NATIONAL GUIDELINES FOR THE PROGRAMMATIC MANAGEMENT OF TUBERCULOSIS

THIRD EDITION 2015
NATIONAL TB CONTROL PROGRAMME
HEALTH PROTECTION AGENCY,
MINISTRY OF HEALTH, MALDIVES

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ABBREVIATIONS

AFB	Acid Fast Bacilli
AIDS	Acquired Immunodeficiency Syndrome
ART	Anti-retroviral treatment
CP	Continuation phase
CSF	Cerebrospinal fluid
DOT	Directly observed treatment
DOTS	Internationally-recommended strategy to control TB
DST	Drug-sensitivity testing
E	Ethambutol
EPTB	Extra-pulmonary tuberculosis
FDC	Fixed-Dose Combination
GDF	Global Drug Facility
H	Isoniazid
HIV	Human Immunodeficiency Virus
HPA	Health protection Agency
IP	Intensive Phase
IGMH	Indira Gandhi Memorial Hospital
IRS	Immune Reconstitution Syndrome
LTBI	Latent Tuberculosis Infection
MDR-TB	Multidrug-resistant tuberculosis
MOH	Ministry of Health
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NTP	National Tuberculosis Programme
PHU	Public Health Unit
PTB	Pulmonary tuberculosis
R	Rifampicin
RMC	Respiratory Medicine Clinic
S	Streptomycin
TB	Tuberculosis
TBM	Tuberculous Meningitis
TST	Tuberculin skin test
WHO	World Health Organization
XDR TB	Extensive drug resistant Tuberculosis
Z	Pyrazinamide

ACKNOWLEDGEMENTS

This edition has been extensively revised to incorporate new information in TB care and control and many have contributed in various ways in the production of this guideline.

We gratefully acknowledge the World Health organization for the continued support to the National TB Programme in terms of technical and financial assistance

Input and feedback on various issues related to the TB Programme were provided by the staff of NTP and the Health Protection Agency in addition to arranging and facilitating the stakeholder meetings

Special thanks go to the following members for their input and contribution to this guideline and to those who reviewed this document and provided guidance by their comments.

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Special thanks also go to the
Dr Ahmed Saeed and Department of Paediatrics /IGM Hospital for their contribution in formulating the guideline on childhood TB
Department of Medicine /IGM Hospital for their feedback and suggestions
Maldivian Medical Association for feedback and comments

1. INTRODUCTION

This revision of the existing guideline was required in view of newer developments in the diagnosis and management of TB over recent years. The current NTP guidelines have not been revised since 2007 and do not reflect recent WHO policy changes in TB diagnosis, treatment and definitions of treatment outcomes.

The purpose of this guideline is for the National TB Programme to optimize management of TB care in alignment with the latest policy recommendations of WHO in TB care and control. This guideline will also act as guidance to clinicians and other health care providers involved in providing TB services across the country.

This guideline constitutes the management of Tuberculosis in Adults. Separate guideline manuals are to be referred for the detailed management of TB in children and management of drug resistant tuberculosis.
The management of TB needs to be standardised to improve patient outcomes, assist monitoring and evaluation efforts and prevent the emergence of MDR-TB. Preventing MDR-TB is critically important since chemotherapy for MDR-TB has more side effects, is expensive and requires a longer duration of treatment. Prevention of MDR-TB can be achieved if health care providers manage TB appropriately and ensure optimal adherence to first-line therapy

With the change in the Stop TB Strategy's objective, to emphasis on universal access to high-quality, patient-centered treatment and protection of TB/HIV and MDRTB patients, the previous Categories I–IV, which were used to prioritize patients for treatment, have been abandoned and patients are now grouped according to the likelihood of their having drug resistance. As for treatment decisions smear-negative patients especially in people living with HIV due to their high mortality and MDR-TB patients, given their high mortality and the urgent need to prevent the spread of these deadly TB strains are equally as important as smear positive new patients.

This guideline emphasizes on the critical role of the identification of Mycobacterium tuberculosis and of rapid DST. Use of rapid DST methods will render the 8-month retreatment regimen of first-line drugs obsolete.
In Maldives till now, sputum for conventional DST was being sent to neighboring India for all previously treated patients and new patients who are sputum positive at end of intensive phase. The 8-month retreatment regimen is being used for the retreatment group on an interim basis until DST results are available which takes about 3 months.
Providing the 8-month retreatment regimen with first line drugs to patients with a high likelihood of MDR due to unavailability of DST is not acceptable, as this regimen is ineffective in treating MDR-TB and may result in amplification of drug resistance. Hence it is vital that these rapid DST techniques be introduced in line with comprehensive, laboratory capacity

strengthening. Establishing local availability of rapid DST is among the priorities of NTP at present.

The Process of making this guideline took into review of the existing protocols, guidelines and standard operating procedures being followed by the National TB Programme, formation of a technical committee to facilitate the development of the guideline followed by peer review of the draft guideline. The situation analysis also included interviews and discussions with service providers both public and private, meetings with stake holders and visits to laboratory, DOT centers and RMC and isolation facility at IGM Hospital.

The NTP will review and update these guidelines after 3- 5 years or as needed when new evidence, treatment regimens or diagnostic tests become available.

2. HEALTH SERVICE DELIVERY AND THE NATIONAL TB PROGRAMME

The public sector conforms to the largest share of the health system in Maldives which is supported by a number of private health care providers, mainly providing curative and diagnostic services and medicines and medical products.

The public system extends to all inhabited islands while the private services are concentrated in Male', mostly as clinics providing outpatient care. The ADK hospital is a 50 bedded, private tertiary hospital located in Male' providing a wide range of medical and surgical facilities with outpatient visits at ADK close to the levels seen at IGMH, the only tertiary public sector facility in Male'.

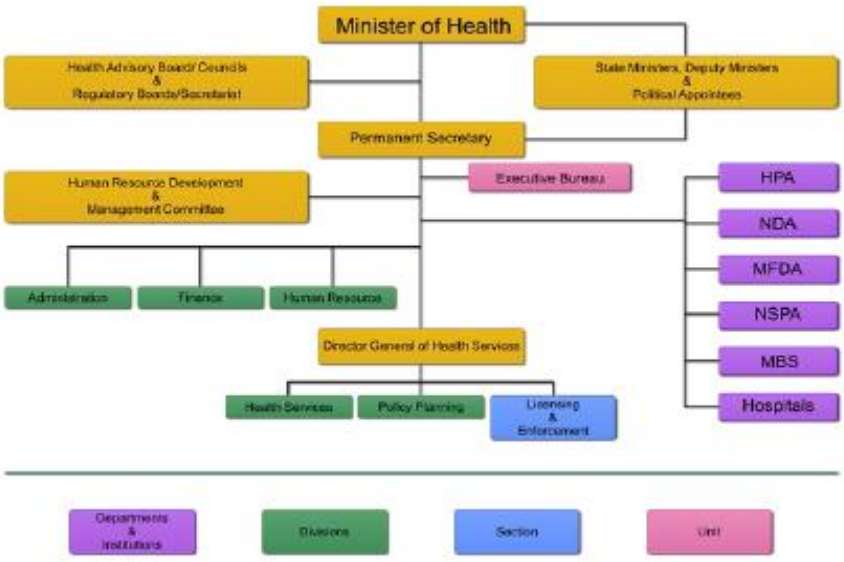
2.1 HEALTH SERVICE DELIVERY IN THE PUBLIC SECTOR

The Ministry of Health is responsible for the provision of health and health related services in the country and formulates the overall health policy, planning, monitoring and evaluation of health services.

There are six departments under the MOH, namely the Health Protection Agency, Maldives food and drug Authority, National Drug Agency, National Social Protection Agency, Maldives Blood Services and Hospitals.

The Health Protection Agency (HPA) under the Ministry of Health is responsible for delivering public health related programmes across the country through atoll and island level Public Health Units based in Atoll Hospital and Island Health Centres. HPA is responsible for the National tuberculosis control programme across the country.

Figure 1: organizational chart of Ministry of Health



Health service in the country is delivered by a four tier referral system comprising of island, atoll, regional and central level services.

The Indira Gandhi memorial Hospital in Male' is the tertiary referral hospital at the central level of the referral system. There are six regional hospitals in six strategic locations across the country. Each of the six regional hospitals serve as the referral centre for 2 to 4 atolls, providing services in a number of specialty areas of medical care. Atoll hospitals provide basic medical care, though some of these thirteen atoll hospitals do have provision for general specialist care. The lowest level of health service delivery in the system is the health care centres and health posts at the island level which account to 176 in number providing primary care.

The NTP under the Health protection Agency, at the central level is responsible for overall program coordination including planning, awareness, IEC and training. NTP is also responsible for DOTs implementation, registration, reporting, monitoring and evaluation of the programme

2.2 NATIONAL TUBERCULOSIS CONTROL PROGRAMME

Tuberculosis (TB) used to be a significant public health problem in Maldives, causing a considerable burden of disease. For this reason the national TB control programme (NTP) was created in 1962 though the proper functioning of the TB control programme started during the first half of 1976 in collaboration with the World Health Organization (WHO) and the Scout Association of Denmark. The activities of the NTP have been well integrated in to the general health care system and Continuous support has been received from WHO and from curative services both in public and private sector in TB care and control

Maldives has a population of about 345 000 and though dispersed over 200 islands, 38% of this population is concentrated in the capital. Maldives had an estimated prevalence and incidence rate of all forms of TB respectively of 57 and 40 per 100 000 population respectively in 2012. The notification rate of all forms TB and new smear positive cases were respectively 33 and 23, showing an increase compared to the steady decrease over the previous 5 years (Mainly smear negative and extra pulmonary cases). Treatment success rate among new smear positive cases is 79 % for the cohort of patients registered in 2011.

DOTS, the internationally recommended strategy for TB control was introduced in 1994 and nationwide coverage of DOTS was achieved by 1996.
NTP maintains the national register of TB patients which is updated monthly by input of reports from central, Regional and Atoll Health facilities. There has been a clear policy that all TB suspects reporting to the various health facilities will have three sputum samples examined and cases confirmed where smears are negative, by radiology and other tests as indicated clinically. Facilities for sputum Smear examination are available at the Central and Regional level and at some of the Atoll Hospital and Health centres. Laboratory capacity strengthening along with availability of rapid diagnostic tests for TB as well as establishing a functioning QA system are vital requirements for effective TB control.

Till now the practice has been to put all new patients including those that are sputum smear positive, smear negative as well as extra-pulmonary TB patients on a daily regimen of 2RHEZ/4RH which is also classified as Category I and treatment failures, relapse and defaulters treated with 2 months of 2SRHEZ/1RHEZ/5HRE which is also classified as Category II. Number of patients started on Cat II regimen (retreatment) is very low (3-5 per year). Culture and DST (conventional) is currently being done for all patients with treatment failure, at the start of Category 2 treatment and new patients who are sputum positive at the end of intensive phase. These treatment categories have been revised in this guideline in accordance with latest policy recommendations of WHO.

Entire treatment is given as DOT. All patients receive fixed drug dose combination through NTP and anti TB medicines are free of charge for residents as well as migrant workers.
Anti tuberculosis drugs are available only through the NTP, as the government in 2001 prohibited the sale of anti-TB drugs throughout the country, thereby ensuring that TB drugs are available only patients through NTP.
Patient kits using fixed drug formulations are being used that is currently purchased through a direct purchase mechanism from the Global Drug Facility.

A policy of contact tracing is actively pursued; lists of contacts at home and at work are made and advice given to undergo Mantoux examination. For symptomatic contacts and those asymptomatic with positive mantoux, further investigations with chest X-Ray and sputum examinations are done. Children under 5 years are provided treatment for latent infection with TB after screening for active disease.

Work has started on Intensification of case finding through regular targeted screening of populations potentially at higher risk of developing TB such as those in accommodation setups for labourers, construction workers and reprimand facilities.

2.3 TB BURDEN AND PERFORMANCE OF THE NTP

Maldives is one of only 5 countries in the world to have achieved the global targets of 70% case detection and 85% cure. This information is referred from WHO referral letter no. T/26 dated on 27th April 1998.

At present priority has been given to improve and strengthen the TB control preventive activities and to cure as many patients as possible and to give better services to the community. In this regard efforts have been made to improve the quality of services in terms of case holding and case management.

Work has been initiated to establish and strengthen diagnostic facilities and as a result of the intensified activities, the program has maintained the prevalence of TB in the same trend for past 7 years.

Between 2007 and 2011, the number of notified TB cases (new cases and relapses) is steadily decreasing from reported 121 to 86. Since 2006, worsening in treatment outcomes is observed: treatment success rate which was above 85% until 2006 is 80-81 percent for the last 5 years. Death rate, 9 percent was highest ever reported in 2010 and default of 13 percent in 2009. Paediatric TB notification is around 6% of all cases notified and it can be assumed that many paediatric TB cases are under diagnosed or/and not reported to NTP.

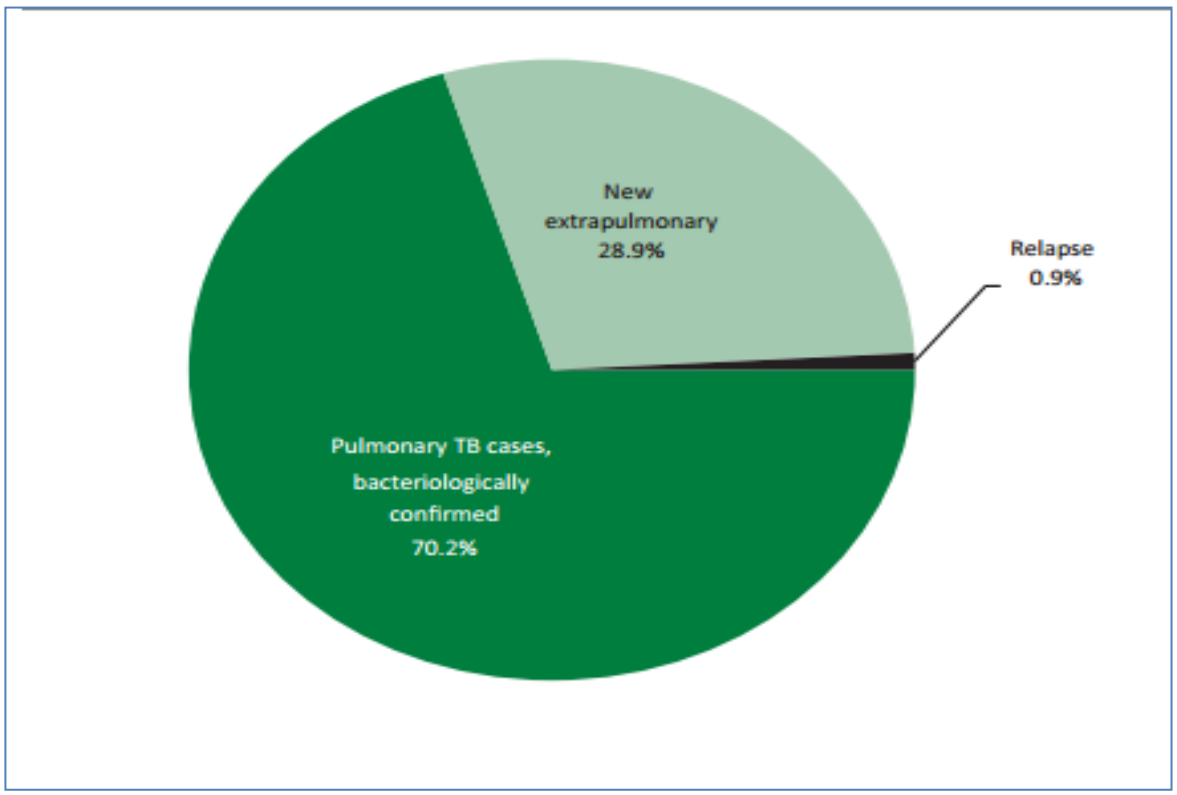
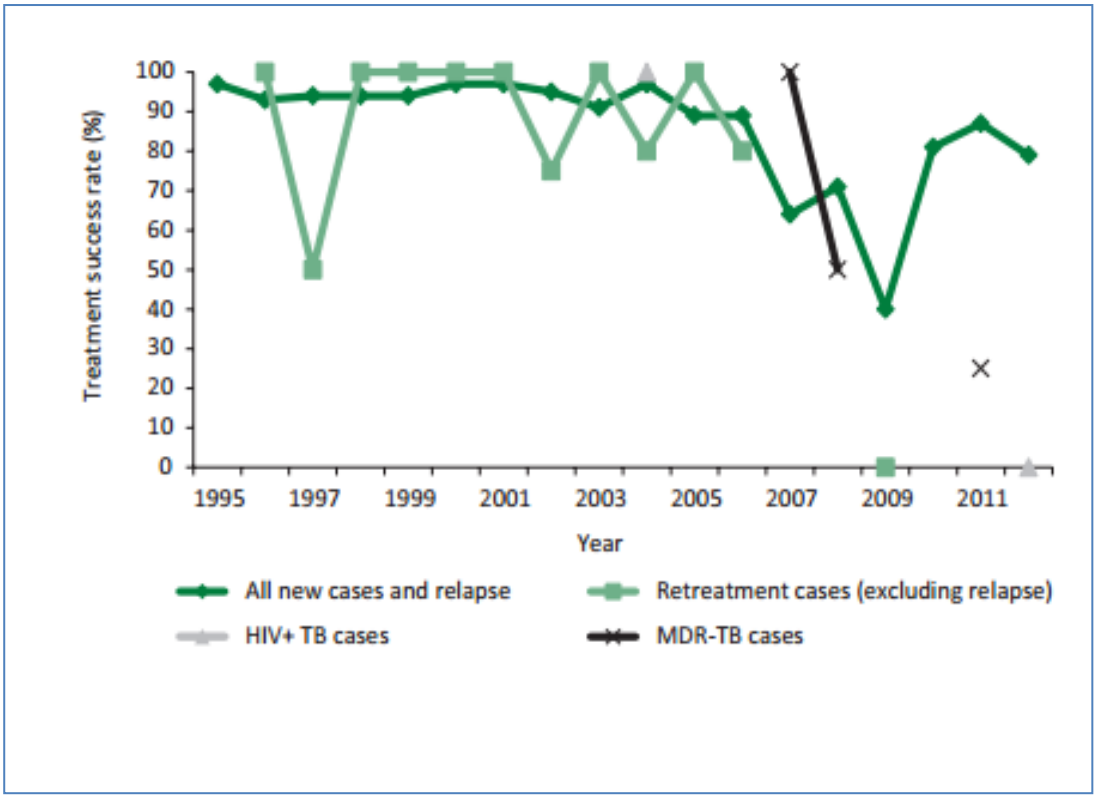


Fig : SEAR TB annual report 2015



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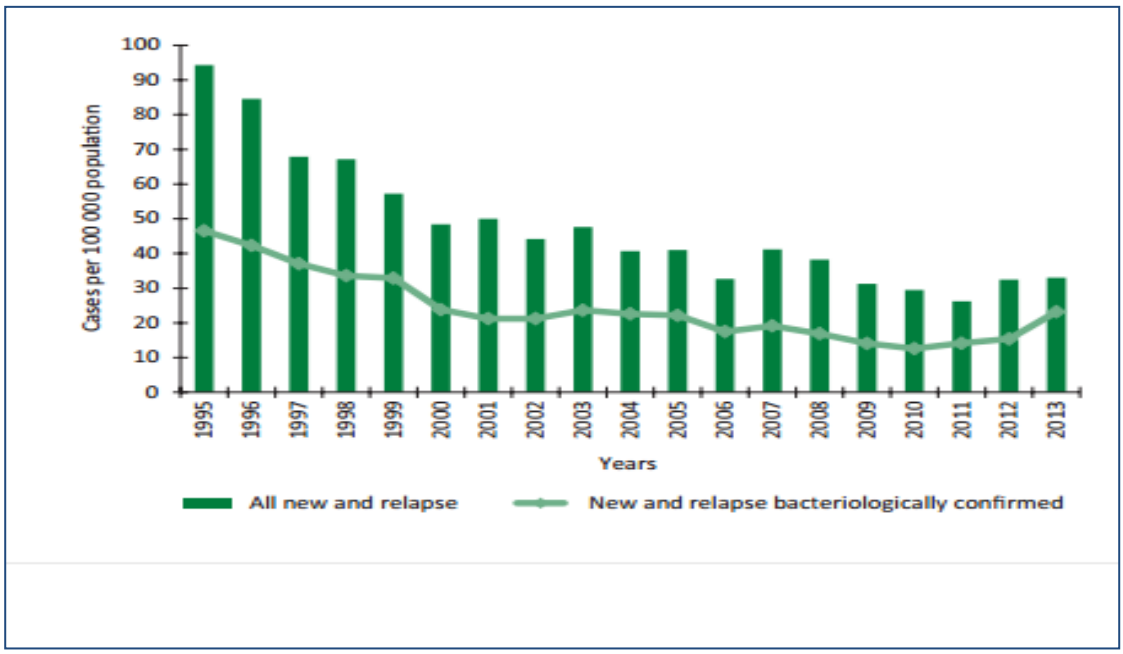

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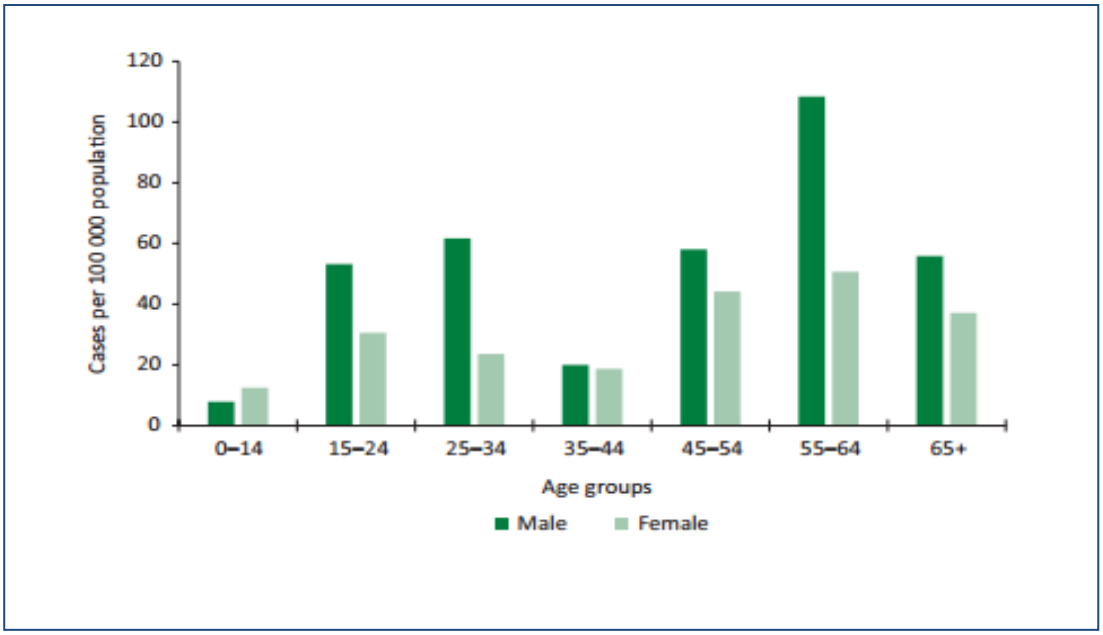

Fig : SEAR TB annual report 2015

Migrants from neighbouring countries with high TB prevalence and TB among substance users and in incarcerated settings are challenges being faced by NTP at present. Work has started in regard to increasing awareness among the migrant population and discussions are ongoing to strengthen the system for screening of migrants for TB during the medical clearance for work visa and also establish screening at penitentiary institutions

Furthermore, the stigma associated with TB in the Maldives remains high. Some people are very scared about receiving a diagnosis of TB, and especially about having other members of the community know the diagnosis. As a result, many cases present in advanced stages of the disease, and some of these patients also travel to neighbouring countries to obtain TB treatment. Such treatments may consist of inadequate drug combinations, given for insufficient time periods, thereby increasing the risk for the development of MDR TB.

In addition to all this, inadequate financial and human resources also contribute a major challenge to the TB control programme.

MDR TB: Very few MDR-TB cases have been identified. So far 7 cases of MDR-TB have been registered since 1995 to 2012. However there is a risk that this trend may change as the country employs a large expatriate workforce from neighbouring countries with high MDR TB prevalence

TB/HIV co infection: Though Maldives remains among the low prevalent countries for HIV in the region, risk factors that might contribute to spread HIV are high and are increasing at an

alarming rate. So far only 19 HIV positives have been detected among locals out of whom 7 are alive and 6 of them are on ART treatment. HIV positives among TB patient also remain low and two TB / HIV cases have been recorded so far.
Screening of all HIV positives for TB infection and TB patient for HIV infection started as a collaborative effort of both the program since 2007.

2.4 NTP STRUCTURE AND FUNCTIONS

Vision of NTP: Elimination of TB for a TB free Maldives
Goal: The goal of NTP is in line with WHO's global TB strategy and as per the National Strategic Plan 2014-2019, the goal is to decrease the prevalence of TB by 25% by 2019

Objectives:

- Ensure availability of quality assured TB services, in line with current international standards and provided by qualified personnel, at 100% of all MOH facilities by 2016

- Detect 80% of incident cases (based on a recalculation of incident cases to be performed in 2014) by 2016, and 90% by 2018; successfully treat 85% of detected cases by 2016 and 90% by 2018

- Provide diagnostic services for MDR-TB for 50% of MDR-TB-suspects by 2016, and 100% of suspects by 2018; successfully treat 70% of detected MDR-TB cases by 2018

- Provide effective ACSM activities to ensure that 50% of the population has adequate knowledge about TB and a positive attitude towards NTP services by 2016, and 100% of the population by 2018

CENTRAL LEVEL

1. National TB control Program

Functions:

- Over all program coordination and planning
- Develop guidelines, SOPs and Training
- Coordinating IEC preparation and awareness programmes
- Ensuring availability of drugs and monitoring rational usage of second-line drugs
- Facilitate referral of patients with MDR and XDR-TB, severe ADRs, and complicated disease to RMC
- Providing technical assistance and capacity building to health facilities
- Ensure mechanism of transport of sputum for culiure and Xpert/MTBRif to IGMH Laboratory
- Country wide implementation of DOTS Strategy
- Ensuring an efficient Reporting and recording mechanism
- Mass contact screening and arranging follow up
- Monitoring and evaluation
- Strengthen collaboration with HIV programme

- Collaboration with private sector and NGOs
- Promote, coordinate and support operational research

2. IGM Hospital (tertiary referral hospital)

a) Respiratory Medicine Clinic (RMC)

- Provide technical assistance to NTP'
- Implement TB programme policies and procedures
- Ensure adequate supplies of diagnostics and drugs at all times
- Collection of sputum samples and follow up of patients who self report and referrals from islands, atoll and regional level
- Early case detection and Treatment
- Admission, workup and Initiation of treatment for MDR TB and XDR TB
- Patient education and counselling
- Establishing and maintaining functional DOTS PLUS Committee
- Ensure continuity of care for all TB clients until treatment completion
- Providing DOTS to Patients in Male.
- Family screening
- Manage drug resistant TB
- Maintain updated patient records and TB registers
- Submit monthly reports on case finding, enrolment in treatment, drug stock etc to NTP

b)IGMH Laboratory

- Diagnostic testing – Mantoux, Smear microscopy, X pertMTB/Rif and Sputum Culture.
- External Quality assurance for peripheral labs
- Maintaining sputum register

REGIONAL LEVEL

Regional hospital& Public health Unit

- Diagnosis by Mantoux and smear microscopy
- Patient education and counselling
- Early case-detection and treatment
- Treatment under DOTS and follow up
- Drug Distribution
- To maintain an adequate supply of drugs and laboratory supplies
- Quality assurance for Atoll Hospital laboratories and microscopy centres
- Family screening
- Establish proper referral systems for tertiary care
- Maintain regional level registers for patients and contacts
- Prepare monthly reports on case detection, drug stock etc send to NTP

ATOLL LEVEL

a) Atoll hospital & PHU

- Diagnosis by Mantoux and smear microscopy
- Early case-detection and treatment
- Treatment under DOTS and follow up
- Motivation and counseling
- Establish proper referral systems for tertiary care
- Drug Distribution
- Family screening
- Maintain atoll level registers patients and contacts
- Awareness programs
- HIV counseling and testing for contacts
- Conduct household assessments prior to receiving patients discharged from RMC
- Ensure on-going psychosocial support for patients

b) Atoll councils

- Awareness for reduction of Stigma and discrimination among the community

ISLAND LEVEL

a) Health centers

- Referring TB suspects and contacts to Regional, Atoll or central level for diagnosis and initiating treatment.
- Continue treatment under DOTS and follow up
- Counseling and motivation to patient and family
- Contact tracing
- Tracing treatment interrupters
- Monitoring treatment side effects
- Ensuring referral of patients with severe ADRs, and complicated disease to the RMC
- Ensure communication with clinician at RMC prior to transfer of patients
- Ensure effective infection control measures in place for transfer of patient
- Ensure effective infection control measures in the health facility
- Maintain Island level TB registers for patients and contact registers
- Monthly Recording and reporting to the NTP

b)Island councils

- Awareness for reduction of Stigma and discrimination among the community

3. TUBERCULOSIS

Tuberculosis is caused by Mycobacterium tuberculosis and is transmitted between humans through the airborne route.

The diagnosis of TB refers to the recognition by clinician of an active case, i.e. a patient with current disease due to M. Tuberculosis but the role of the National TB control programme is more extensive as they are responsible for ensuring that diagnosed cases are notified , meet the case definition and are treated appropriately and that outcomes are evaluated.

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3.1 TRANSMISSION

- Tuberculosis is usually spread from person to person through the air by droplet nuclei that are produced when a person with pulmonary or laryngeal tuberculosis coughs, sneezes or sings.
- The likelihood of transmission of M. Tuberculosis depends on the number of organisms expelled into the air, the concentration of organisms in the air, determined by the volume of the space and its ventilation and the length of time an exposed person breathes the contaminated air
- One cough can produce 3,000 droplet nuclei and a sneeze up to a million droplets. Micro-droplets, which are small particles of 1 to 5 µm in diameter containing 1-5 bacilli, are highly infectious and may remain suspended in the air for several hours. Infection occurs if the inhaled bacilli in these droplet nuclei enter and settle in the lungs of a healthy person and begin to multiply.
- Droplet nuclei may also be produced by aerosol-producing investigations such as sputum induction, bronchoscopy and through manipulation of lesions or processing of tissue or secretions in the laboratory
- The degree of exposure is extensive for those who are in close and prolonged contact with an infectious case (i.e. persons who are living in the same household with infectious TB cases). The chance of becoming infected from a single contact is comparatively small. An untreated smear positive PTB case may infect up to ten people per year on average.
- Patients with smear positive pulmonary TB are the most infectious particularly those with lung cavities. Smear negative pulmonary TB cases are much less infectious. Smear positive cases are those in whom TB bacilli are identified on sputum microscopy whereas smear negative cases are those in whom TB bacilli cannot be identified on sputum microscopy
- Extra pulmonary cases are almost never infectious, unless they have pulmonary tuberculosis as well. Individuals with latent tuberculosis infection are not infectious, as they do not have replicating bacteria and cannot transmit the organism.
- Once infected, the progression to active disease is dependent on the immune status of the individual. In those with normal immunity, 90% will not progress and only 10% will

develop active disease (half of these now and half later on in life). The risk is highest in the first two years after infection, when half the cases will occur. Those most at risk include children <5 years of age and the elderly.

3.2 DIAGNOSIS

XpertMTB/Rif will be used as the initial diagnostic test for all TB suspects

Concomitant smear microscopy will be undertaken as this efficiently identifies cases that are most infectious

Sample for Conventional Culture and DST to be send at the start of treatment so that results of resistance to drugs other than rifampicin if present will be available earlier

For EPTB, Xpert MTB/RIF assay can be used directly on CSF specimens and homogenized extra pulmonary specimens

In TB Pleural effusion, pleural biopsy is the preferred specimen. Pleural fluid is a suboptimal specimen for the bacterial confirmation of pleural TB using any method

Individuals suspected of having EPTB with a single negative result from Xpert MTB/Rif and also HIV infected patients with ongoing symptoms should undergo further diagnostic testing

Detecting TB rapidly and identifying drug resistance early are very essential for TB care and to reduce TB transmission in the community. Diagnosis and optimal management of TB requires both mycobacteriology and clinical laboratory services

In order to ensure quality and reliability of laboratory results, it is necessary for laboratories to implement a quality management system to ensure that all aspects of laboratory diagnostic services are performed properly and allow for the detection of any laboratory errors.These systems must include standard operating procedures and both internal quality control and external quality assessment protocols, which are necessary to ensure accurate detection of TB and drug resistance for subsequent treatment decisions and avoid false diagnoses.

All persons with symptoms or signs suggestive of TB should undergo investigations to establish the diagnosis of TB. and should be investigated for bacteriological confirmation of TB using XpertMTB/Rif, sputum microscopy or culture

Symptoms of pulmonary TB:

- Persistent cough for more than 2 weeks accompanied by systemic symptoms
- Haemoptysis
- Fever for more than 2 weeks
- Drenching night sweats
- Loss of appetite
- Unexplained weight loss (more than 5 kg in a month)
- A general feeling of illness (malaise) and tiredness
- Shortness of breath, chest pain

Symptoms of extra-pulmonary tuberculosis depend on the organ involved. Chest pain from tuberculosis pleurisy, enlarged lymph nodes in the neck and armpit and sharp angular deformity of the spine are frequent signs of extra-pulmonary tuberculosis

A history of contact with a person with PTB increases the likelihood for the diagnosis of TB

Available tests for bacteriological confirmation of TB

Test	Strength	Weakness
microscopy	High specificity Short Turn Around time	Low sensitivity with low bacillary load(children/PLWHA)
culture	High sensitivity	Long Turn Around time High contamination rates(liquid culture)
Line Probe Assay	Short Turn Around time Detects Rif and INH resistance	Reduced sensitivity in smear negative
Xpert MTB/RIF	Very Short Turn Around time Detects Rif resistance High sensitivity for Rif resistance	Does not detect INH resistance Reduced sensitivity in smear negative

XPERT MTB/RIF

The assay has similar sensitivity, specificity and accuracy as culture on solid media and results are available within 2 hours to guide the choice of regimen for the patient. Detects mutations in the rpoB region of M. tuberculosis DNA, which are responsible for >95% of rifampicin resistant strains, hence serves as a reliable (though not complete) proxy for MDR-TB

XpertMTB/Rif has a very high specificity for detection of rifampicin resistance but when used in a population with a low prevalence of the condition can result in a lower positive predictive value (number of false-positive results are present)

For EPTB, XpertMTB/RIF not applicable to specimens of blood, urine, and stool as the validity of these not established with XpertMTB/RIF

ADVANTAGES OF THE XPERTMTB/RIF:

- It detects MTB and Rifampicin resistance from one specimen at the same time.
- Processing time for the test itself is approx. 2 hours.
- It is specific for MTB complex; (it can differentiate MTB from other mycobacteria).
- It can also be used on the following processed samples - CSF, aspirates (gastric, lymph node) and tissue (i.e. pleural biospy)
- Xpert MTB/RIF is a more sensitive test than smear microscopy, therefore it is possible for a TB patient to be Xpert MTB positive but smear negative.
- The test for each specimen is carried out in a closed system (cartridge), so there is a reduced risk of cross-contamination and human error

THE LIMITATIONS OF XPERT MTB/RIF:

- It cannot be used for monitoring treatment and its use is limited to diagnosis
- A small proportion of Rifampicin resistance detected may not correlate with physiological resistance (leading to discordance between Xpert and DST results)
- The test might be unsuccessful due to laboratory test errors, test failure or invalid results. In these instances a second specimen must be collected for a repeat Xpert test.

INTERPRETING RESULTS FROM XPERT MTB/RIF

An Xpert MTB/RIF result can indicate that

- MTB was not detected
- MTB was detected and was not resistant to rifampicin (rifampicin susceptible)
- MTB was detected and it was resistant to rifampicin.
- A small proportion of tests may result in an error or invalid result; these tests need to be repeated.

WHEN XPERT MTB/RIF DOES NOT DETECT MTB:

- The disease can be ruled out in most cases unless there is still a strong suspicion of TB (special attention is required in people living with HIV who have signs and symptoms of

TB) that may warrant further investigation (such as a chest X-ray, culture, another Xpert MTB/RIF test, or a trial of antibiotics)

- The ability of any diagnostic test to detect TB depends on the quality of the specimen collected

WHEN XPERT MTB/RIF DETECTS MTB WITHOUT RIFAMPICIN RESISTANCE:-

- Patient should be started on first line regimen and registered as a case with susceptible bacteriologically confirmed TB.

WHEN XPERT MTB/RIF DETECTS MTB WITH RIFAMPICIN RESISTANCE:-

In Patients considered being at high risk of MDR-TB:

- A regimen for MDR-TB with the addition of isoniazid should be initiated and the patient should be registered as having bacteriologically confirmed rifampicin resistant TB (RR-TB)

- Another sputum sample should be taken immediately to be sent for phenotypic DST for at least isoniazid, fluoroquinolones and second-line injectables and when the DST results are available, treatment can be modified if necessary and the patient's registration can be updated accordingly.

- Treatment modifications may include stopping isoniazid if resistance has been found, changing the quinolone and/or second-line injectable, or, in the case of XDRTB, placing the patient on an appropriately designed regimen that includes group 5 drugs.

In patients considered to be at low risk of MDR-TB:

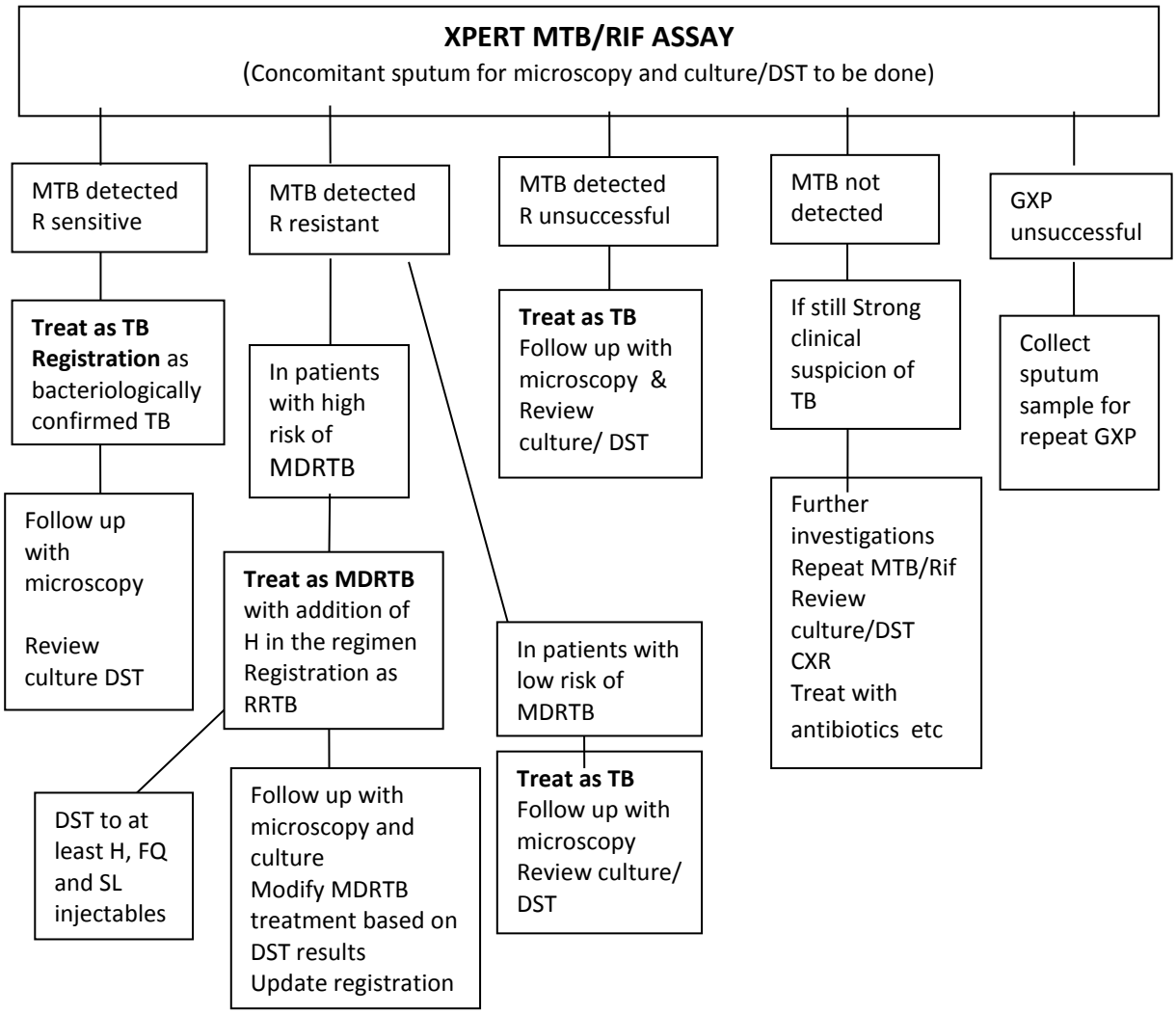
- Rifampicin resistance may be unexpected and clinicians may be hesitant to enroll patients on a treatment regimen requiring second-line drugs (mostly because of the treatment length and concerns about toxicity)

- An unexpected Xpert MTB/ RIF result may be attributed to the PPV for rifampicin resistance due to low underlying prevalence, or may also result from nonsystematic or random errors at the pre analytical or post analytical stages of testing (clerical errors made when information about specimens or test results is recorded, or administrative errors that result in specimens being mixed up, etc)

- Recommended regimen for TB with first line drugs should be started and the patient should be registered as having bacteriologically susceptible TB

- Additional specimen should be taken for phenotypic DST to reconfirm resistance to rifampicin and also to test for susceptibility to isoniazid, fluoroquinolones and second line injectables. When DST results are available, the treatment regimen and patient registration should be adjusted as appropriate

3.3 ALGORITHM USING XPERTMTB/RIF FOR DIAGNOSIS OF TB AND RIFAMPICIN RESISTANCE



3.4 SPUTUM COLLECTION

> All patients suspected of having pulmonary TB should submit at least two sputum specimens of which if possible, at least one should be an early morning specimen

- All patients suspected of having pulmonary TB should submit at least two sputum specimens for microscopic examination and when possible, at least one early morning specimen should be obtained, as sputum collected at this time has the highest yield.

- Sputum collection should occur at the designated sputum collection areas within the hospital premises and should not be collected in waiting rooms, toilets and laboratories

- DOT provider should ensure the correct labeling of the sputum containers before handing it over to the patient for sputum collection

- Containers for sputum collection should have a wide mouth, be sterile, clear and leak proof
- The DOT provider should supervise the collection and guide the patient regarding collection of the sputum sample. Patient should be advised to:
    - Rinse out the mouth with water
    - To be careful and direct the sputum into the container so as not to contaminate the outside of the container.
    - Take a deep cough from the bottom of the chest, beginning with deep breathing
    - Replace the lid on the container immediately after collection of sample and close the lid securely
    - Wash hands after handling the sputum specimen

- The laboratory form to be send along with sputum sample should be filled by the DOT provider and it should include the name, age, hospital number, diagnosis of the patient and the appearance of the sputum (eg: mucoid, green, etc).

  Sputum samples should be sent as soon as possible to the laboratory after collection and if there is a delay it should be stored in a refrigerator

- If patient has difficulty producing sputum. Sputum production may be induced by inhalation of a warm aerosol of sterile 5-10% sodium chloride via a nebulizer. Such samples are watery in consistency and can be mistaken for saliva, so on the request form it should be marked as induced sputum

Methods of obtaining a sputum sample

Method	description	advantages	Limitations
Sputum sample	Patient coughs up sputum into sterile container	Easy to perform	Patient may not be able to cough up sputum Education and supervision of the patient required
Nebulisation/ Sputum induction	Patient inhales a saline mist which causes them to cough	Used to obtain sputum in patients with non productive cough Easy to perform	Specimen may be watery and confused with saliva Requires special equipment May cause bronchospasm
Gastric washing/ aspirate	A tube is inserted into the stomach through the patients mouth or nose to obtain swallowed sputum	Used to obtain sputum in children who do not cough up sputum	Must be done early morning before eating Patient may need to be hospitalised It is an uncomfortable procedure for the patient
Bronchoscopy		Used to obtain sputum when the patient cannot cough and gastric aspirate cannot be done	Invasive procedure Requires special equipment Must be done in a hospital by a specialist Requires anaesthesia

SPUTUM SMEAR MICROSCOPY

When a TB suspect reports to the laboratory the first time, a sputum specimen is collected on the spot. This specimen is called a spot specimen. The patient is then given a marked empty sputum container to collect a specimen early next morning and bring it to the laboratory. This specimen is called an early morning specimen.
The early morning specimen brought by the patient is received and checked if needed a further spot specimen can be collected

Smear microscopy is a low cost, frontline tool for TB but not for diagnosis of drug resistant TB. Microscopy cannot distinguish viable from non viable organisms nor differentiate between drug susceptible and drug resistant M. tuberculosis bacteria, or between different species of mycobacteria

The main purposes of microscopy for drug-resistant TB:

- assess initial bacterial load (infectiousness)
- triage to different diagnostic algorithms ie sputum positive TB
- monitor response to therapy

The LED fluorescence microscopy is recommended for use by WHO as it has increased test sensitivity and reduced turnaround time required allowing the screening of a larger number of slides

Smear-positive cases are the most infectious and most likely to transmit their disease in their surroundings; they are the focus for infection control measures and contact investigations
Bacteriological monitoring of treatment progress is most feasible and practicable in these patients

Sputum Smear preparation, Staining and Reading
All specimens should be examined as a rule, by the Ziehl–Neelsen method.

ZIEHL-NEELSEN STAINING PROCEDURE

1. A new unscratched slide is selected and the slide is labelled with the Laboratory Serial Number
2. A smear is made from yellow purulent portion of the sputum using a broom stick. A good smear is spread evenly, 2 cms x 3 cms in size and is neither too thick nor too thin. Smear preparation should be done near a flame. This is required, as six inches around the flame is considered as a sterile zone which coagulates the aerosol raised during the smear preparation.
3. The slide is allowed to air dry for 15–30 minutes.
4. The slide is fixed by passing it over a flame 3–5 times for 3–4 seconds each time.
5. 1% filtered carbol fuchsin is poured to cover the entire slide.
6. The slide is gently heated with carbol fuchsin on it, until vapours rise. Do not boil.
7. Carbol fuchsin is left on the slide for 5 minutes.
8. The slide is gently rinsed with tap water until all free carbol fuchsin stain is washed away. At this point, the smear on the slide looks red in colour.
9. 25% sulphuric acid is poured onto the slide and allowed to stand for 2–4 minutes.
10. The slide is gently rinsed with tap water and tilted to drain off the water.
11. A properly decolourised slide appears light pink in color .If the slide is still red, sulphuric acid is reapplied for 1–3 minutes and then rinsed gently with tap water. The back of the slide is wiped clean with a swab dipped in sulphuric acid,
12. 0.1% methylene blue is poured onto the slide and left for 30 seconds. Then the slide is rinsed gently with tap water and allowed to dry.
13. The slide is examined under the binocular microscope using x40 lens to select the suitable area and then examined under x100 lens using a drop of immersion oil.
14. The results are recorded in the Laboratory Form and the Laboratory Register.
15. The slides are inverted on a tissue paper till the immersion oil is completely absorbed. Xylene is not to be used for cleaning the slides, as it may give false results at repeat examination after storage.

The number of bacilli (AFB) seen in a smear reflects the client's infectivity. The laboratory records the number of bacilli seen on each smear as follows

Reporting of sputum smear results

Number of bacilli seen on smear		Results
No AFB	Per 100 oil immersion field	0
1-9 AFB	Per 100 oil immersion field	Scanty
10-99 AFB	Per 100 oil immersion field	1+
1-10 AFB	Per 1 oil immersion field (min 50 fields)	2++
>10 AFB	Per 1 oil immersion field (min 20 fields)	3+++

It should be kept in mind that the results of laboratory reports are subject to various sources of error including poor quality of specimens, clerical errors, handling errors, process errors and poor quality control.

Follow up Smear examination

During follow up of treatment, two sputum samples are to be tested each time.
For smear positive TB patients: 2 sputum samples (Morning - Spot) have to be tested each time on three occasions:

At the end of the intensive phase
Two months into the continuation phase (at the end of 4 months for new cases
At the end of treatment

For smear negative patients, two sputum samples have to be tested on two occasions – at the end of IP and at the end of treatment

CULTURE AND DST

Culture and DST plays an important role to identify and treat patients with drug resistant TB. NTP should develop the capacity to provide access to DST for any patient for whom resistance is considered likely.

For culture and DST, sputum samples are at present send abroad through the NTP to India. The samples are collected at Respiratory Medicine clinic at IGMH and send to IGMH laboratory where the sample undergoes triple packing for transport to India as per the international protocol for transfer of biological materials.

Traditional culture uses a solid medium such as coagulated egg (e.g. Lowenstein-Jensen) or agar as a base. Solid media are simple and cost effective to use. Disadvantages include slow bacterial growth (3-4 weeks) and errors due to manual reading of results. The development of more sensitive liquid medium culture techniques, has allowed for the more rapid detection of TB bacilli, within 7 to 14 days. Automated systems are used to culture mycobacteria in liquid

media. These systems use specialised vials/ tubes which are inoculated with the patients specimens. Liquid culture is more prone to contamination than solid culture

Culture in liquid media is the current reference method for bacteriological confirmation of TB. In general, the recovery of tubercle bacilli is higher and the time to detection is shorter with liquid culture than with solid culture methods. However, liquid culture media being a more sensitive culture system has higher contamination rates than solid media.

Culture is also required to monitor MDRTB treatment, for cases diagnosed as Rifampicin resistant on Gene Xpert, for DST of other drugs and for DST in XDRTB

Good quality specimen, prompt transport to the laboratory and quality of laboratory processing, as well as good quality culture media and incubation conditions are essential to optimize the yield of culture
Laboratory errors, such as mislabeling or cross contamination between specimens may lead to false-negative or false-positive results. Therefore, laboratory findings should be always correlated with the patient's clinical condition and any diagnostic test should be repeated if necessary

DST plays an important role to identify and treat patients with drug resistant TB. The reliability of DST (performed under optimal circumstances) varies with the drug tested

First line DST:
- most reliable for rifampicin and isoniazid
- less reliable and reproducible for streptomycin, ethambutol and pyrazinamide.

Second line DST:
- good reliability and reproducibility for second line injectable drugs (amikacin, kanamycin, capreomycin) and fluoroquinolones
- Data on the reproducibility and reliability of DST for the other second-line drugs are limited, and for several of them methods have not been established or standardized

For rifampicin resistance there is not complete concordance between phenotypic and genotypic detection methods. Emerging evidence suggests that DNA sequencing of the rpoB gene (the gold standard method for genotypic DST) may be a better although not perfect reference method than the phenotypic DST.

Line Probe Assays
These tests have been approved for direct testing on smear positive specimens and on isolates from solid and liquid culture. This is not available within the country at present and samples are send to a established laboratory in India through IGMH laboratory for phenotypic DST. PCR based hybridisation assay by LPA simultaneously detects MTB complex and specific mutations in the rpoB gene conferring rifampicin resistance and mutations on the katG gene which is associated with higher levels of isoniazid resistance and inhA gene mutations which is associated with lower levels of isoniazid resistance. Some studies have shown an association

between the inhA mutation and ethionamide resistance. These associations can be used as a guide whilst awaiting phenotypic confirmation.

Compared to phenotypic DST this provides rapid diagnosis of drug resistant TB and results should be available within 7days in health facilities for smear positive TB. For smear negative TB, this depends on the time to positive culture before the LPA can be performed.

Advantages of the test are:

- It detects MTB and resistance to RIF & INH at the same time from one specimen
- It reduces time to diagnosis of MDR-TB to 7 days
- It is specific for MTB complex; it can differentiate MTB from other mycobacteria

The limitations of the test are:

- It cannot be used for monitoring patients on treatment because it does not distinguish between live and dead bacilli; therefore its use is limited to diagnosis
- It is dependent on smear results, can only be performed on smear positive or culture positive sputum specimen
- The test is labour intensive and is prone to contamination and human error
- It requires a lot of space - at least 3 separate rooms for the different steps

CHEST X-RAY

- The primary method of TB diagnosis is bacterial confirmation by Xpert/MTBRif, smear microscopy and culture. Chest X-Rays assist in the diagnosis of TB as well as diagnosis of suspected complications of TB such as pneumothorax. It also aids in monitoring during treatment or at the end of treatment where response to treatment is not adequate.

- Chest X-Ray must be interpreted in the light of patient's history and clinical findings

- Reliance on chest X-Ray as the only diagnostic test results both in over diagnosis and missed diagnosis of TB. Many diseases mimic TB on chest x-rays and this may lead to an incorrect diagnosis. Chest X-rays may also show lung fibrosis or destruction due to old TB, leading to over diagnosing pulmonary TB.

TUBERCULIN SKIN TEST

The test shows hypersensitivity to proteins of the TB bacillus, as a result either of infection with M. tuberculosis or induced by BCG vaccination. Infection is one of the criteria used in the diagnosis of TB in children.

A positive TST does not indicate TB disease, only infection. A negative result does not rule out the diagnosis of TB disease as various conditions, including HIV, may suppress the reaction.

Interferon gamma Release Assays (IGRA)

IGRAs are blood tests that detect MTB infection but cannot distinguish latent TB from active TB. They are not affected by previous BCG vaccination unlike TST.

Other Investigations in the Diagnosis and Assessment of EPTB			
Site	**Imaging**	**Biopsy**	**Culture**
Lymph node		Node	Node or aspirate
Bone/Joint	Plain X-ray and computed tomography Magnetic resonance imaging	Site of disease	Biopsy or paraspinal abscess Site or joint fluid
Gastrointestinal	Ultrasound CT abdomen	Omentum Bowel	Biopsy Ascites
Genitourinary	Intravenous urography Ultrasound	Site of disease	Early morning urine Site of disease Endometrial curettings
Disseminated	High resolution CT thorax Ultrasound abdomen	Lung Liver Bone marrow	Bronchial wash Liver Bone marrow Blood
Central nervous system	CT brain MRI	Tuberculoma	Cerebrospinal fluid
Skin		Site of disease	Site of disease
Pericardium	Echocardiogram	Pericardium	Pericardial fluid
Cold/liver abscess	Ultrasound	Site of disease	Site of disease

4. CASE DEFINITIONS AND REGISTRATION

Uniform criteria are required to define a TB case for proper patient registration and case notification. In addition it is also needed for:

- selecting appropriate standard treatment regimens
- standardizing the process of data collection for TB control
- evaluating the proportion of cases according to site, bacteriology and treatment history
- cohort analysis of treatment outcomes
- accurate monitoring of trends and evaluation of the effectiveness of TB programmes within and across districts, countries and global regions

4.1 CASE DEFINITIONS FOR TB (Based on the level of certainty of the diagnosis and availability of laboratory confirmation)

- **Presumptive TB**: Any person who presents with symptoms or signs suggestive of TB

  The most common symptom of pulmonary TB is a productive cough for more than 2 weeks which may be accompanied by other respiratory symptoms (shortness of breath, chest pain, haemoptysis) and/or constitutional symptoms (loss of appetite, weight loss, fever, night sweats, fatigue)

- **Clinically diagnosed TB:** A case of TB that does not fulfill criteria for bacteriological confirmation but one in which a health care worker has diagnosed TB and has decided to treat the patient with a full course of TB treatment.

  Any person given treatment for TB should be recorded as a case. Incomplete "trial" TB treatment should not be given as a method for diagnosis.

- **Bacteriologically confirmed TB:** A patient with Mycobacterium tuberculosis complex identified from a clinical specimen, either by smear /culture or by a newer method such as molecular line probe assay

4.2 CLASSIFICATION OF TB

Bacteriologically confirmed or clinically diagnosed cases of TB are also classified according to the:

a. anatomical site of disease
b. bacteriological results
c. history of previous treatment
d. HIV status of the patient
e. Drug susceptibility testing

a) ANATOMICAL SITE:

Pulmonary tuberculosis: A case of TB (defined above) involving the lung parenchyma**.**

- Miliary tuberculosis is classified as PTB because there are lesions in the lungs.
- Tuberculous intrathoracic lymphadenopathy (mediastinal and/or hilar) or TB pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of extra pulmonary TB
- A patient with both pulmonary and extra pulmonary TB should be classified as a case of pulmonary TB

Extra pulmonary tuberculosis: A case of TB (defined above) involving organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones and meninges

- Diagnosis should be based on at least one specimen with confirmed M*.* tuberculosis or histological or strong clinical evidence consistent with active EPTB, followed by a decision by a clinician to treat with a full course of tuberculosis chemotherapy.
- The case definition of an EPTB case with several sites affected depends on the site representing the most severe form of disease.
- Unless a case of EPTB is confirmed by culture as caused by *M. tuberculosis*, it cannot meet the "definite case" definition

b) BACTERIOLOGICAL RESULTS

Bacteriology refers to the smear status of pulmonary cases and the identification of *M.* tuberculosis for any case by culture or newer methods. The definition of a new sputum smear positive pulmonary TB case is based on the presence of at least one acid fast bacillus (AFB+) in at least one sputum sample

Smear positive: A case of pulmonary TB with one or more sputum smear specimens positive for AFB at the start of treatment

Smear negative PTB cases should either:

A. Have sputum that is smear-negative but culture-positive for M. tuberculosis (A case of pulmonary TB is considered to be smear-negative if at least two sputum specimens at the start of treatment are negative for AFB)

OR

B. Meet the following diagnostic criteria:

- Decision by a clinician to treat with a full course of anti-TB therapy and
- radiographic abnormalities consistent with active pulmonary TB and either
- Laboratory or strong clinical evidence of HIV infection or If HIV negative or unknown HIV status, no improvement in response to a course of broad-spectrum antibiotics (excluding anti-TB drugs and fluoroquinolones and aminoglycosides)

Pulmonary TB cases without smear results will not be classified as smear-negative; instead, they will be recorded as "smear not done" on the TB register.

For patients suspected of having EPTB, specimens should be obtained from the suspected sites of involvement, where available, culture and histopathological examination should also be carried out.

c) HISTORY OF PREVIOUS TREATMENT

Patients are also classified according to history of previous treatment ie whether the patient has received TB treatment in the past and if so the outcome of that treatment

New patients: Patients who have never had treatment for TB, or have taken anti-TB drugs for less than 1 month. New patients may have positive or negative bacteriology and may have disease at any anatomical site.

Previously treated patients: Patients who have received 1 month or more of anti -TB drugs in the past and may have positive or negative bacteriology and may have disease at any anatomical site

They are further classified by the outcome of their most recent course of treatment. Patients whose sputum is smear-positive at the end of a second or subsequent Course of treatment should be classified by the outcome of their most recent retreatment course: relapsed, defaulted or failed.

REGISTRATION GROUP BY MOST RECENT TREATMENT OUTCOME

Registration group (any site of disease		**Bacteriology(smear, culture or newer diagnostics)**	**Outcome of the most recent prior treatment**
New		+ or -	-
Previously treated	Relapse	+	Cured
			Treatment completed
	Failure	+	Treatment failed
	Lost to follow up	+	Lost to follow up
Transfer in		+ or -	Still on treatment
Other		+ or -	- All cases that do not fit the above definitions, such as patients for whom it is not known whether they have been previously treated -Who were previously treated but with unknown outcome of that previous treatment and/or -Who have returned to treatment with smear negative PTB or bacteriologically negative EPTB

d) HIV STATUS

HIV positive TB patient: refers to any bacteriologically confirmed or clinically diagnosed case of TB who has a positive result from HIV testing conducted at the time of TB diagnosis or other documented evidence of enrolment in HIV care once ART has to be started.

HIV negative TB patient: refers to any bacteriologically confirmed or clinically diagnosed case of TB who has a negative result from HIV testing conducted at the time of TB diagnosis. Any HIV negative TB patient subsequently found to be HIV positive should be reclassified accordingly.

HIV status unknown TB patient: refers to any bacteriologically confirmed or clinically diagnosed case of TB who has no result of HIV testing and no other documented evidence of enrolment in HIV care.
If the patient's HIV status is subsequently determined, he or she should be reclassified accordingly

e) CLASSIFICATION BASED ON DRUG SUSCEPTIBILITY TESTING

Different patterns of drug resistance carry different implications for treatment and management and drug-resistant cases are classified in categories based on DST in clinical isolates confirmed to be M. Tuberculosis

Mono-resistance: - Tuberculosis in patients who's infecting isolates of M. tuberculosis are confirmed to be resistant in vitro to one first-line anti tuberculosis drug only

P**oly-resistance:-**Tuberculosis in patients who's infecting isolates are resistant in vitro to more than one first-line anti tuberculosis drug, other than both isoniazid and rifampicin

MDR-TB: - Tuberculosis in patients who's infecting isolates are resistant in vitro to at least isoniazid and rifampicin

XDR-TB :-(Extensive drug resistant): In addition to multi drug resistance; resistance to any one of the FQs and one of the three second line injectable drugs (Cm, Am, Km)

Rifampicin resistance (RR): resistance 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, poly-resistance, MDR or XDR

4.3 DEFINITIONS OF TREATMENT OUTCOMES FOR TB

Outcome	**Definition**
Cured	A patient whose sputum smear or culture was positive at the beginning of the treatment but who was smear or culture negative in the last month of treatment and on at least on one previous occasion
Treatment completed	A patient who completed treatment but who does not have a negative sputum smear or culture result in the last month of treatment and on at least one previous occasion (sputum not done or results not available)
Treatment failure	A patient whose sputum smear or culture is positive at 5 months or later during treatment.
Died	A patient who dies for any reason during the course of treatment
Lost to follow up	A patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.
Treatment success	The sum of cured and treatment completed

5. MANAGEMENT OF TB

5.1 DIRECTLY OBSERVED THERAPY (DOT)

All patients diagnosed with TB should receive daily DOT for the entire duration of therapy as per policy recommendations of the NTP

DOT may be provided by a person who is accessible and acceptable to the patient but who is also accountable to the health system

Family members should not be used as DOT providers in patients with drug resistant TB and patients at a high risk for non adherence

As all patients are on a daily regimen, DOT will be given for 6 days in a week with a non DOT day (weekend)

- DOT is a component of case management that helps to ensure that patients adhere to treatment and is the most effective strategy for making sure that patients take their medicines.
- DOT means that a health care worker or other designated individual watches the patient swallow every dose of the prescribed drugs.
- DOT should be considered for all patients because it is difficult to reliably predict which patients will be adherent. Even patients who intend to take their medicine might have trouble remembering to take their pills every time
- Studies show that 86-90% of patients receiving DOT complete therapy, compared to 61% for those on self administered therapy.

ADVANTAGES AND DISADVANTAGES OF DOT

Advantages	Disadvantages
It ensures that the patient completes an adequate regimen	Is time consuming
It lets the health care worker monitor the patient regularly for side effects and response to therapy	Is labor intensive
Decreases the risk of drug-resistance resulting from erratic or incomplete treatment	Can be perceived as demeaning or punitive
It helps the health care worker solve problems that might interrupt treatment	Can be insulting to some patients
By ensuring the patient takes every dose of medicine, it helps the patient become non infectious sooner	Can imply that the patient is incapable or irresponsible

Who can deliver DOT?

Treatment observation must be performed by a person who is accessible and acceptable to the patient, but who is also accountable to the health system. People outside the family structure, who are subject to greater supervision by NTP, are more likely to report valid information to the programme and take appropriate action when patients decline or forget treatment,

Family members are discouraged, as the DOT provider must remain objective. Because of strong emotional ties, the family may be unwilling to ensure the patient takes treatment if he or she refuses treatment. And if adherence to treatment creates tension in the family, the simplest way to eliminate the source of that tension may be to discontinue treatment observation.

The DOT provider should build rapport and trust with the patient, protect patient confidentiality, be consistent and adopt and reflect a nonjudgmental attitude

- DOT is usually given by a trained DOT provider, community or family health worker or nurse involved in TB services in the hospital or health centre

- Sometimes staff at other health care settings, such as outpatient clinics, correctional facilities and school health personnel can be asked to give DOT to a patient who can get to the alternative health care setting more easily than to the DOT clinic. Such an arrangement if decided should be closely supervised by the NTP.

- Other non health care persons such as work supervisors or other responsible persons who do not have strong emotional ties with the patient can provide DOT in situations when the person is unable to attend the DOT clinic due to work etc, if the patient agrees to this arrangement. These arrangements must be approved in advance by the supervisory clinician and should be monitored closely to ensure that there are no problems.

- Family members should be used to provide DOT only as a last option if the patient does not agree to any of the above arrangements and there is a possibility for the patient not to report to NTP but obtain ATT from pharmacies from neighboring countries and do self administered therapy. This must again be decided by the supervisory clinician and should be very closely monitored by NTP. Not more than 2 weeks of medicines should be handed over to the family or work supervisor at a time

- Family members should not be used as DOT providers in patients with drug resistant TB and patients at a high risk for non adherence

Who should receive DOT?

All patients diagnosed with TB should receive DOT. Self administered therapy is not an option under the NTP. Ideally all patients should receive DOT by a trained DOT provider but in certain situations as described above work supervisors etc can provide DOT to the patient under close monitoring by NTP.

However, there are certain groups of patients for whom DOTs by a trained DOT provider is a must:

- Patients with drug resistant TB
- Persons at high risk for non adherence, such as
    - Unstably housed persons
    - Persons who abuse alcohol or illicit drugs
    - Persons who are unable to take pills on their own due to mental or physical disabilities
    - Persons with a history of non adherence

ADMINISTRATION OF DOT

- DOT should be initiated when TB treatment starts. It is important to explain the benefits of DOT to each patient at the time of diagnosis and stress the fact that DOT is not punitive; rather, DOT is a highly effective way for the patient and health care worker to collaborate so that the patient will successfully complete an adequate regimen

- The prescribing physician should show support for DOT by explaining to the patient that DOT is widely used and very effective. The DOT provider should reinforce this message.

- DOT works best when used with a patient centered case management approach, including such things as:
    - helping patients keep medical appointments
    - providing ongoing patient education
    - offering incentives and/or enablers

- Patients visit the health facility for DOT provision daily except Friday (weekend) to take the pills under the observation of the DOT provider. As all patients are on a daily regimen, patient can self administer their dose on Friday (weekend). This means that after taking DOT on Thursday, the patient is handed over a small container with Friday's pills by the DOT provider.

- DOT can be given anywhere the patient and health care worker agree upon, provided the time and location are convenient and safe.

- For some patients due to the work schedule, disability etc, patient may be unable to attend the DOT clinic and if so, DOT can be provided in a nonclinical setting during non working hours which may be the patients home etc (field-based DOT)
  Regardless of the arrangement, it is always important to protect the patient's confidentiality and another critical consideration for conducting field DOT is the health care worker's own security.

Tasks Involved in Delivering DOT

DOT for TB is more than watching the patient swallows each pill, although that is the crucial component of a DOT program. At each DOT encounter, the health care worker should perform the following tasks:

1- Check for side effects:

- At each visit, before the drugs are given, the DOT provider should ask if the patient is having any adverse side effects.
- Patients should be educated about symptoms indicating adverse reactions to the drugs they are taking, whether minor or serious.
- If the patient has symptoms of serious adverse reactions, a new drug supply should not be given
- The supervisor should be told that the drugs were not given and the prescribing clinician should be notified about the adverse reaction.
- The DOT provider should arrange for the patient to see the clinician as soon as possible

2. Verify medication:- Each time DOT is delivered, the DOT provider/ health care worker should verify that the right drugs are delivered to the right patient, and that he or she has the correct amount of medication.

3. Deliver the prescribed medication

4 Watch patient take pills: -

- Medication should not be left for the patient to take on his or her own unless self-administered therapy has been prescribed for non-DOT days, such as weekends.

- The health care worker or the patient should get a glass of water before the patient is given the pills. The health care worker should watch the patient continuously from the time each pill is given to the time he or she swallows it.

- Health care workers should watch for tricks or techniques some patients may use to avoid swallowing medication, such as hiding pills in the mouth and spitting them out later, hiding medicine in clothing, or vomiting the pills after leaving the clinic.

- If it is necessary to make sure that the patient swallows the pills, the health care worker may have to check the patient's mouth, or ask the patient to wait for a half hour before leaving the clinic so the medication can dissolve in the patient's stomach.

5. Answer questions

6. Document the visit

5.2 TREATMENT

New patients presumed or known to have drug susceptible pulmonary and EPTB will receive a rifampicin based daily regimen of 6 months duration: 2HRZE/4HR

For TB Meningitis and TB of bone/joint, the duration of therapy is longer: 12 months

In TB meningitis, ethambutol should be replaced by streptomycin in adults

Anti TB drugs are available from the NTP for free to both expatriates and locals alike

For retreatment patients rapid DST of Rifampicin with XpertMTB/RIF will guide the choice of regimen

All patients should receive daily DOT throughout the treatment

The aims of treatment of tuberculosis are:

- to cure the patient and restore quality of life
- to prevent death from active TB
- to prevent relapse of TB;
- to reduce transmission of TB to others
- to prevent the development and transmission of drug resistance

5.3 ANTI TB DRUGS

Fixed dose combinations of first line oral drugs are available under the NTP as per WHO recommended formulations and administered as a daily regimen.
Anti TB drugs are available only through the NTP within the country as the government has prohibited sale of Anti TBdrugs. (Two second line agents ie quinolones and Amikacin are available in the pharmacies due to their use in the treatment of other infections as well)

TB medicines are free of charge for all TB patients in the country (locals and expatriates alike) through the National TB Programme

CLASSES OF ANTI TUBERCULOSIS DRUGS

Group 1 **First line Anti tuberculosis agents**	**Isoniazid (H)** **Rifampicin (R)** **Ethambutol (E)** **Pyrazinamide (Z)** **Rifabutin(Rfb) (Rifabutin added here as routinely used in patients on protease inhibitors in many settings)**
Group 2 **Injectable anti tuberculosis agents**	**Streptomycin (S) (high rates of streptomycin resistance in MDRTB strains, so not considered as a 2nd line agent)** **Kanamycin (Km)** **Amikacin (Am)** **Capreomycin (Cm)**
Group3 **Fluroquinolones**	**Levofloxacin (Lfx)** **Moxifloxacin (Mfx)** **Gatifloxacin**
Group4 **Oral bacteriostatic second-line anti tuberculosis drugs**	**Ethionamide (Eto)** **Prothionamide (Pto)** **Cycloserine (Cs)** **Terizidone (Trd): (limited program & effectiveness data than Cs)** **P-aminosalicylic acid (PAS)**
Group5: **Anti tuberculosis agents with limited data on efficacy and/or long term safety in the treatment of DR-TB. (includes new anti- TB drugs)**	**Bedaquiline (Bdq)** **Delamanid(Dlm)** **Clofazimine (Cfz)** **Amoxicillin/Clavulanate (Amx/Clv): (As adjuvant to Imp and Mpm)** **Linezolid(Lzd)** **Thioacetazone(Thz); Clarithromycin(Clr): (limited data)** **Imipenem(Imp);Meropenem(Mpm)** **High dose INH(H) : (defined as 16-20mg/kg per day)**

RECOMMENDED DOSES OF THE FIRST LINE ATT FOR ADULTS

Drug	Recommended dose	
	Daily	
	Dose and range(mg/kg)	**Maximum(mg)**
Isoniazid	5 (4-6)	300mg
Rifampicin	10 (8-12)	600mg
Pyrazinamide	25 (20-30)	-
Ethambutol	15 (15-20)	-
Streptomycin	15 (12-18)	-

Properties of individual TB Drugs

DRUG	DRUG PROPERTY	TARGET BACILLI	PH	SITE OF ACTION
Isoniazid (H) .	Bactericidal after 24 hours. High potency: kills >90% bacilli in first few days of treatment.	Rapid and intermediate growing bacilli	Alkaline and acid media.	Intracellular and extracellular.
Rifampicin (R)	Bactericidal within 1 hour. High potency. Most effective sterilising agent	All populations including dormant bacilli.	Alkaline and acid media.	Intracellular and extracellular
Pyrazinamide (Z	Bactericidal with a low potency. Achieves its sterilising action within 2-3 months	Slow growing bacilli	Acid medium	intracellular bacilli only (macrophages)
Ethambutol (E	Bacteriostatic. Low potency. Minimises the emergence of drug resistance	All bacterial populations	Alkaline and acid media	Intracellular and extracellular
Streptomycin (S	Bactericidal with a low potency	Rapidly growing bacilli	Alkaline medium.	Extracellular bacilli

5.4 STANDARD REGIMENS FOR DEFINED PATIENT GROUPS:

Standardized treatment means that all patients in a defined group receive the same treatment regimen. Standard regimens have the following advantages over individualized prescription of drugs:

- errors in prescription are less likely and thus the risk of development of drug resistance are reduced
- estimating drug needs, purchasing, distribution and monitoring are facilitated
- staff training is facilitated
- costs are reduced
- maintaining a regular drug supply when patients move from one area to an-other is made easier
- outcome evaluation is convenient and results are comparable

For assigning standard regimens, patients are grouped by the same patient registration groups used for recording and reporting, which differentiate new patients from those who have had

prior treatment. Registration groups for previously treated patients are based on the outcome of their prior treatment course: failure, relapse and default

NEW PATIENTS: New patients are defined as those who have no history of prior TB treatment or who received less than 1 month of anti-TB drugs regardless of their smear or culture status. New patients are presumed to have drug-susceptible TB with the exception that if they have developed active TB after known contact with a patient documented to have drug-resistant TB in which case they are likely to have a similar drug resistance pattern to the source case.

New patients presumed or known to have drug-susceptible pulmonary TB should receive a daily regimen containing 6 months of rifampicin: 2HRZE/4HR
This also applies to extra pulmonary TB except TB of the central nervous system, bone or joint for which the duration of therapy is longer. In TB meningitis, ethambutol should be replaced by streptomycin
The standard treatment regimen for all patients is made up of an intensive phase lasting 2 months and a continuation phase lasting 4 months and all patients will receive daily DOT throughout the treatment

Intensive phase: 2 months duration of 4 drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol) are used to rapidly kill the tubercle bacilli. Infectious patients become less infectious within approximately 10-14 days of starting treatment and symptoms abate. However, the majority of patients with sputum smear-positive TB will become smear-negative within 2 months.

Continuation phase: follows the intensive phase and 2 drugs (isoniazid, rifampicin) are used, over a period of 4 months. The sterilizing effect of these drugs eliminates the remaining bacilli and prevents subsequent relapse.

Standard regimen for new TB patients presumed or known, to have drug-susceptible TB

	Intensive phase	Continuation phase
PTB (Smear positive and smear negative)	2 months of HRZE	4 months of HR
EPTB (except TBM and osteoarticular TB)	2 months of HRZE	4 months of HR
TBM	2 months of HRZS (HRZE in children)	10 months of HR
Osteoarticular TB	2 months of HRZE	10 months of HR

5.5 PREVIOUSLY TREATED PATIENTS AND MULTI DRUG RESISTANCE

For retreatment patients rapid DST of Rifampicin with XpertMTB/RIF will guide the choice of regimen

Previous TB treatment is a strong determinant of drug resistance. At the global level, 15% of previously treated patients have MDR, which is five times higher than the global average of 3% in new patients

Of all the forms of drug resistance, it is most critical to detect multidrug resistance because it makes regimens with first line drugs much less effective and resistance can be further amplified. If MDR is not detected and treated with second line drugs, these retreatment patients will suffer poor outcomes and spread MDR in the community.

For all retreatment patients,Xpert MTB/Rif will be used as the initial diagnostic test to detect Rifampicin resistance and the results obtained would be used to guide the choice of regimen for the patient.

This would ensure that patients with a likelihood of MDR TB would not be put on the 8 month retreatment regimen as this regimen would be ineffective in a patient with MDR and in addition may lead to amplification of resistance.

Specimens for culture and conventional DST should be obtained from all previously treated TB patients at or before the start of treatment to look for resistance to other drugs

6. MONITORING DURING TREATMENT

All patients should be monitored during the course of treatment to assess their response to therapy.
Regular monitoring of patients also facilitates treatment completion, manages treatment interruption and allows for the identification and management of adverse drug reactions

All patients, treatment supporters and DOT providers should be instructed to report:

-the persistence or reappearance of symptoms of TB (including weight loss)
- Symptoms due to adverse drug reactions
-treatment interruptions

Patient weight should be monitored monthly and dosages should be adjusted if changes in weight occur.
A written record should be maintained for each individual patient on the treatment card, of medications given, bacteriological response and adverse reactions

SPUTUM MONITORING:

Smear positive patients

For smear-positive pulmonary TB patients treated with first-line drugs, sputum smear microscopy is to be performed at completion of the intensive phase and if this smear is positive, it should be repeated at the end of the third month.

Culture /DST send at the onset of treatment should be reviewed.
Further sputum smears should be done at the fifth month and the end of treatment. Smear positivity at fifth month or later is declared as treatment failure

Once treatment failure is declared, the TB Treatment Card is closed (Outcome = treatment failure) and a new one is opened (Type of patient = treatment after failure)
If a patient is found to harbor a multidrug-resistant strain of TB at any point of time during therapy, then also the treatment is declared a failure.

Sputum monitoring by smear microscopy

MONTHS OF TREATMENT						
Smear at the start of treatment	**INTENSIVE PHASE (months)**		**CONTINUATION PHASE (months)**			
	1	2	3	4	5	6
Smear +ve (send culture/DST)		Smear +ve	Smear +ve(review culture/ DST)		Smear +ve= treatment failure (send culture/ DST)	Smear +ve= treatment failure (send culture/DST)
		Smear -ve			Smear +ve= treatment failure(send culture/ DST)	Smear +ve= treatment failure (send culture/DST)
Smear -ve or not done		Smear -ve				
		Smear +ve	Smear +ve (review culture/DST)		Smear +ve = treatment failure(send culture/DST)	Smear +ve = treatment failure(send culture/ DST)

Pulmonary TB patients whose sputum smear microscopy was negative (or not done) at the start of treatment

It is important to recheck a sputum specimen at the end of the intensive phase in case of disease progression (due to non-adherence or drug resistance) or an error at the time of initial diagnosis (i.e. a true smear-positive patient was misdiagnosed as smear-negative)

If sputum smears are negative at 2 months, there is no need for further sputum monitoring. These patients should be monitored clinically; body weight is a useful progress indicator

Sputum should be collected when the patient is given the last dose of the intensive-phase treatment.

Note that a positive sputum smear at the end of the intensive phase may indicate any of the following:

- the initial phase of therapy was poorly supervised and patient adherence was poor
- poor quality of anti-TB drugs
- doses of anti-TB drugs are below the recommended range

- Resolution is slow because the patient had extensive cavitation and a heavy initial bacillary load
- there are co-morbid conditions that interfere either with adherence or with response
- the patient may have drug resistant M. tuberculosis that is not responding to first-line treatment
- non-viable bacteria remain visible by microscopy

Prevention of adverse effects of drugs

Some drug induced side effects can be prevented; for example INH induced peripheral Neuropathy which usually presents as numbness or a tingling or burning sensation of the hands or feet and occurs more commonly in pregnant women and in people with HIV infection, alcohol dependency, malnutrition, diabetes, chronic liver disease and renal failure.

These patients should receive preventive treatment with pyridoxine, 10 mg/day along with their anti TB drugs

7. MANAGEMENT OF ADVERSE EFFECTS

Below is a symptom based approach to the management of the most common adverse effects which are classified as major or minor. In general, a patient who develops minor adverse effects should continue TB treatment and be given symptomatic treatment.
If a patient develops a major side effect, the treatment or the responsible drug is stopped; the patient should be urgently referred to the clinician for further assessment and treatment. Patients with major adverse reactions should be managed in a hospital.

7.1 MANAGEMENT OF CUTANEOUS REACTIONS

If a patient develops itching without a rash and there is no other obvious cause, the recommended approach is to try symptomatic treatment with antihistamines and skin moisturizing and continue TB treatment while observing the patient closely. If a skin rash develops, however, all anti-TB drugs must be stopped.
Once the reaction has resolved, anti-TB drugs are reintroduced one by one, starting with the drug least likely to be responsible for the reaction (rifampicin or isoniazid) at a small challenge dose, such as 50mg INH. The dose is gradually increased over 3 days. This procedure is repeated adding in one drug at a time.
A reaction after adding in a particular drug identifies that drug as the one responsible for the reaction.

7.2 Symptom-based approach to managing side effects of anti TB drugs

Side-effects	**Drug(s) probably responsible**	**Management**
Major		**Stop responsible drug(s) and refer to clinician urgently**
Skin rash with or without itching	Streptomycin, isoniazid, rifampicin, pyrazinamide	Stop anti-TB drugs
Deafness (no wax on otoscopy)	Streptomycin	Stop streptomycin
Dizziness (vertigo and nystagmus)	Streptomycin	Stop streptomycin
Jaundice (other causes excluded), hepatitis	Isoniazid, pyrazinamide, rifampicin	Stop anti-TB drugs
Confusion (suspect drug-induced acute liver failure if there is jaundice)	Most anti-TB drugs	Stop anti-TB drugs
Visual impairment (other causes excluded)	Ethambutol	Stop ethambutol
Shock, purpura, acute renal failure	Rifampicin	Stop rifampicin
Decreased urine output	Streptomycin	Stop streptomycin

Minor side effect	Probable Drug responsible	Continue anti TB drugs and check Doses
Anorexia, nausea, abdominal pain	Pyrazinamide, rifampicin isoniazid	Give drugs with small meals or just before bedtime, and advice patient to swallow pills slowly with small sips of water. If symptoms persist or worsen, or there is protracted vomiting or any sign of bleeding, consider the side effect to be major and refer to clinician urgently.
Joint pains	Pyrazinamide	Aspirin or NSAIDs, or paracetamol
Burning, numbness or tingling sensation in the hands or feet	INH	Pyridoxine 50–75 mg daily
Drowsiness	Isoniazid	Reassurance. Give drugs before bedtime
Orange/red urine	Rifampicin	Reassurance. Patients should be told when starting treatment that this may happen and is normal
Flu syndrome (fever, chills, malaise, headache, bone pain)	If Intermittent dosing of rifampicin	Change from intermittent to daily rifampicin administration

7.3 Management of drug induced hepatitis

- Of the first line anti TB drugs, isoniazid, pyrazinamide and rifampicin can all cause liver damage. In addition, rifampicin can cause asymptomatic jaundice without evidence of hepatitis.
- It is important to try to rule out other possible causes before deciding that the hepatitis is induced by the TB regimen

- If the patient is severely ill with TB and it is considered unsafe to stop TB treatment or the signs and symptoms do not resolve and the liver disease is severe, then a non hepatotoxic regimen consisting of streptomycin, ethambutol and a fluoroquinolone should be started and continued for a total of 18–24 months

- If TB treatment has been stopped, it is necessary to wait for liver function tests to revert to normal and clinical symptoms (nausea, abdominal pain) to resolve before reintroducing the anti-TB drugs

- If it is not possible to perform liver function tests, it is advisable to wait an extra 2 weeks after resolution of jaundice and upper abdominal tenderness before restarting TB treatment.

- Once drug-induced hepatitis has resolved, the drugs are reintroduced one at a time. If symptoms recur or liver function tests become abnormal as the drugs are reintroduced, the last drug added should be stopped

- It is advised to start with rifampicin because it is less likely than isoniazid or pyrazinamide to cause hepatotoxicity and is the most effective agent. After 3–7 days, isoniazid may be reintroduced. In patients who have experienced jaundice but tolerate the reintroduction of rifampicin and isoniazid, it is advisable to avoid pyrazinamide.

- Alternative regimens depend on which drug is implicated as the cause of the hepatitis. If rifampicin is implicated, a suggested regimen without rifampicin is 2 months of isoniazid, ethambutol and streptomycin followed by 10 months of isoniazid and ethambutol.

- If isoniazid cannot be used, 6–9 months of rifampicin, PZA and ethambutol to be considered

- If PZA is discontinued before the patient has completed the intensive phase, the total duration of isoniazid and rifampicin therapy may be extended to 9 months.

- If neither INH nor rifampicin can be used, the non-hepatotoxic regimen consisting of streptomycin, ethambutol and a fluoroquinolone should be continued for a total of 18–24 months.

- If loose anti TB drugs are not available, the following approach has been successful, which depends on whether the hepatitis with jaundice occurred during the intensive or the continuation phase.

- When hepatitis with jaundice occurs during the intensive phase with HREZ, once hepatitis has resolved, restart the same drugs EXCEPT replace pyrazinamide with streptomycin to complete the 2-month course of initial therapy, followed by rifampicin and isoniazid for the 6-month continuation phase.

- When hepatitis with jaundice occurs during the continuation phase: once hepatitis has resolved, restart INH and rifampicin to complete the 4-month continuation phase of therapy.

8. CO - MANAGEMENT OF HIV AND TB

People living with HIV are more likely to present with extra pulmonary or sputum smear negative TB, especially as immunosuppression advances. This can result in misdiagnosis or delays in diagnosis and in turn, higher morbidity and mortality

Three approaches can help to minimise the impact of TB on those with HIV:

1. TB preventive therapy to reduce an individual 's risk of developing TB
2. Early, prompt diagnosis of TB through intensified case-finding
3. Appropriate case management of TB including the provision of comprehensive HIV care to the co-infected

HIV testing and counseling of all patients known or suspected to have TB

TB is often the first clinical indication that a person has underlying HIV infection, and TB services can be an extremely important entry point to HIV prevention, care and treatment. In addition, the HIV status of TB patients makes a difference to their TB treatment.

Detecting HIV infection in a TB patient is also critical for the TB patient's household members: HIV-positive TB patients may have household members who are also living with HIV.

Household contacts of an infectious TB case are a high priority for TB screening and treatment, especially if they are living with HIV and those who are found to have active TB disease need prompt treatment.

Among household contacts, people living with HIV (and children, regardless of their HIV status) who do not have active TB are candidates for isoniazid treatment to prevent the development of active TB "provider-initiated" testing is recommended, which means that the clinician recommends HIV testing and counseling as a standard component of care.

As in the case of client-initiated HIV testing, informed consent, counseling and confidentiality are essential. WHO recommends that providers use "opt-out" approaches, meaning that individuals must specifically decline the HIV test after receiving pretest information if they do not want the test to be performed

8.1 HIV PREVENTION FOR TB PATIENTS

Appropriate prevention messages and methods should be provided to patients with confirmed or suspected TB, according to their HIV status. Harm-reduction measures for TB patients who are injecting drug users should be provide through referral linkages to the HIV programme

The benefits of counselling and testing for TB clients include:

- The opportunity for clients to know their HIV status and prognosis
- Early diagnosis and management of other HIV-related illnesses
- Opportunities for prevention of other infections (e.g. using cotrimoxazole)
- Access to HIV care (psychosocial, medical)
- Decreased HIV transmission and re-infection through behavioural modification

8.2 TB PREVENTIVE THERAPY IN HIV POSITIVES

TB preventive therapy with isoniazid (INH 5mg/kg daily up to a maximum 300mg per day) for 6 months has been shown to decrease the risk of TB disease in those with latent TB and is part of the package of care for people living with HIV

It is critical to exclude active TB before starting preventive therapy. This avoids the provision of INH monotherapy to clients with active TB who require a full course of TB treatment.

TB preventive therapy is beneficial to HIV positive people with latent TB as indicated by a positive tuberculin skin test. Clients requiring or on ART are not eligible as the added benefits of INH prophylaxis are unclear and the additional pill burden undesirable. Clients already on INH preventive therapy who start ART can complete their INH preventive therapy

The patient should be screened for TB symptoms to exclude active tuberculosis and should be specifically enquired about all of the signs and symptoms of TB. If symptomatic, the patient should be investigated for TB.

If the patient has no symptoms of TB, has not had TB in the last 2 years, does not have liver disease or alcoholism and is not eligible for ART, a tuberculin (Mantoux) skin test should be done and if positive to be started on INH preventive therapy.

DIAGNOSIS OF TB

Generally there is little difference between the clinical presentation of TB in HIV positive and HIV negative patients. However, among HIV positive clients cough is reported less frequently, probably because there is less cavitation, inflammation and endobronchial irritation as a result of decreased cell mediated immunity. Similarly, haemoptysis, which results from caseous necrosis of the bronchial arteries, is less common.

In addition to Sputum smears, sputum culture and DST should be done at the start of TB therapy in all HIV-positive TB patients, to avoid mortality due to unrecognized drug resistant TB and it is strongly advised for the use of XpertMTB/Rif in persons living with

HIV.

High mortality rates have been reported among people living with HIV who have drug resistant-TB, and rates can exceed 90% in patients co infected with extensively drug resistant TB (XDR-TB) and HIV. Prompt initiation of appropriate TB treatment and subsequent initiation of ART can reduce mortality among people living with HIV who have drug-resistant TB.

Extra-pulmonary disease has been reported in up to 70% of HIV-related TB cases when the CD4 count is less than 100 cells/mm3. The main types of extra-pulmonary TB seen in HIV infected clients are lymphadenopathy, pleural effusion, pericardial effusion and miliary TB.

The definitive diagnosis of extra pulmonary TB is often difficult because of the scarcity of diagnostic facilities

In HIV-related TB lymphadenopathy, diagnosis can be made by needle aspiration and examination of direct smears.

Pericardial TB is not rare and may be diagnosed presumptively based on the characteristic balloon shaped appearance of cardiac shadow on chest X-ray.

In TB meningitis, the CSF may be completely normal in HIV-infected persons and disseminated TB may also be difficult to diagnose

8.3 TREATMENT OF TB IN PEOPLE LIVING WITH HIV

In general, TB treatment is the same for HIV positive and HIV-negative patients and TB patients with known positive HIV status should receive daily TB treatment and should receive at least the same duration of TB treatment as HIV-negative TB patients

Case-fatality is higher in people living with HIV with smear-negative pulmonary and extra pulmonary TB, as these patients are generally more immunosuppressed than those with smear-positive TB. The case fatality rate is reduced in patients who receive concurrent ART. The first priority for HIV-positive TB patients is to initiate TB treatment, followed by co-trimoxazole and ART

Providing cotrimoxazole preventive therapy to all HIV positive TB patients

In all HIV-positive TB patients, cotrimoxazole preventive therapy should be initiated as soon as possible and given throughout TB treatment.

Cotrimoxazole preventive therapy substantially reduces mortality in HIV-positive TB patients. The exact mode of activity is not clear but cotrimoxazole is known to prevent Pneumocystis jirovecii and malaria and is likely to have an impact on a range of bacterial infections in HIV-positive TB patients

When to start ART and what antiretroviral agents to use

Treatment of all patients will be in collaboration with the National HIV programme and ART will be initiated in collaboration with the National HIV Programme

Antiretroviral therapy improves survival in HIV-positive patients. In addition, antiretroviral therapy reduces TB rates by up to 90% at an individual level, by 60% at a population level and it reduces TB recurrence rates by 50%.ART should be initiated for all people living with HIV with active TB disease irrespective of CD4 cell count.

TB treatment should be started first, followed by ART as soon as possible and within the first 8 weeks of starting TB treatment. However, early initiation of ART (within a few weeks of starting TB treatment) means a large number of tablets to ingest, which may discourage treatment adherence; there may also be complications, adverse effects, drug–drug interactions and IRIS.

Mild to moderate IRIS is relatively common in patients with TB started on ART: it has been reported in up to one-third of patients in some studies. However, it is relatively rare in its severe forms. The syndrome can present as fever, enlarging lymph nodes, worsening pulmonary infiltrates, or exacerbation of inflammatory changes at other sites. It generally presents within 3 months of the start of ART and is more common when CD4 cell count is low (<50 cells/mm3). Most cases resolve without intervention and ART can be safely continued

IRIS is a diagnosis of exclusion. Patients with advanced AIDS may show clinical deterioration for a number of other reasons. New opportunistic infections or previously subclinical infections may be unmasked following immune reconstitution and cause clinical worsening. IRIS can also be confused with TB treatment failure.

In addition, HIV-positive TB patients may be demonstrating progression of TB disease due to TB drug resistance. IRIS is not a reason to switch patients to second-line ART, although the ART treatment regimen may need to be adjusted to ensure compatibility with the TB treatment

The first-line ART regimen contain two nucleoside reverse transcriptase inhibitors (NRTIs) plus one non-nucleoside reverse transcriptase inhibitor (NNRTI) will be used to treat these patients. The recommended NRTI is Efavirenz as drug interactions with anti TB drugs are minimal.

Because of concerns related to teratogenicity, efavirenz should not be used in women of childbearing potential without adequate contraception, nor should it be used for women who are in the first trimester of pregnancy. Alternatives are also needed for patients who

are intolerant to efavirenz or are infected with a strain of HIV that is resistant to NNRTIs. For these patients a nevirapine based regimen or a triple NRTI regimen is to be used.

Adverse drug effects are common in HIV-positive TB patients and some toxicities are common to both ART and TB drugs. Overlapping toxicities between ART, TB therapy and co-trimoxazole include rash (and more rarely, hepatic dysfunction) and vigilant monitoring of side-effects is therefore essential

Ensure that comprehensive HIV care and support services are available in collaboration with the HIV programme

9. TREATMENT OF EXTRAPULMONARY TB AND TB IN SPECIAL SITUATIONS

Pulmonary and extra pulmonary(EPTB)disease should be treated with the same regimens
Note that some experts recommend 12 months of treatment for TB meningitis (given the serious risk of disability and mortality) and TB of bones/ joints (because of the difficulties of assessing treatment response)
Unless drug resistance is suspected, adjuvant corticosteroid treatment is recommended for TB meningitis and pericarditis. In tuberculous meningitis, ethambutol should be replaced by streptomycin.

Although sometimes required for diagnosis, surgery plays little role in the treatment of EPTB and is reserved for management of late complications of disease such as hydrocephalus, obstructive uropathy, constrictive pericarditis and neurological involvement from Pott's disease (spinal TB).
For large, fluctuant lymph nodes that appear to be about to drain spontaneously, aspiration or incision and drainage appear beneficial

9.1 IMPORTANT DRUG INTERACTIONS

Many TB patients have concomitant illnesses and at the start of TB treatment, all patients should be asked about medicines they are currently taking. The most important interactions with anti-TB drugs are due to rifampicin.

Rifampicin induces pathways that metabolize other drugs, thereby reducing the concentration and effect of those drugs. To maintain a therapeutic effect, dosages of the other drugs may need to be increased. When rifampicin is discontinued, its metabolism inducing effect resolves within about 2 weeks, and dosages of the other drugs will need to be reduced.

Rifampicin substantially reduces the concentration and effect of the following drugs:

- —anti-infectives (mefloquine,azoleantifungal agents,clarithromycin, erythromycin, doxycycline, atovaquone, chloramphenicol)
- —hormone therapy(ethinylestradiol, norethindrone, tamoxifen, levothyroxine)
- —methadone
- —warfarin
- —cyclosporine/ corticosteroids
- —anticonvulsants including phenytoin
- —cardiovascular agents including digoxin (among patients with renal insufficiency), digitoxin, verapamil, nifedipine, diltiazem, propranolol, metoprorol, enalapril, losartan, quinidine, mexiletine, tocainide, propafenone
- —theophylline
- —sulfonylurea hypoglycaemics/ hypolipidaemics including simvastatin and fluvastatin
- — nortriptyline, haloperidol, quetiapine, benzodiazepines, zolpidem, buspirone

9.2 PREGNANCY AND BREASTFEEDING

Women of childbearing age should be asked about current or planned pregnancy before starting TB treatment.

A pregnant woman should be advised that successful treatment of TB with the standard regimen is important for successful outcome of pregnancy. With the exception of streptomycin, the first line anti-TB drugs are safe for use in pregnancy. Streptomycin is ototoxic to the fetus and should not be used during pregnancy

A breastfeeding woman who has TB should receive a full course of TB treatment

Mother and baby should stay together and the baby should continue to breastfeed. After active TB in the baby is ruled out, the baby should be given 6 months of INH preventive therapy, followed by BCG vaccination

Pyridoxine supplementation is recommended for all pregnant or breastfeeding women taking INH

9.3 LIVER DISORDERS

Patients with the following conditions can receive the usual TB regimens provided that there is no clinical evidence of chronic liver disease: hepatitis virus carriage, a past history of acute hepatitis, current excessive alcohol consumption. However, hepatotoxic reactions to anti-TB drugs may be more common among these patients and should therefore be anticipated

In patients with unstable or advanced liver disease, liver function tests should be done at the start of treatment, if possible. If the serum ALT level is more than 3 times normal before the initiation of treatment, the following regimens should be considered. The more unstable or severe the liver disease is, the fewer hepatotoxic drugs should be used.

Possible regimens include:

- Two hepatotoxic drugs (rather than the three in the standard regimen):
  - 9 months of isoniazid and rifampicin, plus ethambutol (until or unless isoniazid susceptibility is documented);
  - 2 months of isoniazid, rifampicin, streptomycin and ethambutol, followed by 6 months of isoniazid and rifampicin
  - 6–9 months of rifampicin, pyrazinamide and ethambutol.
- One hepatotoxic drug:
  - 2 months of isoniazid, ethambutol and streptomycin, followed by 10 months of isoniazid and ethambutol.
- No hepatotoxic drugs:
  - 18–24 months of streptomycin, ethambutol and a fluoroquinolone

9.4 RENAL FAILURE AND SEVERE RENAL INSUFFICIENCY

The recommended initial TB treatment regimen for patients with renal failure or severe renal insufficiency is 2 months of isoniazid, rifampicin, pyrazinamide and ethambutol followed by 4 months of isoniazid and rifampicin.

Isoniazid and rifampicin are eliminated by biliary excretion, so no change in dosing is necessary.

There is significant renal excretion of ethambutol and metabolites of pyrazinamide and doses should therefore be adjusted. Three times per week administration of these two drugs at the following doses is recommended: pyrazinamide (25 mg/kg), and ethambutol (15 mg/kg).

While receiving INH, patients with severe renal insufficiency or failure should also be given pyridoxine in order to prevent peripheral neuropathy.

Because of an increased risk of nephrotoxicity and ototoxicity, streptomycin should be avoided in patients with renal failure. If streptomycin must be used, the dosage is 15 mg/kg, two or three times per week, to a maximum of 1 gram per dose, and serum levels of the drug should be monitored.

10. MANAGEMENT OF MULTI DRUG RESISTANT TUBERCULOSIS

For the detailed management of MDRTB, to refer to separate guidelines on management of Multi drug resistant tuberculosis

10.1 CAUSES OF DRUG RESISTANCE

Health care provider	drugs	patients
Inadequate regimens	Inadequate Supply/unavailability	Inadequate Drug intake/ Poor adherence
Inappropriate guidelines	Poor Quality	Lack of information
Noncompliance with guidelines	Poor storage conditions	Lack of money
Absence of guidelines	Poor regulation of medicines	Lack of means to adhere to treatment (transportation,food}
Poor patient education	Wrong dose or combination	HIV
Poor management of adverse reactions		Psychiatric conditions
Poor training of health staff		Adverse Effects
No monitoring of treatment		Social barriers eg: Substance dependence
Poorly organized or funded TB Control programs		Malabsorption

DEFINITIONS OF RESISTANCE

Mono-resistance: - Tuberculosis in patients who's infecting isolates of M. tuberculosis are confirmed to be resistant in vitro to one first-line anti tuberculosis drug only

P**oly-resistance:-** Tuberculosis in patients who's infecting isolates are resistant in vitro to more than one first-line anti tuberculosis drug, other than both isoniazid and rifampicin

MDR-TB: - Tuberculosis in patients who's infecting isolates are resistant in vitro to at least isoniazid and rifampicin

XDR-TB:- (Extensive drug resistant):In addition to multi drug resistance; resistance to any one of the FQs and one of the three second line injectable drugs(Cm, Am, Km)

Rifampicin resistance (RR): resistance 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, poly-resistance, MDR or XDR

10.2 CASE FINDING STRATEGIES

A strategy for case finding and diagnosis of patients with suspected MDR-TB is needed for timely identification and prompt initiation of treatment, prevent the patient from spreading the disease to others, acquiring further resistance and progressing to a state of permanent lung damage.

As the numbers of new smear positive patients are around 50-60 per year, it is possible to undertake culture DST for all these patients so that resistance, if present can be identified earlier

Culture capacity is essential for monitoring drug resistant TB patients' response to therapy and Capacity to reliably identify M. tuberculosis and detect resistance to rifampicin and isoniazid remains a minimum requirement for drug resistant TB management.

Xpert MTB/Rif (rapid DST of rifampicin) should be used over conventional DST at initial diagnosis. Concomitant smear microscopy and samples for conventional culture/ DST would be done for all patients at the time of diagnosis.

Target Groups for drug susceptibility testing:

1. Failure of treatment regimen (new and retreatment): defined as patients who are still sputum smear-positive at the end of treatment regimen.
2. Exposure to a known MDR-TB case
3. Relapse and return after lost to follow up**:** Evidence suggests that most of the relapse and defaults do not have DRTB, however history of erratic drug use etc may point more strongly to Drug resistant TB
4. All smear positive patients at the time of initial diagnosis

Diagnosing XDR-TB

All patients diagnosed with MDR-TB and all patients with risk factors for XDR-TB should be tested for XDR-TB:

- failure of an MDR-TB treatment regimen, which contains second-line drugs including an injectable agent and a FQ
- close contact with an individual with documented XDR-TB
- Close contact with an individual for whom treatment with a regimen including second-line drugs is failing or has failed.

XDR-TB is diagnosed through conventional phenotypic DST and all individuals presumed to have XDR-TB should have DST to isoniazid (H), rifampicin (R), the three second-line injectable agents (kanamycin, amikacin, and capreomycin) and levofloxacin

10.3 TREATMENT OUTCOME DEFINITIONS FOR MDRTB

Cured: Treatment completed as recommended by the national guideline without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase

Treatment completed: Treatment completed as recommended by the national guideline without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase

Treatment Failed: Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of:

- Lack of conversion by the end of the intensive phase
- Bacteriological reversion in the continuation phase after conversion to negative
- Evidence of additional acquired resistance to FQ or second-line injectable drugs
- Adverse drug reactions

(**Conversion:** culture is considered to have converted to negative when two consecutive cultures, taken at least 30 days apart, are found to be negative. In such a case, the specimen collection date of the first negative culture is used as the date of conversion)

(Reversion): culture is considered to have reverted to 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 occurs in the continuation phase

Died: A patient who dies for any reason during the course of DR-TB treatment

Lost to follow up: A patient whose treatment was interrupted for 2 consecutive months or more

Not evaluated: A patient for whom no treatment outcome is assigned. (This includes cases “transferred out” to another treatment unit and whose treatment outcome is unknown)

Treatment success: The sum of cured and completed

10.4 MANAGEMENT OF MDRTB AND XDRTB

For all MDR and XDR TB patients, treatment will be initiated at Respiratory medicine Clinic at IGM Hospital and all patients would be admitted for the initial 4 weeks of treatment as this will help in counseling and other necessary tasks needed for adherence

All MDR TB patients will be subjected to pretreatment evaluation prior to start of treatment .Since the drugs used for the treatment of MDR-TB are known to produce adverse effects, a proper pretreatment evaluation is essential to identify patients who are at increased risk of developing such adverse effects.

In addition to a thorough clinical evaluation , a chest radiograph, Audiometry and relevant hematological and bio-chemical tests including screening for diabetes mellitus, liver disease, drug or alcohol use, mental illness, renal insufficiency, thyroid function, pregnancy and lactation

DOTS-PLUS COMMITTEE

The hospital based **DOTS-Plus committee** at RMC will review the patient details, including previous history, sputum results and concurrent illnesses, and make a decision in relation to treatment with MDRTB regimen. The committee will also decide on all issues pertaining to these cases including changes in treatment regimen, treatment failures, suspension of treatment and surgical intervention

The DOTS plus committee would consist of the focal point for NTP plus respiratory consultants , a physician, pediatrician and surgeon/cardiothoracic surgeon

TREATMENT REGIMEN FOR MDRTB

Suspected MDRTB patients would be started on a Standardized Treatment Regimen that would be changed to Individualized treatment once individual DST results are obtained

Standardized treatment regimen	
Intensive phase:	**8 Km + Lfx + Eto + Cs +Z**
Continuation phase:	**12 + Lfx + Eto + Cs +Z**

Treatment of XDR TB

Likelihood of cure has proven to be much lower than in other MDR-TB cases and deaths are higher, especially in HIV-infected patients. There is very limited data on the different

clinical approaches to XDR-TB and it is observed that that success in XDR-TB patients is highest if at least six drugs are used in the intensive phase and four in the continuation phase and the use of later-generation FQs, significantly improved treatment outcomes, even though DST demonstrated resistance to a representative fluoroquinolone

- Use PZA and any group1 agents that may be effective
- Use an injectable to which the strain is susceptible and consider an extended duration of use (12 months) or possibly entire treatment. If resistant to all, use an injectable the patient has not used before or consider regimen without an injectable agent
- Use a later generation quinolone such as moxifloxacin/gatifloxacin
- Use all group 4 agents that have not been used extensively in a previous regimen or any that are likely to be effective
- Use 2 or more agents from group 5
- Consider adding a new investigational drug eligible for use if WHO policy endorses its use for XDR-TB
- Consider high dose INH
- Consider adjuvant surgery if localized disease
- Consider the option of treatment in a hospital if the clinical condition of the patient is poor or major comorbidities exist
- Manage HIV coinfection
- 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
- Ensure rigorous respiratory infection control measures at the site where the patient is being treated

10.5 TREATMENT OF MONO AND POLY RESISTANT TB

Pattern of resistance	Suggested regimen	Minimum duration of treatment	Remarks
H (+_ S)	R,Z and E (+/- FQ)	6-9 months	A FQ may strengthen the regimen for those with extensive disease Monitoring for R resistance at month 0,2,3
H and E(+/-S)	R,Z and FQ	9-12 months	Monitoring for R resistance at month 0,2,3 Second line injectable agent may be added for 1st 3 months (recommended by experts)
H,E,Z(+-S)	R, FQ, plus Eto plus a second line injectable agent for the first 2-3 months(+/-Z)	18 months	A longer course(6 months) of the second line injectable agent may strengthen the regimen in extensive disease Z to be added if resistance uncertain Monitor R resistance at month 0,2,3
R mono or poly drug resistance	MDR regimen plus H	20 months	

10.6 TREATMENT DELIVERY AND ADHERENCE

Treatment delivery strategies are important in management of MDR-TB patients as it will improve patient adherence. Patients with MDR-TB may be more likely to have problems with non-adherence due to prolonged duration of treatment, drug side effects and large number of drugs

Health education should be carried on a continuous basis at all visits by the patient to a health facility. The counseling and motivation is required to be done not only of the patient but also of the family members since family support is an essential component in the management

Because MDR-TB treatment is the last therapeutic chance for patients for a cure and there is a high public health consequence if a patient with MDR-TB fails therapy, it is recommended that all patients receiving treatment for MDR-TB receive daily DOT

Adverse drug reaction among patients on MDR-TB treatment may be one reason for non-adherence. So management of adverse drug reaction should be done in a simple and cost effective way without compromising the MDR-TB treatment regimen

11. ADHERENCE TO TREATMENT

- Adherence to TB treatment is crucial to achieving cure while avoiding the emergence of drug resistance. It means following the recommended course of treatment by taking all the medication, as prescribed, for the entire length of time necessary

- Regular and complete medication intake gives individual TB patients the best chance of cure and also protects the community from the spread of TB. The emergence and spread of MDR and XDRTB further reinforces the absolute necessity of helping a TB patient to not miss any drug doses. Hence supervision and patient support remain the cornerstone of DOTS

- At the initiation of TB treatment, it is important for the clinician to set aside enough time to meet with the patient and family. This is an opportunity to counsel, identify potential problems that the patient may face during treatment and plan for optimal adherence.

- Whenever the patient visits the health facility, the need for regular and complete intake of treatment should be reinforced by the DOT provider and any problems that may cause interruption should be identified

- It is essential for the DOT provider/ health worker to record the patients correct contact details as well as other contact addresses (e.g. spouse, parents, work place) so that patients can be readily located

- The consequences of inadequate and incomplete treatment can lead to prolonged illness and disability, increased mortality, continued TB transmission in the community, and development of drug resistant TB.

- Clear instructions should be provided about how to take the medication, possible side effects and what to do about these. A discussion about the difficulty in remaining motivated to continue with TB treatment once the client starts to feel better can help prevent treatment interruption

- Highlight important steps in the treatment plan such as dates when sputum are due, medication changed and treatment completed.

- Ensuring good adherence requires careful monitoring. Unless adequate records are kept of daily treatment, it is difficult to identify when treatment interruption occurs and to take remedial action.

Factors that Influence Adherence and Treatment Outcomes

Patient related factors	Treatment related factors
• **Stigma** • **Depression** • **Disempowerment** • **Poor knowledge about TB and the efficacy of treatment**	• **Complex treatment regimens** • **Large pill burden** • **Adverse effects of medication** • **Long treatment duration**
Health System related Factors	**Social and Economic Factors**
• **Poor health infrastructure** • **Poorly trained or supervised health care personnel** • **Low levels of accountability of health staff** • **Poor relationships with patients** • **Inadequate development of community based support for patient**	• Financial limitations • Poor support networks • Unstable living circumstances • Substance abuse • Beliefs about TB and its treatment

11.1 MANAGEMENT OF TREATMENT INTERRUPTION

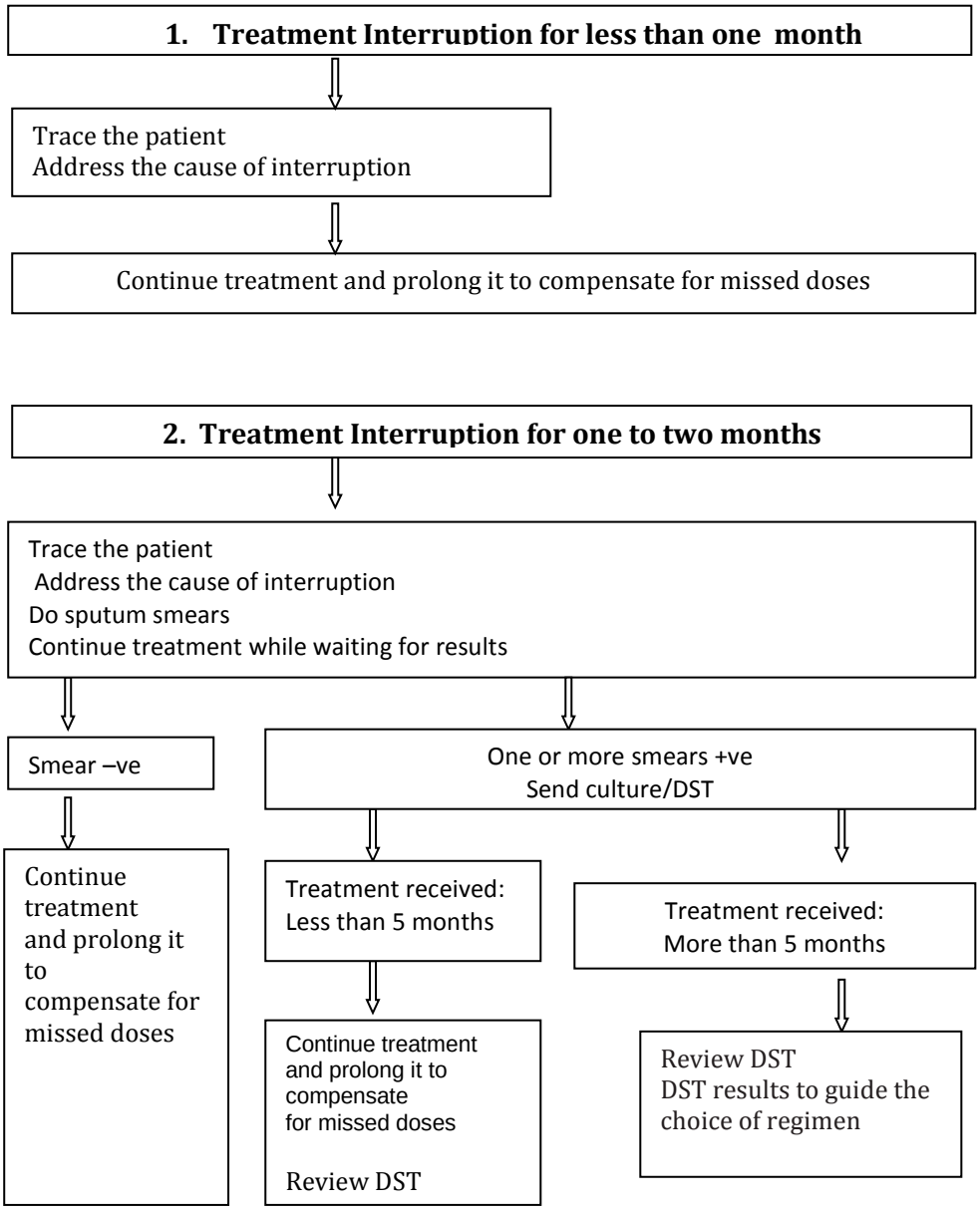
Directly observed treatment adapted to patient needs and accommodating the working conditions of DOT provider is certainly the best method of avoiding treatment interruption. However, even with directly observed treatment, there may be treatment interruptions that need to be addressed.

If a patient misses an arranged appointment to receive treatment, the DOT provider should ensure that the patient is contacted within a day after missing treatment and try to find the cause for it. The NTP should be informed if the patient cannot be contacted or repeated treatment interruptions or lost to follow up.

The management of patients who have interrupted treatment takes into consideration mmseveral factors:

- The patient is found to be smear or culture positive upon returning from default.
- Interruption occurs in the intensive, rather than the continuation, phase
- Interruption occurs early (rather than later) in the continuation phase.
- The interruption is of long duration.
- The patient is immune compromised (living with HIV or another condition)
- The patient had poor response to treatment before the interruption
- Drug-resistant disease is known or suspected.

All patients returning after treatment interruption should have their sputum send for culture and DST


1. Treatment Interruption for less than one month
Trace the patient
Address the cause of interruption
Continue treatment and prolong it to compensate for missed doses
2. Treatment Interruption for one to two months
Trace the patient
Address the cause of interruption
Do sputum smears
Continue treatment while waiting for results
Smear –ve
Continue treatment and prolong it to compensate for missed doses
One or more smears +ve
Send culture/DST
Treatment received: Less than 5 months
Continue treatment and prolong it to compensate for missed doses
Review DST
Treatment received: More than 5 months
Review DST
DST results to guide the choice of regimen
3. Treatment Interruption for two months or more
Trace the patient
Address the cause of interruption
Do sputum smears / culture/DST
Smear –ve
Clinical decision to continue/restart
Review DST
One or more smears +ve
Review DST
DST results to guide the choice of regimen

11.2 ADMISSION OF TB PATIENTS

TB patients do not routinely require admission and can be managed in the community as out patients.TB patients will be admitted to hospital care when either their clinical condition warrants it or due to social or socio-medical reasons

Reasons for admission include:

- when TB patient is too ill or too weak to go home, including severely emaciated TB patients
- severe forms of TB such as TBM
- Extra pulmonary TB for diagnostic workup
- previously non compliant patients
- high risk groups likely to default such as drug dependence, migrant workers
- All MDRTB/XDRTB patients for the initial 4 weeks of treatment for patient and family counselling and adherence promoting strategies
- severe adverse reactions requiring admission

It is equally important that TB clients be discharged to outpatient care as soon possible as they can be managed effectively in the community with DOT support.

11.3 PATIENT REFERRAL

Patients from island and Atoll levels should be referred to a regional or tertiary hospital (IGMH) if their clinical condition warrants more specialised care than the hospital can provide. This includes:

- All severe complications of TB disease e.g. massive haemoptysis, Severe dyspnoea
- TB meningitis
- Empyema.
- Severe drug reactions e.g. acute liver failure, Steven Johnson syndrome
- Unavailability of diagnostic facilities especially for EPTB such as FNAC etc
- Suspected MDRTB to be referred to IGM Hospital

Referral to another hospital should always be done by completing the referral form in detail with all the relevant information and getting a copy of the treatment card to accompany the patient to the referral hospital. The referral Hospital should be contacted and informed in advance regarding the transfer.

12. CONTACT SCREENING AND MANAGEMENT

Contact investigation is to be conducted for house hold and close contacts when the index case has Pulmonary TB or has MDR or XDRTB or is a child < 5years of age

PLHIV and Children <5 years of age who are household or close contacts should be treated for LTBI after ruling out active TB with INH for 6 months

Adults and children >5 years diagnosed with LTBI should be evaluated for risk status and if high risk, to recommend prophylactic chemotherapy. If low risk, to advice to watch for TB symptoms and review if any symptoms develop

Treatment of latent MDRTB with second line anti B drugs is not recommended

The objective of screening is to ensure that active TB is detected early and treatment is initiated promptly thus helping to reduce TB transmission. It also identifies contacts that were recently infected and because the risk for developing TB is increased for 1–2 years after infection, all contacts should be informed about the increased risk and about the symptoms that could indicate TB.

The diagnosis of LTBI is based on information gathered from the medical history, TST or IGRA result, chest radiograph, physical examination, and in certain circumstances, sputum examinations. The presence of TB disease must be excluded before treatment for LTBI is initiated because failure to do so may result in inadequate treatment and development of drug resistance

DEFINITIONS

Index case (index patient): The initially identified case of new or recurrent TB in a person of any age in a specific household or other comparable setting in which others may have been exposed

Contact: Any person who has been exposed to an index case (as defined above)

Household contact: A person who shared the same enclosed living space for one or more nights or for frequent or extended periods during the day with the index case during the 3 months before commencement of the current treatment episode

Close contact: A person who is not in the household but shared an enclosed space, such as a social gathering place, workplace or facility, for extended periods during the day with the index case during the 3 months before commencement of the current treatment episode.

Contact investigation: A systematic process intended to identify previously undiagnosed cases of TB among the contacts of an index case. In some settings, the goal also includes testing for LTBI to identify possible candidates for preventive treatment. Contact investigation consists of two components: identification and prioritization, and clinical evaluation.

Contact clinical evaluation: A systematic process for the diagnosis or exclusion of active TB among contacts.

Clinical evaluation of household and close contacts for active TB is recommended as a priority on the basis of their risk for developing active TB or for the potential consequences of the disease if it develops.

It is recommended that contact investigation be conducted for house hold and close contacts when the index case has any of the following characteristics:

- **pulmonary TB**: Patients with pulmonary TB can transmit M. tuberculosis but people with a positive sputum smear are more infectious than people with negative smears, contact investigation may be limited to new or recurrent cases with positive sputum smears if resources are limited
- **MDR-TB or XDR-TB**
- **PLHIV**
- **Child < 5 years of age**: Generally, children do not have highly infectious forms of TB; however, when a child <5 years of age develops TB, it is likely that the infection was acquired from a person in the household. The rationale for assigning high priority to contacts of index cases < 5 years of age is to find the source of the infection, not to find secondary cases from the child

Contacts should always be informed about the procedure, the implications of the test results, including the potential benefits and harms of screening and the potential harm of not being screened. For migrants this should be done in a language that has been adapted to and is suitable for the participants to ensure that they understand the information.

Timing of interviews and identification of contacts

If contact investigation is to be initiated, the index case should be interviewed as soon as possible after diagnosis to elicit the names of household and close contacts.

The focus should be on household members, but people in the workplace and other settings in which there is exposure should not be ignored. Moreover, contacts in residential care facilities, prisons and acute medical care facilities, especially when exposure is by coughing, should be

evaluated. Occasionally, a second interview is useful to elicit additional contacts. Information from the interview should be recorded

Contacts of known or suspected cases of MDR-TB and XDR-TB should be evaluated with greater urgency because of the potential consequences of drug resistant TB should it develop in the contact and children < 5 years of age who are highly vulnerable to TB and may have more severe forms of the disease, should also be evaluated promptly.

TREATMENT FOR TB INFECTION

PLHIV who are household or close contacts of people with TB and who after an appropriate clinical evaluation, are found not to have active TB should be treated for LTBI

Children <5 years of age who are household or close contacts of people with TB and who, after an appropriate clinical evaluation, are found not to have active TB should be treated for LTBI

Adults and children above 5 years diagnosed with LTBI should be evaluated for risk status and if high risk, to recommend prophylactic chemotherapy. If low-risk, to advice to watch for TB symptoms and review if any symptoms develop to re-assess.

Mass screening:
Indiscriminate mass screening should be avoided
Prioritization of risk groups for screening should be based on assessments made for each risk group of the potential benefits and harms, the number needed to screen and the cost effectiveness of screening

- Household contacts and other close contacts should be systematically screened for active TB
- Systemic screening should be considered in prisons and other penitentiary institutions
- screening for active TB among migrant workers and among alcohol use disorder and IV drug users
- Systematic screening for active TB should be considered in people with an untreated fibrotic chest X-ray lesion

12.1 TUBERCULIN SKIN TESTING
TSTs have been used worldwide for more than a century to determine TB infection. A positive TST result is associated with an increased risk for current or future active tuberculosis Limitations of TSTs:

- requires proper administration
- patients must return to a health-care provider for test reading

- inaccuracies and bias exist reading the test
- false-positive TSTs can result from contact with NTM or BCG vaccination

The only internationally recommended method of tuberculin skin testing is the Mantoux technique, which consists of intradermal injection of 0.1ml of 5TU purified protein derivative solution

ADMINISTRATION

Handling the tuberculin solution

- The solution should be stored at 2° to 8°C, and should discard if frozen
- Do not transfer from one container to another {potency of the PPD may be diminished)
- Draw up the solution just before injecting it. Do not preload syringes for later use as the potency of the PPD may be diminished.
- The solution can be adversely affected by exposure to light. PPD should be stored in the dark except when doses are actually being withdrawn from the vial.
- Discard the solution if the vial has been in use for longer than 1 month or for an undetermined amount of time (the potency of the solution may be diminished)

Preparing the person to be tested

- Seat the person comfortably, and explain the procedure
- Use the inner aspect of the forearm, preferably the non dominant arm (where administration and reading of the reaction is easiest), about 10 cm (4 inches) below the elbow; avoid areas with abrasions, swelling, visible veins or lesions. If there is a localized rash, a burn or localized eczema, avoid this area.
- If neither forearm is suitable, use the outside of the forearm or the upper arm. In this case mark the location clearly in the record. Cleanse the area to be injected with an alcohol swab and let it dry.
- Do not use local anesthetic cream, as application has been reported to cause localized edema, which could easily be confused with a positive TST result

Injecting the PPD tuberculin solution

- Use a 0.6 to 1.3, 26- or 27-gauge needle with a disposable plastic syringe
- Position the bevel of the needle so that it opens facing up.
- While holding the skin of the inner aspect of the forearm taut, insert the needle at a 5°-15°angle to the skin without aspirating. The tip of the needle will be visible just below the surface of the skin. The needle is inserted until the entire bevel is covered
- Administer the PPD by the slow intradermal injection of 0.1 mL of 5-TU.
- A wheal of 6-10 mm in diameter should appear. The wheal will typically disappear in 10-15 minutes. The size of the wheal is not completely reliable, but if a lot of liquid runs out at the time of injection and there is no wheal, then repeat the injection on the opposite

forearm, or on the same forearm as before, but at least 5 cm from the previous injection site.

- A drop of blood may be seen – this is normal. The person tested should be offered gauze to remove the blood but should be advised not to massage the site in order to avoid squeezing out the PPD and disrupting the test
- Do not cover the site with a bandage
- Tell the patient that he or she should not scratch the site but may perform all normal activities

MEASURING INDURATION

- The TST should be read by a trained health professional. Individuals without experience in reading a TST may not feel slight induration and the TST would be mistakenly recorded as 0 mm.
- Reading should be performed 48 to 72 hours after administration, as maximum induration can take up to 48 hours to develop, but after 72 hours it is difficult to interpret a reaction.
- If the TST cannot be read within 72 hours because of unforeseen circumstances, it should be repeated at an injection site far enough from that of the previous test that the reactions do not overlap. No minimum wait is required before the repeat test.
- The forearm should be supported on a firm surface and slightly flexed at the elbow
- Induration is not always visible, so palpate with fingertips to check whether induration is present. If there is induration, mark the border of induration by moving the tip of a pen at a 45° angle laterally toward the site of the injection

PRECAUTIONS

- Acute allergic reactions, including anaphylaxis, angioedema, urticaria and/or dyspnea, have been very rarely reported

The following people should not receive a TST:

- Those with positive, severe blistering TST reactions in the past or with extensive burns or eczema present over TST testing sites, because of the greater likelihood of adverse reactions or severe reactions.
- Those with documented active TB or a well documented history of adequate treatment for TB infection or disease in the past. In such patients, the test is of no clinical utility.
- Those with current major viral infections (e.g. measles, mumps, varicella).
- Those who have received measles or other live virus immunization within the past 4 weeks, as this has been shown to increase the likelihood of false-negative TST results. (Note that only measles vaccination has been shown to cause false-negative TST results,

but it would seem prudent to follow the same 4 week guideline for other live virus immunizations –mumps, rubella, varicella (chickenpox) and yellow fever.

However, if the opportunity to perform the TST might be missed, the TST should not be delayed for live virus vaccines since these are theoretical considerations.
(NOTE that a TST may be administered before or even on the same day as the immunizations but at a different site.)

The following people can receive a TST:

- Those with a history of receiving BCG vaccination
- Those with a common cold
- Those who are pregnant or are breastfeeding
- Those immunized with any vaccine on the same day
- Those immunized within the previous 4 weeks with vaccines other than the ones listed earlier
- Those who give a history of a positive TST reaction (other than blistering) that is not documented
- Those taking low doses of systemic corticosteroids, <15 mg prednisone (or equivalent) daily. It generally takes a steroid dose equivalent to ≥15 mg prednisone daily for 2-4 weeks to suppress tuberculin reactivity.

Classification of Tuberculin Skin Test Reactions

Interpretation of TST results is based on the measurement of the reaction in millimeters, the person's risk of acquiring TB infection, or the risk of progression to disease if infected

12.2 INTERFERON–GAMMA RELEASE ASSAYS (IGRAs)

IGRAs are used to determine if a person is infected with *M. tuberculosis* by measuring the immune response to TB proteins in whole blood. Specimens are mixed with peptides that simulate antigens derived from *M. tuberculosis* and controls. In a person infected with M. tuberculosis, the white blood cells recognize the simulated antigens and release interferon-gamma (IFN- γ); results are based on the amount of IFN- γ released.

- Advantages of IGRAs include the following:
    - Requires a single patient visit to conduct the test
    - Does not cause booster phenomenon.
    - Laboratory test not affected by health care worker perception or bias.
    - Results can be available within 24 hours.
    - Unaffected by BCG and most environmental mycobacteria

- Limitations of IGRAs include the following:
    - Blood sample must be processed within 8-30 hours after collection.

- Limited data exist on use in groups such as children younger than 5 years of age, persons recently exposed to TB, immune compromised persons, and those who will be tested repeatedly (serial testing)

Interpretation of IGRA Results

- Qualitative results are reported as positive, negative, indeterminate or borderline.
- Quantitative results are reported as numerical values that include a response to the TB antigen and 2 controls, nil and mitogen. Quantitative results may be useful for clinical decision making in individual cases, in combination with risk factors.

SELECTING A TEST TO DETECT TB INFECTION

- IGRAs are the preferred method of testing for:
  - Groups of people who have poor rates of return for TST reading and intepretation
  - Persons who have received BCG vaccination. IGRAs *use* M. tuberculosis specific antigens that do not cross react with BCG, and therefore, do not cause false positive reactions in BCG recipients.

- TST is the preferred method for testing for
  - Children under the age of 5 years

- Either TST or IGRA may be used without preference for all other groups

- Some may have a negative reaction to the TST if many years have passed since they became infected and may have a positive reaction to a subsequent TST because the initial test stimulates their ability to react to the test. This "booster phenomenon" may incorrectly be interpreted as a skin test conversion (going from negative to positive). For this reason, the "two-step method" is recommended at the time of initial testing for individuals who may be tested periodically
  If the first test result is negative, the TST should be repeated in 1–3 weeks and If the second test is positive, consider the person infected and evaluate and treat the person accordingly.
  When IGRAs are used for serial testing, there is no need for a second test because boosting does not occur.

13. RECORDING AND REPORTING

A standardized recording and reporting system is an important component of DOTS. It allows for assessment of case detection and treatment outcome against the targets set. It also allows for maintaining surveillance and monitoring with a regular two-way communication between central and peripheral levels. The NTP uses specific forms and registers for this purpose.

Laboratory request form for AFB microscopy
This form is to be filled in by the DOT provider/health worker who suspects TB in a patient and requests for a sputum examination from the laboratory. This form should be available in all health facilities and is to be filled and send along with the sputum specimen to the laboratory.

The form contains the bio-data of the patient/ date and time of sputum collection/ diagnosis/ physical appearance of sputum (ie : mucoid, purulent etc)

This form will be completed by the laboratory technician and returned to the requesting person as soon as the sputum examination is completed. One form will be used to communicate the two or three smear results of one patient. However when a sputum smear is positive, efforts will be made by the laboratory technician to inform the requesting clinician even before all two or three sample results are available.

TB Laboratory Register
This register is kept in every laboratory where AFB tests are performed. Each set of two sputum slides is given a laboratory serial number. All laboratories should be identified through their health facility code. This code should precede the slide number.

The results of the smear examinations must be recorded in the same line of the register. The Patient Registration Number of patients on treatment (in case of follow-up smears) should be noted in the appropriate column.

Tuberculosis Patient Treatment Card
This card contains all the information related to the patient and is opened at the initiation of treatment. A new card must be completed for every new registration and a copy of it will be sent to the NTP.

The card contains the Patient Registration Number. This is a unique number allocated to every TB patient at the time of registration. The number is allocated by the Male' NTP for all patients in the country. This implies that for every diagnosed TB patient, the Male' NTP needs to be informed so that the patient can be registered and allocated a serial number.

TB is a notifiable disease in Maldives. It is required to notify to NTP every patient as soon as the diagnosis is established.

The card needs to be updated with all tick marks for drug intake, as well as for follow up sputum results and treatment outcome. At the end of the treatment a copy of the completed treatment card will be sent to the NTP for updating the TB Treatment Register and archiving.

Tuberculosis Treatment Register

A Tuberculosis Treatment Register will be maintained at all Regional, Atoll hospitals and IGMH to keep track of their patients. All patients on treatment should be entered on the treatment register.

The treatment register contains all information of all patients with regard to diagnosis, disease classification, patient type, treatment regimen, sputum results (diagnosis and follow up) and treatment outcome.

Reporting

All TB reports from the Regional Hospitals and IGMH must be submitted to the NTP in for compilation, proper evaluation and further planning.
The reports to be submitted are:

-monthly report on cases registered, cases on treatment, no of slides checked and no. of slides found to be positive
-monthly TB Drug Stock Report
- Six Monthly Report on TB Buffer stock

Monitoring and evaluation the programme performance is done by the NTP and involves assessing activities, monitoring costs and expenditure, determining the extent of programme coverage and evaluating treatment outcomes.

At the central level the data collected will be analyzed by NTP and quarterly reports will be made on case finding, sputum conversion and treatment outcomes are generated and in addition the data is used for resource mobilization, international reporting requirements ,formulate program policy and advocacy for the programme

14. INFECTION CONTROL

Infection control measures should be established to reduce the risk of TB transmission to both the general population and to health care personnel

There are three types of infection control measures:

- Administrative control, including appropriate work practices
- Environmental control
- Personal respiratory protection

Administrative measures aim to reduce droplet nuclei containing Mycobacterium tuberculosis in health facilities and thus to reduce the exposure of staff and patients. These include:

-A comprehensive, written infection control plan

-Early recognition of TB suspects or confirmed TB cases through screening all clients entering facility with a cough for 2 weeks or more and ensuring that TB-suspects spend as little time as possible in the facility by fast tracking their process through reception

-Educating clients with a cough on respiratory hygiene:
Covering the nose and mouth with a tissue when coughing
Spitting / coughing into a tissue and discarding it into a designated bin
Use of disposable surgical masks by patients/staff who are coughing to reduce the spread of droplets when coughing

-Prompt investigation for TB in symptomatic clients

-Appropriate Collection of sputum samples

-Prompt follow-up of sputum results and commencing treatment if diagnosed with TB

-Educating health care personnel and patients to seek health care early when signs or symptoms of TB are present

-All health care personnel need to be trained to ensure that they understand the importance of infection control and how best to protect themselves and their clients

-All health care personnel should also be trained on the screening of TB suspects; this will help to reduce screening and diagnostic delays and improve TB case finding

Environmental control measures

Ventilation (natural and mechanical): Natural ventilation relies on open doors and windows and there should be adequate numbers of windows and doors opening to the outside to allow good ventilation. Windows on opposite sides of the room allow good cross ventilation.
Assisted ventilation using propeller fans on the ceiling, desk, and floor is an inexpensive way to improve natural ventilation.
Mechanical ventilation can be used in areas where there may be high concentrations of infectious droplets. The most cost effective are exhaust fans that are placed in windows.

Ultraviolet germicidal irradiation (UVGI): may be used as an adjunctive measure. For this to be effective the contaminated air has to come into contact with the rays; therefore circulation of air is important. It is ineffective in humid and dusty environments.

UVGI lamps are expensive, have to be installed properly for maximum effect and require a regular programme of maintenance. If not adequately maintained, lamps are ineffective and can cause acute or chronic skin and eye problems

Personal respiratory protection
Personal protection refers to the use of respirators that contain a special filter material that protects the wearer from inhaling the bacilli. They are most appropriately used for short-term protection against high-risk exposures e.g. during sputum inducing procedures and bronchoscopy.

The recommended respirator is the type that covers the mouth and nose and is fitted with a special particulate filter to filter out very small particles such as U.S. certified N95 or E.U. specified FFP2 should be recommended for use in health care settings.

Surgical masks do not protect the person wearing it from inhaling infectious particles as they are not sealed and have a limited filtration capacity. They are meant to prevent the spread of infectious particles from the person wearing the mask to others and are recommended for infectious patients.

Although less effective, using a tissue to capture large wet particles near the mouth and nose when coughing should be promoted

Protection of health care personnel
All categories of health care personnel have an increased risk of TB when compared to the general population. In addition to reducing their exposure, specific measures that target health care personnel are required

Health care personnel should be informed of the signs and symptoms of TB for early recognition of symptoms and if symptomatic should be evaluated as high risk TB suspects.

Health care personnel diagnosed with TB, should be provided VCT and encouraged to know their HIV status

HIV positive staff should receive precautionary measures, such as TB preventive therapy and antiretroviral therapy and should be placed in low TB risk areas of the facility.

Annexe 1.Weight based dosing of ATT in Adults

DRUGS	WEIGHT CLASS				
	30-35 Kg	**36-45kg**	**46-55kg**	**56-70kg**	**>70kgkg**
ORAL ATT					
Isoniazid (4-6mg/kg once daily)	150mg	200mg	300 mg	300 mg	300mg
Rifampicin(8-12mg/kg once daily)	300 mg	450mg	450mg	600mg	600mg
Ethambutol(15-25mg/kg once daily)	600mg	800mg	1000mg	1200mg	1200mg
PZA (20-30mg/kg once daily)	800mg	1000mg	1200mg	1600mg	2000mg
Levofloxacin (750-1000mg daily)	750mg	750mg	1000mg	1000mg	1000mg
Moxifloxacin (400mg daily)	400mg	400mg	400mg	400mg	400mg
Ethionamide(500-750mg/day in 2 divided doses)	500mg	500mg	750mg	750mg	1000mg
Prothionamide(500-750mg/day in 2 divided doses)	500mg	500mg	750mg	750mg	1000mg
Cycloserine(500-750mg/day in 2 divided doses)	500mg	500mg	500mg	750mg	750mg
P-aminosalicylic acid(8g/day in2 divided doses)	8g	8g	8g	8g	8-12g
Rifabutin(5-10mg/kg once daily)	300 mg	300 mg	300 mg	300 mg	300 mg
High dose INH(16-20mg /kg daily	600-1000mg	1000-1500mg	1500mg	1500mg	1500mg
Clofazimine	200-300mg daily (first 2 months) then 100mg				
Imipenem/cilastatin	1000mg twice daily				
Meropenem	1000mg three times daily (alternative twice daily)				
Linezolid	600 mg once daily.				

INJECTABLE ATT						
DRUG	**30-33kg**	**34-40kg**	**41-45kg**	**46-50kg**	**51-70kg**	**>70kg**
Streptomycin(12-18mg/kg daily)	500mg	600mg	700mg	800mg	900mg	1000mg
Kanamycin(15-20mg/kg daily)	500mg	625mg	750mg	875mg	1000mg	1000mg
Amikacin(15-20mg/kg daily)	500mg	625mg	750mg	875mg	1000mg	1000mg
Capreomycin(15-20mg/kg daily)	500mg	600mg	750mg	800mg	1000mg	1000mg

Anexxe 2: Pediatric dosing of ATT

Drug	Daily Dose(MG/KG)	Frequency	Max.daily dose
isoniazid	7-15mg/kg	Once daily	300mg
rifampicin	10-20mg/kg	Once daily	600mg
ethambutol	15-25mg/kg	Once daily	1200mg
pyrazinamide	30-40mg/kg	Once daily	2000mg
Streptomycin	20–40mg/kg	Once daily	1000mg
Kanamycin	15–30 mg/kg	Once daily	1000mg
Amikacin	15–30 mg/kg	Once daily	1000mg
Capreomycin	15–30 mg/kg	Once daily	1000mg
Levofloxacin	15-20mg/kg<5years	twice daily	750 mg
	10-15mg/kg>5 years	Once daily	
Moxifloxacin	7.5–10mg/kg	Once daily	400 mg
Ethionamide	15-20mg/kg	Twicedaily	1000mg
Prothionamide	15–20mg/kg	Twicedaily	1000m g
Cycloserine	10–20mg/kg	Once or twice daily	1 g
PAS	200-300mg/kg for <30kg	Twice daily	12 g

Annexe3 : TB contact screening and management SOP

Number: HPA/SOP/CD/TB/01

Date: 24th April 2013	**SOP-01**
First Edition	

Tuberculosis Contact Screening and Management SOP

Contact screening will be carried out by the Respiratory Medicine Clinic (RMC) at IGHM or the Tuberculosis focal points at all atoll hospitals.

Mass contact screenings will be coordinated by NTP central unit at HPA for Male', and NTP atoll focal points for atolls. A mass screening session may be organized for the initial screening as below, to be followed up and screening completed at RMC or atoll hospitals. An information session should be carried out before the mass screening session, and also after completing the screenings. Additional information sessions may be required following the initiation of screenings, as it is difficult for lay people to understand all the information about TB at one sitting.

Indications for Contact Investigation and Screening

Contact investigation is required for all cases of TB who are infective, and for children diagnosed with TB to identify a source of infection and treat the person. Contact investigation is indicated for all patients diagnosed with:

1. Sputum positive TB
2. TB in a person living with HIV/AIDS
3. Children < 5 years (to identify source and treat)
4. Multi-drug resistant TB (MDR-TB or XDR-TB (proven or suspected)

Contact investigation should be commenced as soon as possible once the patient has been started on treatment and counseled, and is ready to cooperate. A new patient may be expected to take upto about a week to adjust and be ready to cooperate. Investigation should begin at least within the first 1-2 weeks. A separate guideline will be available for contact investigation and identification.

Initial Contact screening (Step 1):

Requires a **Symptoms survey** + **Mantoux test** for all contacts.

Symptom survey:

- Cough > 3 weeks
- Weight loss
- Fever
- Blood in sputum or coughing blood

- Shortness of breath
- Chest pain
- Enlarged cervical lymph nodes

1. If symptoms (esp, cough) (+)ve, investigate as suspected patient (as in guideline). Give Mantoux and immediately arrange for Sputum test and CXR (for children <15yrs both AP+lat view) without waiting for Mantoux results.
   Arrange doctor consultation with test results.

2. If symptoms (-)ve, go to step 2:

   Step 2 of contact screening for asymptomatic persons:
   a. Mantoux negative, --> check exposure period –
      i. If more than 8 weeks after exposure, can be reassured and discharged with advice.
      ii. If less than 8 weeks from exposure - repeat screening with symptom survey and Mantoux after 8-12 weeks.

   b. Mantoux (+)ve→ do CXR.
      i. CXR abnormal → do sputum tests
      ii. CXR normal, - Latent TB (LTBI)

   ESR has no role in contact investigation or follow-up.

   Arrange doctor consultation with test results. Same day consultation if sputum (+)ve.

Note: If there is any practical difficulty in obtaining test results within the expected time (72 hours for Mantoux and 3-4 days for 3 sputum samples), NPT focal point and hospital care provider should facilitate an early doctor consultation to sort out any problems and get an early diagnosis.

NTP at atoll and central level is responsible for facilitating early diagnosis and treatment.

Prioritization for large number of contacts:

Where facilities are limited, early completion of tests and consultation should be prioritized in the following order:

1. Symptomatic contacts who are severely ill or have cough
2. Symptomatic contacts without cough and not severely ill
3. Asymptomatic contacts with high risk of TB disease (children below 5 years or immunocompromised)
4. Asymptomatic contacts with low risk of developing TB disease

Expected Outcomes from contact screening:

1. Well (No TB infection) – discharge with advice (should include advice on TB symptoms). If exposure is less than 10 weeks, follow-up and repeat screen after 8-12 weeks.
2. LTBI – Not all persons with LTBI need chemoprophylaxis. For high risk groups, see protocol below for prophylactic treatment.
3. TB disease- Start anti-TB treatment according to protocol.

Prophylactic treatment for high risk contacts:

1. All children below ≤5 years and persons who are immunocompromised (persons living with HIV, or on immunosuppressant therapy) should receive chemoprophylaxis with single drug regime of isoniazid for the prescribed period according to the national guidelines.
2. Immunocompromised persons should be followed up closely to watch for development of TB diisease.
3. Adults and children above 5 years diagnosed with LTBI should be evaluated for risk status and if high risk, to recommend prophylactic chemotherapy. If low-risk, to advice to watch for TB symptoms and review if any symptoms develop to re-assess.

Annexe 4: TB treatment card

NATIONAL TUBERCULOSIS CONTROL PROGRAMME
HEALTH PROTECTION AGENCY
MINISTRY OF HEALTH

TUBERCULOSIS TREATMENT CARD

TB NO.:	REGISTRATION DATE: …… DD/MM/YYYY	Treating Center:……	Type of TB: ☐ PTB - Sputum smear Positive (P+) ☐ PTB - Sputum smear Negative (P-) ☐ EP TB (site): ……..
Name: …… ……. Age: YY/MM Sex: ☐ Male ☐ Female		Permanent Address: …… Residential Address…… Treatment Supervisor: …… Supervisor Contact Address: ……	

Any TB Treatment before? ☐ **YES** ☐ **NO** Last regimen ☐ Was full treatment completed? ☐ **YES** ☐ **NO**

(Rx category)

Previous TB No:	Treatment Completed/Cured/Stopped	Day	Month	Year
Details on Patient Movements Referred to : …… ……Referred Date : …… …… Reference Chit No.: ……	…….... …….... ……....	…… ……... ……...	…… …… ……	…… …… …… …… ……

Registration Category		Treatment Category	Planned duration (mths)	Month	Results of sputum examination								Weight (kg)
					Local Lab			Reference Lab					
					Date	Smear	Lab. No.	Smear	Cult	Sensitivity			
										Sens	Res.		
New		New		0									
Relapse		Retreatment		4 wks									
Failure		Retreatment		2 mnth									
Returned Defaulter		OTHERS		4 mnth									
Transfer In				6 mnth									
Other				Rx End									

TB Treatment card……

TREATMENT SCHEDULE: (place a tick (✓) for each date after giving drugs as DOTS)

1. Intensive Phase

Treatment Start Date: _DD_/_MM_/_YYYY **Planned duration (mths):_____**
Planned End Date: _DD_/_MM_/_YYYY
Medicines: ☐ INH, ☐ RIF ☐ ETH, ☐ PRZ, ☐ _____ ☐ _____
No. of Tabs

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

2. Continuation Phase

Treatment Start Date: _DD_/_MM_/_YYYY **Planned duration (mths):_____** **Planned End Date:** _DD_/_MM_/_YYYY
Medicines: ☐ INH, ☐ RIF ☐ _____ ☐ _____ ☐ _____
No. of Tabs

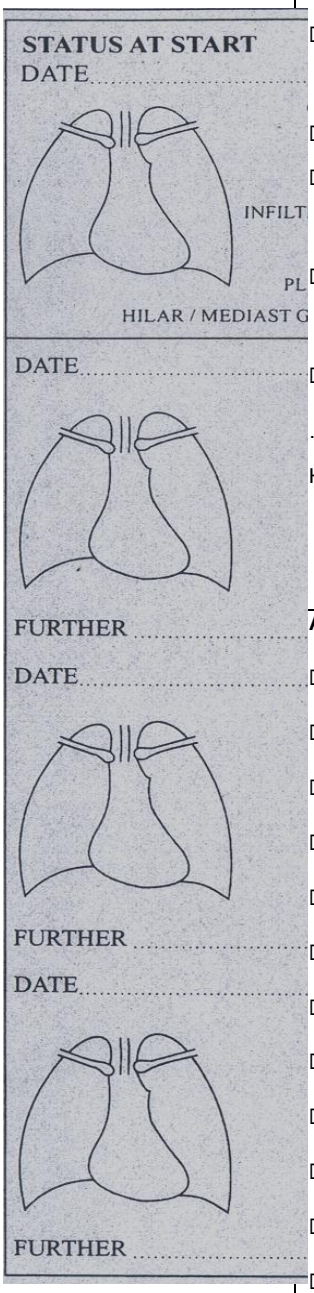
MONTH	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

TREATMENT OUTCOME:

Treatment stopped date:	D	M	Y

Outcome category	**Please tick and write date (DD/MM/YYYY)**
Cured	
Completed treatment	
Treatment Failure	
Death	
Lost to follow up	

Treatment card……



RISK FACTORS – ACTION TAKEN

☐ Smoker ☐ Quit Advice Given

☐ Referred for cessation

☐ Drug user ☐ Referred for Rx or rehab.

☐Alcohol user ☐ Quit Advice Given

☐ Referred for cessation

☐ Diabetes ☐ Referred for treatment

☐ Good control

☐Other (specify)☐ Referred for treatment

…….... ☐ Good control

HIV test done ☐ DO NOT write result here!

ADVERSE EVENTS OF MEDICINES

☐ Fever

☐ Rash

☐ Joint pains

☐ Peripheral neuropathy

☐ Abdominal pain, discomfort or nausea

☐ Vomiting

☐ Loss of appetite

☐ Jaundice

☐ Elevated AST/ALT

☐ Blurred vision

☐ Altered hearing or tinnitus

☐ Dizziness

☐ Tingling or numbness around the mouth

☐ Bleeding tendency

☐ Other (specify): …….....

DOCTORS NOTES AND RECOMMENDATIONS

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Treatment card,,,,,,,,,

CONTACT INFORMATION FOR CONTACT TRACING

NO.	NAME	RELATIONSHIP To PATIENT	AGE	ADDRESS	CONTACT NUMBER	CONTACT TRACING ACTION	
						Completed DATE DD/MM/YY	Cannot Trace (After Repeated Attempt) DD/MM/YY

Annexe5: Case Notification form

Health Protection Agency
Republic Of Maldives
Phone: 3014494 Fax:3014484 email: ntp.maldives@gmail.com
TB Case Notification Form

This form is to be used to report newly infected TB case to Health Protection Agency

1. Name of the Facility

Name of Facility: _____ Date of Submission: ____/_____/_____
DD MM YYYY

Email/Telephone Number: _____

2. Case Details

Case Classification: Suspect ☐ Probable ☐ Confirmed ☐

Full Name: _____ Permanent Address: _____
Current Address: _____ Contact No : _____
Sex: Male ☐ Female ☐ Age (Years): ___ Type of TB: Pulmonary ☐ Extra Pulmonary ☐
Site : _____
Date of Consultation: _____
Occupation: _____

4. Classification of current diagnosis (Please tick)

New ☐ Relapse ☐ Re-treatment ☐ Failure ☐

5.Treatment Category

New ☐ retreatmentl ☐ 2nd line Drugs

6. Details of Drugs (as prescribed)

7. Investigation Report

Sputum result

	Date	Result
1st Sample		
2nd Sample		
3rd Sample		

X-Ray result

Date	Findings (+/-)

Reporter Details
Name: **Designation:** **Signature:**

Instructions

- All the Health facilities should fill the first three parts of the form. This includes
  1. Name of the facility
  2. Case details
  3. Patient information
- If the case is a confirmed case the health facility should fill the entire form.
  Including the:
  4. Classification of current diagnosis
  5. Treatment Category
  6. Details of category drugs
     - Name of the drugs, dosage ,route and the duration of the treatment should be specified.
  7. Investigation Report
     - Sputum result should be written for all three samples with the date
     - If X-ray done specify the date and in the findings column write if positive(+) or Negative.
     - '***Positive***' means the X-ray has features that are compatible with pulmonary TB
     - '***Negative***' means that the X-ray has no features that are suggestive or compatible with pulmonary TB.

Annexe 6: Sputum request and reporting form

Sputum Examination Result for AFB

SPUTUM EXAMINATION RESULT FOR AFB

Name of requesting Health Centre:_____ Date: _____

Name of patient: _____ Age: _____ Sex: ☐M ☐ F

Permanent address: _____

_____

Type of TB: ☐ Pulmonary

☐ Extra-pulmonary Site: _____

Reason for examination ☐ Diagnosis

☐ Follow-up

For follow-up smears: Patient's register number _____

Laboratory Serial Number: _____

Visual appearance of sputum:	Mucopurulent	Blood-stained	Saliva
Specimen 1	☐	☐	☐
Specimen 2	☐	☐	☐
Specimen 3	☐	☐	☐

Microscopy Result (staining method: Ziehl-Neelsen)

Date	Specimen	Result*	Positive (grading)			
			3+	2+	1+	AFB#(1-9)
	A					
	B					
	C					

* Write "neg" (negative) or "pos" (positive)

1-9 AFB grading column: write the exact numbers per 100 hpf

Date: _____ Signature _____

Annexe7: National TB register

TB REGISTER FOR SPUTUM POPSITIVE PUMONARY PATIENTS

NTB NO	NAME	AGE	GENDER	TYPE (P/NP)	CLASSIFY (NEW,RELAPSE,DEFAULT,RE-TREATMENT)	PERMENANT ADDRESS		REFFERED FROM	DATE REGISTERED	STATUS	DISCHARGE DATE
						ADDRESS	ISLAND				

TB REGISTER FOR SPUTUM NEGATIVE PUMONARY /EXTRA PULMONARY PATIENTS

NTB NO	NAME	AGE	GENDER	TYPE (EP/NP)	TYPE (IFEP)	CLASSIFY (NEW,PREVIO TREATMENT)	PERMINET ADDRESS		REFFERED FROM	DATE REGISTERED	STATUS	DISCHARGE DATE
							ADDRESS	ISLAND				

NTB NO National TB Regiter Number
P Pulomonary
New
NP pulmonary
EP EXTRA- PULMONARY

Annexe8: Register for chemoprophylaxis

Chemoprophylaxis Register

ChP No:	Name	Age	Sex	INDEX case	Address	Island Address	Register Date	Status	Discharged Date

Annexe 9: TB monthly reporting form

بسم الله الرحمن الرحيم

Health Protection Agency

Republic Of Maldives

Phone: 3014494 Fax: 3014484 email: ntp.maldives@gmail.com

TB MONTHLY REPORTING FORM

Name of the Facility:……

Reporting Period:……/……/…… to ……/……/……

TB BUFFER STOCK

DRUGS/COMMODITY	STOCK RECEIVED		DURING MONTH		BALANCE
	DATE RECEIVED	EXPIRY DATE	AMOUNT USED	EXPIRY DATE	
TB KITS					
MANTOUX					

TB PATIENTS CURRENTLY ONTREATMENT

TBPATIENT No	NAME	ADDRESS	ISLAND	TREATMENT STARTED	
				DATE	FACILITY

TB PATIENTS WHO DEFAULTED

TB PATIENT NO	NAME	ADDRESS AND ISLAND	DEFAULT DATE	REASON

Report prepared by: Designation:

Date: Signature:

INSTRUCTIONS

This entire form is to be completed by the Atoll hospital with relevent information collected from the islands in the Atoll·

- TB Buffer Stock is kept in every Atoll hospital for easy access to the drugs if any patient is been diagnosed within the Atolls·
- All TB patients currently on treatment in the Atoll (including island level) should be listed in this form·
- If Any deafults are recorded in any island of the Atoll, it should be mentioned in this form with the relevent reason for the deafult·

  (For monitoring purposes in this form,**treatment outcome="default" if a patient has not taken anti-TB drugs for 3 or more consecutive days after starting treatment, or has missed receiving treatment intermittently more than 3 times for a period of 2 weeks)**

  If a patient has defaulted as in the above definitions, every effort must be taken to trace the person and continue regular treatment· If patient cannot be traced within 1 week of the date of defaulting, **please report this patient to NTP immediately** by phone and fax or email without waiting to send as monthly report·

Annexe 10: TB monthly reporting form RMC

National TB Control Programme

Health Protection Agency

Telephone: 3014494 Fax, 3014484

TB MONTHLY REPORTING FORM (RMC)

Name of the Facility: Respiratory Medicine Clinic

Repoting Period: ……/……/…… to ……/……/……

COUNTS OF TB PATIENT	Pulomonary		Extra-Pulomonary	Under 5 years	5 Years & Above	Total
	+ve	-ve				
No of TB Patients on-treatment						
No of TB patients newly registered						
No of patients attending for DOTs treatment						
No of TB patients completed treatment						
No of defaults						
No of relapse cases						
No of re-treatment cases						
No of MDR TB patients						
No of XDR TB patients						
No of Poly-treatment cases						
No of Mono resistant cases						
No of patients Diagnosis changed						
No of patients refered to other health facilities						
No of Patients on 2nd line Drug						
No of patients on prophylaxis treatment						
No of patients newly started prophylaxis						
No of Contacts identified						
No of Contacts screened						
No of Contacts to be followed up						
No of Sputum samples collected						
No of Sputum samples "Positive"						
No of Consultations						
No of Patient Consultations						
Total						

Annexe11: Medicine stock reporting form

TB MEDICINES STOCK

DRUGS/COMMODITY	Stock received			During month		Balance
	Date received	Amount received	Expiry date	Amount used	Expiry date	
First line drugs						
Ethambutol 400mg						
Ethambutol 600mg						
Pyrazinamide 400mg						
Pyradoxine 40mg						
INH 300mg						
INH 100mg						
Rifampicine 150mg						
Rifampicine 300mg						
Rifampicine Syrup 200ml						
Second line drugs						
Cycloserine 250mg						
Levofloxacine 500mg						
Levofloxacine 250mg						
Kanamycine 1g						
Water for Injection 5ml						
Ethiniomide 250mg						

Prepared by

Name:

Signature:

Approved by

Name:

Signature:

2

Annexe 12. INFORMATION SHEET FOR SCREENING ACTIVE TB

NO	NAME	ADDRESS	AGE	Weigh t	BCG Scar	Cough > 2 wks	Feve r	Wei ght Loss	Short ness of Breat h	Lymp node Enlarge ment	Fatig ue	Othe r Sym pto ms	Manto ux readin g mm
1													
2													
3													
4													
5													
7													
8													
9													
10													
11													
12													

References

- Treatment of tuberculosis guidelines. 4th edition. Geneva: World Health Organization; 2010 (http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pd

- Definitions and reporting framework for tuberculosis – 2013 revision. Geneva: World Health Organization

- TB CARE I. International Standards for Tuberculosis Care, Edition 3. TB CARE , The Hague, 2014

  Treatment of tuberculosis: guidelines for national programmes, 3rd ed. Geneva, WHO, 2003 (WHO/CDS/TB/2003.313).

  Enarson DA et al. Management of tuberculosis: a guide for low-income countries, 5th ed. Paris, International Union against Tuberculosis and Lung Disease, 2000.

- Guidelines for establishing DOTS-Plus pilot projects for the management of multidrug resistant tuberculosis (MDR-TB). Geneva: World Health Organization; 2000 (WHO/CDS/TB/2000.279) (whqlibdoc.who.int/hq/2000/WHO_CDS_TB_2000.279.pdf

- Lawn SD, Nicol MP. Xpert ®MTB/RIF assay: development, evaluation and implementation of a new rapid molecular diagnostic for tuberculosis and rifampicin resistance. Future Microbiology 2011;6(9):1067–1082

- Policy statement on molecular line probe assays for rapid screening of patients at risk of multidrug-resistant tuberculosis (MDR-TB). Geneva: World Health Organization; 2008

- Prerequisites to country implementation of Xpert MTB/RIF and key action points at country level. Geneva:WorldHealthOrganization;2011

- Guidelines for the programmatic management of drug-resistant tuberculosis. 2011.. Geneva: WorldHealthOrganization;2011

- Revision of the case definition for sputum smear-positive tuberculosis: background document. Geneva:WorldHealthOrganization;2011

- Guidance for national tuberculosis programmes on the management of tuberculosis in children. 2nd edition. Geneva: World Health Organization; 2014

- Policy guidance on drug susceptibility testing (DST) of second-line anti-tuberculosis drugs. Geneva: World Health Organization

- Guidance on regulations for the transport of infectious substances 2013–2014. Geneva: World Health Organization; 2012

- Policy statement on fluorescence light-emitting diode (LED) microscopy for diagnosis of tuberculosis. Geneva: World Health Organization; 2011

- XpertMTB/RIF implementation manual. Technical and operational 'how-to': practical considerations. Geneva: World Health Organization;2014

- Policy guidance on drug-susceptibility testing (DST) of second-line antituberculosis drugs. Geneva: World Health Organization; 2008

- Guidelines for the programmatic management of drug-resistant tuberculosis, 2011 update. Geneva: World Health Organization; 2011

- Guidelines for the programmatic management of drug-resistant tuberculosis, Emergency update 2008. Geneva: World Health Organization; 2008

- Companion handbook to the WHO guidelines programmatic management of drug-resistant tuberculosis,2014; World Health Organization