complications: patient has a QT interval greater than 500ms history of torsades de pointes or cardiac ventricular arrhythmias or severe coronary artery diseases. • History of severe allergic reaction to bedaquiline
Relative Contraindications	• Children or persons under 18yrs of age • Pregnancy • Nursing mothers
Monitoring	• ECGs should be monitored closely. • Monitor symptoms and liver-related laboratory tests at baseline, monthly while on treatment, and as needed • An increase of serum aminotransferases to >3x upper limit of normal (ULN) should be followed by repeat testing within 48 hours. • Testing for viral hepatitis should be performed and other hepatotoxic medications discontinued **Discontinue Bedaquline if:** • Aminotransferase elevations are accompanied by • Total bilirubin elevation >2x ULN • Aminotransferase elevations are >8x ULN • Aminotransferase elevations persist beyond 2 weeks
Missed Doses	• Compliance with the full course of therapy must be emphasized • If a dose is missed during the first 2 weeks of treatment, patients should not make up the missed dose but should continue the usual dosing schedule • From week 3 onwards, if a 200 mg dose is missed, patients should take the missed dose as soon as possible, and then resume the 3 times a week regimen

CLARITHROMYCIN	
Drug class	• Macrolides
Activity against TB	• Much more active against non-tuberculosis mycobacterium (NTM), but some isolates of TB are susceptible in vitro
Dose (adult)	• 500mg twice daily
Dose (children)	• 7.5mg/kg / 12 hours up to 500mg
Preparation	• Oral tablets of 250mg and 500mg • Oral suspension 125mg/5ml and 250mg/5ml
Renal failure/dialysis:	• The drug is cleared both hepatically and renally; in severe renal impairment , the interval doses should be increased, i.e. 500mg/day
Route of administration	• Oral administration
Oral absorption	• The drug is rapidly absorbed after oral administration and is about 50% bioavailable
CSF penetration	• There is no information available
Storage	• Store tablets and unmixed granules for suspensions at room temperature
Use in pregnancy	• Pregnancy category C and generally should not be used

Use with breastfeeding	• It is not known if the drug is excreted in human breast milk
Use in renal disease	• In severe renal impairment, the interval between doses should be increased i.e. 500mg daily
Use in hepatic disease	• Not adjustment necessary
Adverse reactions	• Common: diarrhoea, nausea, abnormal taste, dyspepsia, abdominal pain/ discomfort, headache • Rare: allergic skin reactions, liver toxicity, QT prolongation, hearing loss
Contraindications	• Patients with known hypersensitivity to macrolide antibiotics should not be given with any of the following drugs:bedaquiline, atemizaole, ergotamine, cisapride, pimozide, and terfenadine
Patient instructions	• Clarithromycin should not be taken with the above mentioned drugs

5.2.2 Treatment regimen for DR –TB cases

In line with WHO/The Union recommendation and available local evidence, Drug-resistant TB in Nigeria is currently treated with a standardized second-line anti-TB drugs for a minimum period of 20 months.The Standardized Regimen for treating DR-TB in Nigeria comprises five drugs - Kanamycin, Levofloxacin, Prothionamide, Pyrazinamide, and Cycloserine

- The treatment regimen is for 20months with an intensive and continuation phases.
- The intensive phase lasts 8 months**;** during this period, the injectable agent Kanamycin/Capreomycin/Amikacin is used in addition to pyrazinamide, Cycloserine, Levofloxacin and Prothionamide.
- The continuation phase spans 12 months, during which the injectable is stopped and the other four drugs mentioned above are continued.

8 Km-Z-Cs-Lfx-Pto / 12 Z-Lfx-Cs-Pto

Table 5.3: Adult dosing of Second Line anti-TB medicines in Nigeria

Drug	Formulation	<33Kg	33-50	51-70	>1000
Amikacin/Kanamycin	500 mg vial	15–20 mg/kg/day	500–750 mg	1000 mg **(1vial)**	1000 mg **(1vial)**
Levofloxacin	250 mg tablet	Adult -750 mg/day	750 mg **(3 tab)**	750 mg **(3 tab)**	1000 mg **(3 tab)**
Prothionamide	250 mg tablet	15–20 mg/kg/day	500 mg (2 tab)	750 mg **(3 tab)**	1000 mg **(4 tab)**
Cycloserine	250 mg capsule	15 mg/kg/day	500 mg **(2 cap)**	750 mg **(3 cap/tabs)**	1000 mg **(4 cap)**
Pyrazinamide	400mg tablet	30–40 mg/kg/day	1000-1750mg **(3 tabs)**	1750-2000mg **(4tabs)**	2000 mg **(5tabs)**
Pyrazinamide	500mg tablet	30–40 mg/kg/day	1000-1750mg **(3 tabs)**	1750-2000mg **(4tabs)**	2000 mg **(4tabs)**

Pyridoxine (B6)	50mg tablet	**Give one tablet of 50mg Pyridoxine per each 250 mg capsule of Cycloserine**			

Table 5.4: Paediatric dosing of Second Line anti-TB medicines in Nigeria

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

5.2.3 Steps for initiating DR-TB cases on treatment

In the Management of an already diagnosed DR-TB case, health workers should follow the following steps:

1. All MTB detected RIF resistant detected cases should be notified immediately to the State control programme
2. The State team should then decide which model of treatment is available to the patient through a patient centred approach
3. Patient should be counselled and provided with health education on the risk factors, mode of transmission, treatment modalities for DR-TB
4. Ensure that patient sign the informed consent form before enrolment for DR-TB treatment (this is a compulsory step)
5. At the point of initiation of treatment, collect sample for Culture and DST
6. At the point of initiation of treatment, perform baseline investigation
7. After the above process, commence patient on standardized DR-TB regimen
8. Then the consilium should adjust treatment based on DST results

5.2.4 Some important points to bear in mind when managing drug resistant TB cases

- A single new drug should never be added to a failing regimen.
- When initiating or revising therapy, always attempt to employ at least three previously unused drugs to which there is demonstrated in vitro susceptibility. One of these should be an injectable agent.
- Sufficient numbers of oral drugs should be started at the onset of therapy to make sure there is an adequate regimen once the injectable agent is discontinued.
- Do not limit the regimen to four agents if other previously unused drugs that are likely to be active are available.

- Ensure directly observed therapy (DOT) throughout the treatment period.
- Intermittent therapy should not be used in treating TB caused by multidrug-resistant organisms, except perhaps for injectable agents after an initial period (usually 2 to 3 months) of daily therapy.
- Cross-resistance between amikacin and kanamycin is nearly universal. There is emerging data that certain mutations may confer cross-resistance between amikacin, kanamycin and capreomycin.
- Determination of resistance to Pyrazinamide (Z) is technically problematic and thus, is not determined in all laboratories. However, resistance to Z is uncommon in the absence of resistance to other first-line drugs. Pyrazinamide mono-resistance in vitro is essentially universal for Mycobacterium bovis isolates.

5.2.5 Health education and adherence counsellingin DR-TBmanagement

Strict adherence to treatment is critical for the success of the DR-TB Programme. The treatment programme must therefore ensure informed patient consent before starting treatment. Information should be provided on all the aspects of the treatment. This information will include:

- Nature of the disease;
- Available treatments with their side effects;
- Duration and places of treatment;
- Referral levels; and
- Infection control within the health facility and upon discharge back home.

It is recommended that adherence counselling and health education is upon diagnosis and result disclosure. It should be a continuous process during the intensive phase and documented every other month during the clinical encounters in the follow-up phase of the treatment.

5.2.5.1 Health Education and adherence counsellors' checklist

- Discuss the disease condition with the patient and relatives.
- Inform patient on his/her current diagnosis and treatment centre options
- Inform patient of appropriate IC measures
- Discuss with patient the procedure for accessing treatment and the available support.
- Inform patient of decentralized treatment options for continuation phase of the treatment
- Inform patient about the treatment duration and all expected follow up test.
- Inform patients about the side-effects of the drug and its management

5.3 Treatment strategies for mono-resistant and poly-resistant TB

The NTBLCP recognizes that the treatment of patients with mono-and poly-resistant strains using standardized short-course chemotherapy (SCC) has been associated with an increased risk of treatment failure and further acquired resistance, including the development of DR-TB. The

NTBLCP therefore adopts the following regimens for mono-and poly-resistance based on different drug susceptibility patterns as outlined intable 5.5.

Table 5.5: Treatment regimens for the management of mono and poly-resistant TB cases

Pattern Of Drug Resistance	Suggested Regimen	Minimum Duration Of Treatment	Comments
H(±S)	R,ZE (+/-FQ)	6-9	Use Xpert MTB/RIF at months 0, 2 and 3and if rifampicin resistance is found switch to full MDR-TB treatment. Some experts add a FQ to the regimen
H and E (+/-S)	R, Z and FQ	9-12	Use Xpert MTB/RIF at months 0, 2 and 3 and if rifampicin resistance is found switch to full MDR-TB treatment and check DST to first and second-line anti-TB drugs. Some experts recommend using a second-line injectable agent for the first three months.
H, E, Z (±S)	R, FQ plus ethionamide plus a second-line injectable agent for the first 2-3 months. (+/-Z)	18	A longer course (6months) of the second-line injectable may strengthen the regimen for patients with extensive disease. Z should be added if resistance is uncertain. Use Xpert MTB/RIF at months 0, 2 and 3 and if rifampicin resistance is found switch to full MDR-TB treatment and check DST to second-line anti-TB drugs. If culture positive after month 2, repeat DST to first-and second-line anti-TB drugs.
R mono or poly-drug resistant	Full MDR-TB regimen plus H	20	Use standardized MDR-TB treatment and monitor patient appropriately.

The use of Xpert MTB/RIF at month 0, 2 and 3 is not intended for monitoring response to therapy as the test may be positive for mycobacterium tuberculosis for patients with a positive response and even after cure. Rather, it is intended only to detect rifampicin amplification during therapy.
H=Isionazid; S=Strptomycin; R=Rifampicin; Z=Pyrazinamide; E=Ethanbutol; FQ=Fluoroquinolone.

Note:

- If DST shows susceptibility to isoniazid, it should be added to the regimen.
- The suggested regimen assumes that pyrazinamide susceptibility is being tested. If DST of pyrazinamide is not being done, then pyrazinamide could be used but should not be considered as core drug and could be stopped after intensive phase if it shows severe adverse reactions.
- Individualized regimen for mono and poly-resistant should be determined by theclinical expert committee at the DR-TB treatment centre based on the table above.

In the case of an adverse reaction,treatment may be modified as outlined in table 5.6.

Intolerance to:	Substitute by:
• Kanamycin	• Capreomycin
• Cycloserine	• PAS/Terizidone
• Baseline Kanamycin monoresistance	• Capreomycin
• Baseline Levofloxacin mono – resistance	• Combination of Moxifloxacin and PAS
• Baseline Levofloxacin and Kanamycin resistance	• XDR-TB regimen
• Amoxyclav (Amx/Clv) and Clarithromycin could be added if patient develop adverse reaction to any of the drugs	

- If intolerance occurs to the drugs, Prothionamide, Cycloserine and PAS may be split into two dosages and should be administered under DOT.

Table 5.6: Modification of treatment in cases of adverse drug reactions

5.4 Adjunctive therapies in DR-TB

5.4.1 Nutritional support

Nutritional support is particularly important for DR-TB patients because:

- DR-TB patients often are extremely wasted and have poor nutritional status.
- Second-line drugs can also decrease appetite, making adequate nutrition a greater challenge.

Without nutritional support, patients, especially those already suffering from baseline nutritional deficiency, can become enmeshed in a vicious cycle of malnutrition and disease. Therefore, it is important that health care providers ensure:

- Regular nutritional support through purchase of a nutritious diet for patients or cash support to ensure access to good nutrition are indicated in all patients with poor economic resources.
- Ready-to-use therapeutic food such as a fortified peanut paste is excellent for use in children and has no secondary cost to the family in terms of cooking fuel for its use.
- Patients should be given a balanced diet rich in protein, carbohydrates, minerals and vitamins.

5.4.2 Use of corticosteroids

In severe respiratory insufficiency, pericarditis, pleuraleffusion and central nervous system involvement, prednisolone is recommended, starting the dose at 1mg/kg, with gradual decrease in the daily dose by 10mg per week (when a longer course is indicated).

In patients with exacerbation of obstructive disease, prednisolone should be given in a short tapering over 1-2 weeks, starting with 1mg/kg and decreasing the dose by 5-10mg per day.

5.5 Management options for XDR-TB

- Use pyrazinamide and any other group 1 agent that may be effective
- Use an injectable agent to which the strain susceptible and consider an extended duration of use (12 months or possibly the whole treatment). If resistant to all injectable agents it is recommended to use one the patient has never used before or consider designing the regimen without an injectable agent. If toxicity is a limiting factor for the use of the injectable agent, and one of the injectable agents is considered effective, consider using inhaled version via a nebulizer.
- Use a higher-generation fluoroquinolone such as moxifloxacin or gatifloxacin.
- Use all group 4 agents that have not been used extensively in a previous regimen or any that are likely to be effective.

- Add two or more group 5 drugs (consider adding bedaquiline).
- Consider adding a new investigational drug eligible for use under the compassionate use scheme if policy of the WHO endorses its use for XDR-TB.
- Consider high-dose isoniazid treatment if low-level resistance or absence of the katG gene is documented.
- Consider adjuvant surgery if there is localized disease.
- Ensure rigorous respiratory infection control measures at the site where the patient is been treated.
- Consider the option of treatment in a hospital if the clinical condition of the patient is poor or major comorbidities coexist, or a shelter if the social condition of the patient prevents proper home care.
- Manage HIV co-infection as per national guideline.
- Provide comprehensive monitoring and full social support to enable adherence to treatment.
- Ensure that all patients have full access to palliative and end-of-life care services, with a patient-centred approach to relieve the suffering of the disease and its treatment.

6. Treatment of DR-TB in special conditions and situations

6.1 Drug resistant TB during pregnancy

Managing DR-TB during pregnancy creates anxiety not only for patients but also for clinicians, especially considering the toxicity of the drugs used. Nonetheless, aggressive management of gestational DR-TB may benefit both mother and child.

All women of childbearing age who are diagnosed with DR-TB should be tested for pregnancy and HIV prior to treatment start.

If testing is negative, family planning is highly recommended for the entire length of treatment and all patients should be informed about potential problems and risks of pregnancy while receiving DR-TB treatment.

If the pregnancy test is positive, all routine prenatal care used should be followed. Pregnancy is not a contraindication for DR-TB management. Moreover, not treating DR or susceptible TB during pregnancy would put the mother and/or foetus at risk.

Clinical presentation of TB during pregnancy does not differ from typical presentations; and pregnancy does not increase the likelihood of resistance or worsen treatment outcomes. However, if TB remains untreated, maternal mortality increases, as do low birth weight, premature births, foetal loss and transmission to children after delivery. When DR-TB is adequately treated, these risks for mother and child are much reduced.

6.2 Fundamentals of drug-resistant tuberculosis treatment during pregnancy

- After the diagnosis of DR-TB in a pregnant woman, treatment strategy decisions must weigh risks and benefits for mother and foetus. There is vast experience in the use of first-line drugs (FLDs) during pregnancy, but limited knowledge regarding the safety of second-line drugs (SLDs).
- DR-TB treatment should preferably be started during the second trimester of pregnancy in the HIV-negative patient if clinical conditions are stable.
- Deferring treatment reduces the risks of teratogenesis or toxicity, which are greater during the first trimester of pregnancy, and allows enough time during the second and third trimesters for the mother to achieve sputum or culture conversion prior to delivery.
- In life-threatening situations (respiratory failure, advanced disease, HIV-positive, etc.), DR-TB treatment is recommended immediately, even in the first trimester, given the risks that exist for both mother and/or foetus.
- The patient should be informed and the risks and benefits of treatment vs. lack of treatment must be thoroughly explained. The mother should understand and be involved in all clinical decisions.

6.2.1 Pregnancy and anti-tuberculosis drugs

There is vast evidence on the safe use of FLDs during pregnancy, showing that all but streptomycin (S) are permitted and recommended.

Aminoglycosides, namely kanamycin (Km) and amikacin (Am) are potentially teratogenic drugs and care is required when used during pregnancy. These drugs are pregnancy safety class D according to the U.S. Food and Drug Administration classification and are not recommended during pregnancy, especially within the first 20 weeks.

In approximately 10% of cases for which Streptomycin (S) was prescribed, ototoxicity and malformation in the foetus were seen. Km and Am likely induce similar teratogenic effects to S.
If there is no other option, these can be used, but preferably after the 20th week and always taking risks and benefits into account with the patient. Their use should be limited to patients whose poor clinical state and resistance pattern justify such risk.

Capreomycin (Cm) has a similar action to S but less teratogenic effect. Cm is an alternative to aminoglycosides as the toxic profile is much reduced in terms of ototoxicity.Fluoroquinolones (FQs) are considered safety class C and have no documented teratogenicity in human studies. Data on prolonged use in pregnancy are limited.All drugs from Group 4 Ethionamide (Eto), Cycloserine (Cs) and p-aminosalicylate (PAS)) are safety class C. Nonetheless, Pto/Eto administration can result in significant vomiting and exacerbate the nausea and vomiting usually associated with pregnancy.

6.3 Drug-resistant tuberculosis treatment during pregnancy

- Pregnant DR-TB women should receive a similar regimen to other patients, combining at least four effective drugs with one FQ as a core drug.
- The main difference relates to the use of Cm as the injectable of choice. If this is not possible or Cm is not available, Km should be used, but preferably starting during the second trimester.
- The use of Cm three times weekly instead of daily can be considered during the first trimester.
- Vitamin B6 (pyridoxine) should be used in all pregnant women with TB in doses not higher than 150 mg. Higher doses may interfere with FQ absorption and, after birth, the child may experience vitamin B6 withdrawal manifesting as seizures and other neurological presentations.

6.3.1 Recommendations for the management of drug-resistant tuberculosis and pregnancy

- Encourage family planning if not pregnant
- If pregnant:
  1. Close follow-up of the pregnancy with regular care
  2. Patient involvement in therapeutic decisions
  3. Individualized management
- Ideally, avoid treatment during first trimester, but consider treatment regardless of trimester if life-threatening conditions are present
- During first 20 weeks, avoid injectables if possible or use Capreomycin preferentially
- Initiate DR-TB therapy during second or third trimester to achieve smear conversion prior to delivery
- Consider risks and benefits to mother and foetus

6.4 Special care to be taken after birth and during breastfeeding

During and after delivery, one of the most important issues is the risk of DR-TB transmission from mother to child. Unlike HIV, transmission from mother to child of congenital DR-TB may occur through blood or during delivery, but this is extraordinarily rare. Infection via breast milk is also extremely rare. The most common source of contagion by far is airborne transmission.

If the mother is not undergoing appropriate treatment or still has positive cultures, contacts between mother and child should be limited for the wellbeing of the child. Contact should occur in an open-air space if possible, with the mother wearing a N95 respirator. Breastfeeding is permitted especially when the mother is smear-negative (and ideally culture-negative).

If the mother is smear-positive, she should be separated from the child (different bedrooms) and

preferably use formula feeding or extracted (pumped) breast milk to avoid close contact. Breast milk will present some level of anti-TB drugs but not high enough to be deleterious for the child (or to protect him/her against DR-TB infection). All children born to a mother with DR-TB should be closely monitored.

6.4.1Management of paediatric DR-TB Cases

DR-TB in children is usually classified as new cases and are presumptive in the following circumstances:

- The child is a close contact of a DR-TB patient;
- A child who is a contact of a TB patient, who died during treatment & there are reasons to presume that the disease was DR-TB; and/or
- There is bacteriologically proven TB not responding to first line anti-TB drugs.

The diagnosis of DR-TB in children is usually quite difficult, because of the pauci-bacillary nature of the disease and difficulty in obtaining quality sputum. The diagnosis of DR-TB in children often relies on clinical suspicion and contact history. However attempts should be made to confirm the disease bacteriologically (sputum, induced sputum, gastric aspirate, biopsy specimen, etc.) before exposing the child to toxic second line anti-TBdrugs.

Symptomatic household paediatric contacts should receive:

1. An evaluation by a physician with history and clinical examination
2. Tuberculin skin testing with purified protein derivative
3. If the child can produce quality sputum, GeneXpert testing is useful method
4. Sputum smear, culture & DST - effort should be made to obtain bacteriological confirmation
5. HIV counselling& testing in areas of high HIV prevalence or if parents are known or suspected to be HIV positive

If a child's clinical condition is highly suggestive of TB & the child has a history of contact to a bacteriologically confirmed DR-TB case, treatment can be started on the basis of the DST of index case.

In general anti-TB drugs should be dosed according to body weight. Monthly monitoring of body weight is especially important in paediatric cases, with adjustment of doses according to change in body weight.

All drugs, including fluoroquinolones, should be dosed at the higher end of the recommended ranges whenever possible, except ethambutol. Ethambutol should be dosed at 15 mg/kg, and not at 25 mg/kg as sometimes used in adultswith DR-TB, as it is more difficult to monitor for optic neuritis in children.

In children, weight loss or, more commonly, failure to gain weight adequately, is of particular concern.

Table6.1:Weight-based dosing of anti-TB medications for MDR paediatrics

Drug	Daily dose (mg/kg)	Frequency	Maximum daily dose
Kanamycin	15-30	Once daily	1g
Amikacin	15-22.5	Once daily	1g
Capreomycin	15-30	Once daily	[1]g
Levofloxacin	7.5-10	Twice daily	750mg
Moxifloxacin	7.5-10	Once daily	400mg
Ethionamide	15-20	Once daily	1g
Protionamide	15-20	Once daily	1g
Cycloserine	10-20	Once or Twice daily	1g
PAS	150	Twice or thrice daily	12g

7. MANAGING DR-TB CO-MORBIDITY

7.1 DR-TB and renal insufficiency

Compared to the general population, patients with chronic renal failure undergoing haemodialysis are at a 10 to 25-fold increased risk of developing TB once infected. These patients require careful monitoring for treatment of TB, and drug-resistant TB in particular. In addition to the effects on drug clearance, the diseases that cause renal failure and concomitant treatments can also impact drug levels by altering absorption or drug interactions. Table 8.1 below describes dosing changes for patients with renal insufficiency.

For TB drugs that are cleared by the kidney, the general strategy is to increase the interval between dosing rather than to decrease the dose.

Table 7.1: Adjustment of anti-TB drugs in renal insufficiency

DRUGS	RECOMMENDED DOSE AND FREQUENCY FOR PATIENTS WITH CREATININE CLEARANCE <30ML/MIN OR FOR PATIENTS RECEIVING HAEMODIALYSIS (UNLESS OTHERWISE INDICATED DOSE AFTER DIALYSIS)
Isoniazid	No adjustment necessary
Rifampicin	No adjustment necessary
Pyrazinamide	25-35 mg/kg per dose three times per week (not daily)
Ethambutol	15-25 mg/kg per dose three times per week (not daily)
Rifabutin	Normal dose can be used, if possible monitor drug concentration to avoid toxicity.
Rifapentine	No adjustment necessary
Streptomycin	12-15 mg/kg per dose two or three times per week (not daily)
Capreomycin	12-15 mg/kg per dose three times per week (not daily)
Kanamycin	12-15 mg/kg per dose three times per week (not daily)
Amikacin	12-15 mg/kg per dose three times per week (not daily)
Ofloxacin	600-800 mg per dose three times per week (not daily)
Levofloxacin	750-1000 mg per dose three times per week (not daily)
Mixofloxacin	No adjustment necessary
Gatifloxacin	400 mg three times a week
Cycloserine	250 mg once daily, or 500 mg/dose three times per week
Terizidone	Recommendations not available
Prothionamide	No adjustment necessary
Ethionamide	No adjustment necessary
Para-aminosalicylic acid	4g/dose, twice daily maximum dose
Bedaquiline	No dosage adjustment is required in patients with mild to moderate renal impairment (dosing not established in severe renal impairment, use with caution).
Linezolid	No adjustment necessary
Clofazimine	No adjustment necessary
Amoxicillin/clavulanate	For creatinine clearance 10-30ml/min dose 1000mg as amoxicillin component twice daily; for creatinine clearance <10ml/min dose

	1000mg as amoxicillin component once daily
Imipenem/cilastin	For creatinine clearance 20-40ml/min dose 500mg every 8 hours; for creatinine clearance <20ml/min dose 500mg every 12 hours
Meropenem	For creatinine clearance 20-40ml/min dose 750mg every 12 hours; for creatinine clearance <20ml/min dose 500mg every 12 hours
High dose isoniazid	Recommendations not available
Clarithromycin	500 mg daily

[a] Adapted from Tuberculosis drug information guide. 2nd edition, 2012 (13).

[b] Caution should be used with injectable agents in patients with renal function impairment because of the increased risk of both ototoxicity nephrotoxicity. If on dialysis, dose after dialysis.

[c] The appropriateness of 250mg daily doses has not been established. There should be careful monitoring for evidence of neurotoxicity (if possible measure serum concentrations and adjust accordingly).

[d] 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 and are the preferred formulation in patient with renal insufficiency.

7.1.1 Calculating creatinine clearance

The following calculation below show how to calculate creatinine clearance

$$\textbf{Estimated glomerular filtration} = \frac{\textbf{weight (kg)} \times (\textbf{140} - \boldsymbol{age}) \times \boldsymbol{constant}}{\textbf{serum creatinine } \left(\frac{\textbf{µmol}}{\textbf{L}}\right)}$$

The creatinine is measured in the serum.

The constant in the formula is = 1.23 for men and 1.04 for women

If creatinine is reported in conventional units (mg/dl) from the laboratory, it can be converted it to a SI Unit (µmol/l) by multiplying by 88.4.

(For example a creatinine = 1.2mg/dl is equivalent to (88.4 x 1.2) =106.1 µmol/l.

Normal values for creatinine clearance are:

Men: 97 to 137ml/min

Women: 88 to 128 ml/min

Example: if a female patient (age =46 years, weight = 50kg) has serum creatinine =212 µmol/l, what is the creatinine clearance?

Calculation of creatinine clearance:

Weight (kg) x (140 - age) x (constant/serum creatinine) = 50 x (140 - 46) x (1.04 for women/212) = **23.0 ml/min**

The creatinine clearance is below 30: every drug in the regimen should be examined and adjusted if necessary according to table 8.1.

Note:
Creatinine clearance can also be calculated with a 24 hour urine and serum creatinine, but that is usually more cumbersome.

7.2 DR-TB and liver disease

Many TB medications have the potential to cause hepatotoxicity, and their use must be contemplated in the setting of severe liver dysfunction. Fortunately, the most important second-line anti-TBdrugs used for treatment of resistant diseasehave less hepatotoxicity. Refer to table 8.1below for more details

Treatment of drug-resistant TB in the setting of liver failure is complicated and depends on the degree of liver damage.

- If the patient has end-stage liver disease and further worsening could be life-threatening, consider avoiding all hepatotoxic drugs.
- The use of levofloxacin, ethambutol, an aminoglycoside, and cycloserine should be considered, if appropriate.
- If the liver disease is not imminently life-threatening, the use of a Rifamycin in the regimen is advised if the isolate is susceptible**.**

Table 7.2: List of anti-TB medications and their effects on the liver

Isoniazid (H)	• Isoniazid is most likely to cause hepatitis • In individuals with normal hepatic function, the hepatotoxic effects are usually reversible if the drug is stopped as soon as symptoms are evident • Isonazid hepatotoxicity appears to be increased when rifampicin is used
Pyrazinamide	• Pyrazinamide causes fewer episodes of hepatotoxicity than isonazid, but the events can be severe and prolonged, and worsen even after stopping therapy • Pyrazinamide is thought to cause the most severe liver toxicity
Rifampin (R)	• Rifampcin more commonly causes a cholestatic jaundice, but can potentiate the hepatocyte damage caused by Isoniazid
Fluoroquinolones	• Some of the fluoroquinolone drugs (Moxifloxacin) have been associated with occasional cases of liver damage. Travafloxacin has been associated with severe liver toxicity in rare cases • Levofloxacin not commonly associated with liver dysfunction
Prothionamide	• Has also been implicated in hepatotoxic drug reactions
PAS	• Has also been implicated in hepatotoxic drug reactions
Cycloserine	• Not commonly associated with liver dysfunction
Aminoglycosides	• Not commonly associated with liver dysfunction
Ethambutol	• Not commonly associated with liver dysfunction

Note:

- Isonaizd and Pyrazinamide are the anti-TB medications most often associated with hepatotoxicity
- Second-line anti-TB medications are less commonly associated with hepatotoxicity

7.3 DR-TB and additional health conditions

Considerations for treating DR-TB in patients with other heath conditions, such as diabetes mellitus, seizure disorders, psychiatric disorders, and substance disorders, are summarized in table

8.3 below.

Table 7.3: Important considerations to note in DR-TB patients with other heath conditions

Diabetes mellitus	Diabetes should be monitored using fasting blood sugar twice a month and whenever indicated. The dose of oral hypoglycemics may need to be increased during treatment with anti-TB drugs. Use of Ethionamide or Prothionamide may make the control of insulin levels difficult. Creatinine and potassium levels should be monitored frequently, often weekly for the first month and then at least monthly thereafter.
Seizure disorders	Ensure seizure is controlled before initiation of anti-TB drugs. Avoid use of Cycloserine in patients with active seizures or adjust anti-seizure medication to control the seizure.
Psychiatric disorders	Any psychiatric illness identified at the start or during treatment with anti-TB drugs should be fully addressed. Cycloserine should be used with care in a patient with psychiatric illness.
Substance dependence	Substance dependence disorders should be treated for addiction. Complete abstinence from alcohol or other substances should be encouraged. For non-compliant patients, anti-TB treatment should be suspended until measures are put in place to ensure adherence.

7.4 Management of MDR-TB in Extrapulmonary TB cases

The guidelines for management of MDR-TB in extra pulmonary cases are as follows:

- Management of bacteriologically confirmed extra pulmonary (EP)DR-TB patients will be considered provided the diagnosis confirmed by culture &DST.
- Treatment regimen and schedule for EP DR-TB cases will remain the same as for pulmonary MDR-TB.
- Data regarding treatment of extra pulmonary drug-resistant TB are limited. A few cases are described within larger series of DR-TB cases.
- Patients with extra pulmonary TB are at risk of treatment failure due to poor drug penetration to the affected tissue and the lack of accessibility of tissue for serial cultures.
- Surgical resection (scrofula) and drainage (empyema, abscesses, and arthritis) may decrease bacterial burden and improve outcome. Full medical treatment is still indicated.
- Drug-resistant TB meningitis is challenging to treat due to the incomplete CSF penetration of many second-line drugs.
- Intra-thecal administration of medications and the use of newer fluoroquinolones may improve outcome and should be evaluated prospectively.

7.4.1 Investigations and pre-treatment evaluation

Patients should be admitted to a DR-TB centre, preferably for at least short period, for pre-treatment evaluation and Cat-IV treatment initiation.

EPDR-TB patients will undergo all those pre-treatment investigations as done for pulmonary DR-TB patients as a part of the pre-treatment evaluation prior to initiating regimen for DR-TB.

Consider other investigation if necessary such as GeneXpert, tissue culture and ultrasound of abdomen to rule out involvement of other organs and abdominal nodes.

7.4.2 Initiation of treatment

After baseline investigations, treatment for extra pulmonary DR-TB should be initiated based on weight of the patient.

Treatment regimen, weight band and duration of treatment for EP DR-TB cases will remain the same as for pulmonary DR-TB.

7.4.3 Clinical monitoring

Clinical monitoring is the most important criteria for the follow up of patients with extra pulmonary DR-TB. Regular patient monitoring and periodic follow up of nodes and other extra pulmonary symptoms with culture from the discharging node/sinus is the key in monitoring of treatment in extra pulmonary lymph nodal DR-TB.

7.4.4 Bacteriological monitoring

Two specimens from the discharging sinus/pus in the lymph node should be collected, one for smear and one for culture. The sample should be taken at the every month during intensive phase then every three months during the continuation phase until there is no pus/discharge from sinus (in the node).

Unlike sputum smear and culture, culture from the node can be given only till the pus/discharging sinus is present from the node. The follow up is mainly based on clinical parameters.

7.4.5 Monitoring of treatment

This is important in the case of EP DR-TB. Monitoring and follow up can be done clinically based on the following:

- Weight gain
- Decrease or increase in symptoms (e.g. healing of ulcer/scrofuloderma)
- Increase or regression in size of nodes (possibility of Immune Reconstitution Inflammatory Syndrome [IRIS] should be considered and differentiated from disease progression)
- Appearance of new nodes
- If chest is symptomatic, monthly sputum for AFB and chest x-ray (to rule out pulmonary involvement)
- Other extra pulmonary sites should be monitored
- Serum creatinine – monthly while receiving an injectable agent.

- Liver function test – monitoring every three months in patients receiving pyrazinamide or for patients at risk of or with symptoms of hepatitis.
- Ultrasound of abdomen – if necessary
- Monitoring for drug adverse reactions

7.4.6 Outcome definitions

The same outcome definition is used for extra pulmonary DR-TB patients as for pulmonary DR-TB patients. The treatment outcome will depend on availability of culture reports of specimens taken from discharging sinuses, treatment completion and clinical improvement of the patient.

7.5 Treatment of DR-TB in HIV co-infected patients

There are a number of new developments in the management of DR-TB & HIV co-infected clients, drug-drug interactions and some special precautions during the management. The below guidelines incorporate the latest evidence.

- Provider initiated HIV testing &counselling is an essential component in the management of all presumptive DR-TB cases.
- The sputum of all TB/HIV co-infected presumptive cases is sent to the nearest GeneXpert site for the diagnosis of DR-TB.
- Thorough clinical examination & necessary investigations (biopsy specimen, pleural or peritoneal or meningeal fluid) are performed in all presumptive extra pulmonary DR-TB cases.
- Once diagnosis of DR-TB is confirmed, initiate second line anti-TB drugs.
- As soon as the patient beginsto tolerate second line anti-TB drugs, initiate cotrimoxazole preventive therapy (CPT).
- Antiretroviral therapy (ART) is recommended for all co-infected cases of HIV & DR-TB requiring second line anti-tuberculosis drugs, irrespective of CD4 cell counts, as early as possible, preferably within the first eight weeks after starting anti-tuberculosis treatment.
- Ensure strict adherence to TB IC.
- Provide additional nutritional support.

Successful implementation of the above guidelines depends on availability of trained healthcare workers and management of drug-drug interactions.The need for increased integration of HIV and TB care services for effective case management is the most important aspect of treatment.

Table 7.4: Potential overlying & additive toxicities ARV &anti-TB therapy

Potential toxicity	Antiretroviral agents	Anti-TB agent	Suggested management strategies	Comments
Peripheral neuropathy	d4T, ddI,	Lzd, Cs, H, aminoglycosides, Eto/Pto,, E	1) Increase pyridoxine to maximum daily dose of 200 mg/day. 2) Changing injectable to capreomycin if there is documented susceptibility. 3) Initiate therapy with	Avoid use of d4T or ddI in combination with Cs or Lzd because of theoretically increased peripheral neuropathy.

			tricyclic antidepressants like amitryptiline; NSAID or acetaminophen may alleviate symptoms. 4) Lower dose of suspected agent if this can be done without compromising regimen. 5) Discontinue suspected agent if this can be done without compromising regimen.	
Central nervous system toxicity (Confusion, impaired concentration, depersonalization, abnormal dreams, insomnia and dizziness etc.)	EFV	Cs, H, Eto/Pto, Fluoroquinolones	1) Consult a psychiatrist. 2) Withhold suspected anti-TB agent for a short period of time (one to four weeks) while psychotic symptoms are brought under control. 3) Increasing pyridoxine to maximum daily dose (200mg per day) if cycloserine is the likely cause. 4) EFV-related CNS symptoms abate after tw to four weeks in the majority of patients; symptomatic treatment is required;initiate anti-psychotic drugs; adminis haloperidol 1-5 mg PO or IM, repeat every hour if needed. 5) Administer benzodiazepines if concomitant anxiety (use benzodiazepines with caution if tenuous respiratory status and at risk of retaining CO^2). 6) Paradoxical effect of increased psychosis may be observed with benzodiazepine use, especially in elderly patients. 7) Administer benzodiazepines with	Efavirenz has a high rate of CNS adverse effects in the first 2–3 weeks, which typically resolve on their own. If these effects do not resolve on their own, consider treatment options. If still not resolved, then change the drug.

			diphenhydramine 25 mg to alleviate extrapyramidal symptoms. 8) Continue to adjust antipsychotic therapy in consultation with psychiatrist if psychosis continues. 9) Lower dose of suspected agent, if this can be done without compromising regimen. 10) In severe condition, discontinue suspected agent if this can be done without compromising the regimen.	
Depression	EFV	Cs, H, Eto/Pto, fluoroquinolones	Initiate therapy with tricyclic antidepressants like amitryptiline.	Severe depression can be seen in 2.4% of patients receiving EFV consider substituting EFV if severe depression develops. The severe socioeconomic circumstances of many patients with chronic disease can also contribute to depression.
Headache	AZT, EFV	Cs	Use of analgesics (ibuprofen, paracetamol) and good hydration may help; headache secondary to AZT, EFV and Cs is usually self-limited.	Rule out more serious causes of headache such as bacterial meningitis, cryptococcal meningitis, CNS toxoplasmosis, etc.
Nausea and vomiting	d4T, NVP, RTV &others.	Eto/Pto, PAS, H, E, Z & others	1) Assess for dehydration; initiate rehydration if indicated. 2) Initiate anti-emetic therapy. 3) Administer drugs one hour after Metoclopramide 10mg tablet and/or a course of proton pump inhibitor or H2 receptor inhibitor (omeprazole, famotidine, ranitidine).	ARV-induced GI intolerance is generally self-limited except for ddI induced pancreatitis, which requires permanent cessation of therapy. Symptomatic treatment should be offered. (With AZT and Pls, nausea-vomiting can be severe and prolonged and may require a change of

			5) Monitor electrolytes if needed (severe vomiting). 6) Lower dose of suspected anti-TB if this can be done without compromising regimen. 7) In severe condition discontinue suspected agent if this can be done without compromising regimen, rarely necessary.	drugs). 2) Anorexia, nausea and vomiting are frequent in early weeks of therapy and usually abate with time on treatment and supportive therapy.
Abdominal pain	All ART treatment may be associated with abdominal pain	Cfz, Eto/Pto, PAS		Abdominal pain is a common adverse effect and often benign; however, abdominal pain may be an early symptom of severe adverse effects such as pancreatitis, hepatitis or lactic acidosis.
Pancreatitis	d4T, ddI, ddC	Lzd		Avoid use of these agents together. If an agent causes pancreatitis suspend it permanently and do not use any of the pancreatitis producing anti-HIV medications (D4T, ddI, or ddC) inthe future. Also consider gallstones or alcohol as a potential cause of pancreatitis.
Hepatotoxicity	NVP, EFV & all protease inhibitors	H, R, E, Z, PAS, Eto/Pto	1) If ALT is more than five times the basal level stop all therapy pending resolution of hepatitis. 2) Rule out other potential causes of hepatitis. 3) Consider suspending the most likely agent permanently. Re-introduce remaining anti-TB drugs, one at a time with the most hepatotoxic agents	1) History of prior hepatitis should be carefully analyzed to determine most likely causative agent (s); these should be avoided in future regimens. 2) Generally reversible upon discontinuation of suspected agent. 3) Also rule out viral etiologies as cause of hepatitis (hepatitis A, B, C, and CMV).

			first, while monitor liver function. For ART, replace the drug most likely associated with the condition or all three ARVs at the same time if required.	
Lactic acidosis	D4T, ddI, AZT, 3TC	Lzd	Discontinue ART and give supportive treatment. After clinical resolution resume ART replacing the offending drug with ABC, TDF, and 3TC.	Lactic acidosis has been reported with the use of Linezolid.
Diarrhoea	All protease inhibitors, ddI	Eto/Pto, PAS	If severe, take care of hydration and manage electrolyte profile. Continuous counselling is required to adhere to the drug.	Also consider opportunistic infections as a cause of diarrhoea, or clostridium difficile (a cause of pseudomembranous colitis).
Skin rash	ABC, NVP, EFV, d4T	H, R, Z, PAS	If mild, treated with antihistamines. If severe, withdraw the offending agent& treated with steroids, if necessary.	Do not re-challenge with ABC (can result in life-threatening anaphylaxis) Do not re-challenge with an agent that causes Stevens-Johnson syndrome.
Renal toxicity	TDF (rare)	Aminoglycosides, Cm	1) All drugs will be withheld; blood tests for renal parameters ordered and the patient will be referred, if available, to a nephrologist. 2) Re-introduction of drugs will be undertaken by the attending physician, in consultation with either the DOTS-Plus expert committee or nephrologist, along with frequent monitoring of renal parameters throughout treatment. 3) Throughout intensive phase of treatment follow creatinine and blood urea nitrogen every month. 4) Many ARV and TB medications need to be dose adjusted for renalinsufficiency.	Use TDF with caution in patients receiving aminoglycosides or Cm. Even without the concurrent use of TDF, HIV-infected patients have an increased risk ofrenal toxicity secondary to aminoglycosides and Cm.
Bone marrow	AZT	Lzd, R. Rfb	1) If severe (Hg<6.5g	Monitor blood

suppression			%), replace by an ARV with minimal or no bone marrow toxicity (ABC or TDF) and consider blood transfusion. 2) Granulocytopenia also seen with AZT 3) Discontinuation of Linezolid should be considered, if it is the cause.	counts regularly. Also consider TMP/SMX as a cause if the patient is receiving the medication.
Optic neuritis	ddI	E	Suspend agent responsible for optic neuritis permanently and replace with an agent thatdoes not cause optic neuritis.	
Hypothyroidism	d4T	PAS, Eto/Pto	Depending on the level of TSH estimation, thyroxin is replaced and titrated relating to blood levels.	Monitor monthly for signs & symptoms of hypothyroidism.

7.6 Pharmacovigilance in programmatic management of Adverse Drug Reaction in DR-TB

Pharmacovigilance is defined by WHO as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem".Many of the second-line anti-TB drugs are more prone to cause toxic reactions in patients than first-line drugs, making pharmacovigilance more important in the programmatic management of drug-resistant TB. Good pharmacovigilance will also pick up adverse effects quicker from the second-line anti-TB drugs in use and should be considered as a standard of patient care.

WHO recommends that as programmes start to incorporate newly released drugs into treatment regimens they should also improve their capacity to undertake pharmacovigilanceby recording the occurrence of adverse drug reactions for patients on treatment, the country already has data collection inherent to pharmacovigilance. All ADR should be documented using the ADR Form. Refer to the annex for a copy.

7.6.1Basic definitions used in pharmacovigilance

Adverse event (AE): Any untoward medical occurrence that may present during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with this treatment.

Adverse (drug) reaction (ADR): A response to a medicine, which is noxious and unintended, and which occurs at doses normally used in humans.

Risk factor: A characteristic associated with an increased probability of occurrence of an event. In the presence of a risk factor, a patient is more likely to develop an adverse reaction.
Serious reaction: A serious reaction is an adverse drug reaction which involves any of the

following: death or a life-threatening experience; hospitalization or prolongation of hospitalization; persistent significant disability; congenital anomaly.

Signal: Reported information on a possible causal relationship between an adverse event and a medicine; the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending on the seriousness of the event and the quality of the information.

The timely and intensive monitoring for, and management of, adverse effects caused by Second-line drugs are essential components of DR-TB control programmes. Poor management of adverse effects increases the risk of loss to follow up (LTFU) or irregular adherence to treatment, and may result in death or permanent morbidity.

Table 7.5: Common adverse reactions to the anti-TB drugs

Injectables – Kanamycin, Amikacin, Capreomycin
• Ototoxicity • Nephrotoxicity • Vertigo • Electrolyte imbalanceincluding hypokalemia and hypomagnesaemia

Quinolones – Levofloxicin, Moxifloxacin
• Gastro-intestinal symptoms: diarrhoea, vomiting, and abdominal pain • CNS: dizziness and convulsions • Phototoxicity and photosensitivity • Tendinopathy and tendinitis • Skin rash • Cardio toxicity – QT prolongation • Arthralgia

Pyrazinamide
• Arthralgia • Hyperuricaemia • Hepatitis • Pruritis with or without rash

Prothionamide
• Gastro-intestinal: epigastric discomfort, anorexia, nausea, metallic taste, vomiting,excessive salivation, and sulfurous belching • Psychiatric: hallucination and depression • Hepatitis • Hypothyroidism and goiter with prolonged administration • Gynaecomastia • Menstrual disturbances • Impotence • Acne • Headache • Peripheral neuropathy

Cycloserine

- CNS: dizziness, slurred speech, convulsions, headache, tremor, and insomnia
- Psychiatric: confusion, depression, altered behaviour, and suicidal tendency
- Hypersensitivity reaction
- Peripheral neuropathy and skin changes; skin problems include lichenoid eruptions and Stevens-Johnson syndrome

PAS

- Gastro-intestinal: anorexia, nausea, vomiting, and abdominal discomfort
- Skin rash
- Hepatic dysfunction
- Hypokalemia
- Hypothyroidism and goiter with prolonged administration

Clofazamine

- Pink or red discoloration of skin, conjunctiva, cornea, and body fluids
- Gastrointestinal intolerance
- Severe abdominal symptoms, bleeding, and bowel obstruction
- Photosensitivity
- Retinopathy
- Dry skin, pruritus, rash

Linezolid

- Bone marrow suppression (myelosuppression)
- Diarrhoea and nausea
- Optic neuropathy
- Peripheral neuropathy (symptoms of neuropathy (pain, numbness, tingling or weakness in the extremities)
- Lactic acidosis

Amoxicillin/Clavulanate

- Diarrhoea and abdominal discomfort
- Nausea, vomiting, and rash
- Hypersensitivity

Bedaquiline

- Nausea
- Arthralgia
- Headache
- Increase transaminases (aspartate aminotransferase increased, alanine aminotransferase increased, hepatic enzyme increased)
- Blood amylase increase
- Hemoptysis
- Chest pain
- Anorexia
- Rash

7.6.3 Management of adverse drug reactions

Adverse drug reactions should be managed according to the following guidelines:

- Before starting treatment, the patient should be instructed in detail about the potential adverse effects that could be produced by the prescribed drug regimen, and if and when they occur to notify a healthcare provider.
- The Pharmacist, DOT providers, nurses in the hospital and clinician will monitor and record all the adverse events routinely and laboratory screening tests will be done on a routine basis as per the national guidelines.
- All ADR should be documented on the ADR Form.
- The initial base line investigations are important for identify patients who are at increased risk for adverse effects or poor outcomes and may detect certain adverse effects that are more occult, and before serious impairment is done.
- Laboratory screening is important for detecting certain adverse effects that are more occult, and before serious impairment is done.
- The majority of adverse effects are easy to recognize and close monitoring of patients is necessary to ensure that the adverse effects of the drugs are recognized early by healthcare personnel.
- It is important to have a systematic method of patient monitoring since some patients may be silent about reporting even severe adverse effects.
- The ability to monitor patients for adverse effects daily is one of the major advantages of DOT over self-administration of treatment. Commonly, patients will volunteer that they are experiencing adverse effects.
- Nurses and DOT providers should be trained to screen patients regularly for symptoms of common adverse effects: rashes, toxic epidermal necrosis, gastrointestinal symptoms (nausea, vomiting, diarrhoea), psychiatric symptoms (psychosis, depression, anxiety) jaundice, ototoxicity, peripheral neuropathy, symptoms of electrolyte wasting (muscle cramping, palpitations), and convulsions.
- Most ADRs canbe managed by doctors at the LGA level. If required, hospitalization could be done at the state hospital where an inpatient facility is available or referred to a referral hospital for admission.
- The State DR-TB Consilium would be consulted to take decisions regarding reduction/termination of any drug and if any drug is withheld / terminated due to ADR, it would be replaced with the appropriate substitute drug as per the State DR-TB Consilium. If required, the National DR-TB consilium should be consulted.
- Proper management of adverse effects begins with pre-treatment patient counselling and continued health education.

- Depending on the severity of ADRs, the following actions may be indicated:
  - If the adverse effect is mild and not serious, continuing the treatment regimen, with the help of ancillary drugs if needed, is often the best option.
  - Most of the adverse effects of a number of second-line drugs are dose-dependent. Reducing the dosage of the offending drug or terminating the offending drug is another method of managing adverse effects, but should be done after consultation with DR experts or the DR-TB treatment centre.

- Psychosocial support is an important component of the management of adverse effects. This may be provided through patient education and motivation by nurses and DOT providers, patient support groups through group discussions while in the hospital.

Table 7.6: Basic management of adverse drug reactions

Gastro-intestinal symptoms (nausea and vomiting)
• This may be due to the bulk of drugs and/or due to Ethionamide, PAS and Pyrazinamide. • Patients who complain of nausea or vomiting can be advised to take the drugs embedded in a banana or taken with juice. • If vomiting persists, drugs will be administered one hour after one tablet of Domperidone and/or a course of proton pump inhibitor (Omeprazole) or H2 receptor inhibitor (Famotidine, Ranitidine). • Antacids cannot be given within two hours of fluoroquinolonesas they interfere with absorption of fluoroquinolones. • In case of severe vomiting the hydration status of the patient should be monitored and rehydration therapy initiated if required. • If the offending drug is Ethionamide, the drug is more acceptable if it is administered with milk, or after milk, or at bedtime to avoid nausea. • Administer antiemetics or antacids prior to medication or as needed, Promethazine (Phenergen) 12.5 to 25 mg PO, IV, 30 minutes before the dose and every eight hours as needed. • Metoclopramide (Reglan) 10 to 20 mg PO or IV every eight hours or as needed. • If vomiting is severe, drugs can be withheld temporarily and tests should be conducted to rule out other causes of vomiting like hepatitis.

Renal toxicity
• Common offending drug is an aminoglycoside. • Prior to starting treatment, all patients will have renal function evaluated. • During treatment of DR-TB, if the patients presents with symptoms and/or signs of renal impairment (oliguria, anuria, puffiness of face, pedal oedema), renal function tests should be done and, if required, opinion of nephrologist should be sought. • If there is a decrease in renal function, repeat a 24-hour creatinine clearance. • Ensure adequate hydration. • Hold the injectable agent for one to two weeks to allow renal function to stabilize. • Check serum electrolytes and correct if needed. • Evaluate other drugs the patient is taking and adjust dose and/or dosing interval if needed. • If the clearance is less than 30 ml/minute, adjust the doses of prothionamide, Z, some fluoroquinolones, cycloserine, all of the aminoglycosides, and capreomycin. • For a creatinine clearance between 30 and less than 50 ml/min, twice perweek aminoglycoside dosing at 12 mg/kg should be tried. • For a creatinine clearance between 50 and 70 ml/min, the patient may tolerate aminoglycoside dosing at 12 to 15 mg/kg three times per week. • Monitor peak and trough drug concentrations. It is especially important that trough concentrations be less than the critical value before another dose of the drug is given. • Re-introduction of drugs will be undertaken by the DR-TB Centre committee in consultation with a nephrologist, along with frequent monitoring of renal parameters. • During treatment, blood urea and serum creatinine should be done every month for the first three months after treatment initiation and then every three months thereafter whilst injection Kanamycin is being administered. Silent renal toxicity may be picked up by this routine monitoring. • Follow-up on biochemical examinations. If at any time, the blood urea or serum creatinine becomes abnormal, treatment should be withheld and further management decided upon in consultation with the DR-

TB Centre committee.

Arthralgia

- Pain and tenderness of the muscles and joints are relatively common side effects associated with a variety of drugs used to treat drug-resistant TB patients.
  - One or more of the following drugs may be implicated: Pyrazinamide, Fluoroquinolone, Prothionamide, and INH.
  - Electrolyte disturbances associated with the aminoglycosides and capreomycin may also cause muscle pain and cramping.
  - Hypothyroidism may also contribute.
- The most common offending drugs are likely to be Pyrazinamide and/or Fluoroquinolone.
- Do not discontinue medications.
- NSAIDs are usually helpful.
- If acute swelling, erythema, and warmth are present, evaluate for the presence of inflammatory diseases.
- Aspirate joint for diagnosis if fluid is present.
- Evaluate for infection, gout, or autoimmune disease.
- Institute treatment (often indomethacin) if the diagnosis is gout.
- If there is still no improvement, or if the arthralgia worsens, consult with a rheumatologist and evaluate for hypothyroidism or hyperthyroidism the dosage of Pyrazinamide and/or Levofloxacin should be reduced or the drug withheld temporarily without compromising the regimen.

Hypersensitivity reactions

- Hypersensitivity reactions such as pruritus or rash, can occur with any of the drugs used, and are commonly managed with anti-histamines.
- For minor dermatologic reactions, various agents may be helpful and allow continuation of the medication. They can be given prior to the anti-tuberculosis drug or as needed.
- Diphenhydramine (Benadryl) 25 to 50 mg PO, IV, or IM given before the medication,and then every four to six hours as needed may lessen skin irritation.
- Other antihistamines: Chlorpheniramine (Chlor-trimeton) 4 mg PO before themedication and then every four to six hours as needed;
- Hydrocortisone cream can be used topically.
- Low-dose prednisone (10 to 20 mg/day) for several weeks can be tried if other measures are not helpful.
- For severe reactions which do not respond to anti-histamines, attempt to identify the offending drug by challenging with individual drugs.
- The dose of the offending drug may be reduced or the drug terminated if required.
- If there is a generalized erythematous rash, especially if it is associated with fever and/or mucous membrane involvement, all drugs should be withheld immediately.
- When the rashes subside, the medications can be restarted one by one, at intervals of two to three days.
- The order of reintroduction will be Ethambutol, Cycloserine, Ethionamide, Fluoroquinolone, Kanamycin and lastly Pyrazinamide.
- After identification, and patient not recovered the offending drug will be terminated without compromising the regimen.

Evaluate other potential etiologies of rash and pruritus:

- Scabies and insect bites may masquerade as a drug rash.
- Contact dermatitis (question patient about use of new lotions, soaps, perfumes,etc.).
- Phototoxicity (may respond to sunscreens, but these may cause contact dermatitis).
- Other drugs, especially new agents, should be evaluated as possible etiologies.
- Other dermatologic causes; psoriasis, pityriasis, atopic dermatitis, etc.

- Dry skin, especially in diabetic patients, may be the cause of pruritus. Consider liberal
    - use of lotions, such as petroleum jelly and lanolin
- Dry skin is a serious problem with clofazimine.

Hepatitis

- This could be due to the combined effect of potentially hepatotoxic drugs such as Pyrazinamide and Prothionamide.
- If a patient presents with symptoms/signs of hepatitis (anorexia, nausea, vomiting, abdominal discomfort, and/or dark coloured urine), he/she will be examined for clinical jaundice and liver enlargement.
- The ALT (SGPT) is the hepatocellular enzyme most directly associated with hepatocellular damage. If the enzymes are normal, continue medications and treat nauseas and vomiting accordingly.
- The ALT (SGPT) is more specific for hepatocellular injury than the AST (SGOT). Elevations in the AST may indicate abnormalities in the muscle, heart, or kidney.
- If the ALT is elevated more than the AST, this is consistent with liver inflammation.
- When the AST is elevated more than the ALT, the possibility of alcohol-related elevation of the transaminase should be considered.
- Patients will be questioned carefully regarding symptoms suggestive of biliary tract disease and exposures to other potential hepatotoxins, including alcohol and hepatotoxic medications.
- If the hepatocellular enzymes are less than three times the upper limit of normal and there is no evidence of jaundice (total bilirubin < 3.0 mg/dl), continue the medications using strategies for managing nausea and vomiting and observe carefully.
- If symptoms continue, consider repeating liver enzymes again to exclude hepatotoxicity.
- If the bilirubin is increased but the hepatocellular enzymes are only mildly elevated, this could still represent significant drug-induced liver injury.
- An evaluation for causes of direct and indirect hyperbilirubinemia should be done, and if the bilirubin is > 3.0 mg/dl, generally, hepatotoxic medications should be stopped.
- If the enzymes are more than three times the upper limit of normal, hold all potentially hepatotoxic medications.
- If at least three medications remain in the treatment regimen that are not hepatotoxic (for example the aminoglycosides, levofloxacin, or cycloserine), then these can be continued. If not, then all anti-tuberculosis medications should be held.
- If the results of the liver function tests are normal, the treatment will be resumed.
- Patients with abnormal liver function will be reviewed at weekly intervals and liver function repeated when jaundice subsides clinically.

Neurological symptoms

Peripheral neuropathyore likely to occur in patients with diabetes, alcoholism,

- Neuropathy is more likely to occur in patients with diabetes, alcoholism, HIV infection, hypothyroidism, pregnancy, poor nutrition, and with inadequate dietary intake of pyridoxine.
- The common offending drugs are cycloserine, prothionamide, inezolid and INH.
- To prevent the occurrence of such adverse reaction, all patients should receive daily Pyridoxine.
- If peripheral neuropathy develops, increase pyridoxine to maximum daily dose (200 mg)
- If there is no improvement or symptoms worsen, initiate therapy with tricyclic antidepressants such as Amitriptyline 25mg.The dose of amitriptyline may be increased (to 150 mg maximum) if lower doses are not helpful.
- Non-steroidal anti-inflammatory drugs or acetaminophen may help alleviate symptoms.
- Carbamazepine (Tegretol), an anticonvulsant, at 100 to 400 mg PO BID, can be tried. Blood dyscrasias and elevated liver function may complicate therapy, and a complete blood count (CBC)

and liver function should be routinely monitored in patients on this medication.

- Prescribe a lower dose of suspected agent, if this can be done without compromising the regimen.
- Rarely, medication may be discontinued, but only if an alternative drug is available or the regimen is not compromised.

Seizures

- The offending drug could be either Fluoroquinolone or Cycloserine and INH.
- Hold cycloserine, fluoroquinolones, and INH and initiate anticonvulsant therapy Phenytoin, valproic acid).
- Monitor anti-epileptic drug levels as drug interactions and synergistic toxicity are possible.
- Increase pyridoxine to 200 mg daily.
- When seizures have resolved, restart medications one at a time.
- Cycloserine should not be restarted unless it is absolutely essential to the regimen. This will not often be the case.
- Continue anticonvulsant therapy during the remainder of therapy for DR-TB.
- Evaluate for other etiologies of seizures.
- Check serum electrolytes, calcium, and magnesium.
- A history of prior seizures is not an absolute contraindication to the use of cycloserine,
- Fluoroquinolones, and INH.
- Do not include cycloserine if an alternative drug is available.

Psychiatric disturbances

Depression

- The common offending drugs are Cycloserine and Prothionamide.
- Depression can be relatively mild and managed with supportive attention from family and healthcare providers.
- Some level of situational depression is to be expected for most patients who deal with the difficulties of DR-TB therapy.
- Assess and address underlying psycho/social issues. Assess patients for coexisting substance abuse and refer to counselling if appropriate.
- When depression is more significant, give a trial of antidepressant therapy.
- Tricyclic antidepressants should not be given to patients on linezolid.
- Question the patient regarding suicidal ideation anytime depression is judged to be more than mild. Reduce the dose of cycloserine and prothionamide to 500 mg daily to see if depressionis lessened.
- If depression progresses or is not improved by a trial of antidepressant therapy, discontinue Cycloserine and, possibly, Prothionamide as well.
- Cycloserine should not usually be part of an initial treatment regimen if significant depression is present.
- When no alternative drugs are available and depression is controlled on therapy, some patients may tolerate cycloserine and ethionamide.
- INH has been associated with depression, which has been reported as severe in several case reports. Withdrawal of the drug is associated with rapid recovery.
- If no response these drugs will be withheld and further management of the patient will be done in consultation with the psychiatrist.

Psychosis

- If severe psychosis is present, consider psychiatric consultation.
- Hold all medications that possibly contribute until the patient stabilizes.
- The most likely drugs to cause psychosis are cycloserine and fluoroquinolones;INH can occasionally be implicated.
- Pyridoxine (150 mg) should be given if not already part of the treatment.
- Start antipsychotic therapy (haloperidol) PO, IV, or IM 0.5 to 5 mg) at the earliest sign of psychosis.
- When symptoms resolve, the least likely medications that contributed to the symptoms should be reintroduced first, one at a time, with careful observation.

- If no alternative drug is available, cycloserine may be tried at low dose. If any recurrence of psychotic behaviour occurs, promptly and permanently discontinue cycloserine.
- When the patient has stabilized, all medications have been successfully restarted, and all symptoms have resolved, the antipsychotic drugs can be tampered with careful observation of the patient.
- Consider and address all other etiologies, especially illicit drugs, alcohol, and medical problems (meningitis, hypothyroidism, and depression).
- Some patients may tolerate cycloserine with an antipsychotic drug if no other treatment options are available.
- These patients require special observation. Utilize this therapy only after consultation with an expert in the management of drug-resistant TB, and when the cycloserine is determined to be essential to the regimen and no alternative is available.
- In case of suicidal ideation discontinue Cycloserine and request psychiatric consultation.
- Initiate antidepressant therapy and lower the dose of ethionamide to 500 mg daily until the patient is stable.
- If no improvement occurs after holding cycloserine, hold INH and/or ethionamide.

Vestibulo-auditory disturbances

- Offending drug is usually an Aminoglycoside. Patient may present with tinnitus, unsteady gait or loss of hearing.
- Hearing loss is a direct effect of injectable medication toxicity to the eighth cranial nerve.
- Some degree of loss occurs in nearly all patients treated for DR-TB.
- High-frequency loss usually occurs first and the effects are cumulative.
- Hearing loss may be reversible or permanent.
- Perform a baseline audiogram and repeat monthly.
- Monitor the ability of the patient to participate in normal conversation.
- Consider change of the injectable to three times a week, after three to four months, when the cultures are negative.
- Avoid loop diuretics because they increase eighth nerve toxicity.
- Some patients must tolerate significant hearing loss in order to achieve a cure of their DR-TB.
- When significant hearing loss occurs should be discussed with an expert in the management of DR-TB and also with the patient.

Hypothyroidism

- Hypothyroidism may develop with either PAS or prothionamide; when both drugs are used,the incidence of hypothyroidism may be 40% or greater.
- Patients may present with slowing of activities, puffiness of face and/or thyroid enlargement.
- Assess baseline thyroid function prior to start of these medications and correct if needed.
- Assess thyroid function every three months unless clinical assessment indicates the need to evaluate sooner.
- Conduct monthly clinical assessments for hypothyroidism.Clinical assessments may be a better indicator of thyroid function than laboratory values.
- When thyroid stimulating hormone (TSH) begins to increase, evaluate for clinical evidence of hypothyroidism. Begin to monitor more frequently.
- When TSH rises to 1.5 to 2 times above upper limit of normal, begin thyroid hormone replacement:
    - Most adults will require 100 to 150 mcg of thyroxin daily
    - Young healthy adults can be started on 75 to 100 mcg of thyroxin daily
    - Older patients should begin treatment with 50 mcg daily
    - Patients with significant cardiovascular disease should start at 25 mcg

- Adjust thyroid hormone replacement until the patient's TSH is within the normal range.
- When TB treatment is complete, stop thyroid hormone replacement; the thyroid gland will now be able to respond to endocrine stimulation with release of thyroid hormone.

Severe drug reactions

- Anaphylaxis is rare but can occur.
- Anaphylaxis presents within minutes of medication dosing.
- The patient classically has signs of airway compromise, such as stridor, wheezing, a feeling of the throat being closed, swelling of the tongue, and hoarseness.
- Additional symptoms include shock, urticaria, angioedema, confusion, and pruritus. Nausea, vomiting, cramping, and diarrhoea may also occur. It is essential to identify the causativeagent once the patient is stable.
- The use of a small challenge dose of medication may be needed and should be given in the hospital.
- Do not include drugs identified as causing anaphylaxis in the treatment regimen; do not try to desensitize to these agents.
- Severe drug reactions may occur with any medication. Reactions associated with systemic toxicity—high fever, widely distributed urticaria, and bulla, along with mucous membrane involvement—are characteristic of SJS.
- Each of these reactions needs immediate therapy, usually with systemic steroids and care.
- A dermatology consultation and a skin biopsy should be requested if there is any question of the diagnosis. INH, RIF, EMB, streptomycin, Ofloxacin, and Cycloserine have been reported as causative agents.
- If a drug is identified as responsible for one of these reactions, it should never be used again.

Metallic taste

- Metallic taste is reported as an adverse reaction in patients taking prothionamide and clarithromycin.
- Fluoroquinolones may also cause changes in taste.
- Encourage the patient to tolerate this side effect.
- Sucking on lemon drops or other hard candy or chewing gum can be helpful.
- Normal taste returns when treatment is stopped.

Gynaecomastia

- Breast enlargement can be a troublesome side effect of prothionamide therapy, especially for male patients.
- Galactorrhea has also been reported.
- Encourage patients to tolerate this side effect.
- Resolution occurs after treatment is stopped.

Alopecia

- Hair loss can occur with either prothionamide or INH.
- In the first months of treatment, there can be significant thinning of the hair, but this is temporary and not progressive during treatment.
- Significant cosmetic change has not been reported.

8. MONITORING OF TREATMENTAND TREATMENT OUTCOME

8.1 Monitoring progress of treatment

Treatment can be monitored by three methods: 1) clinical monitoring; 2) laboratory monitoring; and 3) monitoring of drug intake. Monitoring of treatment should comprise:

- Regular medical history focusing on the classic symptoms of TB, i.e. coughs, sputum production, fever, weight loss and drug side effects;
- Social History, especially barriers to adherence;
- Physical examination for weight gain; and
- Chest radiographs should be taken every six months, especially when the symptoms worsen.

8.1.1 Bacteriological Monitoring

Both sputum smear and culture should be used concurrently and closely to monitor the patient's progress throughout the course of treatment. The sputum **smear and culture** should be performed **monthly during intensive phase** i.e. at least 8 smears and 8 cultures at the end of intensive phase. During continuation phase of treatment, bacteriological monitoring should be done at least **monthly for smears** and **every two months for culture** i.e. at least 18 smears and 9 cultures during continuation phase of treatment.

8.1.1.1 Sputum Conversion

Sputum conversion is defined as two consecutive negative cultures taken at least 30 days apart.

- If a patient remains smear- and culture-positive at month four during treatment (this is a presumptive case for failure), DST should be repeated for first and second line drugs.
- If a patient is rifampicin resistant and has been commenced on treatment and the culture result taken at baseline (before commencement of treatment) is negative, do another GeneXpert test before discontinuing treatment, and evaluate for other conditions. Then do two monthly culture and DST for one year. If it is positive, manage accordingly.

Table 8.1: Monitoring during treatment of drug-resistant TB

Monitoring evaluation		Recommended frequency
1	Sputum smear	• **At baseline** then monthly throughout duration of treatment
2	Sputum cultures	• **At baseline** then monthly during the intensive phase, then everytwomonths in the continuation phase until the end of treatment
3	Weight	• **At baseline** and weekly for the first three months and then monthly.
4	Drug susceptibility testing	• **At baseline** • Repeat for patients who remain culture-positive more than four months of treatment
5	Chest radiograph	• **At baseline**, and then every six months
7	Serum creatinine	• **At baseline**, then monthly while receiving an injectable drug
8	Serum potassium	• **Monthly** while receiving an injectable agent
9	Thyroid stimulating hormone	• **Every six months** if receiving protionamide • Monitor monthly for signs/ symptoms of hypothyroidism
10	Liver serum enzymes	• **Monitoring every three months** in patients receiving pyrazinamide or for patients at risk of or with symptoms of hepatitis

11	HIV screening	• **At baseline**, and repeat if clinically indicated
12	Pregnancy testing	• **At baseline** for women of childbearing age, and repeat if indicated
13	Audiometry	• **At baseline** and whenever necessary
14	Electrocardiogram	• At base line for patient on bedaquiline and whenever indicated for other conditions
15	Serum amylase	• At base line for patient on bedaquiline

8.1.2 Monitoring of weight

Monitoring of drug intake is done through the assessment of patient's records for regularity of drug intake. Checking the patient treatment card for filling the drug intake column is very essential as proof that there is daily drug intake.

Note:

- If a patient gains weight during treatment and crosses the weight-band range, the DR-TB Centre committee will consider moving the patient to the higher weight band drug dosages.
- Similarly if a patient loses weight during treatment and crosses the weight band the DR-TB Centre committee will consider moving the patient to the lower weight band

8.2 Treatment outcome analysis for patients on second-line anti-TB

Based on the use of laboratory smear and culture as a monitoring tool, six treatment outcomes for DR-TB treatment are recognized. These are summarized in table 8.1.

8.2.1 Treatment outcome cohort analysis

This focuses on treatment outcomes (culture conversion, interim treatment outcome and final treatment outcome) of DR-TB patients started on treatment in a particular period. The NTBLCP expect that all State TBL & BU control managers should ensure that these information are made available whenever it is needed (at least on a quarterly basis) to inform programmatic planning and decisions.

1. **Eight month interim outcome:** This should be carried out nine months after the closure of the quarter.
2. **Final outcome:** The cohort analysis should be carried out at 24 months and repeated at 36 months after the last patient starts treatment. The cohort analysis at 24 months will provide the preliminary assessment of cure rates because most patients would have finished their treatment. The analysis is repeated at 36 months and this presents the final treatment cohort analysis result.

Table 8.2: Definitions of treatment outcomes

Cured:
A DR-TB patient who completed treatment without evidence of failure AND has three or more consecutive cultures taken at least 30 days apart that are negative after the intensive phase.
Treatment completed:
A DR-TB patient who completed treatment without evidence of failure BUT does not have three or more consecutive cultures taken at least 30 days apart which are negative after the intensive phase.
Treatment Failed:

A DR-TB patient in whom treatment was terminated or need for permanent regimen change for at least two anti-TB drugs because of: • Lack of conversion[a] by the end of intensive phase; or • Bacteriological reversion[b] in the continuation phase after conversion[a] to negative; or • Evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs; or • Adverse drug reactions.
Died:
A TB patient who dies for any reason before starting or during the course of treatment.
Lost to follow-up:
A DR-TB patient whose treatment was interrupted for two consecutive months or more.
Not evaluated:
A DR-TB patient for whom no treatment outcome is assigned. (This includes cases "transferred out" to another treatment unit and where the treatment outcome is unknown to the reporting unit).
Treatment success:
The sum total of cured and treatment completed

[a]Lack of conversion at the end of intensive phase (end of 8 months) implies that the patient did not convert from culture positive to negative (i.e. Two consecutive cultures taken at least 30 days apart are found to be negative) at the end of the intensive phase.

[b]For smear- or culture-positive patients only. Culture is considered to have reverted to be positive when, after an initial conversion, two consecutive cultures, taken at least 30 days apart are found to be positive. For the purpose of defining treatment failure, reversion is considered only when it occur in continuation phase

8.3Management of contacts of DR-TB patients

Close contacts of DR-TB patients are defined as people living in the same household, or spending many hours a day with the patient in an indoor living space.

8.3.1 Management of symptomatic adult contacts of a patient with DR-TB

Guidelines for the management of symptomatic adult contacts of a DR-TB patient are as follows:

- All close contacts of DR-TB cases should be supported to come for screening (physical examination and chest-ray).Those that are found to be symptomatic should undergo further investigation using GeneXpert.
- Provide health education on IC for all contacts.
- If the contact has active TB, refer the patient to a DR-TB treatment centre for immediate evaluation. When the investigation of a symptomatic adult contact yields no evidence of TB, a trial of broad spectrum antibiotic, particularly the one which is **not** active against TB can be used.
- If the patient continues to have symptoms, a bronchoscopy for smear **and** culture should be considered if available.
- Where these diagnostic tools are not available or the results are not conclusive, a diagnosis should be based on the available information.
- If the initial investigation is not suggestive of active TB but the contact remains symptomatic, repeat the physical examinations, while smears and cultures should be performed monthly and the chest X-ray repeated if needed.

8.3.2 Management of symptomatic paediatric contacts of patients with DR-TB

DR-TB should be suspected in children with active TB in the following situations:

- A child who is a close contact of a DR-TB patient;
- A child who is a contact of a TB patient who died while on treatment when there are

reasons to suspect that the disease was DR-TB (i.e. the deceased patient had been a contact of another DR-TB case, had a poor adherence to treatment or had received more than two courses of anti-TB treatment); and

- Children with bacteriologically proven TB who are not responding to first-line drugs given with direct observation.

Symptomatic paediatric household contacts should receive:

- An evaluation by a physician, including history and physical examination;
- Tuberculin testing purified protein derivative (PPD) if available;
- A chest x-ray examination to document hilar lymphadenopathy;
- Sputum smear and culture: if the child is aged less than five years, or cannot expectorate, induced sputum, gastric aspiration for smear and culture should be considered;
- DST if possible;
- If the tuberculin skin test result is > 5 mm, but the chest radiograph and gastric aspirate or sputum smear are negative, the symptomatic child can be treated with a broad spectrum antibiotic which is **not** active against TB; and
- If a child's clinical condition is highly suggestive of TB, or progressively deteriorates, empirical therapy designed according to the DST pattern of the strain from the index case can be started.

In line with WHO recommendations, NTBLCP does not advise the use of second-line drugs for chemoprophylaxis in DR-TB contacts. Rather, close contacts of DR-TB patients should be closely monitored for symptoms of TB for a period of at least two years. If active disease develops, then initiate treatment promptly.

8.4DR-TB infection control in health care setting

DR-TB is transmitted in the same manner as drug-susceptible TB. Moreover, because DR-TB patients may respond to treatment slowly and remain sputum smear-positive longer than other TB patients, they may infect more contacts. It is therefore expedient for facilities providing care for DR-TB patients to be aware of this and put in place measures which will prevent transmission of DR-TB within their setting. The type of measures to be instituted will vary from facility to facility depending on the level of care which is provided for DR-TB patients or presumptive casesin the facility.

Measures to reduce transmission of DR-TB in different type of facilities are described below.

8.4.1 Facility with a DOTS Centre

A facility with a DOTS centre should put in place the following measures to minimize transmission of DR-TB in the facility in addition to the existing TB IC practices in the facility:

Strengthen the implementation of IC measures in line with the *National guidelines for TB Infection Control*: The following measures described in the guidelines should be effectively implemented and monitored:

- Administrative controls

- Environmental controls
- Personal protective measure

Note:
Facilities that are yet to start the implementation of IC measures should be supported to commence the implementation in line with the National guidelines.

- Provide health education for presumptive DR-TB cases and patients on how to prevent transmission of TB at home and in the community.
- Separate patients known or presumed to have DR-TB (including the high risk group) from other patients including other TB patients on treatment.
- Strengthen cough etiquettes among the presumptive DR-TB casesto ensure the use face mask while in the hospital.
- Avoid placing HIV-positive patients with known or presumed cases of TB together with presumptive DR-TB cases or patients.
- Ensure sputum from presumptive DR-TB cases or patients is collected in an open space.
- Do not admit smear positive pulmonary TB patients with non TB patients, especially patients with HIVto minimize the risk of nosocomial infection.
- Limit visits to the TB wards and DOTS treatment unit.
- Ensure strict adherence to TB laboratory services SOPs tominimize TB and DR-TB transmission to laboratory workers.
- Patients should use surgical masks during procedures and also during transport from one facility to another.
- Offer HIV counselling and testing to staff working in the TB unit and those who are positive should be moved to other safer areas within the hospital; laboratory workers should be transferred from mycobacterial work.
- Enhance the access of HIV-positive staff to isoniazid prophylaxis therapy.
- Ensure continuous training programme for health workers on TB IC.

8.4.2 Facility providing DR-TB treatment

This facility provides comprehensive care including admission services for DR-TB patients and therefore has the highest potential risk for the transmission of DR-TB. This type of setting should put in place the following measures in addition to the existing IC measures in the facility.

8.4.2.1 Administrative Controls

- Establish a TB IC committee or if this is in existence, incorporate staff from the DR-TB treatment unit into the membership of the committee.
- Identify a staff member from the DR-TB treatment unit to coordinate IC issues in the unit in addition to the identified IC officer in the facility.
- Develop a facility specific comprehensive IC policy and plan or incorporate TB/DR-TB IC issues in the existing plan.
- Ensure separation of patients known or presumed to have DR-TB (especially smear positive cases) from patients with TB and other type of patients.

- Ensure sputum collection from patients or presumptive DR-TB cases is done in well ventilated areas.
- Ensure separation of DR-TB patients in the intensive phase from those in thecontinuation phase.
- Ensure that patients with different DST results do not mix together as much as possible, and when this is not possible the use of personal protective measures described below should be strengthened.
- Admission in the treatment unit should be in such a way that:
    - Patients with similar DST results are placed close to each other as much as possible.
    - Patients that have converted are also placed closed to each other as much as possible.
    - New patients and old DR-TB patients do not mix together.

- Limit visits to the treatment centre and restrict visitor's entry to the wards.
- Ensure a continuous training programme on IC for health workers.
- A DR-TB ppatient's toilet should not be shared with relatives or health workers.
- Health care workers living with HIV and other immunosuppressive conditions should not be allowed to manage DR-TB cases (therefore there is need for routine medical check-up at base line and annually).
- Routine surveillance among health workers includes: HIV testing, TB symptoms screening, chest x-ray, fasting blood sugar)
- IC considerations related to health workers include:
    - Provide adequate signage and materials on IC
    - Monitoring and Caring for caregivers
    - Health workers are at risk for DR-TB in high-burden TB settings because they are constantly exposed to infectious TB patients.
    - Health workers should be provided with the personal protective equipment necessary for caring for DR-TB patients.
    - All healthcare workers working in DR-TB care settings with symptoms suggestive of TB should have their sputum sent for GeneXpert test.

8.4.2.2 Environmental controls

- Evaluation should be conducted to advice on appropriate infrastructural design of the DR-TB wards.
- DR-TB wards should have adequate cross ventilation and upper windows should be open and fixed.
- Patient should be encouraged to stay outside the wards during the daytime (open courtyards).
- Where possible, extractor fans and ultraviolet light should be considered and their functionality ensured.
- TB laboratories should strictly follow appropriate national guidelines and SOPs to minimize TB and DR-TB transmission to laboratory workers.
- Waste disposal practices should be consistent with national guidelines.

8.4.2.3 Personal protective measures

- Health care workers managing DR-TB cases must use an N-95 respirator when in contact with patients.
- N95 respirator should be changed within a maximum duration of two weeks. However, if the N95 respirator is damaged or soiled, or if breathing becomes difficult, healthcare workers should remove the respirator, discard it properly, and replace it with a new one.
- To safely discard the N95 respirator, health workers should place it in a plastic bag, put it in the trash and ensure hand washing after handling the used respirator.
- Patients should use surgical face masks at all times. Patients surgical masks should be changed within a maximum duration of one week, however if the mask is soiled and unsuitable it should be replaced immediately.
- Healthcare workers should ensure the appropriate use of all other personal protective devices such as gloves, gowns, boots and goggles and comply with safe hand washing practice and appropriate disposal of sharps in the course of patient care.
- Healthcare workers should ensure compliance with universal safety precaution at all times.

9. SUPERVISION, MONITORING AND EVALUATION FOR DR-TB

9.1 Introduction

The DR-TB supervisory, monitoring and evaluation system (SME system) is keyed into the existing structure/system of the NTBLCP. However, in order to ensure that task and planned activities are carried out as planned, additional activities specific for DR-TB have been recommended. The SME system will assess:

- Accessibility to laboratory services for diagnosis
- Accessibility to second line anti TB drugs
- Case finding activities
- Treatment outcome
- Drug utilization
- DR-TB/HIV related activities
- Quality of care

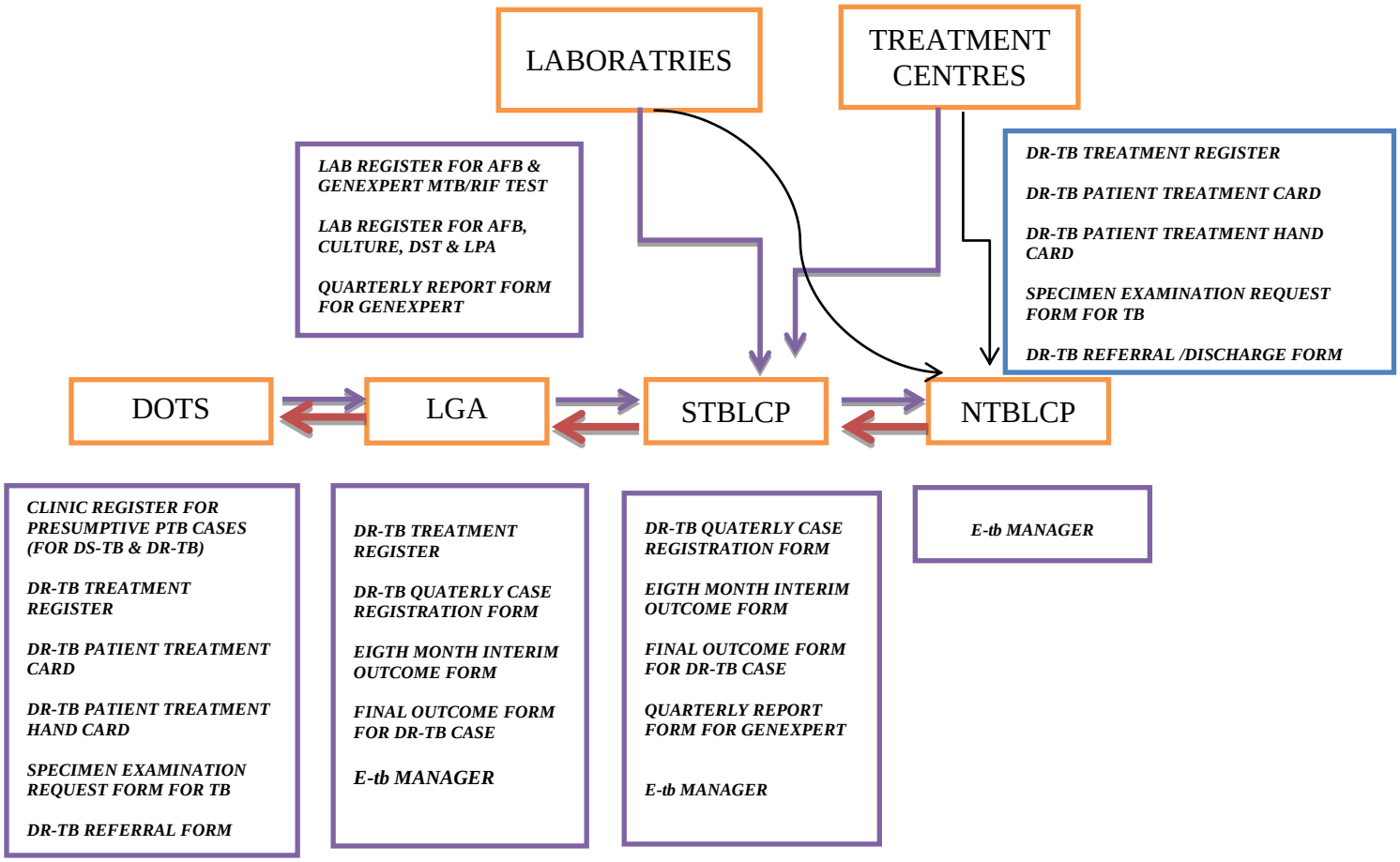
Assessment will be accomplished according to the NTBLCP indicators presented in the below.

9.2 Information flow system

The NTBLCP M&E system starts from the health facility level to the Central Unit of the programme. The M&E responsibilities at the various levels can be summarized as follows:

1. At the DOTS clinic level, health staff records presumptive DR-TB cases and patient information on the Clinic register for Presumptive PTB case.
2. DR-TB treatment centre and staff managing DR-TB cases in the community level complete the DR-TB treatment register and the e-tb manager where applicable.
3. State TBL control programme/LGTBLS collates all presumptive DR-TB case data into the quarterly reporting formats.
4. The State TBL & BU control programmes regularly update the e-tb manager and subsequently complete the quarterly statistical reporting format.
5. The state sends all validated quarterly statistical reports to the M&E unit of the central unit. (Similarly the State is expected to have the statistics of the treatment centre but the M&E unit of the central unit can access the statistical reports of the treatment centre/state data through the electronic web-based data capturing tool (e-tb manager).
6. The State TBL & BU control programme/State QA officer collate all GeneXpert data from the Xpert sites on a quarterly basis, however an aggregated data can been access through the GxAlert system
7. Culture/DST laboratory staff complete laboratory register and quarterly reports.
8. At the national level, M&E unit collates all state DR-TB data on quarterly basis.

Figure 9.1: NTBLCP DR-TB DATA FLOW



9.3 Supervision

Supportive supervision is a way of ensuring staff competence and effectiveness through observation, discussion, support and on-the-job training.

1. The State TBL & BU team with a representative from the State DR-TB team will supervise the DR-TB treatment centre providing initial phase of care at least once in every quarter.
2. The state DR-TB team with a representative from the consilium in the DR-TB treatment centre will supervise the DOTS centre providing continuation of care.
3. The national programme shall also conduct joint supervisory visits to the DR-TB treatment centres, DOTS centre providing continuation of care and the state programme in line with the NTBLCP supervisory system and frequency.

9.4 Programme Monitoring

Monitoring is very essential in a programme if a good outcome is required, hence the following must be considered.

1. The consilium of experts meets monthly and when needs arises to review all cases.
2. DR-TB focal persons: The focal person from each treatment centre and Culture/DST laboratory will meet quarterly to review their records and discuss challenges, lessons learned and develop

action plans. (This involves states that have treatment centres and Reference laboratories domiciled in it.)

3. The National DR-TB Committee shall meet quarterly to review the programme.
4. The annual programme review meeting is a forum where key stakeholders meet to review the progress made, challenges encountered and come up with strategies for the new reporting year as the case may be.

9.5 DR-TB Programme Indicators

Indicators are pointers in a programme which indicates if a programme is performing well or not. The following indicators are used for PMDT monitoring and evaluation in the NTBLCP.

9.5.1 DR-TB Case Notification indicators

- Proportion of presumptive DR-TB cases examined using rapid tests according to the national diagnostic algorithm
- Proportion of DR-TB cases (Rifampicin Resistant TB) diagnosed using rapid tests according to the national diagnostic algorithm
- Proportion of Rifampicin Resistant TB cases (RR-TB)that were confirmed to be MDR-TB cases

Table9.1: DR-TB case Notification indicators

S/N	Indicator	Description	Formula	Source/Freq.
1	Proportion (%) of all presumptive DR-TB cases examined	Total number of all presumptive DR-TB cases examined using rapid tests according to the national diagnostic algorithm among total number of presumptive DR-TB cases notified.	**Numerator:** Total number of all presumptive DR-TB cases examined using rapid tests according to the national diagnostic algorithm. **Denominator:** Total number of presumptive DR-TB cases notified over the same period.	E-tb manager/ NTBLCP quarterly DR-TB case finding reports ***Reported quarterly***
2	Proportion (%) of all DR-TB (RR-TB) cases diagnosed	Total number of all DR-TB (RR-TB) cases diagnosed using rapid tests according to the national diagnostic algorithm among total number of presumptive DR-TB cases examined.	**Numerator:** Total number of all DR-TB (RR-TB) cases diagnosed using rapid tests according to the national diagnostic algorithm. **Denominator:** Total number of presumptive DR-TB cases examined over the same period.	E-tb manager/ NTBLCP quarterly DR-TB case finding reports ***Reported quarterly***
3	Proportion (%)of all DR-TB (RR-TB) cases confirmed to be MDR-TB cases	Total number of all DR-TB (RR-TB) cases confirmed to be MDR-TB cases using culture/DST or LPA according to the national diagnostic algorithm among total number of DR-TB (RR-TB) cases examined.	**Numerator:** Total number of all DR-TB (RR-TB) cases confirmed to be MDR-TB cases using culture/DST or LPA according to the national diagnostic algorithm. **Denominator:** Total number of DR-TB (RR-TB) cases examined over the same period.	E-tb manager/ NTBLCP quarterly DR-TB case finding reports ***Reported quarterly***

9.5.2 DR-TB Enrolment for care Indicators

- Proportion of diagnosed DR-TB (RR-TB) cases started on treatment
- Proportion of diagnosed DR-TB (RR-TB) cases started on treatment in the community

- Proportion of DR-TB (RR-TB) cases started on treatment and eventually confirmed MDR-TB cases.

Table 9.2: Case holding Indicators for TB

S/N	Indicator	Description	Formula	Source/Freq.
1	Proportion (%) of diagnosed DR-TB cases started on treatment	Total number of diagnosed DR-TB (RR-TB) cases started on second-line anti-TB treatment among total number of diagnosed DR-TB cases notified.	**Numerator:**Total number of diagnosed DR-TB (RR-TB) cases started on second-line anti-TB treatment **Denominator:** Total number of diagnosed DR-TB (RR-TB) cases notified over the same period.	e-tb manager/ NTBLCP DR-TB quarterly case finding reports ***Reported Quarterly***
2	Proportion (%) of diagnosed DR-TB cases started on treatment in the community.	Total number of diagnosed DR-TB (RR-TB) cases started on second-line anti-TB treatment in the community among total number of diagnosed DR-TB cases notified.	**Numerator:** Total number of diagnosed DR-TB (RR-TB) cases started on second-line anti-TB treatment in the community **Denominator:** Total number of diagnosed DR-TB (RR-TB) cases notified over the same period.	e-tb manager/ NTBLCP DR-TB quarterly case finding reports ***Reported Quarterly***
3	Proportion (%) of DR-TB (RR-TB) cases started on treatment and eventually confirmed MDR-TB cases.	Total number of DR-TB (RR-TB) cases started on second-line anti-TB treatment and eventually confirmed to be MDR-TB case among total number of DR-TB cases started on second-line anti-TB treatment.	**Numerator:** Total number of DR-TB (RR-TB) cases started on second-line anti-TB treatment and eventually confirmed to be MDR-TB case **Denominator:** Total number of DR-TB cases started on second-line anti-TB treatment over the same period.	e-tb manager/ NTBLCP DR-TB quarterly case finding reports ***Reported Quarterly***

9.5.3 Indicators at the end of intensive phase (Eight Month Interim outcome)

- Proportion of RR/MDR-TB cases started on second-line anti-TB treatment with a negative culture result at the end of 8thmonth of treatment
- Proportion of RR/MDR-TB cases started on second-line anti-TB treatment but died at the end of 8th month of treatment
- Proportion of RR/MDR-TB cases started on second-line anti-TB treatment but lost to follow-up at the end of 8th month of treatment
- Proportion of RR/MDR-TB cases started on second-line anti-TB treatment but not evaluated at the end of 8thmonth of treatment
- Proportion of RR/MDR-TB cases started on second-line anti-TB treatment & had test done but culture result not available at the end of 8thmonth of treatment
- Proportion (%) of culture positive RR/MDR-TB cases initiated on DR-TB treatment later found not to have RR/MDR-TB by the 8th month of treatment

Table 9.3: Case holding Indicators for TB

S/N	Indicator	Description	Formula	Source
1	Proportion (%) of culture positive RR/MDR-TB cases started on second-line anti-TB treatment with a negative culture result at the	Total number of culture positive RR/MDR-TB cases started on second-line anti-TB treatment with a negative culture result at the end of 8thmonth of treatment among total number of culture positive RR/MDR-TB cases started on	**Numerator:**Total number of culture positive RR/MDR-TB cases started on second-line anti-TB treatment with a negative culture result at the end of 8thmonth of treatment **Denominator:** Total number of culture positive RR/MDR-TB cases started on	E-tb manager/ NTBLC DR-TB quarterly eight month interim reports ***Reported Quarterly***

	end of 8th month of treatment	second-line anti-TB treatment	second-line anti-TB treatmentover the same period.	
2	Proportion (%) of culture positive RR/MDR-TB cases started on second-line anti-TB treatment whodied at the end of the 8th month of treatment	Total number of culture positive RR/MDR-TB cases started on second-line anti-TB treatment with no culture result due to death at the end of 8th month of treatment among total number of culture positive RR/MDR-TB cases started on second-line anti-TB treatment	**Numerator:** Total number of culture positive RR/MDR-TB cases started on second-line anti-TB treatment with no culture result due to death at the end of 8th month of treatment **Denominator:** Total number of culture positive RR/MDR-TB cases started on second-line anti-TB treatment over the same period.	E-tb manager/ NTBLC DR-TB quarterly eight month interim reports ***Reported Quarterly***
3	Proportion (%) of culture positive RR/MDR-TB cases started on second-line anti-TB treatment who was lost to follow-up at the end of 8th the month of treatment	Total number of culture positive RR/MDR-TB cases started on second-line anti-TB treatment with no culture result due lost to follow-up at the end of 8th month the treatment among total number of culture positive RR/MDR-TB cases started on second-line anti-TB treatment	**Numerator:** Total number of culture positive RR/MDR-TB cases started on second-line anti-TB treatment with no culture result due lost to follow-up at the end of 8th month the treatment **Denominator:** Total number of culture positive RR/MDR-TB cases started on second-line anti-TB treatment over the same period	E-tb manager/ NTBLC DR-TB quarterly eight month interim reports ***Reported Quarterly***
4	Proportion (%) of culture positive RR/MDR-TB cases started on second-line anti-TB treatment who was not evaluated at the end of 8th the month of treatment	Total number of culture positive RR/MDR-TB cases started on second-line anti-TB treatment with no culture result because case was not evaluated at the end of 8th month the treatment among total number of culture positive RR/MDR-TB cases started on second-line anti-TB treatment	**Numerator:** Total number of culture positive RR/MDR-TB cases started on second-line anti-TB treatment with no culture result because case was not evaluated at the end of 8th month the treatment **Denominator:** Total number of culture positive RR/MDR-TB cases started on second-line anti-TB treatment over the same period	E-tb manager/ NTBLC DR-TB quarterly eight month interim reports ***Reported Quarterly***
5	Proportion (%) of RR/MDR-TB cases started on second-line anti-TB treatment & had test done but culture result not available at the end of eight months of treatment	Total number of RR/MDR-TB cases started on second-line anti-TB treatment & had test done but culture result not available at the end of eight months of treatment among total number of RR/MDR-TB cases started on second-line anti-TB treatment	**Numerator:** Total number of RR/MDR-TB cases started on second-line anti-TB treatment & had test done but culture result not available at the end of eight months of treatment **Denominator:** Total number of RR/MDR-TB cases started on second-line anti-TB treatmentover the same period	E-tb manager/ NTBLC DR-TB quarterly eight month interim reports ***Reported Quarterly***
6	Proportion (%) of culture positive RR/MDR-TB cases initiated on DR-TB treatment later found not to have RR/MDR-TB by the 8th month of treatment	Total number of culture positive RR/MDR-TB cases initiated on DR-TB treatment later found not to have RR/MDR-TB by the 8th month of treatment among total number of RR/MDR-TB cases started on second-line anti-TB treatment	**Numerator:** Total number of culture positive RR/MDR-TB cases initiated on DR-TB treatment later found not to have RR/MDR-TB by the 8th month of treatment **Denominator:** Total number of RR/MDR-TB cases started on second-line anti-TB treatment over the same period	E-tb manager/ NTBLC DR-TB quarterly eight month interim reports ***Reported Quarterly***

9.5.4 Indicators at the end of treatment

- Proportion of DR-TB cases cured (RR/MDR TB cure rate)
- Proportion (%) of DR-TB cases declared treatment completed (RR/MDR-TB treatment completion rate)
- Proportion (%) of DR-TB cases successfully treated (RR/MDR-TB treatment success rate)
- Proportion (%) of DR-TB cases that failed treatment (RR/MDR-TB treatment failure rate)
- Proportion (%) of DR-TB cases that died (RR/MDR-TB death rate)

- Proportion (%) of DR-TB cases loss to follow-up (RR/MDR-TB lost to follow-up rate)
- Proportion (%) of DR-TB cases not evaluated (RR/MDR-TB not evaluated rate)
- Proportion (%) of DR-TB cases still on treatment (RR/MDR-TB still on treatment rate)

Table 9.3: Treatment outcomes indicators for DR-TB cases

S/N	Indicator	Description	Formula	Source/Freq.
1	Proportion (%) of DR-TB cases cured (RR/MDR TB cure rate)	Total number of DR-TB cases initiated on 2nd line anti-TB treatment that was cured at the end of treatment among total number of culture positives cases initiated on 2nd line anti-TB treatment	**Numerator:** Total number of DR-TB cases initiated on 2nd line anti-TB treatment that was cured at the end of treatment **Denominator:** Total number of culture positives cases initiated on 2nd line anti-TB treatment over the same period.	E-tb manager/ NTBLCP quarterly DR-TB preliminary & final treatment outcome reports ***Reported quarterly***
2	Proportion (%) of DR-TB cases declared treatment completed (RR/MDR-TB treatment completion rate)	Total number of MDR-TB cases initiated on 2nd line anti-TB treatment that were declared treatment completed at the end of the treatment among total number of culture positives cases initiated on 2nd line anti-TB treatment.	**Numerator:** Total number of MDR-TB cases initiated on 2nd line anti-TB treatment that were declared treatment completed at the end of the treatment **Denominator:** Total number of culture positives cases initiated on 2nd line anti-TB treatment over the same period.	E E-tb manager/ NTBLCP quarterly DR-TB preliminary & final treatment outcome reports ***Reported quarterly***
3	Proportion (%) of DR-TB cases successfully treated (RR/MDR-TB treatment success rate)	Total number of DR-TB cases initiated on 2nd line anti-TB treatment that were cured plus those declared treatment completed at the end of treatment among total number of culture positives cases initiated on 2nd line anti-TB treatment.	**Numerator:**Total number of DR-TB cases initiated on 2nd line anti-TB treatment that were cured plus those declared treatment completed at the end of treatment **Denominator:** Total number of culture positives cases initiated on 2nd line anti-TB treatment over the same period.	E-tb manager/ NTBLCP quarterly DR-TB preliminary & final treatment outcome reports ***Reported quarterly***
4	Proportion (%) of DR-TB cases that failed treatment (RR/MDR-TB treatment failure rate)	Total number of DR-TB cases initiated on 2nd line anti-TB treatment that failed treatment among total number of culture positives cases initiated on 2nd line anti-TB treatment.	**Numerator:**Total number of DR-TB cases initiated on 2nd line anti-TB treatment that failed treatment **Denominator:** Total number of culture positives cases initiated on 2nd line anti-TB treatment over the same period.	E-tb manager/ NTBLCP quarterly DR-TB preliminary & final treatment outcome reports ***Reported quarterly***
5	Proportion (%) of DR-TB cases that died (RR/MDR-TB death rate)	Total number of DR-TB cases initiated on 2nd line anti-TB treatment that died from any cause while on treatment among total number of culture positives cases initiated on 2nd line anti-TB treatment.	**Numerator:**Total number of DR-TB cases initiated on 2nd line anti-TB treatment that died from any cause while on treatment **Denominator:** Total number of culture positives cases initiated on 2nd line anti-TB treatment over the same period.	E-tb manager/ NTBLCP quarterly DR-TB preliminary & final treatment outcome reports ***Reported quarterly***
6	Proportion (%) of DR-TB cases loss to follow-up (RR/MDR-TB lost to follow-up rate)	Total number of DR-TB cases initiated on 2nd line anti-TB treatment that was lost to follow-up among total number of culture positives cases initiated on 2nd line anti-TB treatment.	**Numerator:** Total number of DR-TB cases initiated on 2nd line anti-TB treatment that was lost to follow-up. **Denominator:** Total number of culture positives cases initiated on 2nd line anti-TB treatment over the same period.	E-tb manager/ NTBLCP quarterly DR-TB preliminary & final treatment outcome reports ***Reported quarterly***
7	Proportion (%) of DR-TB casesnot	Total number of DR-TB cases initiated on 2nd line anti-TB	**Numerator:** Total number of DR-TB cases initiated on 2nd line anti-TB treatment that	E-tb manager/ NTBLCP

	evaluated (RR/MDR-TB not evaluated rate)	treatment that was not evaluatedamong total number of culture positives cases initiated on 2nd line anti-TB treatment.	was not evaluated. **Denominator:** Total number of culture positives cases initiated on 2nd line anti-TB treatment over the same period.	quarterly DR-TB preliminary & final treatment outcome reports ***Reported quarterly***
8	Proportion (%) of DR-TB cases still on treatment (RR/MDR-TB still on treatment rate)	Total number of DR-TB cases initiated on 2nd line anti-TB treatment that are still on treatment among total number of culture positives cases initiated on 2nd line anti-TB treatment.	**Numerator:** Total number of DR-TB cases initiated on 2nd line anti-TB treatment that are still on treatment. **Denominator:** Total number of culture positives cases initiated on 2nd line anti-TB treatment over the same period.	E-tb manager/ NTBLCP quarterly DR-TB preliminary & final treatment outcome reports ***Reported quarterly***

THE RECORDING AND REPORTING TOOLS as printed in separated documents

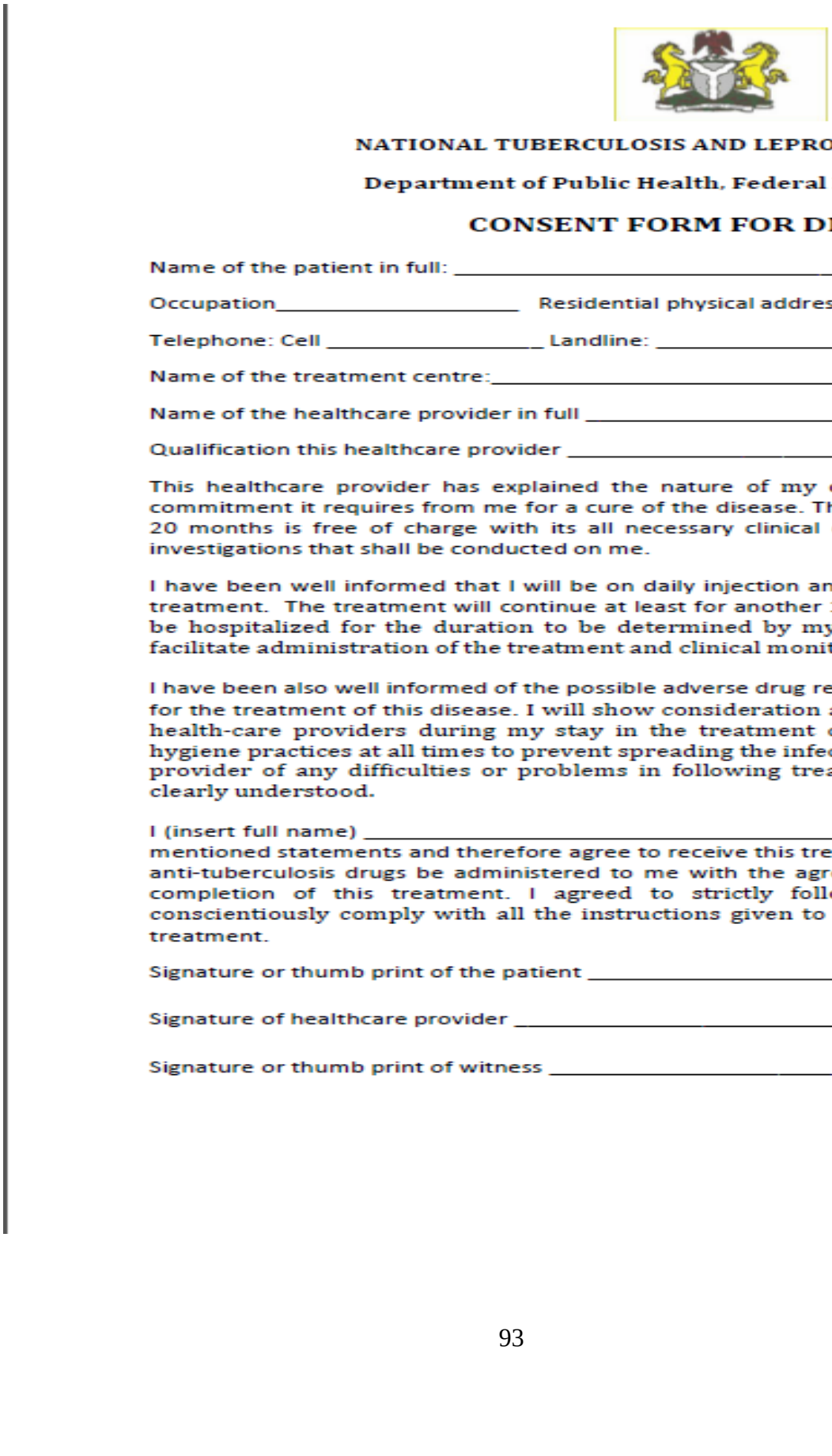
The NTBLCP DR-TB information system is based upon, and is an extension of the basic DOTS information system.

The comprehensive collection of recording and reporting tools are provided as appendices.

10. APPENDIX:

10.1 Recording tools

Figure 10.1: NTBLCP DR-TB Patient Consent Form



NATIONAL TUBERCULOSIS AND LEPROSY CONTROL PROGRAMM

Department of Public Health, Federal Ministry of Health, Niger

CONSENT FORM FOR DR-TB PATIENT

Name of the patient in full: _____ Age (in yrs.) _____ Sex

Occupation_____ Residential physical address: _____

Telephone: Cell _____ Landline: _____ e-mail (if any): _____

Name of the treatment centre:_____

Name of the healthcare provider in full _____

Qualification this healthcare provider _____ and designation_____

This healthcare provider has explained the nature of my disease to me and I've cle commitment it requires from me for a cure of the disease. The treatment which will last 20 months is free of charge with its all necessary clinical consultations, audiometric investigations that shall be conducted on me.

I have been well informed that I will be on daily injection and oral medications for the treatment. The treatment will continue at least for another 12 months with the oral me be hospitalized for the duration to be determined by my healthcare provider is d facilitate administration of the treatment and clinical monitoring.

I have been also well informed of the possible adverse drug reactions that may result fron for the treatment of this disease. I will show consideration and respect for the rights health-care providers during my stay in the treatment center and thereafter. I w hygiene practices at all times to prevent spreading the infection to others. I will also in provider of any difficulties or problems in following treatment, or if any part of t clearly understood.

I (insert full name) _____clearly u mentioned statements and therefore agree to receive this treatment and give my consen anti-tuberculosis drugs be administered to me with the agreement that I will adhere completion of this treatment. I agreed to strictly follow the prescribed treat conscientiously comply with all the instructions given to me by the healthcare pro treatment.

Signature or thumb print of the patient _____ Date ___

Signature of healthcare provider _____ Date ___

Signature or thumb print of witness _____ Date ___

Figure 10.2: NTBLCP DR-TB Patient Referralform

National Tuberculosis and Leprosy Control Programme NTBL

DR-TB Patient Referral Form

1. Date (dd/mm/yyyy) _____ / _____ / 20_____ **2. Patient Name:** _____
Surname

3. Patient Address: _____

Phone No: _____ **Sex:**

4. Health facility no: [ ] **LGA TB No (If applicable)** [ ]

5. Referring from _____ _____
Facility name LGA

6. Referring to _____ _____
Facility name LGA

(Tick as appropriate for questions 7 to 10)

7. Type of patient (initial classification) O New O Relapse O Treatment after failure O T
O Other previously treated patients O Unknown previous TB treatment Hx

8. Reason for referral O DR-TB treatment O Others (specify) _____

9. HIV status O HIV unknown O HIV neg O HIV Pos

10. Current Medication: O None

TB Treatment: O Six months Regimen O Twelve months Regimen

O ART (List): _____ O C

O Other (specify): _____

11. Date current TB regimen began: _____ / _____ / 20_____

12. Additional Clinical Notes: _____

13. Date of last clinical visit at referral site: _____ / _____ / 20_____

14. Date of scheduled first appointment to the receiving site: _____ / _____ / 20_____

15. Name of the person effecting the referral: _____ Designation: _____

Tel number: _____ Sign: _

ACKNOWLEDGEMENT OF ENROLMENT OF PATIENT (to be completed by receiving DR-TB Admiss

16. Received date: _____/ _____ / 20 _____

17. Name of the person receiving the patient: _____ Designation: _____

Tel number: _____ Sign: _____

18. Date of admission to DR-TB centre: _____ / _____ / 20_____

Figure 10.3: NTBLCP DR-TB Treatment card (front page)

National Tuberculosis and Leprosy Control Programme

NTBLCP/DR-TB 03

Second line TB (DR-TB) Treatment Card

Facility/Treatment Unit name: _____ DR-TB Px registration number: DR-TB

Name: _____ Date of Reg. No.: ___/____/ 20__ Etbm uniq. no.

Have been previously treated for TB for at least 4 weeks? Yes No

Age: _____ Date of Birth: ____/____ /___

Sex: O F O M

Address: _____

Tel no: _____

Refering Health facility : _____

LGA: _____ State: _____

LGTBLS No.: _____

Initial weight (kg): _____ Height (cm): _____

Site of disease: O Pulmonary O Extrapulmonary

O Both If extrapulmonary, specific site: _____

Registration group	Tick one only
New	
Relapse	
Treatment after failure	
Treatm. after loss to follow-up	
Other previously treated	
Patients with unknown previous TB treatment history	
Transferred in (from another DR-TB treatment site)	

History of previ

No.	Star unkr

HIV information
HIV testing done: O Y O N O unknown
Date of test: ___/ ____/ ___ Results:
Started on ART O Y O N Date: ___/___/___
Started on CPT O Y O N Date: ___/___/___

Drug

First

H = Is

R = Ri

E = Et

Z = Py

S = St

Review panels meetings: dates and decisions

Date	Decision	Next date

Figure 10.4: NTBLCP DR-TB Treatment card (Inner page 1)

DR-TB REGIMEN (date treatment started and dosage (tablets/ mg), change of dosage (tablets/ mg), and cessation of drugs):

Date	H	R	E	Z	S	Km	Am	Cm	Lfx	Mfx	Rfb/Rbt	Cs/Trd	PAS	Other	Comments

ADMINISTRATION OF DRUGS (one line per month)

Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	2

Figure 10.5: NTBLCP DR-TB Treatment card (Inner page 2)

Month	Sputum Smear microscopy		
Prior**	Date	Sample no.	Result
0			
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			

Month	
Prior**	Date
0	
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	
21	
22	
23	
24	

Drug susceptibility testing (DST/LPA) results

Date *	H	R	E	Z	S	Km	Am	Cm	Lfx

Figure 10.6: NTBLCP DR-TB Treatment card (Back page)

ADMINISTRATION OF DRUGS (continued)

Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	2

Enter X only on the day when medications were swallowed under direct observations of the facility staff.

Enter O only on the day when medications were swallowed without direct observations of the facility staff.

Enter A on day when medications were Missed.

Comments: _____

_____

_____

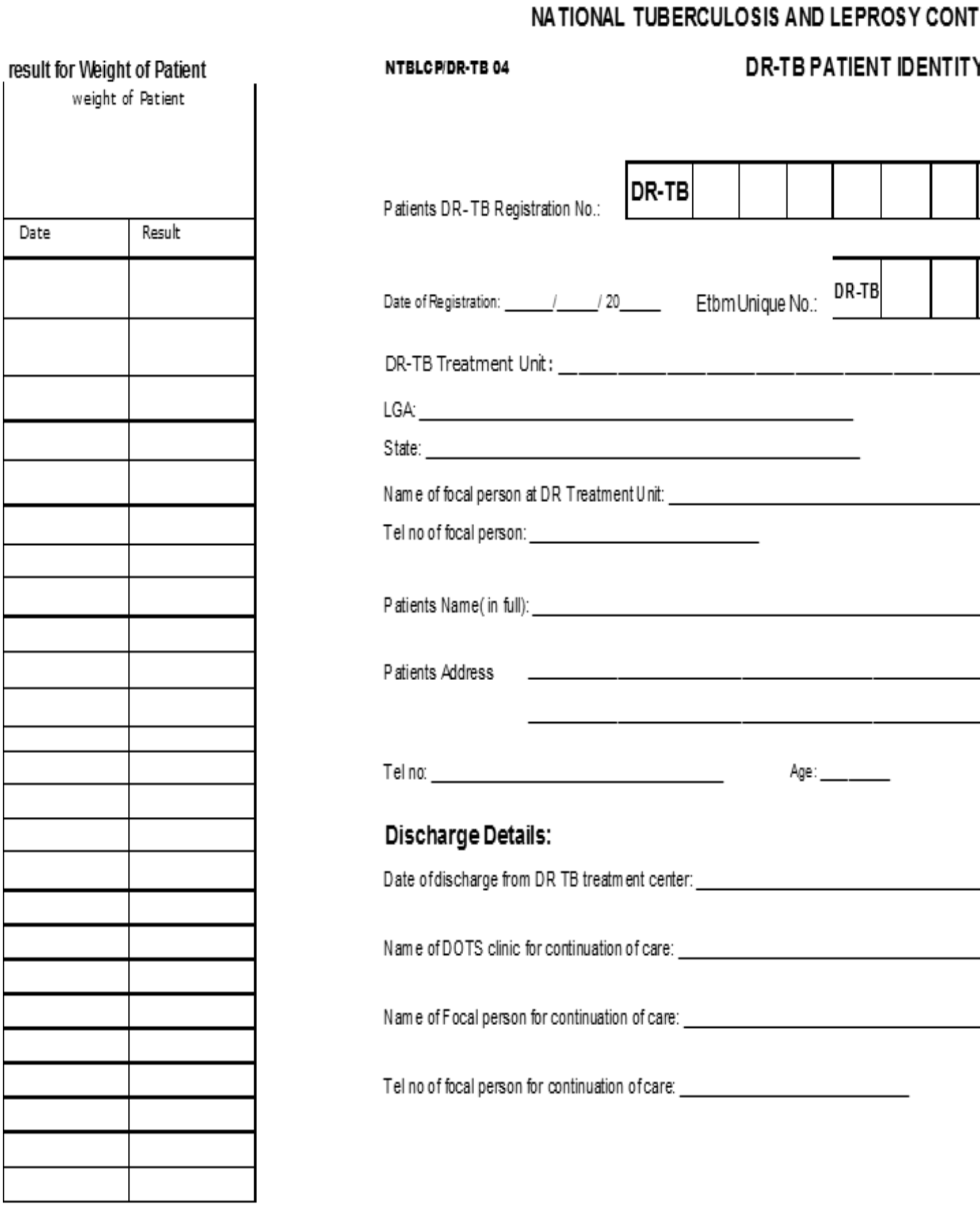
_____

_____

_____

_____

Figure 10.7: NTBLCP DR-TB patient treatment hand card (Front page)



NATIONAL TUBERCULOSIS AND LEPROSY CONT

result for Weight of Patient

weight of Patient

Date	Result

NTBLCP/DR-TB 04

DR-TB PATIENT IDENTITY

Patients DR-TB Registration No.: DR-TB

Date of Registration: _____/_____/ 20_____ Etbm Unique No.: DR-TB

DR-TB Treatment Unit: _____

LGA: _____

State: _____

Name of focal person at DR Treatment Unit: _____

Tel no of focal person: _____

Patients Name(in full): _____

Patients Address _____

_____

Tel no: _____ Age: _____

Discharge Details:

Date of discharge from DR TB treatment center: _____

Name of DOTS clinic for continuation of care: _____

Name of Focal person for continuation of care: _____

Tel no of focal person for continuation of care: _____

Figure 10.8: NTBLCP DR-TB patient treatment hand card (Back page)

Drug susceptibility testing (DST/LPA) results

Date *	H	R	E	Z	S	Km	Am	Cm	Lfx	Mfx	Pto/Eto	Cs/Trd	Other

SECOND-LINE REGIMEN (date treatment started and dosage (tablets/ mg), change of dosage (tablets/ mg), and cessation of drugs):

Date	H	R	E	Z	S	Km	Am	Cm	Lfx	Mfx	Pto/Eto	Cs/Trd	PAS	Other	Comments

ADMINISTRATION OF DRUGS (one line per month)

Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21

ADMINISTRATION OF DRUGS (Continued)

Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21

Enter X only on the day when medications were swallowed under direct observations of the facility staff.
Enter O only on the day when medications were swallowed without direct observations of the facility staff.
Enter A on day when medications were Missed.

Figure 10.9: NTBLCP Laboratory register for AFB Microscopy, Culture, DST and LPA

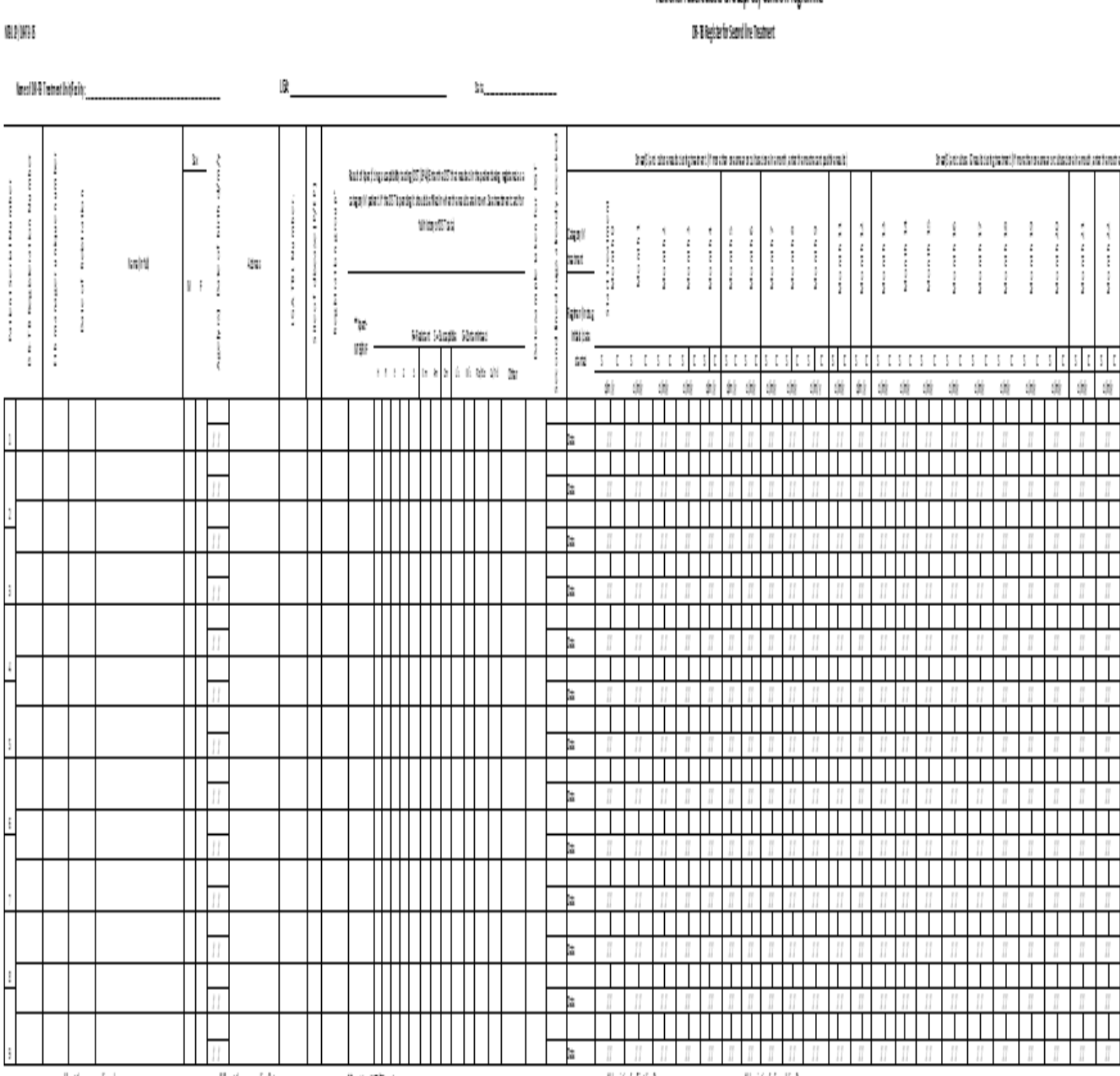


Figure 10.10: NTBLCP DR-TB treatment Register

National Tuberculosis and Leprosy Control Programme
NTBLCP Laboratory Register for AFB smear microscopy, culture, LPA and DST

NTBLCP/DR-TB 01

Name of Laboratory:_____ LGA:_____

Patient Biodata								Laboratory Information								SMActivities[a]	Culture Activities			LPA/DST Activities													
Patient name	Patient adress	Referring health facility[b]	Patient Registration Number LGA TB/DR-TB Registration No.[c]	E-tbmanig No.[d]	M/F	Age	HIV Status (Tick appropriately) Positive	Negative	Unknown	Date specimen was received	Date specimen was collected	Laboratory serial number	Specimen identification number	Type of specimen received (Indicate the code only)[e]	Tick Reason for examination	Follow-up	If Follow-up, Specify Month of Treatment	Specify Test Required (Indicate SM or C/DST)[f]	Specify Reason for Test (Insert alphabet code)[g]	Sputum AFB result	Date specimen was inoculated	Results of Culture (Write the codes only)[h]	Result of confirmatory test for M. Tb (Positive or negative)	Culture sent for DST (Y/N)	Name of reporting officer for culture/ Date of test	Date specimen was received for DST	Specify Type of DST (LPA, Solid or Liquid)	LPA result[i] Rifampicin (R)	Isoniazid (H)	Fluoroquinone	Aminoglycoside/ Cyclic	Ethambutol (E)	Isoniazid (H)	Rifampicin (R)	Ethambutol (E)	Pyrazinamide (Z)							

Keys : 1-6

[a] Facility from which patient was referred

[b] Either the LGA TB No. if the patient is on 1st line treatment or the DR-TB Reg. No. if the patient is on 2nd line treatment

[c] Refers to the patient unique No. in the e-tbmanager applies to both 1st and 2nd line treatment)

[d] Write S for Sputum; GL for Gastric Lavage; CSF for Cerebrospinal Fluids and LN for Lymph nodes tissue

[e] Write "SM for Smear Microscopy and C/DST for Culture/Drug Susceptible Testing

[f] Write Alphabets for reasons for Test

G: Others specify

J: To Confirm MDR-TB (at enrolment)

K: Cases of X-part MTB not detected but smear positive

L: Routine follow-up of 2nd line TB Treatment

M: Smear Positive at (after month 4 of 2nd line TB Treatment

[g] Write Solid culture report as: NTor Negative; STor scanty (1-9); 1+; 2+; 3+; CTor Confluent or contaminated and Write Liquid culture reports as P for Positive; NTor Negative; or CTor Contaminated

[h] Write LPA result as R for Resistant; STor Susceptible; and I for Indeterminate

[i] Write DST results as R for Resistant; STor Susceptible; and CTor Contaminated

10.2 NTBLCP DR-TB Reporting tools

Figure 10.11: NTBLCP Quarterly report form on eight month interim outcome of RR/MDR-TB cases

NATIONAL TUBERCULOSIS AND LEPROSY CONTROL PROGRAMME

NTBLCP/DR-TB 07 **Quarterly report form on GeneXpert/MTB/RIF test performed**

Completion Date	Facility Name	Quarter	Year

Name of State		**Responsible officer**	
Name of LGA		**Telephone number**	
Population Covered		**Email address**	

Block 1: All Patients with TB symptoms who are tested using Xpert/MTB/RIF during quarter_____ of year_____

Result of Xpert test performed	Total Patients Tested	Presumptive DR-TB cases			PLHIV with TB symptoms	Other priority groups at risk			Total by Sex	
		Symptomatic DR-TB Contacts	AFB positive at end of mth 3[1]	Previously treated TB cases[2]		Health Care Worker	EPTB Cases	Other cases[3]	Male	Female
MTB Not Detected										
MTB Detected RIF Resistance Not detected										
MTB Detected RIF Resistance Detected										
MTB Detected RIF Resistance Indeterminate										
Total										

Block 2: Breakdown of total Patients tested using Xpert/MTB/RIF during quarter_____ of year_____ by HIV Status and sex

Result of Xpert test performed	Total Patients Tested	HIV Status			No. with HIV Positive result		No. with HIV Negative result	
		Positive	Negative	Unknown	Male	Female	Female	Male
MTB Not Detected								
MTB Detected RIF Resistance Not detected								
MTB Detected RIF Resistance Detected								
MTB Detected RIF Resistance Indeterminate								
Total								

Block 3: Analysis of Test performed and error codes

Total number of test with successful Result			
Total number of test with Error result		Enter the Error code numbers	
Total no. of test with invalid/incomplete result		Enter the number of errors	

Block 4: Catridge Utilization

Description of Item	UNIT	A	B	C	D	E	F	G	H
		Opening Balance	Quantity Received	Quantity Used	Closing Stock (A+B-C)	Physical Inventory	Losses/ Adjustment(E-D)	AMC (C/3)	Remarks*
CATRIDGES	PIECE								

*Remarks: Indicate the quantity used for EQA here:

[1]All TB Cases with AFB positive result after smear is repeated at the end of month three (3) of Regimen 1 treatment

[2]All previously treated TB (Relapse, Treatment after failure to Regimen 1, Treatment after loss to follow-up, and Other previously treated patients)

[3]All other person tested apart from presumptive DR-TB cases, PLHIV with TB symptoms, Health worker with TB and EPTB

Figure 10.12: NTBLCP Quarterly report form on eight month interim outcome of RR/MDR-TB cases

NATIONAL TUBERCULOSIS AND LEPROSY CONTROL PROGRAMME

Quarterly report on DR-TB cases enrolled for second line treatment

NTBLCP/DR-TB 09

Tick below the appropriate reporting unit

State	Community	Treatment centre

Completion Date	Facility Name	Quarter	Year

Name of State		Responsible officer	
Name of LGA		Telephone number	
Population Covered		Email address	

Block 1: Total DR-TB Cases enrolled for treatment during _____quarter of year_____ by case category

	New Cases	Relapse Cases	Treatment after failure	Treatment after loss to follow-up	Previously treated TB cases	Unknown treatment history[1]	Transferred in DR-TB Patient[2]	Total cases enrolled
MTB Detected RIF Resistance Detected Cases								

Block 2: Breakdown of total DR-TB Cases enrolled by sex and age

Sex	0-4	5-I4	15-24	25-34	35-44	45-54	55-64	≥65	Total
Male									
Female									

Block 3: Breakdown of confirmed DR-TB cases notified during ___quarter[3] of year _____ by culture/DST result

	Total cases enrolled	New	Relapse	Treatment after failure	Treatment after loss to follow-up	Previously treated TB cases	Unknown treatment history[1]	Transferred in DR-TB cases[2]	Total cases evaluated
MDR-TB Cases									
RIF Resistance TB Cases									
Poly-Resistance TB Cases									
XDR-TB Cases									
Others (e.g. Non TB Mycobacterium)									
Total									

Block 4: Breakdown of confirmed MDR-TB cases registered 3-6 months earlier during____quarter of year_____ by HIV status and sex

MDR-TB Confirmed cases	No. with known HIV status		No. that are HIV positive		No. with unknown HIV status		Referred for HIV care & support	No. with HIV positive result placed on CPT		No. with HIV positive result placed on ART	
	M	F	M	F	M	F		M	F	M	F
Male											
Female											

[1]All TB cases with unknown previous TB treatment history

[2]All DR-TB cases transferred in from another DR-TB treatment site

[3]All DR-TB cases enrolled for second-line anti-TB treatment 3-6 months earlier

Figure 10.13: NTBLCP Quarterly report form on eight month interim outcome of RR/MDR-TB cases

NATIONAL TUBERCULOSIS AND LEPROSY CONTROL PROGRAMME

Quarterly Report on eight month assessment of DR-TB Case enrolled for second line treatment

NTBLCP/DR-TB 10

Completion Date	Facility Name	Qaurter	Year

Name of State		Responsible officer	
Name of LGA		Telephone number	
Population Covered		Email address	

Block 1: Breakdown of smear and culture results of MDR-TB cases registered during quarter[1]_____ of Year_____

	Confirmed MDR-TB Cases enrolled for treatment	Bacteriological result at 8 months of treatment			Smear and Culture not done			Total evaluated
		Negative (Smear and culture negative)	Positive (smear and/or culture)	Smear done but result unknown	Died	Lost to follow-up	Not evaluated	
New								
Relapse								
Treatment after failure								
Treatment after loss to follow-up								
Previously treated TB cases								
Unknown treatment history[2]								
Transferred in DR-TB Patient[3]								
Total								

Block 2: Breakdown of smear and culture results of RR-TB cases registered during quarter[4]_____ of Year_____

	Confirmed MDR-TB Cases enrolled for treatment	Bacteriological result at 8 months of treatment			Smear and Culture not done			Total evaluated
		Negative (Smear and culture negative)	Positive (smear and/or culture)	Smear done but result unknown	Died	Lost to follow-up	Not evaluated	
New								
Relapse								
Treatment after failure								
Treatment after loss to follow-up								
Previously treated TB cases								
Unknown treatment history[2]								
Transferred in DR-TB Patient[3]								
Total								

[1]These are confirmed MDR-TB Cases enrolled 9 - 12 months earlier

[2]All TB cases with unknown previous TB treatment history

[3]All DR-TB cases transferred in from another DR-TB treatment site

[4]These are confirmed RR-TB Cases enrolled 9 - 12 months earlier

Figure 10.14: NTBLCP Quarterly report form on treatment outcome of RR/MDR-TB cases

NATIONAL TUBERCULOSIS AND LEPROSY CONTROL PROGRAMME

Quarterly report on treatment outcome of MDR-TB cases enrolled on treatment 24 - 36 months earlier

NTBLCP/DR-TB 11

Tick below the appropriate reporting unit

State	Community	Treatment centre

Completion Date	Facility Name	Qaurter	Year

Name of State		Responsible officer	
Name of LGA		Telephone number	
Population Covered		Email address	

Block 1: Treatment outcome of all confirmed MDR-TB cases registered during ____quarter[1] of year_____ by case category

Case category	Total cases enrolled on treatment	Treatment outcomes							Total cases evaluated
		Cured	Treatment Completed	Treatment failed	Lost to follow-up	Died	Transferred Out	Not evaluated	
New Cases									
Relapse Cases									
Treatment after failure Cases									
Treatment after loss to follow-up Cases									
Previously treated TB cases									
Unknown treatment history Cases[2]									
Transferred in DR-TB Cases[3]									
Total Cases									

Block 2: Treatment outcome of all confirmed MDR-TB cases registered during ____quarter[1] of year_____ by HIV status

Case category	Total cases enrolled on treatment	Treatment outcomes							Total cases evaluated
		Cured	Treatment Completed	Treatment failed	Lost to follow-up	Died	Transferred Out	Not evaluated	
HIV Positive Cases									
HIV Negative Cases									
HIV Status unknown Cases									
Total Cases									

Block 3: Treatment outcome of all confirmed RR-TB cases registered during ____quarter[4] of year_____ by case category

Case category	Total cases enrolled on treatment	Treatment outcomes							Total cases evaluated
		Cured	Treatment Completed	Treatment failed	Lost to follow-up	Died	Transferred Out	Not evaluated	
New Cases									
Relapse Cases									
Treatment after failure Cases									
Treatment after loss to follow-up Cases									
Previously treated TB cases									
Unknown treatment history Cases[2]									
Transferred in DR-TB Cases[3]									
Total Cases									

Block 4: Treatment outcome of all confirmed RR-TB cases registered during ____quarter[4] of year_____ by HIV status

Case category	Total cases enrolled on treatment	Treatment outcomes							Total cases evaluated
		Cured	Treatment Completed	Treatment failed	Lost to follow-up	Died	Transferred Out	Not evaluated	
HIV Positive Cases									
HIV Negative Cases									
unknown Cases									
Total Cases									

[1]These are confirmed MDR-TB Cases enrolled 24 - 36 months earlier

[2]All TB cases with unknown previous TB treatment history

[3]All DR-TB cases transferred in from another DR-TB treatment site

[4]These are confirmed RR-TB Cases enrolled 24 - 36 months earlier