

Primary Care Management of **Rifampicin-Resistant Tuberculosis**



National Clinical Management Training

Participant Manual

10 Oct 2023 v7



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Programme Agenda

Day 1

Module 1: Epidemiology of Drug-Resistant Tuberculosis

Module 2: Overview of Tuberculosis

Module 3: Diagnosing Tuberculosis (All forms)

Module 4: TB Preventive Therapy

Module 5: Treating Active DS-TB

Case Studies

Day 2

Module 6: RR-TB Treatment Initiation

Module 7: RR-TB Regimens

Module 8: RR-TB Pharmacology and Side-Effects

Module 9: Monitoring and management on RR-TB treatment

Case Studies

Day 3

Module 10: RR-TB in Special Populations (incl. HIV)

Module 11: Patient Centred Care

Module 12: Tuberculosis Infection Control

Module 13: Recording & Reporting in RR-TB

Case Studies

Welcome

[Rifampicin-Resistant Tuberculosis in South Africa]

South Africa has the world's highest rate of Mycobacterium Tuberculosis (TB)/Human immunodeficiency virus (HIV) co-infection and ranks third worldwide for rifampicin-resistant (RR-TB) incidence and HIV prevalence. Despite advances made in treatment and diagnosis over the past decade, rifampicin-resistant TB remains a growing threat to public health. South Africa has been a global leader in introducing innovation to the field of RR-TB, including the implementation of shorter 6-month regimens known as BPaL-L and BPaL.

Following the COVID-19 pandemic, TB care cascade gaps have increased with fewer patients tested, diagnosed, and successfully treated. The TB Recovery Plan v2.0 aims to find people with undiagnosed TB in communities, link and retain them in care. The plan also prioritises TB prevention, improvement of TB surveillance systems, advocacy, communication and social mobilisation. The TB Recovery Plan 2.0 is aligned with the SANAC AIDS Council's Strategic Plan (NSP) for HIV, TB and STIs 2023-2028.

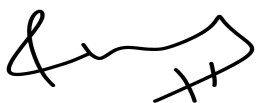
[About This Course]

This RR-TB Clinical Management course is designed for health care workers (HCWs) serving at DR-TB treatment initiation sites, including decentralised sites and centres of excellence, to prepare them to plan and deliver RR-TB care. The course provides a detailed overview of RR-TB management – with a special emphasis on treatment initiation by primary health care (PHC) nurses, clinical nurse practitioners (CNP) and medical officers.

Participants of the course are trained to synthesize theoretical content and apply it to the diagnosis and management of patients with RR-TB, enhancing their capacity to support and strengthen RR-TB and HIV management in primary health care facilities.

Upon completion of the course, medical officers will have the necessary information to begin working with specialized RR-TB physicians to initiate community-management, and PHC/CNPs will be positioned to begin the additional trainings required to manage RR-TB patients.

The interactive didactic curriculum includes 13 modules, focusing on how to diagnose, care, manage and treat RR-TB. The objective of the training is to enhance and strengthen the role of health care professionals in providing quality care to patients.



Prof. Norbert Ndjeka

Chief Director: TB Control & Management

14 Sept 2023

[Course Competencies]

At the end of the course, it is expected that participants will be able to:

- ▶ Describe the epidemiology of drug-resistant TB
- ▶ Diagnose RR-TB infection accurately
- ▶ Manage RR-TB patients in adults, including pregnant women
- ▶ Identify correct treatment regimens for RR-TB management, including the modified short and extended regimens
- ▶ Manage clients presenting with all forms of TB including those co-infected with HIV
- ▶ Recognise and manage all adverse reactions associated with antiretroviral and TB treatment
- ▶ Detail appropriate diagnostic approaches to evaluate adverse drug reactions
- ▶ Recognise possible treatment failure based on clinical symptoms
- ▶ Explain the criteria for RR-TB care
- ▶ Identify strategies to assist clients and patients in improving treatment adherence
- ▶ Identify the recording and reporting systems necessary in RR-TB management
- ▶ Understand how to complete patient's files in full, allocate treatment outcome, compile outcome report of cohorts

[Course Materials]

Course materials include a Participant Manual, and training slides. The participant Manual includes course handouts, worksheets, and activities that correspond to the course content. Job aids may be included in the participant handout or as stand-alone documents.

The course is conducted using the following teaching and learning methods:

- ▶Lecture
- ▶Case studies
- ▶Large- and small-group work and discussions
- ▶Individual work
- ▶Demonstration and practice

[Course Evaluation]

This course will be evaluated based on a pre- and post-training assessment of participants. Evaluations will also be conducted at the end of the training.

Abbreviations

ABC	Abacavir	d4T	Stavudine
ADR	Adverse drug reaction	ddl	Didanosine
aDSM	Active Drug Safety Monitoring & Management	DLM	Delamanid
AE	Adverse event	DNA	Deoxyribonucleic acid
AFB	Acid-fast bacilli	DOTS	Directly observed treatment, short-course
AIDS	Acquired immunodeficiency syndrome	DRS	Drug Resistance Surveillance
ALT	Alanine aminotransferase	DRT	Drug-resistant therapy
Am	Amikacin	DR-TB	Drug-resistant tuberculosis
Amx/Clv	Amoxicillin/Clavulanate	DST	Drug susceptibility testing
ART	Antiretroviral treatment/therapy	DTG	Dolutegravir
ARV	Antiretroviral	E	Ethambutol
AST	Aspartate aminotransferase	ECG	Electrocardiogram
ATV	Atazanavir	EDL	Essential drug list
AZT	Zidovudine (also known as ZDV)	EDST	Extended drug susceptibility test
bd	Twice daily	EFV	Efavirenz
Bdq	Bedaquiline	EPTB	Extrapulmonary Tuberculosis
BPaL	Bedaquiline, Pretomanid, and Linezolid	Eto	Ethionamide
BPaL-L	Bedaquiline, Pretomanid, Linezolid, Levofloxacin	FBC	Full blood count
CBO	Community-based organizations	FDC	Fixed Dose Combination
CC	Culture conversion	FEV1	Forced expiratory volume in 1 second
CDC	Centers for Disease Control and Prevention	FIND	Foundation for Innovative New Diagnostics
Cfz	Clofazimine	FTC	Emtricitabine
Clr	Clarithromycin	Gfx	Gatifloxacin
CMV	Cytomegalovirus	GI	Gastrointestinal
CNP	Clinical nurse practitioner	GXP	GeneXpert
CNS	Central nervous system	H	Isoniazid (regimen abbreviation)
CP	Continuation phase	HAART	Highly active antiretroviral therapy
CPK	Creatinine phosphokinase	HB	Haemoglobin
Cs	Cycloserine	HBV	Hepatitis B virus
CSF	Cerebrospinal fluid	HCT	HIV counseling and testing
CPT	Cotrimoxazole preventive therapy	HCT	Hematocrit
CTX	Cotrimoxazole	HCV	Hepatitis C virus
CXR	Chest x-ray	HCW	Health care worker

HIV	Human immunodeficiency virus	PHCs	Primary health care centres
HPF	High-power field	PI	Protease inhibitor
HR-TB	Isoniazid resistant tuberculosis	PMTCT	Prevention of vertical transmission
Im	Imipenem	PTB	Pulmonary tuberculosis
IND	Indinavir	Pto	Prothionamide
INH / hdINH	Isoniazid / high-dose isoniazid	PZA	Pyrazinamide
INJ	Injectable agent	qd	Once daily
IP	Intensive phase	QTc	Corrected QT interval
IPC	Infection prevention and control	RIF	Rifampicin
IPT	Isoniazid preventive treatment	RNA	Ribonucleic acid
IRIS	Immune reconstitution inflammatory syndrome	RR-TB	Rifampicin-resistant tuberculosis
KS	Kaposi sarcoma	RT	Reverse transcriptase
Lfx	Levofloxacin	S	Streptomycin
LTB	Latent TB infection	SCC	Short-course chemotherapy
LPA	Line Probe Assay	SLD	Second line drug
LZD	Linezolid	SL	Second-line
MC&S	Microscopy, culture and sensitivity	SQV	Saquinavir
MDR-TB	Multidrug-resistant tuberculosis	STIs	Sexually transmitted infections
MGIT	Mycobacterial growth indicator tube	TAT	Turn around time
MO	Medical officer	tds	Three times daily
Mfx	Moxifloxacin	TB	Tuberculosis
NAAT	Nucleic acid amplification testing	TB NAAT	TB Nucleic Acid Amplification Test
NDoH	National Department of Health	TDF	Tenofovir disoproxil fumarate
NFV	Nelfinavir	TDS	Three times a day
NGO	Non-governmental organisation(s)	TEE	Tenofovir + emtricitabine + efavirenz
NIMART	Nurse initiated management of antiretroviral therapy	Th	Thioacetazone
NIMDR	Nurse initiated management of MDR TB	TLC	Total lymphocyte count
NNRTI	Non-nucleoside reverse transcriptase inhibitor	TLD	Tenofovir, Lamivudine, Dolutegravir
NRTI	Nucleoside reverse transcriptase inhibitor	TMP	Trimethoprim
NTM	Non-tuberculosis mycobacteria	Trd	Terizidone
NVP	Nevirapine	TSH	Thyroid stimulating hormone
OHL	Oral hairy leukoplakia	UIF	Unemployment insurance fund
Ofx	Ofloxacin	UTI	Urinary tract infection
OIs	Opportunistic infections	UVGI	Ultraviolet germicidal irradiation
Pa	Pretomanid	Vi	Viomycin
PAS	Para-aminosalicylic acid	VZV	Varicella zoster virus
PCP	<i>Pneumocystis Jiroveci (Carinii)</i> pneumonia	XDR-TB	Extensively drug-resistant tuberculosis
PCR	Polymerase chain reaction	WBC	White blood cells
pDST	Phenotypic DST	WHO	World Health Organization

Key Terms

- a** **acid-fast bacilli (AFB)** – mycobacteria that when stained, retain color even after they have been washed in an acid solution; may be detected under a microscope in a stained smear
- action plan** – a plan to determine what information is missing or pending, where and when to collect this information, and who will need the information
- active case finding** – identifying unreported cases of TB disease by actively searching for them through, for example, laboratory and pharmacy audits
- adherence agreement** – a written understanding between a health care worker and a patient that indicates the activities they both agree to carry out. For some patients, this written commitment increases the likelihood of adherence
- adherence plan** – a written plan that is based on the patient’s understanding and acceptance of the TB diagnosis, that addresses barriers to adherence, and that details the method chosen to deliver treatment and monitor adherence for that specific patient
- adherence to treatment** – following the recommended course of treatment by taking all the prescribed medications for the entire length of time necessary
- administrative controls** – the first level in the hierarchy of TB infection-control measures; managerial measures that reduce the risk for exposure to persons who have or are suspected to have TB disease
- admission note** – patient information recorded at the time of admission to a hospital, usually including the admission diagnosis and initial plan for diagnostic work-up; usually included in the progress notes
- adverse reaction** – negative side effect resulting from the use of a drug (for example, hepatitis, nausea, headache)
- AIDS** – acquired immunodeficiency syndrome, a condition in which the immune system is weakened and therefore less able to fight certain infections and diseases; AIDS is caused by infection with the human immunodeficiency virus (HIV)
- alternative medicine** – health care other than conventional, scientifically tested, medicinal treatment; includes herbal remedies, yoga, meditation, acupuncture, and other practices intended to maintain or improve health
- alveoli** – the small air sacs of the lung that are at the end of the airway; when droplet nuclei reach these air sacs, TB infection begins
- amikacin** - injectable agent that could be used as part of a rescue regimen in DR-TB
- anergy** – the inability to react to a skin test because of a weakened immune system, often caused by HIV infection or severe illness (see **anergy testing**)
- anergy testing** – giving skin tests using substances other than tuberculin; done in select situations to determine whether a person is anergic
- antigen** – protein substances that can produce an immune response (such as CFP-10, ESAT-6, or those in PPD)
- antiretroviral therapy (ART)** – a lifelong combination drug treatment to improve the quality and length of life for a person living with HIV/AIDS
- assessment** – talking to a patient to find out about his or her medical history, knowledge about TB, feelings and beliefs about TB treatment, and other pertinent information
- authorization** – permission given by the patient to allow a third party to have access to the patient’s confidential information
- autonomy** – the right of a patient to determine what will be done with his or her body, personal belongings, and personal information; this concept applies to any adult person who is mentally competent
- b** **bacteriologic examination** – tests done in a laboratory to diagnose TB disease; includes examining a specimen under a microscope, genotypic testing i.e. TB-NAAT (Xpert Ultra etc.), culturing the specimen, and testing for drug susceptibility
- bactericidal** - kills bacteria
- bacteriostatic** - inhibition of the growth of bacteria without killing the bacteria

barrier – anything that can prevent a patient from being able to adhere to a TB treatment regimen behavioral diagnosis – used to find out what is causing a patient to have problems with adherence and to develop strategies to improve the patient's treatment plan

baseline skin test – a tuberculin skin test (TST) given to employees or residents in certain facilities when they start their job or enter the facility (see **TB testing programme** and **two-step testing**)

bedaquiline - new second line drug used in treating RR-TB

BCG – bacille Calmette-Guérin (BCG), a vaccine for TB disease that is used in many countries, but rarely used in the United States; may cause a false-positive reaction to the TST but does not affect QuantiFERON®-TB Gold test (QFT-G) results

bronchoscopy – a procedure used to obtain pulmonary secretions or lung tissue with an instrument called a bronchoscope; used only when patients cannot cough up sputum on their own and induced specimen cannot be obtained

C case - a patient diagnosed to have TB by a clinician, regardless if the diagnosis has been confirmed bacteriologically or not.

case management – a system in which a specific health department employee is assigned primary responsibility for the patient, systematic regular review of patient progress is conducted, and plans are made to address any barriers to adherence

case rate – the number of cases that occur during a certain time period, divided by the size of the population during that time period; the case rate is often expressed in terms of a population size of 100,000 persons

case reporting – informing the state or local health department when a new case (an occurrence) of TB disease has been diagnosed or is suspected

casualty department assessment form – patient information recorded when a patient is brought to an emergency room; may be used instead of an admission note and is usually included in the progress notes

cavity – a hollow space within the lung, visible on a chest x-ray, that may contain many tubercle bacilli; often occurs in people with severe pulmonary TB disease

clinic-based DOT – directly observed therapy delivered in a TB clinic or comparable health care facility

clinical evaluation – an evaluation done to find out whether a patient has symptoms of TB disease or is responding to treatment; also done to check for adverse reaction to TB medications

clinician – a physician, physician's assistant, nurse practitioner, or nurse

close contact – a person who has shared the same air space in a household or other enclosed environment for a prolonged period of time (days or weeks, not minutes or hours) with a person with suspected or confirmed TB disease

colonies – groups of mycobacteria that have grown in a culture

combined pill – fixed-dose combination capsule or tablet that may enhance patient adherence

completion – patient who completed treatment but who does not meet definition of cure or treatment failure

concentric circle approach – a method of testing contacts in order of their exposure time (close vs. other-than-close) and their risk (high priority vs. low priority) with close contacts and other contacts at high risk of developing TB disease tested first; it includes contacts from environments where contact may have taken place (household or residential, work or school, and leisure or recreation environments)

confidentiality – the protection of information revealed during patient and health care worker encounters, including all written or electronic records of these encounters

congregate setting – a setting in which a group of usually unrelated persons reside in close physical proximity. These settings may include hospitals, long term care facilities, assisted living facilities, correctional facilities, or homeless shelters (see residential facilities)

consent – acceptance or approval of what is planned or done; it involves voluntary agreement to an action, whether it is a treatment option or a diagnostic test; the patient and health care worker relationship is founded on the patient's consent to the care being provided

contacts – people exposed to someone with infectious TB disease, generally including family members, roommates or housemates, close friends, coworkers, classmates, and others (see close contacts or other-than-close contacts)

contact investigation – a procedure for interviewing a person who has TB disease to determine who may have been exposed to TB. People who have been exposed to TB are tested for LTBI and TB disease

continuation phase – the period after the first 8 weeks of TB disease treatment, during which tubercle bacilli that remain after the initial phase are treated with at least two drugs

control – a standard of comparison for checking or verifying the results of an experiment. In the QFT-G, the substances mitogen and saline are the controls

corticosteroid – a type of steroid, either natural or man-made, often used to treat arthritis or certain allergies

cough-inducing procedures – procedures that make a patient cough, such as sputum induction and bronchoscopy

culture – to grow organisms on media (substances containing nutrients) so that they or the product of this process can be identified; a positive culture for *M. tuberculosis* contains tubercle bacilli, whereas a negative culture contains no detectable tubercle bacilli

culture conversion – two consecutive negative cultures taken at least 7 days apart. Time of conversion is calculated as the interval between the date of treatment initiation and date of the first of the two negative consecutive cultures

cure – a patient who has had TB culture conversion and at least one additional negative culture (that is 3 negative culture during the entire duration of treatment), with no evidence of clinical deterioration.

cycloserine – second line drug previously used in treating RR-TB

d **daily regimen** – a treatment schedule in which the patient takes a dose of each prescribed medication every day

death – a patient who dies for any reason during the course of treatment

death rate (mortality rate) – a measure of the frequency of occurrence of death among a defined population during a specified time interval

diabetes mellitus – a disease in which the body's ability to use sugar is weakened

diagnostic evaluation – an evaluation used to diagnose TB disease; includes a medical history, a chest x-ray, the collection of specimens for bacteriologic examination

directly observed therapy (DOT) – a strategy devised to help patients adhere to treatment; a designated person watches the TB patient swallow each dose of the prescribed drugs

directly observed therapy for latent TB infection (LTBI) – a strategy devised to help patients at especially high risk of developing TB disease adhere to treatment for LTBI; a health care worker or another designated person watches the patient swallow each dose of the prescribed drugs

discharge planning – the preparation of a detailed plan for comprehensive care of a hospitalized or institutionalized patient after that patient's discharge

discharge summary – a document written by the patient's physician upon discharge; contains a brief summary of all important information from the entire hospitalization or stay in the institution, including the discharge diagnosis and often a plan for follow-up care

disclosure – the act of revealing or distributing personal information

due process – an established course for governmental activities or procedures, designed to safeguard the legal rights of the individual

droplet nuclei – very small droplets (1 to 5 microns in diameter) containing *M. tuberculosis* that may be expelled when a person who has infectious TB coughs, sneezes, speaks, or sings; the droplets can remain suspended in the air for several hours, depending on the environment

drug injection – using a needle and syringe to inject drugs into the body

drug susceptibility pattern – list of drugs to which a strain of tubercle bacilli is susceptible and to which it is resistant

drug-resistant TB – TB caused by organisms that are able to grow in the presence of a particular drug; TB that is resistant to at least one first line antituberculosis drug

e empiric treatment followed by individual treatment – regimen given to patients diagnosed on clinical grounds. Drug sensitivity testing of the presumed RR-TB contact is considered as well as other drug resistance information from the patient population. Often followed by an individual patient regimen when drug sensitivity test info becomes available

enablers – those things that can make it possible or easier for the patients to receive treatment

environmental controls – the second level in the hierarchy of TB infection-control measures; engineering systems used to prevent the transmission of TB in health care settings, including ventilation, high-efficiency particulate air (HEPA) filtration, and ultraviolet germicidal irradiation

epidemiology – study of the distribution & causes of disease and other health problems in different groups of people

erythema – redness around the site of the injection when a TST is done; erythema is not considered when the reaction size is measured, because redness does not indicate that a person has TB infection

ethambutol – a drug used to treat TB disease; may cause vision problems. Ethambutol should be used cautiously in children who are too young to be monitored for changes in their vision

ethionamide – second line drug used in treating RR-TB

exposure to TB – time spent with or near someone who has infectious TB disease

extensively drug-resistant TB (XDR-TB) – a type of RR-TB that is resistant to isoniazid and rifampin, plus resistant to any fluoroquinolone & to at least one additional group A drug, either BDQ or LZD

extrapulmonary TB – TB disease that occurs in places other than the lungs, such as the lymph nodes, the pleura, the brain, the kidneys, or the bones; most types of extrapulmonary TB are not infectious

f failure – A patient whose treatment regimen needed to be terminated or permanently changed to a new regimen or treatment strategy (change of 2 or more drugs). Reasons for change of treatment include: no clinical response and/or no bacteriological response, adverse drug reactions, or evidence of additional drug resistance to medicines in the regimen. When someone is started on a shorter regimen and later it is picked up on the baseline sample that they had a condition that qualified them to be on the longer regimen, the patient may not be captured as a failure. They should be de-registered from the shorter regimen and re-registered in the new group.

false-negative reaction – a negative reaction to the TST in a person who has TB infection; may be caused by HIV or other immunocompromising diseases, immunosuppressive drugs, a live-virus vaccination, recent infection (within the past 10 weeks), or very young age (younger than 6 months old)

false-positive reaction – a positive reaction to the TST in a person who does not have TB infection; may be caused by infection with nontuberculous mycobacteria or by vaccination with BCG

field-based DOT – directly observed therapy delivered in a setting outside the TB clinic or a comparable health care facility; possible sites for field DOT include a doctor's office, the patient's home or workplace, a school, a public park, or a restaurant

field investigation – visiting the patient's home or shelter, workplace (if any), and the other places where the patient said he or she spent time while infectious. The purpose of the field investigation is to identify contacts and evaluate the environmental characteristics of the place in which exposure occurred

first-line TB drugs – the initial drugs used for treating TB disease. Include isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and either ethambutol (EMB)

fit check – see **user check seal fit test** – a method to evaluate the fit of a respirator on a person

folk medicine – medicinal beliefs, knowledge, and practices associated with a particular culture or ethnic group. Folk medicine is usually handed down by cultural tradition and practiced by health care workers specially trained in that tradition; not all members of a given culture or ethnic group will use its folk medicine practices

g gastric washing – a procedure done by inserting a tube through the patient's nose and passing it into the stomach; may be useful for obtaining a specimen for culture from children, who produce little or no sputum when they cough

geneXpert MTB/RIF Ultra (GXP) – A diagnostic tool for TB and rifampin resistant TB that uses nucleic acid amplification techniques (TB-NAAT) and produces results in under 2 hours

h **health care facilities** – places where people receive health care, such as hospitals or clinics

health care setting – a place where health care is delivered; includes inpatient and outpatient settings, TB clinics, settings in which home-based health care and emergency medical services are provided, and laboratories handling TB clinical samples

health care worker – any member of a team of health professionals who care for and manage a TB patient, including physicians, nurses, outreach workers, hospital discharge planners, pharmacists, and social workers

heparin – an anti-clotting agent added to patient's blood samples for conducting a QFT-G

hepatitis – inflammation of the liver, causing symptoms such as nausea, vomiting, abdominal pain, fatigue, and dark urine; hepatitis can be caused by several drugs used to treat LTBI or TB disease

high-risk contacts – the contacts (either close or other-than-close) who are at a particularly high-risk of developing TB disease if they become infected with *M. tuberculosis* (e.g. young children less than 4 years of age, HIV-infected and other immunosuppressed persons and persons with certain medical conditions)

history and physical exam form – a standardized form sometimes used to record patient information at the time of the patient's first evaluation; may be used instead of an admission note and is usually included in the progress notes; it is also referred to as the H&P

HIV – human immunodeficiency virus; the virus that causes AIDS

i **identification data** – includes the patient's name, address, social security number, date of birth, and other demographic information (may be a separate registration form)

immune reconstitution syndrome (IRIS) – occurs when the improving immune system unmasks a previously occult opportunistic infection. Reactions usually occur within a median of 15 days after initiation of antiretroviral therapy

immune system – cells and tissues in the body that protect the body from foreign substances

immunosuppressive therapy – therapy that suppresses or weakens the immune system

incentives – small rewards given to patients to encourage them to either take their own medicines or keep their clinic or field DOT appointments

incident rate – a measure of the frequency with which new cases of illness, injury or other health condition occurs, expressed explicitly per a time frame. Incidence rate is calculated as the number of new cases over a specified period divided either by the average population (usually mid-period) or by the cumulative person-time the population was at risk

index patient – a person with suspected or confirmed TB disease who is the initial case reported to the health department. The index case may or may not be the source case (see source patient)

induced sputum – sputum that is obtained by having the patient inhale a saline (salt water) mist, causing the patient to cough deeply; this procedure is used to help patients cough up sputum if they cannot do so on their own

infection control practitioner – a trained health care professional (often a nurse) who is responsible for controlling and preventing the spread of infectious diseases in a hospital or other health care setting

infection control procedures – measures to prevent the spread of any infectious disease including TB

infection rate – the percentage of contacts with a similar amount of exposure (e.g. close, other- than-close) who have a newly identified positive skin test reaction (5 or more millimeters of induration)

infectious – capable of spreading infection; a person who has infectious TB disease expels droplets containing *M. tuberculosis* into the air when he or she coughs, sneezes, speaks or sings

infiltrate – a collection of fluid & cells in tissues of the lung; visible on a chest x-ray in people with pulmonary TB disease

informed consent – a patient's written consent to a surgical or medical procedure or other course of treatment, given after the health care worker has informed the patient about the potential benefits, risks and alternatives involved

intensive phase – the first 8 weeks of TB disease treatment, during which most of the tubercle bacilli are killed

institutions – residential facilities where groups of people live, such as nursing homes, correctional facilities, or homeless shelters, as well as out-patient facilities, such as drug treatment centers or health department clinics

intermittent therapy – a treatment schedule in which the patient takes each prescribed medication two or three times weekly at the appropriate dosage

isolate – a group of organisms isolated or separated from a specimen; in an *M. tuberculosis* isolate, the organisms have been grown in culture and identified as *M. tuberculosis*

isoniazid – a drug that is used for treating LTBI and TB disease; although relatively safe, it may cause hepatitis and other adverse reaction in some patients

laboratory results – records presenting the results of every laboratory test that has been done on the patient, such as AFB smear examinations, TB-NAAT, cultures, and drug susceptibility tests performed in a laboratory

latent TB infection (LTBI) – refers to the condition when a person is infected with tubercle bacilli but has not developed TB disease. Persons with LTBI carry the organism that causes TB but do not have TB disease symptoms and they cannot spread TB germs to others. Persons with LTBI usually have a positive result to the Mantoux tuberculin skin test and interferon release gamma assays i.e. IGRAs

levofloxacin – second line drug used in treating RR-TB and HR-TB

liver function tests – tests done to detect injury to the liver

local community – the geographic area where a person lives and spends time; may be a residential area or an ethnic community (i.e., groups of people who emigrated from the same geographic area)

Loss to follow-up – treatment interruption for 2 or more consecutive months

LTBI treatment – medication given to people who have TB infection to prevent them from developing TB disease

m **malaise** – a feeling of general discomfort or illness

Mantoux tuberculin skin test (TST) – a method of testing for TB infection; a needle and syringe are used to inject 0.1 ml of 5 tuberculin units of liquid tuberculin between the layers of the skin (intradermally), usually on the forearm; the reaction to this test, usually a small swollen area (induration), is measured 48 to 72 hours after the injection and is interpreted as positive or negative depending on the size of the reaction and the patient's risk factors for TB

media – substances containing special nutrients and used for growing cultures of bacteria found in specimens

medical history – the part of a patient's life history that is important for diagnosing and treating TB infection or disease, including history of exposure, symptoms, previous diagnosis of TB infection or disease, and risk factors for TB disease

medical records department – a department in a hospital or other health care facility that houses the records of patients who have been admitted to the hospital and subsequently have been discharged, transferred to ambulatory care services, left against medical advice, or died

medication record – an information sheet on which the nurses record the date, time, and amount of prescribed medications given to the patient during hospitalization or care in a facility; may not be included in patient's medical record (for example, may be kept in a separate medication logbook)

miliary TB – TB disease that occurs when tubercle bacilli enter the bloodstream and are carried to all parts of the body, where they grow and cause disease in multiple sites; the chest x-ray of patients with miliary TB often looks like millet seeds scattered throughout the lung

mobile teams – also known as mobile MDR-TB units. Based at PHC facility or a satellite MDR-TB unit. They provide injections to patients at their homes, supervise intake of oral tablets, and educate families about infection control

mono-resistant TB – TB that is resistant to one TB treatment drug

moxifloxacin – second line drug used in treating RR-TB

multidrug-resistant TB (MDR-TB) – TB that is resistant to at least the drugs isoniazid and rifampin; MDR-TB is more difficult to treat than drug-susceptible TB

mycobacteriology laboratory – a laboratory that deals specifically with *M. tuberculosis* and other mycobacteria

mycobacterium – a kind of bacterium; mycobacteria can cause a variety of diseases

Mycobacterium africanum – a type of tuberculous mycobacterium, closely related to *M. tuberculosis*, that can cause a disease similar to TB

Mycobacterium avium complex – a common type of nontuberculous mycobacterium that can cause disease in humans

Mycobacterium bovis – a type of tuberculous mycobacterium that can cause a disease similar to TB; usually occurs in cows. Before the pasteurization of milk became common practice, these mycobacteria were often spread to humans through contaminated milk

Mycobacterium canetti – a type of tuberculous mycobacterium that can cause disease in humans

Mycobacterium microti – a type of tuberculous mycobacteria that can cause generalized tuberculosis

Mycobacterium tuberculosis – the organism that causes TB in humans and is sometimes called the tubercle bacillus; belongs to a group of bacteria called mycobacteria

n N95 respirators – special device designed to protect users from inhaling droplet nuclei; used in health care facilities and other settings where TB may be spread

negative pressure – the difference in air-pressure between two areas; room that is under negative pressure has a lower pressure than adjacent areas, which keeps air from flowing out of the room and into adjacent rooms or areas; also used to describe a nonpowered respirator

nonadherence – the patient's inability or refusal to take TB drugs as prescribed

nontuberculous mycobacteria – mycobacteria that do not cause TB disease, e.g., *M. avium complex*

not confirmed case – patients commenced on TB, MDR-TB, or XDR-TB treatment after a decision by a TB practitioner on the basis of clinical presentation, radiologic findings, and medical history indicating a high probability of TB disease

nucleic acid amplification test (NAAT) – a technique that amplifies (copies) DNA and RNA segments, in order to directly identify microorganisms in sputum specimens

nurse's notes – a record in which the nurse who directly cares for the patient continuously records information, including the patient's symptoms, medications given, and scheduled procedures or activities and may be included in the progress notes section

o open-ended question – a question that cannot be answered with a simple "yes" or "no." Open-ended questions are designed to elicit the patient's knowledge, feelings and beliefs, by beginning with words such as "What," "Why," "Who," "How," and "When," that demand an explanation. Such questions are used to explore complex issues that do not have a finite or predetermined set of responses

other-than-close contacts – contacts with less intense, less frequent, or shorter durations of contact to the TB patient than close contacts (see **close contacts**)

outpatient clinic – a clinic that cares for non-hospitalized patients with a particular type of problem (for example, chest, infectious disease, AIDS, pediatric)

p partner notification – activity conducted by HIV/AIDS programmes to identify & counsel the sexual and needle-sharing contacts of HIV-infected persons; this notification is confidential and depends on the voluntary cooperation of the patient

para-aminosalicylic acid – second line drug used in treating MDR-TB

pathogenesis – how an infection or disease develops in the body

pathology laboratory – a laboratory that performs tests and examinations on tissue and biopsy specimens

patient-health care worker relationship – the basis for sharing information, communicating beliefs and feelings that affect care, and building trust in the value of the interaction

patient-identifiable information – info in which the identity of the patient is directly included or can be deduced

period of infectiousness – time period during which a person with TB disease is capable of transmitting *M. tuberculosis*; usually estimated by determining the date of onset of the patient's symptoms (especially coughing)

peripheral neuropathy – damage to the sensory nerves of the hands and feet, causing a tingling sensation or a weakened sense of touch in the hands and feet

physician or provider's orders – a record in which the physician(s) prescribes medications, orders laboratory tests or procedures (for example, bronchoscopy or gastric aspiration), and delivers other patient-care instructions to staff. Medication orders specify date, name of medication, dosage, and duration of treatment (in days or in number of doses)

polymerase chain reaction (PCR) – a technique used to copy small segments of DNA

poly-resistant TB – TB that is resistant to at least two TB treatment drugs (but not both isoniazid and rifampin); but is not MDR-TB

pretomanid - a second line TB drug used only in a regimen that contains bedaquiline and linezolid.

purified protein derivative (PPD) – antigens such as the type of tuberculin used in the TST (see **antigen**)

PPD skin test – a tuberculin skin test that uses PPD tuberculin

prevalence rate – the proportion of a population that has a particular disease, injury, other health condition, or attribute at a specified point in time (point prevalence) or during a specified period (period prevalence)

primary drug-resistant TB – drug-resistant TB caused by person-to-person transmission of drug-resistant organisms

primary TB – primary TB generally affects the mid and lower lung; in children this form of TB is much more common

privileged information – personal information shared by the patient with his or her health care worker

progress notes – a record in which all physicians and other specialists continuously record patient information during a patient's hospital stay and may include nurses' notes and notes from other ancillary staff

public health worker – an employee of the health department (often a public health advisor, DOT outreach worker, or a nurse) whose duties may include either surveillance, case management, or some combination of these activities

pulmonary TB – TB disease that occurs in the lungs typically causing a cough and an abnormal chest x-ray; pulmonary TB is usually infectious if untreated

p-value – the probability of observing an association between two variables or a difference between two or more groups as large or larger than that observed, if the null hypothesis were true. Used in statistical testing to evaluate the plausibility of the null hypothesis (i.e., whether the observed association or difference plausibly might have occurred by chance)

pyridoxine – another name for vitamin B6; it is given to prevent peripheral neuropathy; should always be given to pregnant and breastfeeding women on isoniazid

q **QT interval** - measured from beginning of QRS complex to end of T wave on ECG

r **radiology reports** – reports summarizing all radiology procedures performed on the patient (for example, chest radiographs or CT scans); part of the medical record

reactivation (post-primary) TB – TB that generally affects upper lobes; sometimes with cavities and is usually found in adults. Sometimes called adult-type TB

residential facilities – institutions where people live, such as nursing homes, assisted living facilities, correctional facilities, or homeless shelters (see congregate setting)

resistant – an organism's ability to grow despite the presence of a particular drug

resistance in new patients – formerly called "primary resistance." Resistance in the samples of patients never previously treated for TB or treated for one month or less

resistance in previously treated patients – previously called "acquired resistance." Resistance in samples of patients with one or more previous TB treatment episodes or more than one month each

respiratory-protection controls – the third level in the hierarchy of TB infection control measures; used to minimize the risk for exposure to *M. tuberculosis*

rifabutin – a drug used to treat TB disease; used as a substitute for rifampin (RIF) in the treatment of all forms of TB

rifampicin – a drug used to treat TB disease; also used for LTBI treatment. Rifampin has several possible side effects (for example, hepatitis, turning body fluids orange, drug interactions)

rifampicin-resistant TB - resistance to at least rifampicin, with or without resistance to other drugs. This category includes MDR-TB, rifampicin mono-resistant TB, pre-XDR-TB and XDR-TB

rifapentine – a drug used to treat latent TB infection; used with INH as part of the TPT regimen 3HP

routine case reporting – the required reporting of suspected or confirmed TB cases to a public health authority

S secondary case – a contact who has developed TB disease as a result of transmission from an index patient

secondary drug-resistant TB – also referred to as acquired drug-resistant TB; develops during TB treatment, either because the patient was not treated with the appropriate treatment regimen or because the patient did not follow the treatment regimen as prescribed

second line TB drugs – drugs used to treat TB that are resistant to first-line TB drugs (e.g., bedaquiline, linezolid, pretomanid, levofloxacin, ethionamide, terizidone, or amikacin)

skin test conversion for contacts – defined differently from a standard skin test conversion; for contacts, a skin test conversion is defined as a change from less than 5 mm on the initial skin test to a reaction of greater than or equal to 5 mm on the second test, 10 to 12 weeks after exposure

silicosis – a lung disease caused by inhaling silica dust, which is used in the production of glass and ceramics; occurs most often in mining and foundry workers

skin test conversion – a change in a skin test reaction from negative to positive between testing intervals

smear – a specimen that has been smeared onto a glass slide, stained, washed in an acid solution, and then placed under the microscope for examination; used to detect acid-fast bacilli in a specimen

smear conversion – two consecutive negative smears taken at least 30 days apart. Time of conversion is calculated as the interval between the date of treatment initiation and date of the first of the two negative consecutive smears

SOAP notes – Progress notes can also be referred to as SOAP notes: subjective data, objective data, assessment, and plans

source case investigation – conducted to find the source of transmission when recent transmission is likely; used to determine who transmitted *M. tuberculosis* to an index patient or infected child or persons in the cluster of skin test conversions, whether this person is still infectious, whether the case of TB in this person was reported to the health department, and whether others were infected by the source patient (see source patient)

source patient – a person with infectious TB disease who is responsible for transmitting *M. tuberculosis* to another person or persons. He or she is identified through either a contact or source case investigation and may or may not be the index patient (see index patient)

sputum – phlegm from deep in the lungs, collected in a sterile container for processing and examination

standardized treatment regimen – drug-resistance survey data from all representative patient populations are used to base regimen design in the absence of an individual drug sensitivity test

standardized treatment regimen followed by individualized treatment regimen – patients on standardized treatment regimen may be switched to an individual treatment regimen when drug sensitivity test results become available

statement of disagreement – a statement filed by the patient stating there is a disagreement with the health care worker or institution regarding the patient's record

success – combination of cure and completion

surgical mask – device worn over the nose and mouth of a person with suspected or confirmed infectious TB disease to prevent infectious droplet nuclei from being spread (exhaled) into the air

surveillance – the ongoing systematic collection, analysis, and interpretation of health data essential to the planning, implementation, and evaluation of public health practice, closely integrated with the timely dissemination of these data to those who need to know in public health programmes

susceptible – an organism's ability to be killed by a particular drug

symptoms of TB disease – noticeable conditions caused by TB disease. The symptoms of pulmonary TB disease include coughing, pain in the chest when breathing or coughing, and coughing up sputum or blood. The general symptoms of TB disease (pulmonary or extrapulmonary) include weight loss, fatigue, malaise, fever, and night sweats. The symptoms of extrapulmonary TB disease depend on the part of the body that is affected by the disease

- t** **targeted testing** – a TB control strategy to identify persons at high risk for latent TB infection and persons at high risk for developing TB disease who would benefit from treatment
- TB risk assessment** – an initial and ongoing evaluation of the risk for transmission of *M. tuberculosis* in a particular health care setting
- terizidone** – second line drug used in treating RR-TB
- third party** – a person or an organization not directly involved in the care of a patient’s health problem
- transmission** – the spread of an organism, such as *M. tuberculosis*, from one person to another; probability of transmission depends on the contagiousness of the patient, the type of environment, the length of exposure, and the virulence or strength of the organism
- treatment for LTBI** – medication that is given to people who have LTBI to prevent them from developing TB disease
- treatment plan** – a written plan detailing the medical regimen as ordered by the physician, including periodic monitoring for adverse reactions and other follow-up care
- tuberculin** – a substance made from tubercle bacilli that have been killed by heating; used to determine whether a person has TB infection. Tuberculin is not a vaccine
- tuberculin skin test (TST)** – see Mantoux tuberculin skin test
- tubercle bacilli** – another name for the *Mycobacterium tuberculosis* organisms that cause TB disease
- tuberculin unit** – a standard strength of tuberculin used; a strength of 5 tuberculin units is used for the Mantoux TST
- tuberculous mycobacteria** – mycobacteria that can cause TB disease or other diseases very similar to TB; the tuberculous mycobacteria include *M. tuberculosis*, *M. bovis*, *M. africanum*, *M. canetti*, and *M. microti*
- U** **ultraviolet germicidal irradiation** – the use of special lamps that give off ultraviolet light, which kills the tubercle bacilli contained in droplet nuclei
- user seal check** – formerly called “fit check;” procedure performed to check for the proper seal of a respirator each time a respirator is put on
- V** **ventilation systems** – air systems designed to maintain negative pressure and to exhaust the air properly; designed to minimize the spread of TB in a health care facility
- virulence** – refers to the ability of an organism to produce a disease. The virulence (strength) of a bacteria is associated with the severity of the disease
- W** **waiver** – a form that patients are often asked to sign to allow their health information to be used by third parties
- window period** – the time span between the date of an initial tuberculin skin test with a negative reaction and the date of the follow-up tuberculin skin test that should take place 10 to 12 weeks after exposure; after the window period has ended, a repeat skin test should be administered to each contact who had an initial negative reaction
- window period prophylaxis** – the practice of providing treatment for LTBI to high risk contacts (including young children under 4 years of age, and HIV-infected and other immunosuppressed persons) with an initial negative skin test reaction less than 10 to 12 weeks after their exposure; if the contact has a negative skin test reaction after the window period, treatment for latent TB infection is usually stopped (see window period)
- X** **XDR-TB** – see **extensively drug-resistant TB**

Module

1

Epidemiology of Drug-Resistant Tuberculosis



Global Burden of Tuberculosis

In 2021, there were:

10.6 million people fell ill with *M. tuberculosis*

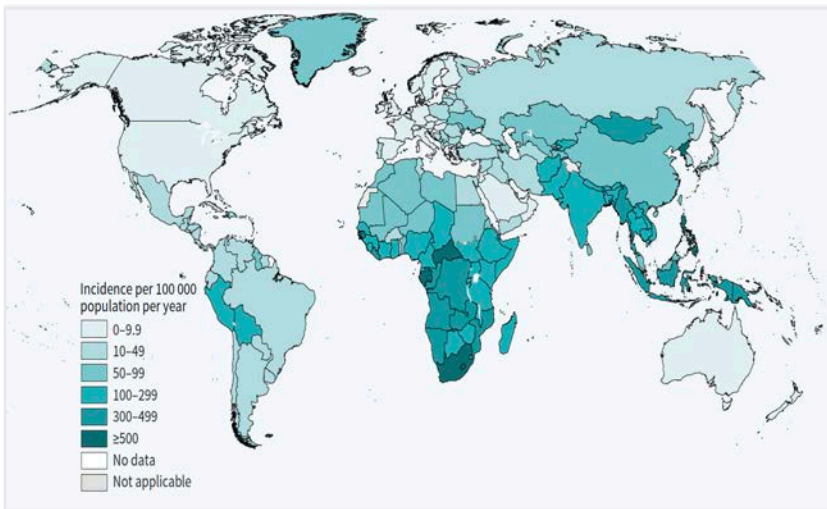
Only 6.4 million people were diagnosed with TB

3.6 % increase in TB incidence in 2021, reversing trend of 2% decrease per year for the past 2 decades

TB mortality increased from 1.3 to 1.4 million between 2020 and 2021

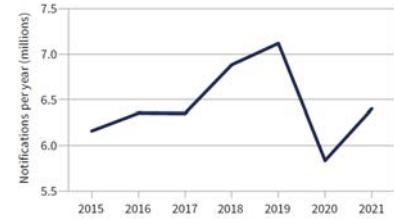
703,000 people living with HIV that developed TB

Estimated TB Incidence Rates, 2021

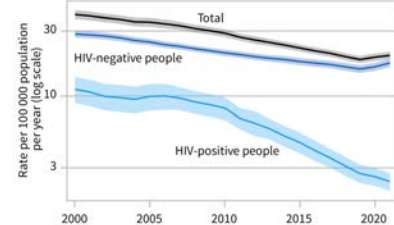


World Health Organization: 2022 Global TB Report

Case notifications of newly diagnosed TB



TB incidence



Despite being both preventable and treatable, TB remains one of the top 10 causes of death globally and the leading cause of death from a single infectious disease. The African continent is significantly affected by TB, accounting for 25% of the global burden and 365,000 deaths in 2021.

Global Burden of Rifampicin-Resistant TB

In 2021, there were:

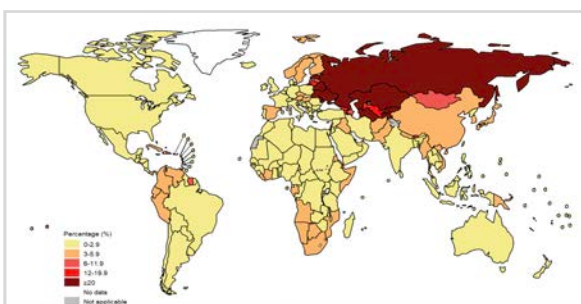


37% case detection rate for RR-TB

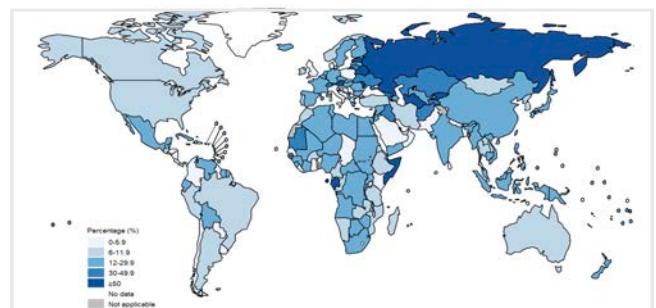
3.6% of new TB cases have RR-TB

18% of previously treated cases have RR-TB

% of new TB cases with RR-TB, 2021

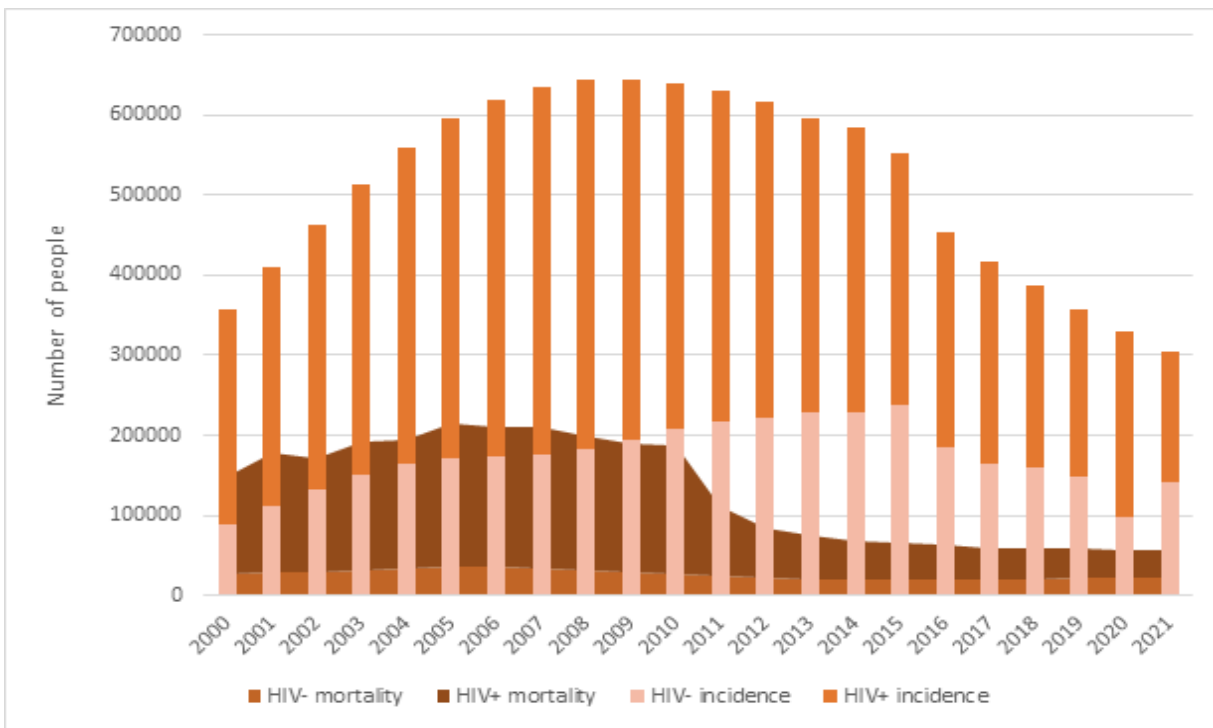


% of previously treated TB cases with RR-TB, 2021



World Health Organization: 2022 Global TB Report

Burden of TB in South Africa (All types)



1. TB incidence and mortality in South Africa increased sharply pre-2009, driven mostly by HIV.
2. The scale up of antiretroviral treatment contributed to a reversal in this trend.
3. TB incidence has declined by 53% between 2009 and 2021, with a higher rate of decline among people living with HIV (PLHIV) (64%) than in HIV-uninfected individuals (28%)
4. TB mortality declined by 71%, between 2009 and 2021, with a higher rate of decline among PLHIV (80%) than in HIV-uninfected individuals (21%)

TB INCIDENCE

All types of TB

304,000

Fell Ill with TB
(207,000 - 421,000)

54% MEN
36% WOMEN
10% CHILDREN

172,194

people with TB notified
(New and relapse)



132,000

people not notified
or not diagnosed

TB Catastrophic Costs



56%

TB patients facing
catastrophic total costs
Year of survey: 2021

TB MORTALITY

55,000

TB Deaths
(32,000 - 86,000)

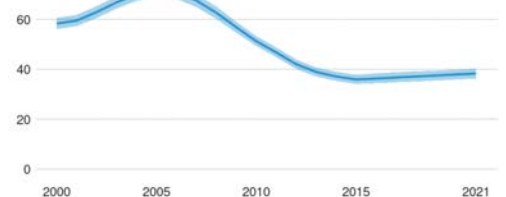
All types of TB



Including

33,000

Deaths among
people with HIV



World Health Organization: 2022 Global TB Report

TB Treatment & Care in South Africa (all types)

Use of WHO-Recommended Rapid Diagnostics

62%

People newly diagnosed with TB using WHO-recommended rapid diagnostics

TB/HIV

163,00

(111,000 - 225,000)

people living with HIV fell ill with TB

73,117

people notified and put on ART

TB Treatment Coverage

57%  **90%**



2025
End TB Target

Treatment success rate **78%**

RR-TB Treatment & Care in South Africa

Drug-Resistant TB

21,000 people fell with drug-resistant TB

(13,000 - 29,000)

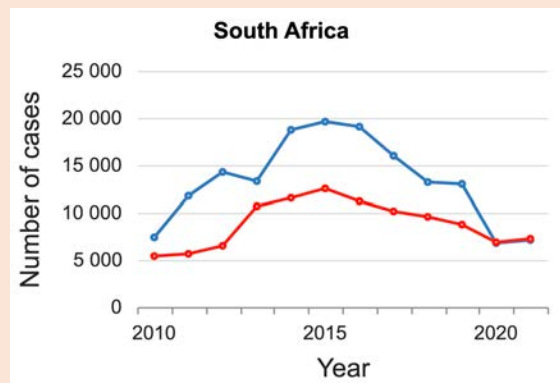
7,239 people started on second-line treatment

4,616 people started on WHO-recommended shorter treatment regimens

57%

Treatment coverage

People **diagnosed** with RR-TB and **enrolled** on MDR-TB treatment



World Health Organization: 2022 Global TB Report.

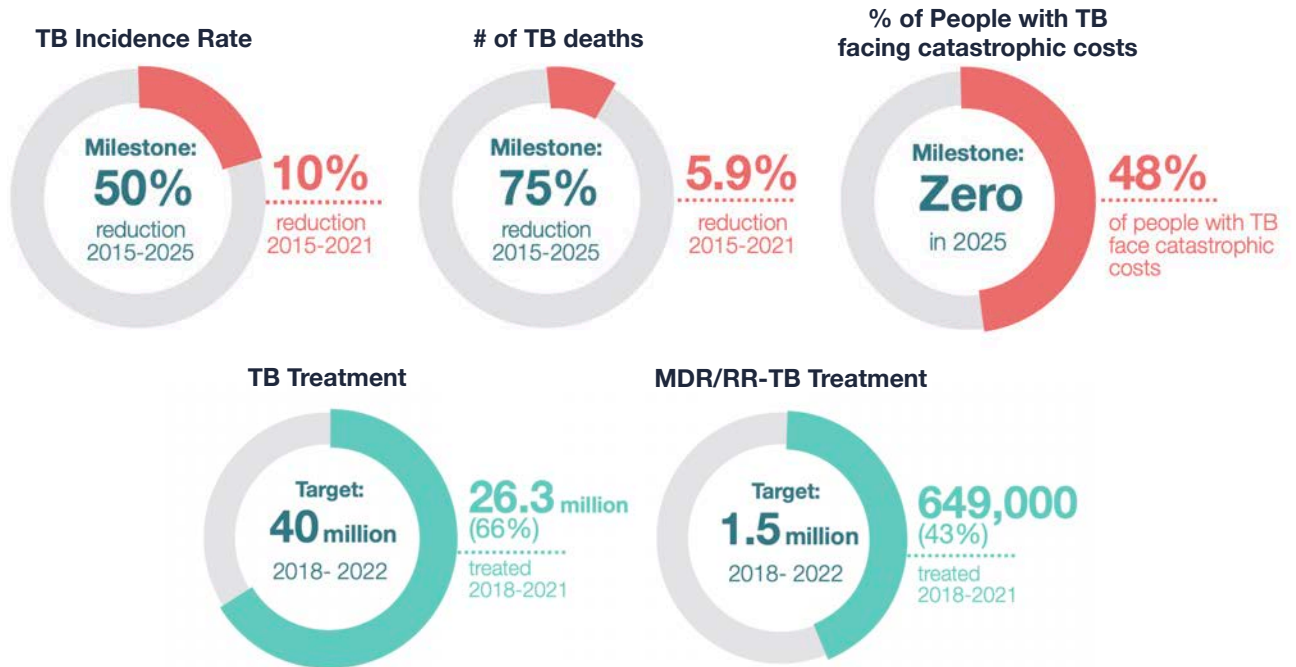
TB Treatment Outcomes in South Africa

Treatment Outcomes (for those who started on Rx)	DS-TB (2019)	DR-TB (2019)
Treatment Success	80,2%	66%
LTFU	11,2%	15,3%
Died	7,9%	17%
Failed	0,7%	1,9%

Global TB Strategies

End TB Strategy: A World Free of TB


ZERO deaths, disease and suffering due to TB



World Health Organization: 2022 Global TB Report

National Strategies for TB in South Africa

National Strategic Plan (NSP) for HIV, TB and STIs: 2023 – 2028

- 
Goal 01 Break down barriers to achieving HIV, TB and STIs solutions
- 
Goal 02 Maximise equitable and equal access to HIV, TB and STIs services and solutions
- 
Goal 03 Fully resource and sustain an efficient NSP led by revitalised, inclusive, and accountable institutions
- 
Goal 04 Build resilient systems for HIV, TB and STIs that are integrated into systems for health, social protection, and pandemic response

SOUTH AFRICA'S TUBERCULOSIS RECOVERY PLAN 2023-2024

A TARGET-DRIVEN APPROACH



health

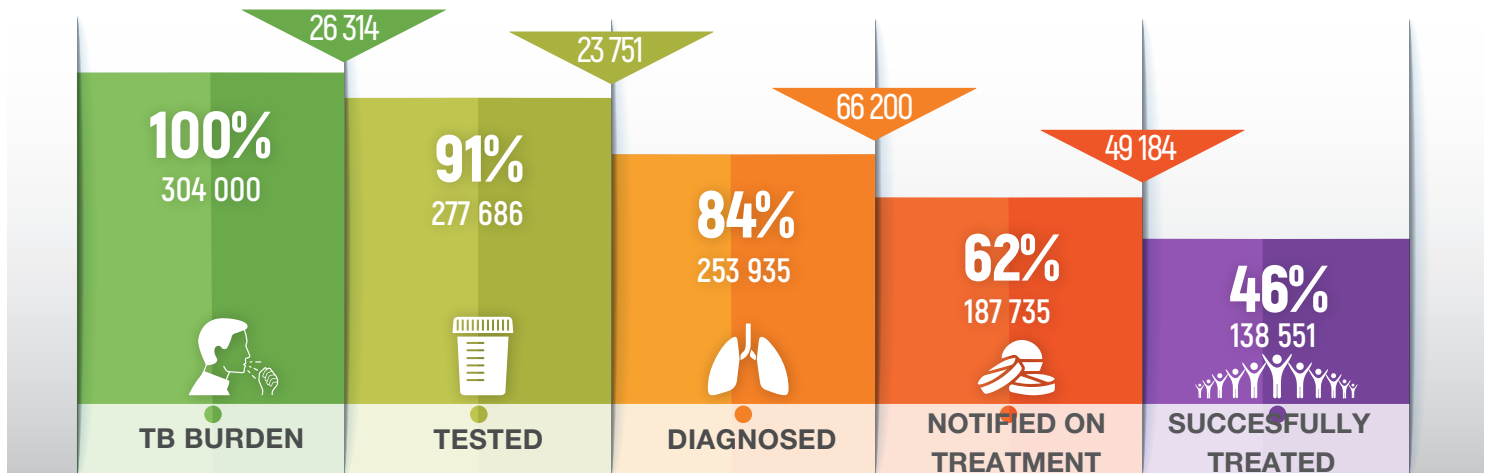
Department:
Health
REPUBLIC OF SOUTH AFRICA



South Africa is yet to close the gaps in the TB care cascade.

Disruptions resulting from COVID-19 have meant fewer patients being tested, diagnosed and successfully treated. Now, more than ever, we recognise the need to act.

SOUTH AFRICA'S TB CARE CASCADE (2021)



The TB Recovery Plan aims to recover losses in TB care due to COVID-19 disruptions and accelerate efforts towards End TB targets

OUR TARGET-DRIVEN PROGRAMMATIC GOALS ARE TO:

1 CREATE DEMAND FOR TB TESTING THROUGH ADVOCACY AND COMMUNICATION TO INCREASE FINDING UNDIAGNOSED TB

- Implement Social & Behaviour Change Communication Strategy in at least 12 districts

2 ACCELERATE IMPLEMENTATION OF TUIT (TARGETED UNIVERSAL TB TESTING)

- Conduct 3,085,166 GeneXpert/molecular TB tests
- Scale up routine testing of high risk groups
- Scale up the use of DCXR screening and ULAM testing

3 ESTABLISH RELIABLE LINKAGE PATHWAYS

- Increase GeneXpert SMS coverage from 30% to 60%
- Initiate 224,776 patients on TB treatment

4 IMPROVE RETENTION IN CARE

- Introduce BPAL-L regimen for eligible RR-TB patients
- Introduce paediatric 4-month regimen for DS-TB
- Achieve a treatment success of 90 % for DS-TB and 78 % for RR-TB

5 STRENGTHEN TB PREVENTION

- Scale up implementation of TB preventive therapy

6 STRENGTHEN TB PROGRAMME IN THE MINES

- Conduct a situational analysis to determine the status of TB programme implementation in the mines

7 IMPROVE TB DATA SYSTEMS, GOVERNANCE AND ACCOUNTABILITY

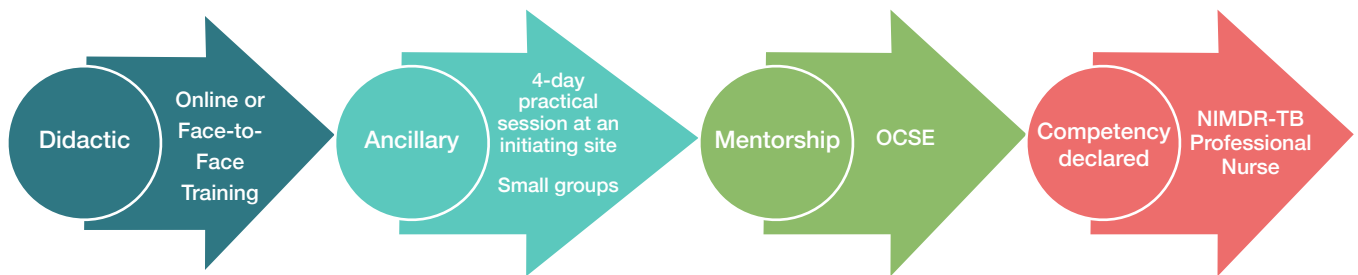
- Compile TB recovery plan report(s)
- Convene regular meetings with provinces and TB partners

We will ensure

SUCCESS = ENGAGE + TRAIN + MONITOR + TROUBLESHOOT + SHARE
 stakeholders staff targets obstacles learnings

Nurse Initiated MDR/RR-TB Treatment (NIMDR)

NIMDR-TB Framework



Who should be trained for NIMDR?

Professional nurses working at PHC facilities that have been earmarked as MDR-TB decentralised sites are to be prioritised. If they are already NIMART trained, this is an advantage. A dispensing license is recommended. Selection must be conducted in partnership with the Provincial and District Departments of Health. Completion of Basic TB & Basic HIV are also a requirement.

What type of patients can undergo NIMDR?

Patients eligible for NIMDR: have limited co-morbidities, can be treated with standardised treatment per the guidelines, and are unlikely to require medication or monitoring adjustments

Training Model for NIMDR

All participants need to undergo a didactic training which may be online or face-to-face. A certificate of completion will be issued upon achieving 70 % during the post-test.

Additional competency in NIMDR-TB is dependent on completing of the NIMDR-TB practical workbook, and passing the OSCE examination and obtaining 70% or more.

Module **2**

Overview of

Tuberculosis



Tuberculosis 101

TB is caused by an organism called *Mycobacterium tuberculosis*

TB can attack the lungs (**Pulmonary TB**) or any other part of the body such as the kidney, spine, and brain (**Extra-Pulmonary TB**)

The probability that TB will be transmitted depends on four factors:

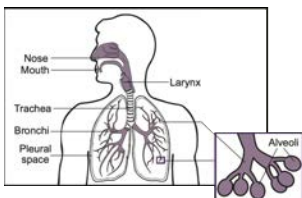
1. Infectiousness of the TB patient
2. Environment in which the exposure occurred
3. Frequency and duration of the exposure
4. Susceptibility (immune status) of the exposed individual

Why is transmission so common in SA?



HIV | Smoking | Malnutrition | Poverty | Diabetes |

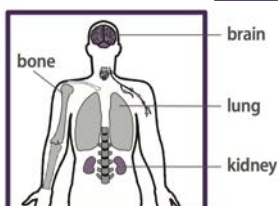
Pathogenesis of TB



1) Person inhales droplet nuclei containing *M. tuberculosis*

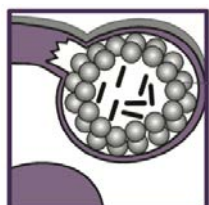
2) Smaller droplet nuclei can reach the small air sacs of the lung (the alveoli), where they multiply and infection can begin

3) Bacilli can enter the bloodstream and may reach any part of the body



4) Within 2-8 weeks, the body's immune system usually intervenes blocking the spread - **latent TB infection (LTBI)**

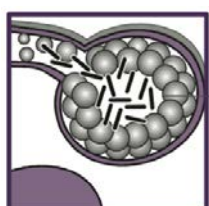
5) If the immune system can't control bacilli - **active TB disease** develops



special immune cells form a barrier shell (in this example, bacilli are in the lungs)

▶ The risk of developing TB disease is the **highest in the first 2 years after infection**

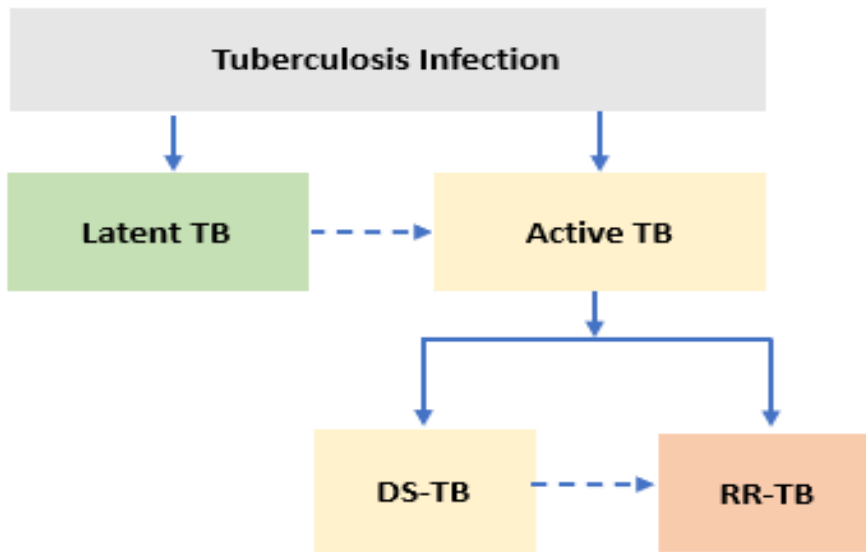
▶ Compromised immune systems increase the risk that LTBI will progress to disease



shell breaks down and tubercle bacilli escape and multiply (in this example, TB disease develops in the lungs)

▶ People who are infected with HIV are **20 to 30 times more likely to develop active TB**

Broad Overview of Types of TB



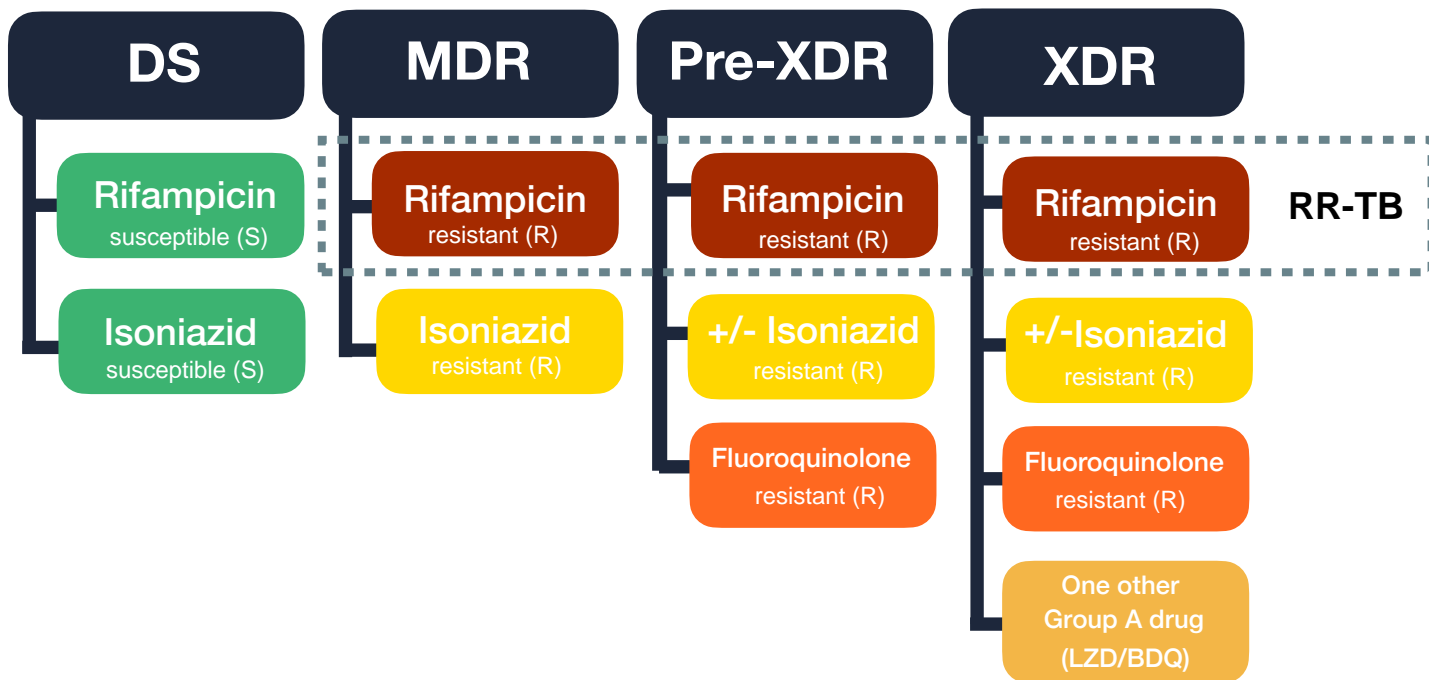
Latent vs. Active TB

Persons with Latent TB Infection	Persons with Active TB Infection
Small # of TB bacteria in the body that are alive, but under control	Has a large # of active TB bacteria in the body
Cannot spread TB bacteria to others	May spread TB bacteria to others
Does not feel sick, but may become sick if the bacteria become active in the body	May feel sick and may have symptoms such as a cough, fever, or weight loss
TST usually positive	TST usually positive
Chest x-ray usually normal	Chest x-ray usually abnormal
Sputum smears and cultures negative	Sputum smears and cultures usually positive
Should consider treatment for LTBI to prevent TB disease	Needs treatment for TB disease
Does not require respiratory isolation	May require respiratory isolation

Drug Susceptible (DS) TB

In drug susceptible TB, the MTB strain is susceptible to the first line agents rifampicin and isoniazid

Drug Susceptible (DS) TB vs. Drug Resistant TB (DR-TB)



Categories of Drug Resistant TB

Mono-resistance

Resistance to only one anti-TB drug, without resistance to other drugs.

Poly-resistance

TB strains that are resistant to two or more anti-TB first-line drugs (R or H or Z or E) – other than both R and H (e.g. resistance to H and E)

Multidrug-Resistant TB (MDR-TB):

TB strains resistant to rifampicin and isoniazid with or without resistance to other first-line TB drugs

Rifampicin Resistant TB (RR-TB):

TB strains resistant to Rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. RR-TB includes any resistance to Rifampicin, whether mono-resistance, poly-resistance, MDR-TB, PreXDR-TB or XDR-TB (categories are not all mutually exclusive)

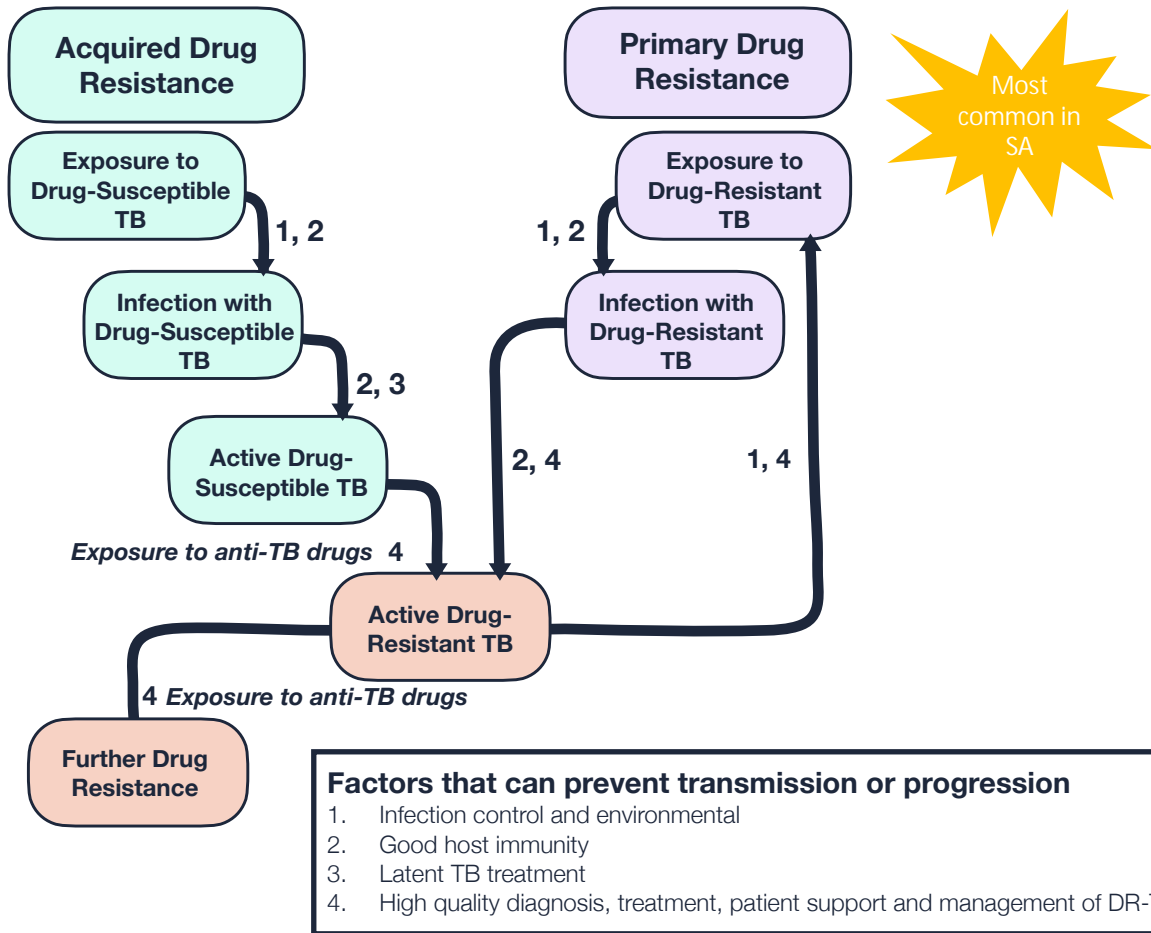
Pre-XDR:

TB caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) strains that fulfill the definition of MDR/ RR-TB and which are also resistant to any fluoroquinolone.

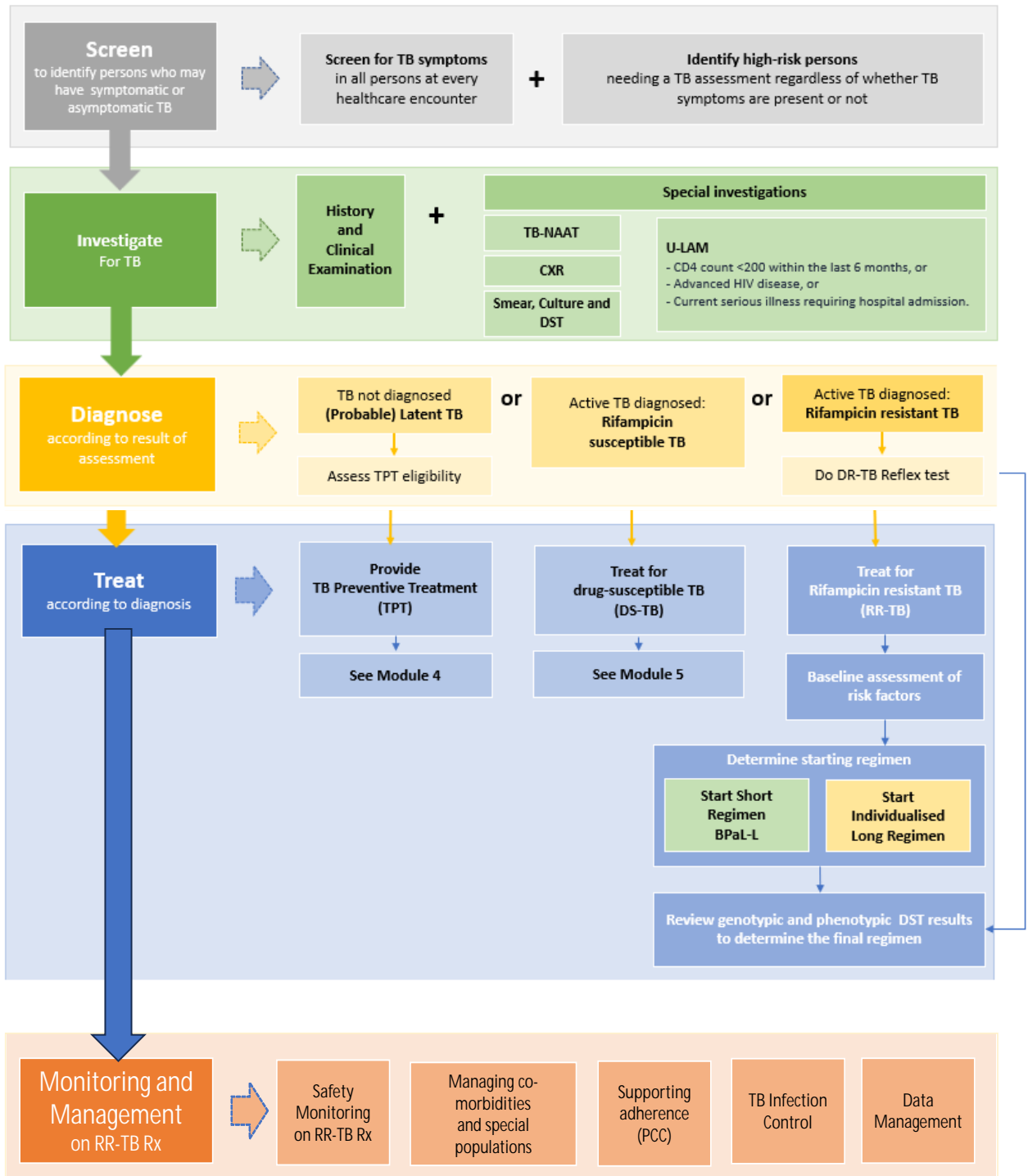
Extensively-drug resistant TB (XDR-TB):

TB caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) strains that fulfil the definition of MDR/ RR-TB and which are also resistant to any fluoroquinolone and at least one additional Group A drug (Group A drugs are the most potent group of drugs in the ranking of second-line medicines for the treatment of drug-resistant forms of TB using longer treatment regimens and comprise levofloxacin, moxifloxacin, bedaquiline and linezolid).

Two Pathways to Drug-Resistant TB



Overview of the TB diagnostic and management process

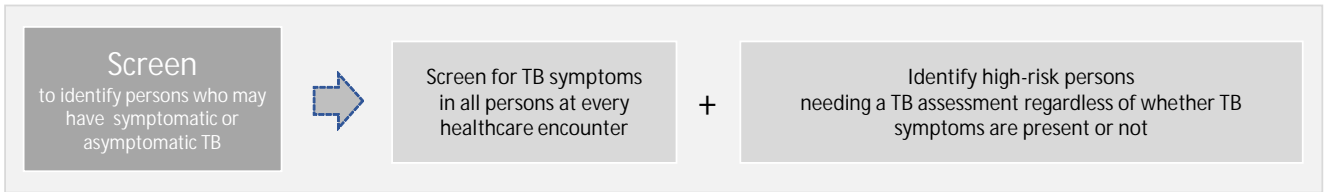


Module **3**

Diagnosing Tuberculosis



Intensified Case Finding



Identify persons requiring further assessment for TB

All persons attending a health facility or receiving care in the community should be screened for TB using the WHO TB symptom screen. All persons with TB symptoms requires additional investigations for TB.

WHO: 4 Critical Screening Questions

Cough

Night Sweats

Fever

Unintentional or unexplained weight loss

In addition to those persons with TB symptoms, the following high-risk persons should also receive further TB investigations, regardless of whether they have TB symptoms or not:

- Persons newly diagnosed with HIV or starting ART
- Annually for persons on ART (at their annual VL assessments)
- Persons with who completed TB treatment in the last 2 years
- Household and close contacts of known TB clients
- Inmates
- People exposed to silica in workplaces in areas with a high TB prevalence.

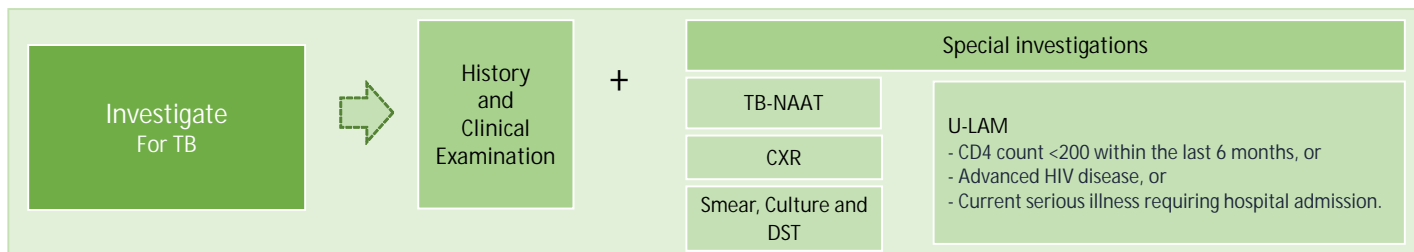
When should a provider suspect RR-TB

- In all re-treatment patients
- In all treatment failures
 - Treatment adherent patient whose condition deteriorates
 - Patient whose smear does not convert after 3 months of treatment
 - Patient whose smear becomes positive again after initial conversion
 - Patient whose smear is negative but not responding to treatment
- In symptomatic contacts of a RR-TB patient
- In HCWs when infection control measures are not in place

If a patient has a positive symptom screen or is considered a "high-risk" person, they require further evaluation for TB

- Send at least one sputum specimen for bacteriological confirmation (TB-NAAT)
- Perform other diagnostic tests if available and clinically indicated, as listed on page 34

Investigate for TB



Evaluating a client for TB requires a history and clinical examination, as well as the applicable special investigations for TB and HIV.

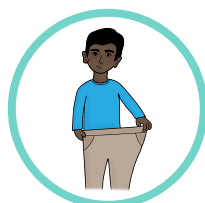
Symptoms and Signs of TB



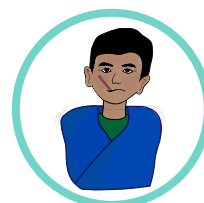
Persistent cough of 2 weeks or more (or any duration if HIV positive)



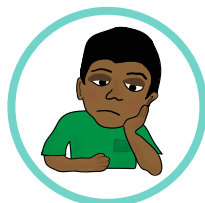
Drenching night sweats



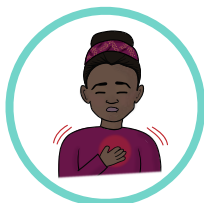
Unexplained weight loss



Fever for more than 2 weeks



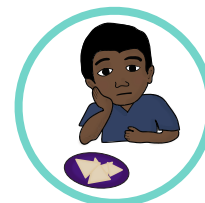
Malaise/Fatigue



Chest Pain



Hemoptysis



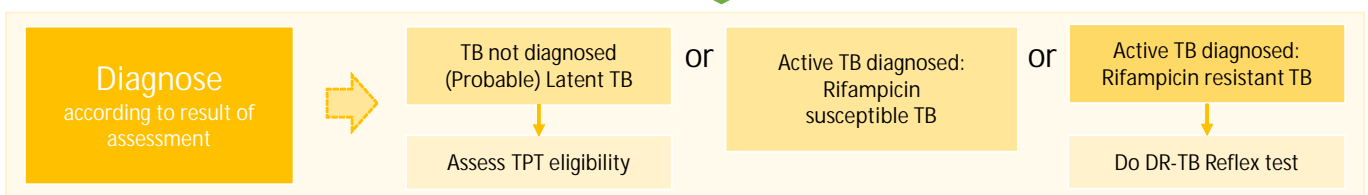
Anorexia

NOTE:

- PLHIV present with pauci-bacillary PTB or EPTB therefore a negative TB-NAAT (e.g., Xpert MTB/RIF Ultra) result must be followed by clinical assessment, chest x-ray and culture and DST to confirm the diagnosis of TB.
- In people who completed TB treatment in the past two years, a “Positive” or “Trace” TB-NAAT result may indicate presence of live (active TB disease) or dead (left over from previous TB episode) bacilli or DNA. Therefore, the test result must be considered along with the clinical findings before treatment initiation and a TB culture conducted to confirm active TB disease

Types of special investigations used to assess for and diagnose TB

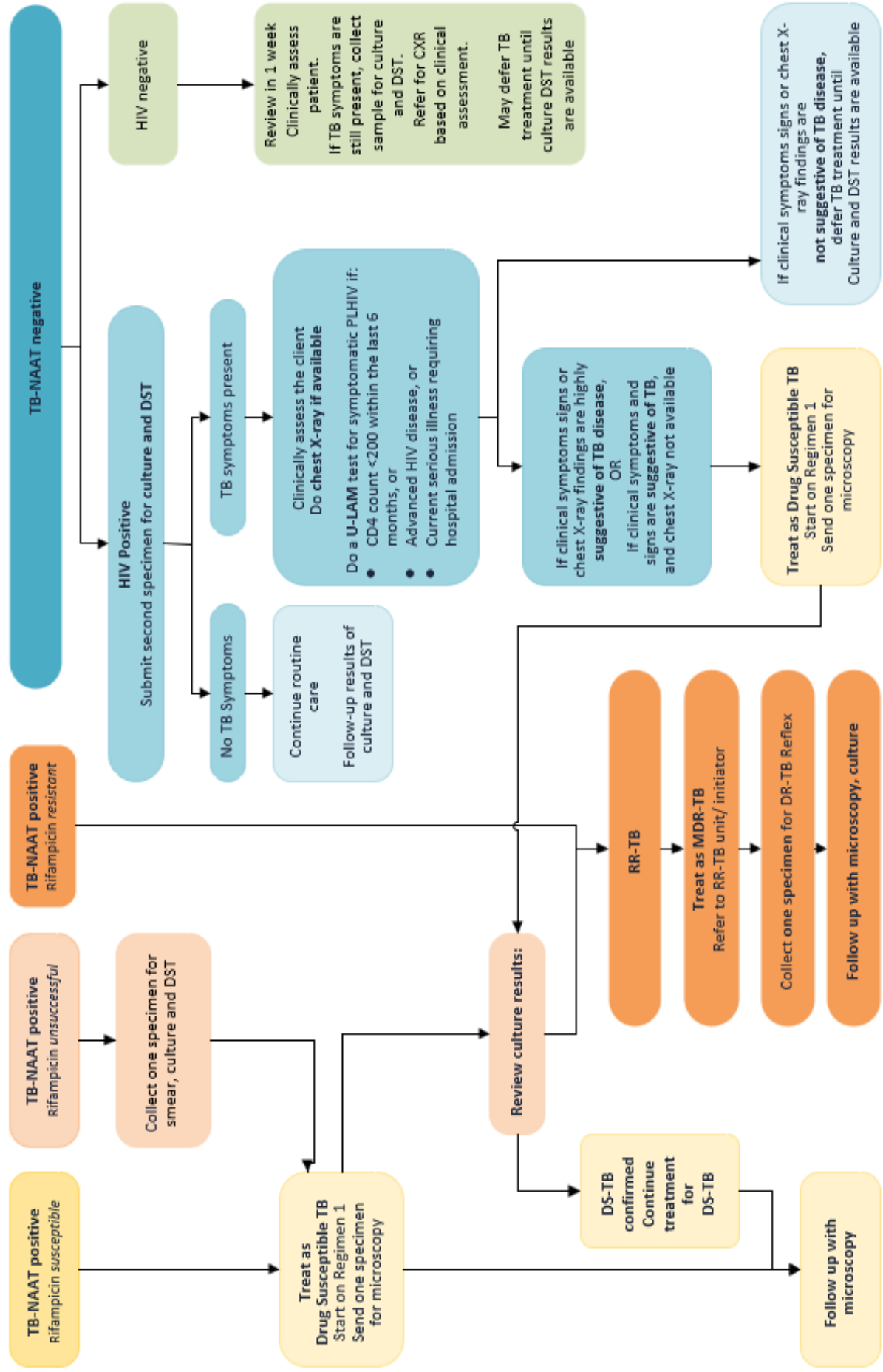
	TB Investigations	Purpose	When done	Estimated TAT	Possible outcomes
Investigations to make the diagnosis of TB	TB Nucleic Acid Amplification Tests (TB-NAAT)	Bacteriological confirmation of TB Identification of rifampicin resistance	At primary diagnosis of TB At any point if RR-TB is suspected*	48 hours	MTB detected/ not detected Rif susceptible/ Rif resistant
	Smear microscopy	To determine infectiousness To monitor response to treatment	At primary diagnosis of TB, after a positive GXP result and before treatment initiation	48 hours	AFB negative AFB positive: + ++ +++
	Chest Xray	To identify radiological changes due to TB	At primary diagnosis of TB, when available At the time of any clinical deterioration		
	Urinary-LAM	To facilitate the diagnosis of TB in PLHIV with symptoms of TB who are severely immunocompromised and/or seriously ill	Do a U-LAM test if: - CD4 count <200 within the last 6 months, or - advanced HIV disease, or - current serious illness	30 min	Negative/ positive
Investigations to determine drug susceptibility	TB-NAAT (GeneXpert XDR cartridge) -Genotypic DST	Detects resistance to second-line TB drugs: INH & FLQ	Done automatically as part of RR-TB reflex test when GXP positive and rifampicin-resistant	48 hours	INH S/R FLQ S/R
	Culture and Phenotypic DST	Phenotypic DST: INH, BDQ, LZD, +-Pa		6 – 9 weeks	INH S/R BDQ S/R LZD S/R +- Pa S/R
	Individualised Extended Phenotypic DST	Identifies susceptibility to multiple TB drugs used to construct a rescue regimen	Requested when RR-TB regimen failing, resistant to BDQ or LZD or previous exposure to second-line drugs		



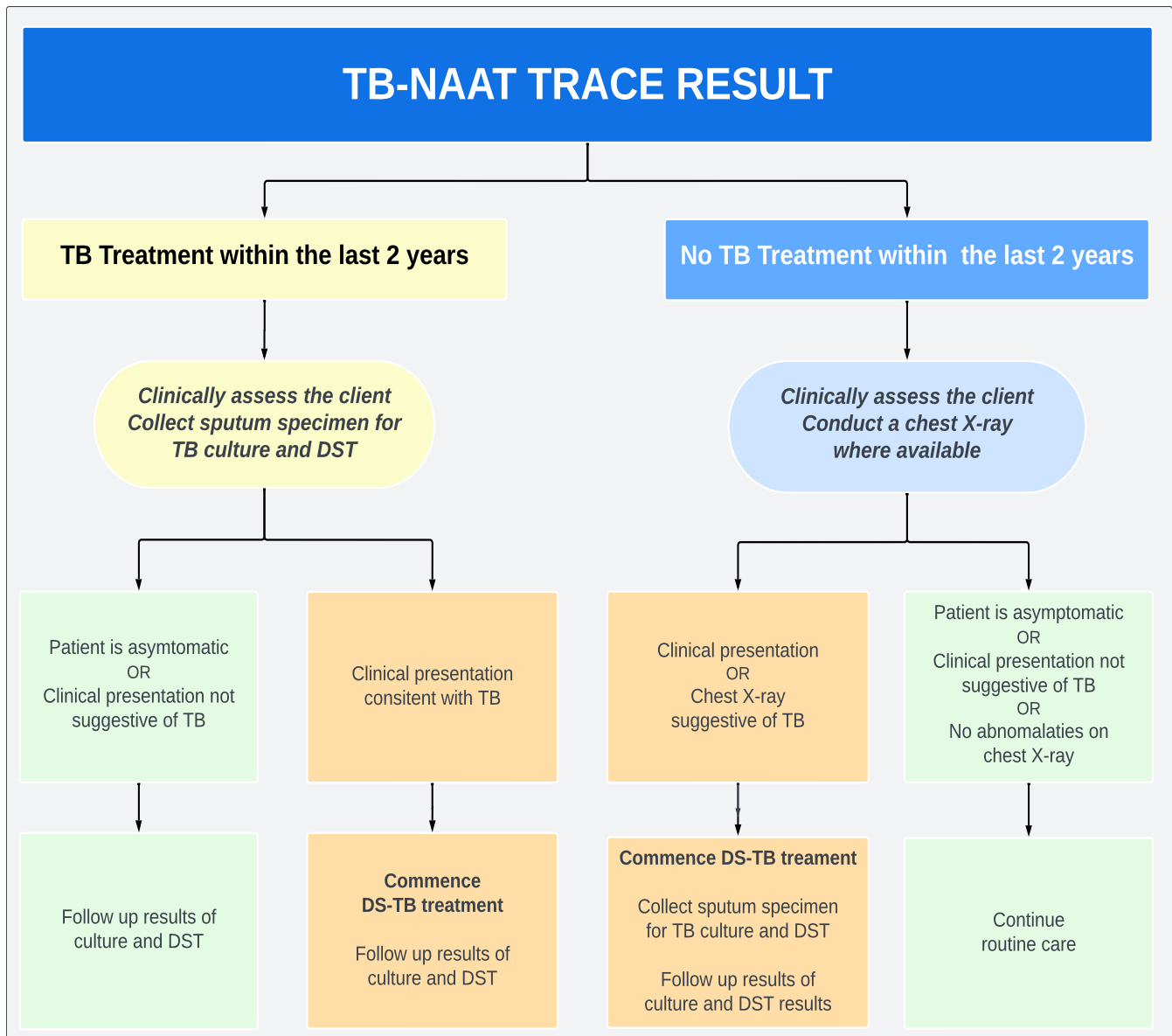
TB-NAAT Diagnostic Algorithm

Presumptive TB in clients who have not received TB treatment within the previous two years
 TB and DR-TB contacts, non-contact symptomatic high-risk individuals, and re-treatment after relapse, failure and lost to follow up

Collect one sputum specimen at the health facility under supervision



Diagnostic Algorithm for TB-NAAT Trace result



DR-TB Reflex Testing

DR-TB Reflex testing is required to determine which other drugs a client is resistant to (other than rifampicin). The type of DR-TB (i.e. MDR, Pre-XDR, or XDR) can then be determined based on the resistance profile (refer to Module 2).

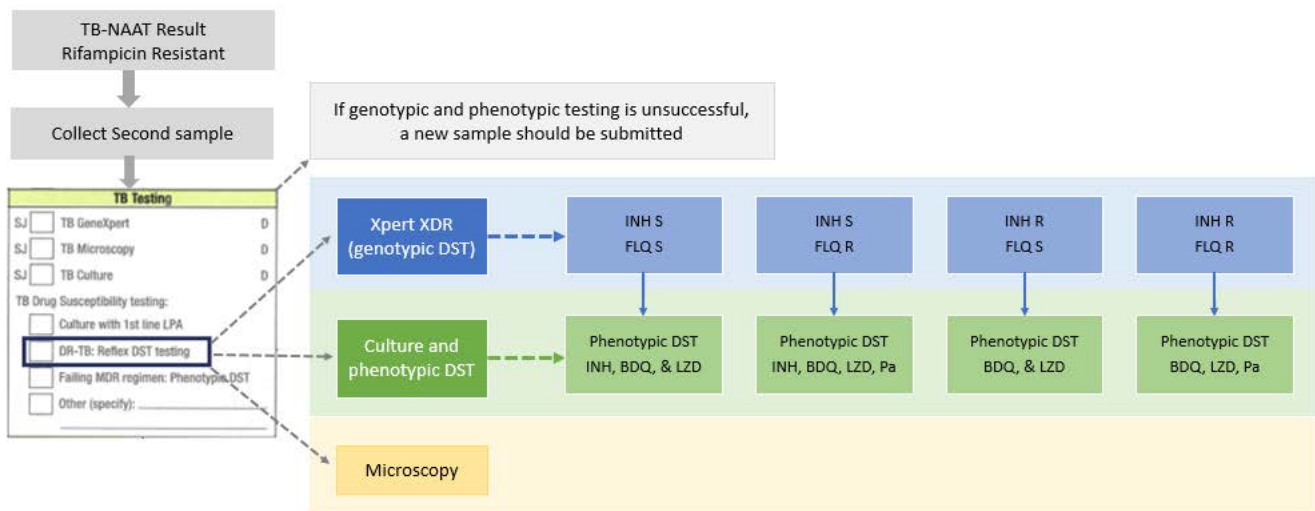
Persons who test positive for *M. tuberculosis* with rifampicin resistance will have DR-TB reflex testing that includes **TB microscopy, second-line genotypic testing for Isoniazid (INH) and Fluoroquinolone (FLQ) resistance (currently using Xpert XDR cartridge) , and TB culture and phenotypic DST for bedaquiline (BDQ) and linezolid (LZD).**

Samples or isolates with FLQ-resistance on genotypic DST will be automatically sent for phenotypic DST for pretomanid (Pa). Clinicians should call the laboratory to discuss any discordant results.

Laboratory surveillance will determine the need for upfront phenotypic testing of drugs such as delamanid and pretomanid.

DR-TB reflex testing done at baseline must not delay the initiation of treatment.

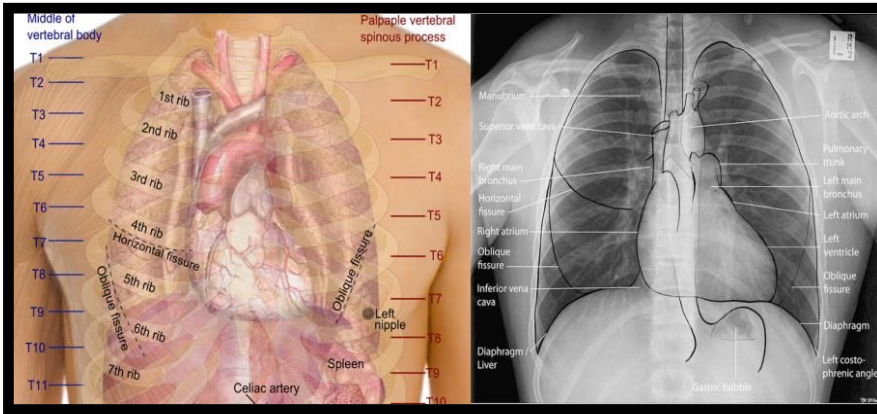
DR-TB Reflex Testing Algorithm



Principles of Chest X-Ray (CXR)

Basics of X-Ray Interpretation (RIP-Q)

1. **Rotation** - Does the spine align with midline; are clavicles even?
2. **Inspiration** - Can you see 6 anterior ribs and 10 posterior ribs?
3. **Penetration/Exposure** - Can you see the spinal processes through the chest?
4. **Quality** - Can you see all areas of the thoracic cavity?

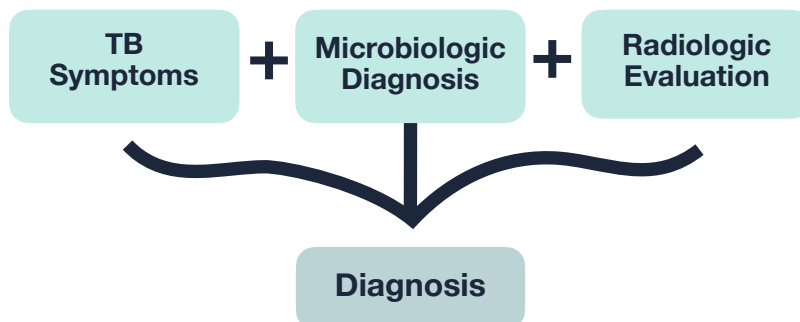


Systematic Approach

- | | |
|---------------------------|-------------------|
| 1. Clinical Context | 6. Mediastinum |
| 2. Validity: RIP-Q | 7. Lungs |
| 3. Bones and Soft Tissues | a. Hilum |
| 4. Diaphragm | b. Parenchyma |
| 5. Cardiac Silhouette | c. Pleura |
| | 8. Interpretation |



CXR in TB - Many findings are possible!



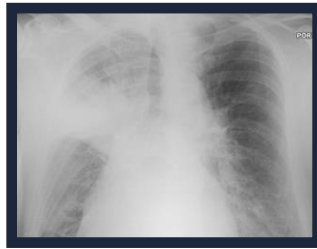
Normal CXR in a patient who has symptoms & microbiologic diagnosis is POSSIBLE
 TB is not the only cause of an abnormal chest x-ray finding

Interpreting Chest X-Rays

Findings Suggestive of ACTIVE TB

Infiltrate/Consolidation:

- Whiteness (opacification) of airspaces
- May be dense or patchy
- May be irregular, ill-defined or hazy borders



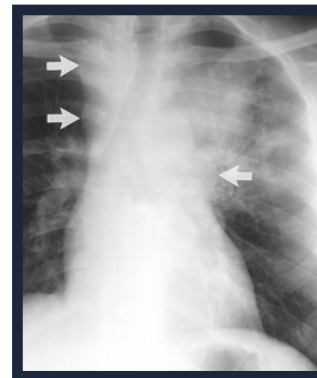
Cavitary Lesion:

- Lucency (darkened area) within lung
- Walls may be thick or thin
- Calcification may exist around it



Pleural Effusion:

- Fluid in pleural space
- Must distinguish fluid from other causes of costophrenic angle blunting (i.e., volume loss)



Hilar or mediastinal lymphadenopathy:

- Enlargement of lymph nodes in hilar area
- Mediastinal widening

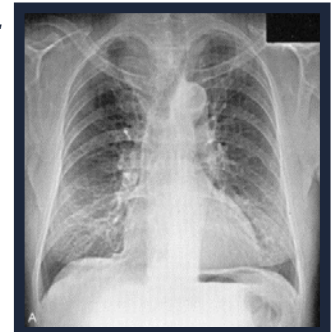
Nodules:

- Round density (tuberculoma)
- This may have poorly defined margins
- May have surrounding haziness which suggests air space consolidation



Tracheal deviation:

- Is trachea being "pushed" or "pulled"



CXR monitoring

Chest x-ray should be obtained:

- **At Baseline** and **Every 6 months**
- Consider chest x-ray for patients with acute worsening of condition

CXR vs CT Scan

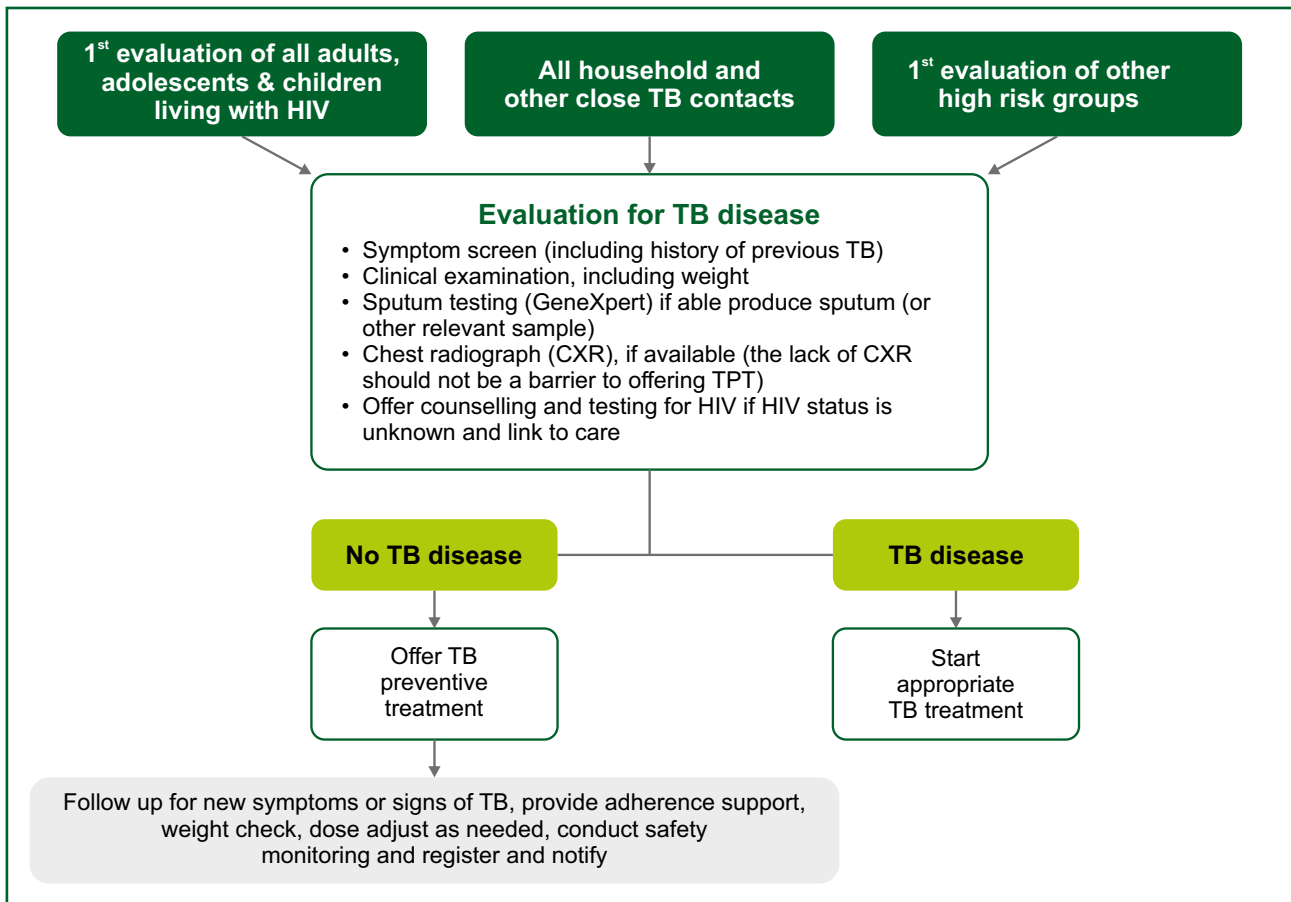


Module **4**

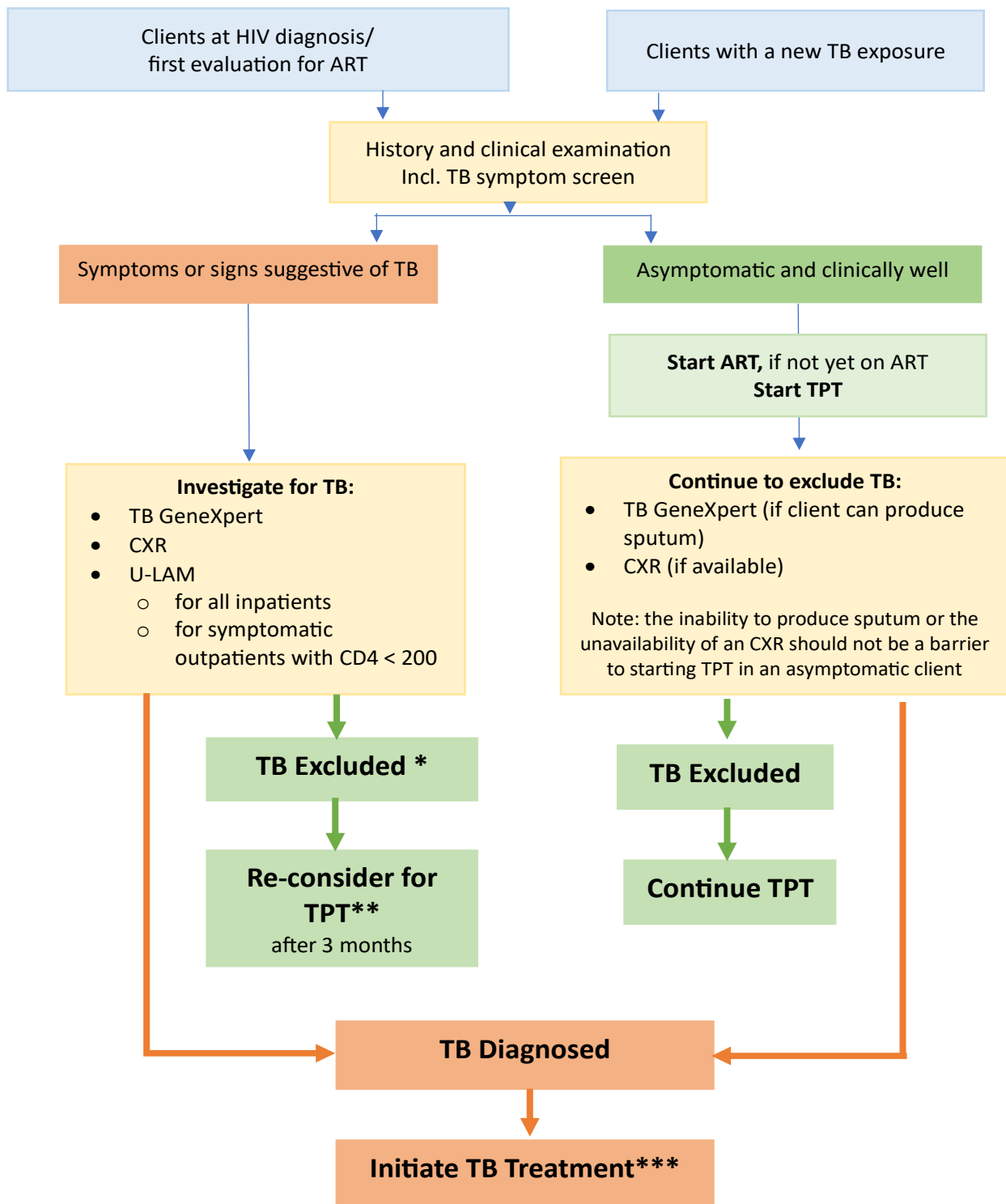
TB Preventive Therapy (TPT)



General algorithm for provision of TB preventive treatment



TB Assessment Process for PLHIV



* Based on a clinician's assessment of the symptomatic client's clinical condition and all special investigations, and subsequently deciding that the client does not have TB

** Symptomatic clients who were who subsequently considered NOT to have TB, should not immediately be initiated on TPT. They can be reconsidered for TPT 3 months later. However, at this later time, they should be screened and tested for TB again, before being considered for TPT

*** Clients who are asymptomatic and were initiated on TPT, and who were then subsequently diagnosed with TB, can stop TPT and initiate TB treatment. There is no risk of developing INH resistance in the short period of time that the client would have taken INH alone

Summary of TPT regimen options by patient type

PATIENT CATEGORY		WHAT TO DO	REGIMEN
Adults and adolescents including children ≥25kg	HIV-positive	PLHIV: Test for TB regardless of ART status and give TPT once TB disease is excluded. If newly diagnosed with HIV, start ART immediately and TPT within the next two weeks.	3HP* or 12H
		Post TB treatment: Offer TPT to all PLHIV ≥25 kg after successfully completing treatment for TB disease, after active TB disease has again been excluded.	
		Previously treated with TPT: If re-exposed to any close contact with TB, retest for TB and give TPT once TB disease has been excluded.	
		Evaluate all HIV-positive pregnant women regardless of CD4 count and give TPT once TB disease has been excluded.	
	HIV-negative	Contacts: Evaluate all HIV-negative adults, adolescents and children ≥25kg in close contact with people diagnosed with TB and start TPT once TB disease has been excluded.	3HP, 3RH or 6H
		Evaluate all HIV-negative at-risk groups (on anti-TNF treatment, on dialysis, diabetes, preparing for organ or haematological transplant, or with silicosis). Once TB disease is excluded, start TPT.	
		Evaluate HIV-negative adults and adolescents who previously received TPT , if re-exposed to a close contact with TB and start TPT once active TB has been excluded.	
		Evaluate all TB exposed HIV-negative pregnant women and give TPT once TB disease has been excluded.	
Infants and children <25kg	HIV-positive	Children living with HIV (CLHIV): Evaluate all children older than 14 weeks of age living with HIV for TB and start TPT once active TB has been excluded. ART should be started immediately if newly diagnosed with HIV. TPT should be started within two weeks of ART initiation.	6H**
		Contacts: Evaluate all TB-exposed CLHIV and start TPT after TB disease has been excluded, regardless of previous treatment or TPT.	
	HIV-negative	Contacts: Evaluate HIV-negative children in close contact with a TB patient and start TPT after active TB disease has been excluded.	3RH
		Test other HIV-negative at-risk children (weakened immune system e.g., cancer, diabetes, autoimmune diseases, transplant patients on immunosuppressive drugs, receiving dialysis, or inherited immunodeficiencies) for TB and start TPT once TB disease has been excluded	

* For adults, adolescents and children ≥25kg *initiating* a dolutegravir-containing ART regimen, 12H is preferred. For PLHIV who are virally suppressed (VL<50 copies/mL) on a dolutegravir-containing regimen, 3HP is preferred.,

** In children <25kg initiating a dolutegravir-containing ART regimen, 6H is preferred.

Once the dolutegravir levels from the DOLPHIN-2, DOLPHIN-kids and TBTC Study 35 trials are available, 3HP will likely be the preferred option in all PLHIV. If 3HP is not available, use either 6H (children<25kg) or 12H (adults, adolescents and children ≥25kg).

TPT for Rifampicin Resistant Household Contacts

Principles of TPT for RR-TB

- All adults, adolescents and children who are household contacts of a person with RR-TB, irrespective of HIV status, should be screened for TB symptoms and signs and if found to be asymptomatic, assessed for eligibility for TPT
- Preventive treatment should be individualised after a careful assessment of the intensity of exposure, the certainty of the source case, reliable information on the resistance pattern of the source case and potential adverse events.
- Those at high-risk to be treated (children, adolescents and PLWHIV and individuals receiving immunosuppressive therapy).
- Drugs to be selected according to the drug susceptibility profile of the source case.

Inclusion criteria

- All household contacts of Rifampicin Resistant TB (RR- TB) patients
 - Including those with Multi- drug Resistant TB (MDR- TB) and Extensively Drug Resistant TB (XDR - TB)
- Irrespective of HIV status and age, but with no other exclusion criteria

Exclusion criteria

- Confirmed DS-TB or RR-TB (MDR-TB and XDR-TB) disease
- Presence of symptoms and signs of TB
- Active liver disease (acute or chronic)
- Presence of symptoms and signs of severe peripheral neuropathy
- History of adverse reaction to any of the drugs used for TPT

Category Definitions for Clients Starting TPT

New	A contact who has never had treatment for TB infection (IPT or other) or who took treatment for less than 4 weeks.
Previously treated	A contact who has taken treatment for TB infection (IPT or other) for 4 weeks or more in the past and either completed or stopped for whatever reason (adverse events, developed TB, lost to follow up)

TPT Regimen Options for RR-TB

Regimen Option 1

- For contacts exposed to a patient with fluoroquinolone -susceptible RR-TB:
- A fluoroquinolone-based regimen (ideally levofloxacin) given alone or in combination with other medicines that are likely to be efficacious (e.g., high-dose INH)

Type of Exposure	TPT Medicines	Patient Type	Dosage	Frequency	Duration
Fluoroquinolone susceptible RR-TB	Levofloxacin	Adult	15 – 20 mg/kg [max 1,5 g]	Once daily	6 months
		Child	15 - 20 mg/kg [max = 1.5 g]	Once, daily	6 months

Regimen Option 2

- For contacts who are exposed to an index patient with fluoroquinolone resistant MDR TB:
- Single drug regimen of high-dose INH for 6 months

Type of Exposure	TPT Medicines	Patient Type	Dosage	Frequency	Duration
Fluoroquinolone resistant RR-TB	High-dose INH*	Adult	10 – 15 mg/kg	Once, daily	6 months
		Child	15 – 20 mg/kg	Once, daily	6 months

* Given with Pyridoxine (vitamin B6): 25-50mg per day

Note that current evidence for TPT regimens for clients exposed to RR-TB is weak, but updated recommendations will follow as the evidence evolves.

For further information, please also refer to the 2019 Clinical Reference Guide.

Counselling when TPT for RR-TB is initiated

Persons should be educated and counselled about:

- the risk of developing TB disease
- the importance of taking the TPT medication as prescribed for the complete duration
- TB signs and symptoms
- the importance of reporting to health facilities for an assessment for TB once these develop

Monitoring on TPT for RR-TB

Persons on TPT should have the following checked at their follow-up visits:

- Assess for any TB symptoms and signs
- Assess for treatment side-effects
- Assess their level of adherence

Outcome Definitions for TPT for RR-TB

Classification	Definition
Treatment completed	A contact who has taken treatment and completed treatment within the prescribed period.
Lost to follow up	A contact whose treatment was interrupted for three consecutive months or more during the treatment period
Treatment stopped	A contact whose treatment was stopped during the treatment period, as a result of serious adverse events or development of TB disease.
Died	A contact who dies for any reason during the course of TB treatment

There are currently no reporting mechanisms for TPT outcomes, but these outcomes should be documented in the client's file

Module **5**

Treating Active DS-TB



Drug-Sensitive TB Treatment

Standardised treatment with fixed dose combination medicines are used for DS-TB Treatment

2 month intensive phase
+
4 month continuation phase

There are 3 standardised treatment regimens for DS-TB:

- Regimen 1:** for new and previously treated adults and children >8yrs/>30kg
- Regimen 3A:** for children < 8yrs and < 30kg with uncomplicated TB disease
- Regimen 3B:** for children < 8yrs and < 30kg with complicated TB disease

DS-TB Treatment: Regimen 1

Regimen 1: For Adults and Children >8 years or weighing >30kg			
Pre-Treatment Body Weight	Intensive Phase 7 days a week for 2 months	Continuation Phase 7 days a week for 4 months	
	RHZE (150, 75, 400, 275)	RH (150, 75)	RH (300, 150)
30-37kg	2 tabs	2 tabs	--
38-54kg	3 tabs	3 tabs	--
55-70kg	4 tabs	--	2 tabs
>70kg	5 tabs	--	2 tabs

R: Rifampicin **H:** Isoniazid **Z:** Pyrazinamide **E:** Ethambutol

Adjunctive Treatment:

Pyridoxine is given to prevent peripheral neuropathy, most commonly caused by INH:

- 25mg daily for all adult patients started on TB treatment
- If peripheral neuropathy develops increase to 50-75mg (up to maximum of 200mg) until symptoms subside then reduce to 25 mg daily

Please refer to the most recent DS-TB Guideline for updated recommendations

DS-TB Treatment Side Effects

Side Effects	Drug(s)	Responsible Management
Minor		
Anorexia, nausea, abdominal pains	Rifampicin	Exclude hepatitis. Treat symptomatically. Take Rifampicin at least 30 minutes before meals or before going to bed. Use antacids at least 2 hours before or after taking treatment
Joint pains	Pyrazinamide	Continue TB drugs, treat symptomatically (e.g. aspirin or panadol). If severe, allopurinol may be required for the treatment of gout
Burning sensation in feet/ fingers	Isoniazid	Increase Pyridoxine to 50-75mg (up to maximum of 200mg daily) Ensure that patient is receiving the correct dose according to weight
Orange/red coloured urine	Rifampicin	Warn patients of this possible side-effect before commencing treatment. Reassure if it occurs
Major		
Skin itching/rash	Rifampicin, Isoniazid	Take careful history regarding onset. Consider other drugs (e.g. ART), underlying causes or infectious conditions. If petechial rash, may be due to Rifampicin - check platelet count. If erythematous rash with fever, stop all drugs
Jaundice	Isoniazid, Rifampicin, Pyrazinamide	Check liver tests immediately and evaluate for drug-induced and other causes of hepatitis. If likely drug-induced hepatitis, stop all TB drugs. If possible, eliminate the most likely agent from regimen
Peripheral Neuropathy	Isoniazid (also HIV)	Continue TB drugs. Pyridoxine 50-75mg daily, can increase to 200mg daily in HIV positive patient
Vomiting, confusion	Isoniazid, Rifampicin, Pyrazinamide	Refer for supportive treatment if severe
Visual Impairment/Loss	Ethambutol	Stop ethambutol immediately and never re-introduce. First, rule out other causes
Generalised purpura and shock	Rifampicin	Stop rifampicin. Administer Vitamin K at birth to infant of mother taking Rifampicin

Definitions of DS-TB Treatment Outcomes

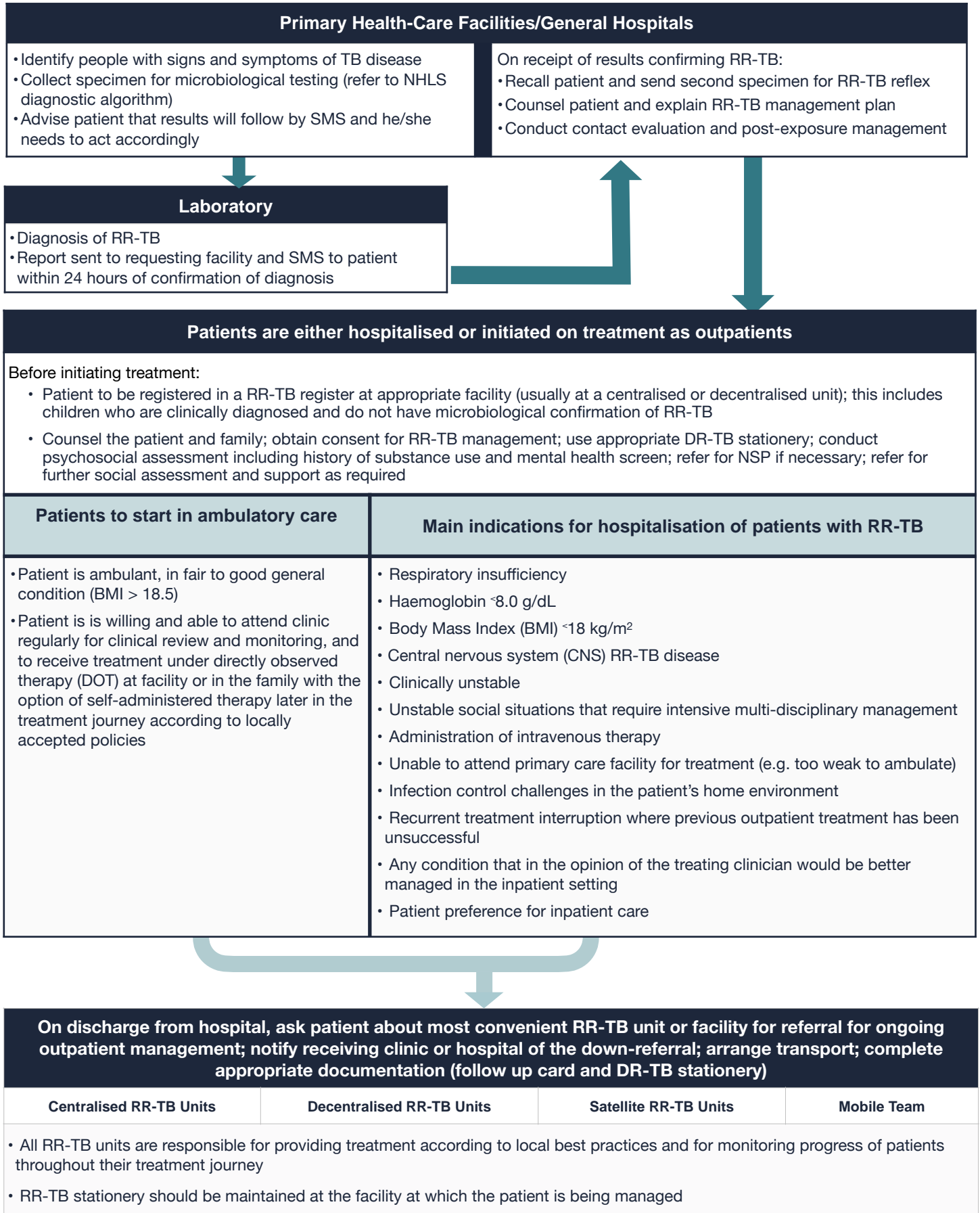
Outcome	Definition
Cure	Patient whose baseline smear (or culture) was positive at the beginning of the treatment and is smear/culture negative in the last month of treatment and on at least one previous occasion at least 30 days prior.
Treatment Completed	A patient who may have had a positive or negative baseline smear (or culture) at the beginning of treatment, and who has completed treatment, but does not have a negative smear/culture in the last month of treatment and on at least one previous occasion more than 30 days prior. The smear examination may not have been done or the results may not be available at the end of treatment.
Treatment Failure	Patient whose baseline smear (or culture) was positive and remains or becomes positive again at 5 months or later during treatment. This definition excludes those patients who are diagnosed with RR-TB or MDR-TB during treatment.
Died	Patient who dies for any reason during the course of TB treatment.
Lost To Follow Up	Patient whose treatment was interrupted for two consecutive months or more during the treatment period.
Transfer Out	Patient who was referred to a facility in another district to continue treatment and for whom the treatment outcome is not known.

Module

Initiating the Treatment & Care Process for RR-TB



Flow of RR-TB Patients



RR-TB Identification & Notification

After there has been a laboratory diagnosis of RR-TB, the patient should be **notified** and **brought in** to the clinic for further evaluation and treatment initiation

If the patient does not return or call within 48 hours of notification, send a TB tracer or community health worker (CHW) to locate the patient



Screening of Close Contacts

All close contacts of RR-TB patients should be identified through contact tracing, and evaluated for active TB by a health-care provider

If symptomatic:

- Investigate contacts promptly using GeneXpert

If asymptomatic:

- If high risk: Investigate promptly using TB-NAAT (e.g. Xpert Ultra)
- Screen close contacts at six-monthly intervals for up to two years
- Follow up HIV positive contacts six-monthly
- Educate contacts about signs & symptoms of TB and inform them that they should present at a health facility immediately if these develop
- If active RR-TB develops refer immediately for treatment



Pre-Treatment Evaluation

The objective of the pretreatment evaluation is to identify those patients at a greater risk of adverse effects and to **establish a baseline for monitoring**

The pretreatment evaluation should include:

- ▶ counselling & informed consent
- ▶ a comprehensive medical history & physical examination
- ▶ laboratory and diagnostic testing



History Taking

Interview the patients and review their medical and social history to detect any of the following conditions or situations that may require individualized decisions to be made about treatment

Ask the patient about:

- ▶ Prior TB infection and treatment history
- ▶ Exposure to RR-TB
- ▶ HIV status
- ▶ Current medications
- ▶ Mental health and other medical conditions

Nutritional Support

In addition to causing malnutrition, DR-TB can be exacerbated by poor nutritional status

- ▶ DR-TB management should contain integrated nutritional assessment, counselling, and support for the duration of treatment

- ▶ Substance abuse history
- ▶ Occupational hazards
- ▶ Support systems

RR-TB Pre-Treatment Checklist

Baseline Investigations for RR-TB		
<input type="checkbox"/>	DR-TB Reflex Test Smear, Culture, and DST to determine resistance profile	All patients
<input type="checkbox"/>	Height	All patients
<input type="checkbox"/>	Weight	All patients
<input type="checkbox"/>	Body Mass Index (BMI) and NSP, if BMI <18.5	All patients
<input type="checkbox"/>	HIV Test/Screening	Patients with unknown HIV status or those who have not been tested in the past 3 months
<input type="checkbox"/>	CD4 Count and HIV Viral Load	HIV positive patients
<input type="checkbox"/>	Hepatitis B Screening	All patients
<input type="checkbox"/>	Pregnancy Test	Women of child bearing age, presenting with history of amenorrhea and not on contraception
<input type="checkbox"/>	Family Planning Discussion	All patients
<input type="checkbox"/>	Full Blood Count	All patients (<i>May substitute for Haemoglobin if unable to obtain</i>)
<input type="checkbox"/>	Urea & Electrolytes	All patients
<input type="checkbox"/>	Serum Creatinine	All patients
<input type="checkbox"/>	Serum Calcium, Magnesium	All patients
<input type="checkbox"/>	Blood Glucose	All patients: Urine glucose & Ketones Symptomatic patients: Blood glucose (If elevated, obtain Haemoglobin A1c)
<input type="checkbox"/>	Substance Use and Mental Health Screening	All patients
<input type="checkbox"/>	Liver Function Tests	ALT: All Patients Full LFTs: In patients with history of liver disease or excessive alcohol use
<input type="checkbox"/>	Chest X-ray	All patients
<input type="checkbox"/>	Vision Test (using Snellen chart)	All patients
<input type="checkbox"/>	ECG	All patients who will be receiving Bedaquiline or Delamanid

Module

RR-TB Treatment Regimens



RR-TB Treatment Regimens in South Africa

In May 2022 the WHO announced the introduction of the **6-month BPaL-M regimen for RR-TB**, comprising of bedaquiline, pretomanid, linezolid, with or without moxifloxacin. In clinical trials the BPaL-M regimen showed up to 90% efficacy.

Following a review by NEMLC, a decision was taken to adopt BPaL-M, and it was further concluded that levofloxacin will be used in replacement of moxifloxacin in South Africa.



BPaL-L will be used in place of the 9-month or longer (≥ 18 months) regimens in clients (aged ≥ 15 years) with multidrug-resistant (MDR)/RR-TB who are eligible.

Short Regimen for RR-TB (BPaL-L)

Most people with a diagnosis of RR-TB will be eligible to receive the short regimen BPaL-L.

This contains:



If fluoroquinolone resistance is detected, BPaL can be used without levofloxacin for 6 months. Prior use of bedaquiline and linezolid (>1 month) is not a contraindication for BPaL-L, but resistance to BDQ, LZD, pretomanid or delamanid must be excluded.

DST should not delay treatment initiation.

BPaL-L must not be used if there is confirmed resistance to bedaquiline or linezolid or pretomanid or delamanid

Criteria for BPaL-L

INCLUSION Criteria	EXCLUSION Criteria
<p>Individuals with RR-TB Resistance based on initial TB-NAAT result, while awaiting further susceptibility results</p>	<p>Persons with severe extra-pulmonary RR-TB: meningitis, pericarditis, osteoarticular, abdominal or disseminated/miliary disease</p>
<p>Non-severe extra-pulmonary RR-TB, including lymphadenopathy or pleural effusion</p>	<p>RR-TB with additional resistance to BDQ or LZD, or pretomanid or delamanid</p>
<p>Persons with extensive pulmonary disease (i.e. bilateral, cavitary disease with significant fibrosis, scarring or cavities in 3 or more lung zones) should have their treatment extended to 9 months</p>	<p>Children under the age of 15 years (pretomanid safety is not yet confirmed in this population)</p>
	<p>Pregnant women (pretomanid safety is not yet confirmed in this population)</p>

BPaL-L for HIV/TB Co-infected Clients

HIV-positive patients with any CD4 count, regardless of ART status, qualify to receive the short RR-TB regimen if they meet the inclusion criteria. See also Module 10 on RR-TB in Special Populations.

BPaL-L Dosing for Adults/Adolescents ≥ 15 years of age

Drug	Dose
Bedaquiline (100mg tablet)	400mg once daily for 2 weeks, then 200mg 3 times per week afterwards
Pretomanid (200mg tablet)	200mg once daily
Linezolid (600mg tablet)	600mg once daily
Levofloxacin (250/500 mg tablet)	750 mg (30 kg to < 46 kg) OR 1000 mg (≥ 46 kg) once daily

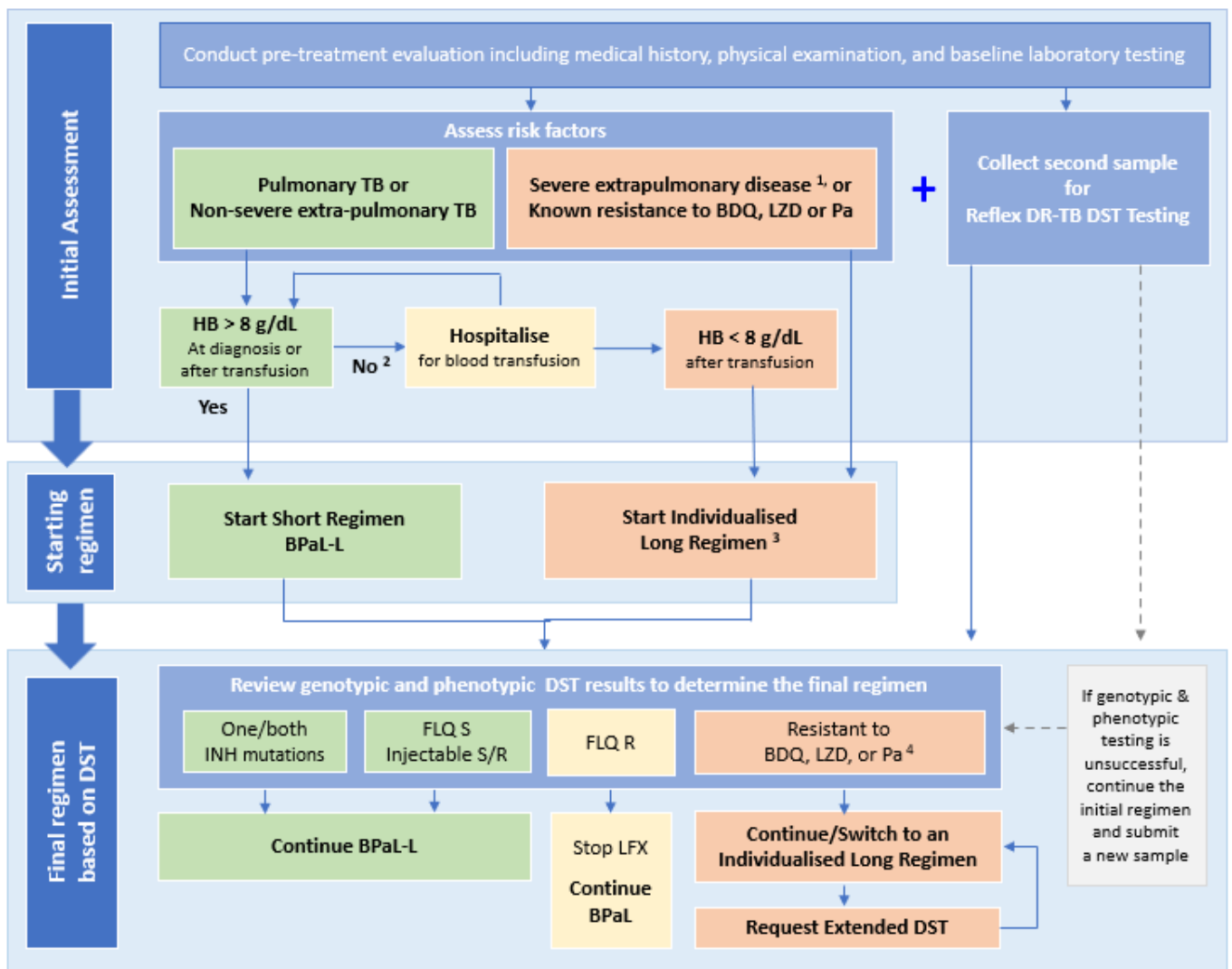
BPaL-L is given for 6 months, extended to 9 months at the clinician's discretion

- ▶ There is no specified intensive or continuation phase for these regimens and all drugs should be continued throughout treatment if possible, unless limited by toxicity or intolerance.
- ▶ Linezolid dose is 600 mg/daily. This should be given for at least 8 weeks. In the case of toxicity or intolerability the dose can be interrupted (while other medicines in the regimen are continued) for a total of a maximum of 8 weeks throughout the treatment course. Interruptions should, where possible, be minimized during the initial phase of treatment.
- ▶ Pyridoxine does not need to be prescribed in patients receiving BPaL-L

Bedaquiline Interruptions

Duration of interruption	Instructions for reloading
< 2 weeks	No reloading needed
2 - 4 weeks	3 days 400mg* bedaquiline daily
1 - 12 months	7 days 400mg* bedaquiline daily
> 12 months	14 days 400mg* bedaquiline daily
If the patient weighs between 16 and 30kg, reload with 200mg daily	

Overview of RR-TB Regimen Selection Process



1. Severe extrapulmonary disease includes forms of tuberculosis such as TB meningitis, pericarditis, osteoarticular TB, and abdominal or disseminated/miliary TB.
2. For management of an HB < 8g/dL in a client who is not in hospital, see section "Specific Adverse Events: Haematological" in Module 9.
3. Individualised long regimens should be designed according to WHO drug groupings. If RR-TB meningitis: include DLM, PZA, and [hdINH or ETO]. If the client switches to an individualised long regimen, a new treatment episode should be registered.
4. If resistance to BDQ, LZD, Pa or CFZ: discuss with NCAC.

Switching from BPaL-L to Long Individualised Regimen

A switch to a long individual regimen should be strongly considered in the following situations:

- There is a **positive culture result at month 4** (delayed culture conversion or reversion back to positive). Resistance to bedaquiline, pretomanid, delamanid or linezolid must be excluded.
- **Resistance** to bedaquiline, pretomanid, delamanid or linezolid is detected
- Bedaquiline, or pretomanid, or linezolid is prematurely and permanently **discontinued because of toxicity**
- The patient is **clinically deteriorating or has not clinically improved**. Other causes must be excluded in a culture negative patient

Extended DST is required. Delamanid testing is currently not being routinely done, the NTBRL is planning on starting to test for pretomanid. Clofazimine will also not be routinely tested, it will only be tested as part of EDST.

If the patient switches to a longer regimen due to short RR-TB regimen treatment failure, the treatment episode should be registered as “treatment failure” and the patient should be assigned a new treatment episode.

Long Individualised Regimens for RR-TB

New WHO TB Drug Grouping

A.	Levofloxacin	Lfx
	Moxifloxacin	Mfx
	Bedaquiline	Bdq
	Linezolid	Lzd

B.	Clofazimine	Cfz
	Terizidone	Trd
	Cycloserine	Cs

C.	Ethambutol	E
	Delamanid	DIm
	Pyrazinamide	Z
	Imipenem-cilastatin	lpm
	Meropenem	Mpm
	Ertapenem	Epm
	Amikacin	Am
	Streptomycin	S
	Ethionamide	Eto
	Prothionamide	Pto
	Para-aminosalicylic acid	PAS

Considerations when designing a Long-Individualised Treatment Regimen

Groups and Steps	Medicine	Comments
Group A Include all three medicines, where possible	Levofloxacin or Moxifloxacin	Include for CNS disease. Omit in fluoroquinolone resistant RR-TB
	Bedaquiline	Include if no resistance
	Linezolid	Include for all including CNS disease, unless contraindication or resistance. If Hb <8g/dL, neutrophils <0.75 x 10 ⁹ /L and/or platelets <50 x 10 ⁹ /L, only consider reintroducing or initiating in hospital under close monitoring
Group B Add one or both medicines if possible	Clofazimine	Possible cross resistance to bedaquiline
	Terizidone	Include for CNS disease
Group C Add to complete the regimen and when medicines from Group A and B cannot be used	Ethambutol	Only use as a reliably effective drug if susceptibility demonstrated on DST
	Delamanid	Include for CNS disease
	Pyrazinamide	Include for CNS disease. Only use as a reliably effective drug if susceptibility demonstrated on DST
	Imipenem-cilastatin	Adequate CNS penetration. Must be giving in combination with amoxicillin/clavulanic acid
	Amikacin	Administer if not enough other drug options to compose an effective regimen. Only administer if there is documented susceptibility, if formal hearing tests can be done, and if the patient consents to its use after the risks and benefits of the drug have been explained
	Ethionamide	Consider for CNS disease. Should only be given if inhA mutation is not present
	Para-aminosalicylic acid	Use in rescue regimens

The choice and number of Group C medicines to include depends upon the confidence in the effectiveness of medicines in this group and the other components of the regimen, thus:

- If 4 Group A and B agents are included and there is confidence in all of them then Group C agents are not needed.
- If 3 Group A and B agents are included and there is confidence in all of them then at least one Group C agent is added.
- If 2 Group A and B agents are included and there is confidence in all of them then at least three Group C agents are added.

Summary algorithm for longer MDR-TB regimen composition

	Medicines to which there is resistance or contraindication of use	Consider adding medicines likely or confirmed to be effective			Examples of regimens
		Group A	Group B	Group C ^b	
1	Two Group A medicines	Remaining medicine	Both medicines	At least 1 medicine	<p>18 Bdq_(6 m or longer)-Cfz-Cs-Dlm_(6 m or longer)-(Z or E)</p> <p>18 Lzd-Cfz-Cs-Dlm_(6 m or longer)-(Z or E)</p> <p>18 Lfx-Cfz-Cs-Dlm_(6 m or longer)-(Z or E)</p> <p>If there is a suspected resistance to E or Z, replace with Group C drugs</p>
2	One Group B medicine	All 3 medicines	Remaining medicine	May not be needed	<p>18 Bdq_(6 m or longer)-(Lfx or Mfx)-Lzd-(Cfz or Cs)</p>
3	Both Group B medicines	All 3 medicines	None	1 or 2 medicines	<p>18 Bdq_(6 m or longer)-(Lfx or Mfx)-Lzd – Dlm_(6 m or longer)-(Z or E)</p> <p>If there is a suspected resistance to E or Z, replace with Group C drugs</p>
4	One Group A and both Group B medicines	Remaining 2 medicines	None	At least 3 medicines	<p>18 Bdq_(6 m or longer)-(Lfx or Mfx)-Dlm_(6 m or longer)-Z-E</p> <hr/> <p>18 (Lfx or Mfx)-Lzd-Dlm_(6 m or longer)-Z-E</p> <hr/> <p>18 Bdq_(6 m or longer)-Lzd-Dlm_(6 m or longer)-Z-E</p> <p>If there is a suspected resistance to E or Z, replace with Group C drugs</p>
5	All Group A medicines	None ^c	Both	3 or more medicines	<p>18–20 Cfz-Cs-Dlm-Z-E</p> <p>or other combinations of Group C drugs, depending on known or suspected resistance</p>

Source: WHO [operational handbook on tuberculosis](#). Module 4: treatment drug-resistant tuberculosis treatment, 2022 update, Page 62

In South Africa terizidone (TRD) is used instead of cycloserine (Cs)

Pyridoxine 50 mg should be prescribed for patients receiving a regimen containing TRD or hdINH

For persons ≥ 15 years of age without CNS RR-TB disease, select a regimen consisting of as many category A drugs that are still considered to be susceptible, with terizidone and clofazimine. In addition, select drugs from category C, based on likely efficacy: consider an individual's prior drug exposure, toxicity history and documented resistance.

If a CNS regimen is needed, select drugs that penetrate the CNS and have suspected efficacy.

Special Considerations for Persons on Long Regimens

Situation	Possible Actions
<p>Persons not responding to treatment</p>	<ul style="list-style-type: none"> - Careful assessment in any persons with a positive culture at month 3, clinical worsening or poor weight gain - Review adherence, screen for any contributing factors that could relate to non-adherence (substance use, mental health, socio-economic factors), and ensure adherence support in place - Confirm BDQ and LZD sensitivity - Request extended DST and perform chest X-ray - Offer long individualized regimen
<p>Persons who are lost to follow-up (LTFU) during treatment then return to care</p>	<ul style="list-style-type: none"> - "Welcome back" counselling and additional adherence support - Thorough assessment on reasons for LTFU (e.g. substance use, mental health, undisclosed adverse events, socio-economic factors) - Send sputum for reflex testing and request extended DST - Regimen selection to consider patient's clinical status, extent of disease, comorbidities, bacteriologic status at time of LTFU (i.e. smear and culture status), length of therapy received, and length of time between LTFU and return to care - In patients who have a microbiological/radiological and clinical picture confirming TB disease, an empiric long treatment regimen may be started while awaiting extended DST results, with input from PCAC/NCAC as needed

Module 8

RR-TB Treatment Pharmacology & Side Effects



RR-TB Adult Dosing Tables

	Medicine	Weight				
		30 - <36kg	36 - <46kg	46 - <56kg	56 - <70kg	≥ 70kg
Group A	Levofloxacin	750mg		1000mg		
	Moxifloxacin	400mg				
	Bedaquiline	400mg daily for 2 weeks, then 200mg 3 times per week				
	Linzeolid	300mg	450mg	600mg		
Group B	Clofazimine	100mg				
	Terizidone	500mg		750mg		
Group C	Ethambutol	800mg		1200mg		1600mg
	Delamanid	50mg twice daily				
	Pyrazinamide	1200mg	1600mg			2000mg
	Imipenem-cilastatin*	1000mg twice daily				
	Meropenem*	1000mg three times daily or 2000mg twice daily				
	Ertapenem*	500 mg once daily				
	Amikacin	—		750-1000mg	1000mg	
	Streptomycin	—		Calculate according to dilution		
	Ethionamide	500mg		750mg		1000mg
	Prothionamide	500mg		750mg		1000mg
	Para-aminosalicylic acid	4000mg twice daily 4g-6g twice daily				
	High-Dose Isoniazid	450mg 600mg				
	Pretomanid	200mg				

* Given with Amoxicillin-clavulanate: 250 mg / 125 mg given 30 minutes prior to Imipenem/ertapenem/meropenem

[Group A]

Levofloxacin (LFX)

Contraindications: Known hypersensitivity, QTc prolongation. Caution with CNS disease/seizures

Adverse Reactions:

Common: Generally well-tolerated, well-absorbed. GI upset (nausea, diarrhea), headache

Less common: Insomnia, photosensitivity, rash, vaginitis, tendonitis, psychosis, seizure (CNS effects seen almost exclusively in elderly)

Monitoring: Symptom evaluation

Comments: Do not administer with antacids, sucralfate, iron, zinc, calcium, or oral potassium and magnesium replacements. Use caution in patients known with tendon disorders

Moxifloxacin (Mfx)

Contraindications: Known hypersensitivity, myasthenia gravis, QTc prolongation. Caution with CNS disease/seizures

Adverse Reactions:

Common: Generally well-tolerated, well-absorbed. GI upset (nausea, diarrhea), headache

Less common: Insomnia, photosensitivity, rash, vaginitis, tendonitis, psychosis, seizure (CNS effects seen almost exclusively in elderly)

Monitoring: Symptom Evaluation. ECG if on BDQ

Comments: Do not administer with antacids, sucralfate, iron, zinc, calcium, or oral potassium and magnesium replacements. Use caution in patients known with tendon disorders

Bedaquiline (BDQ)

Contraindications: Cardiac disease, ventricular arrhythmias, prolonged QTc interval (>500ms), severe liver disease, abnormal electrolytes

Adverse Reactions:

Common: GI distress (nausea, vomiting, abdominal pain, loss of appetite); joint pain; headache.

Less common: QT prolongation, hyperuricemia, hypersensitivity, elevated ALT, chest pain, hemoptysis. Possibly an increased risk of pancreatitis

Monitoring: ECG monitoring at baseline, weeks 2, 4, 8, 12, 24. ECG should be monitored until 6 months after last dose of BDQ. Monthly LFTs

Comments: Monitor with use with other QT prolonging agents (e.g. Cfz).

Linezolid (LZD)

Contraindications: Hypersensitivity; Caution in patients with uncontrolled HTN

Adverse Reactions:

Common: Diarrhea, nausea, headache, metallic taste

Less common: Myelosuppression, lactic acidosis, optic and peripheral neuropathy, Serotonin syndrome, hypoglycemia

Monitoring: Monitor for peripheral neuropathy and optic neuritis. Monitor with a full blood count

Comments: Do not use with patients taking serotonergic drugs (MAOIs, SSRIs). Patients should not be on AZT while on LZD

[Group B]

Clofazimine (Cfz)

Contraindications: Acquired or congenital QT prolongation, hypersensitivity to clofazimine

Adverse Reactions:

Common: Hyperpigmentation, conjunctiva, cornea, and body fluids; dry skin, pruritus, rash; gastrointestinal intolerance; photosensitivity

Less common: Retinopathy, severe abdominal symptoms, bleeding, and bowel obstruction; QT prolongation

Monitoring: Symptomatic monitoring only

Comments: Discolours skin and body secretions orange, red, or brownish-black; this should go away after stopping the medicine, but may take a long time; avoid sun; use strong sunscreens

Terizidone (TRD)

Contraindications: Porphyria, hypersensitivity, alcohol abuse, seizure disorder, mental illness, severe renal impairment

Adverse Reactions:

Common: Peripheral neuropathy, CNS toxicity, including inability to concentrate, lethargy, insomnia

Less common: Seizure, Depression, Psychosis, Hepatitis

Monitoring: Monitor CNS effects, carefully monitor mood/personality

Comments: Phasing out in South Africa. Pyridoxine 50mg should be given to prevent neurological SE

[Group C]

Ethambutol (E)

Contraindications: Hypersensitivity, optic neuritis, advanced renal failure

Adverse Reactions:

Common: Nausea, Vomiting

Less common: Optic neuritis, GI distress, peripheral neuropathy, arthritis/arthralgia

Monitoring: Baseline and monthly visual acuity and red/green color vision test when dosed at greater than 15 mg/kg daily (more than 10 percent loss is considered significant); regularly question patient about visual symptoms

Comments: May divide doses for issues with nausea or vomiting. Stop drug immediately if patient reports visual disturbance

Delamanid (DIm)

Contraindications: Cardiac disease/arrhythmias, prolonged QT interval, severe liver disease, renal dysfunction, hypothyroidism, age >65, alcohol or substance use, hypersensitivity

Adverse Reactions:

Common: Nausea, vomiting, dizziness

Less common: QT prolongation

Monitoring: ECG monitoring at baseline, weeks 2, 4, 8, 12, 24

Comments: Don't use with other QT prolonging agents

Pyrazinamide (Z)

Contraindications: Known hypersensitivity, severe hepatic damage, acute gout, porphyria, alcohol abuse

Adverse Reactions:

Common: Arthritis/arthralgias, myalgias, hepatotoxicity, hyperuricemia, abdominal distress

Less common: Impaired diabetic control, rash

Monitoring: Monthly LFTs, uric acid can be measured if arthralgias, arthritis, or symptoms of gout are present. Careful monitoring of diabetic patients (labile glucose)

Comments: Usually given once daily, but can split dose initially to improve tolerance. If ALT > 5 times the upper limit of normal without symptoms or if > 3 times the upper limit of normal with symptoms, stop Pyrazinamide

Imipenem-Cilastatin (Ipm)

Contraindications: Carbapenem intolerance

Adverse Reactions:

Common: Diarrhea, nausea, or vomiting

Less common: Seizure (but less is seen than with imipenem), palpitations, pseudomembranous colitis

Monitoring: Symptom evaluation

Comments: Imipenem is rapidly degraded by renal proximal tubule dipeptidases, so it is used in combination with the dipeptidase inhibitor cilastatin. Use with caution in impaired kidney function

Amikacin (Am)

Contraindications: Pregnancy, Myasthenia Gravis, hypersensitivity. Caution with renal, hepatic, vestibular or auditory impairment

Adverse Reactions:

Common: Local pain, proteinuria, (protein in urine), ototoxicity (hearing loss)

Less common: Nephrotoxicity, vestibular toxicity (vertigo, ataxia, dizziness). All increases with advanced age and prolonged use. Electrolyte abnormalities, including hypokalaemia, hypocalcaemia, and hypomagnesaemia.

Monitoring: Monitor renal function, LFTs and audiometry monthly

Comments: Given IM or IV (not absorbed orally). Strains resistant to streptomycin are usually susceptible to amikacin

Ethionamide (ETO)

Contraindications: Do not use with inhA mutation. Hypersensitivity, severe hepatic disease, porphyria, Use with caution in psychiatric illness. Should only be used in pregnancy if there are no other options since it has been associated with neural tube defects and can exacerbate pregnancy-associated nausea and vomiting. Use with caution in diabetics

Adverse Reactions:

Common: GI distress (nausea, vomiting, diarrhoea, abdominal pain, loss of appetite); dysgeusia (metallic taste); hypothyroidism (especially when taken with PAS)

Less common: Arthralgia, dermatitis, gynaecomastia, hepatitis, impotence, peripheral neuropathy, photosensitivity, hypoglycaemia. CNS effects include seizures, pellagra-like encephalopathy responsive to niacin, acute psychosis, anxiety and depression

Monitoring: TSH monitoring, LFTs

Comments: May split dose or give at bedtime to improve tolerability; Eto efficacies are considered similar.

P-Aminosalicylic Acid (PAS)

Contraindications: Severe renal disease, pregnancy

Adverse Reactions:

Common: Severe GI effects (anorexia, nausea, vomiting, diarrhea, abdominal pain); hypersensitivity reaction; hypothyroidism (especially when taken with Eto)

Less common: Hepatitis, electrolyte abnormalities

Monitoring: Monitor TSH, electrolytes, blood counts and liver function tests

Comments: Generally poorly tolerated. Must be taken with acid drink for absorption. Often reserved for pre-XDR and XDR treatment

[Other]

High-Dose Isoniazid (H^h)

Contraindications: Patients with high-level isoniazid resistance who have failed an isoniazid-containing regimen should not receive isoniazid. History of allergic reaction to isoniazid. Porphyrin mutation.

Adverse Reactions:

Common: Peripheral neuropathy (more common with increased doses of INH); GI distress (nausea, vomiting, diarrhea, abdominal pain, loss of appetite); hypothyroidism (especially when taken with PAS)

Neurotoxicity – dose-related and more common in slow acetylators and malnourished patients – presents as peripheral neuropathy, seizures, psychosis, ataxia and optic neuritis. Neurotoxicity is reversed by pyridoxine

Less common: Arthralgias, dermatitis, gynecomastia, hepatitis, impotence, photosensitivity

Monitoring: Baseline and monthly liver enzymes, especially if age > 50 yrs

Comments: Give with pyridoxine 50 mg/day

Pretomanid (Pa)

Contraindications: Hypersensitivity; Caution with impaired liver function; potential for myelosuppression. Contraindicated in pregnancy due to limited data

Adverse Reactions: Only studied in combination with BDQ/LZD

Common: Diarrhea, nausea, headache

Less common: Myelosuppression (most likely LZD), lactic acidosis, optic and peripheral neuropathy. QT prolongation has been reported

Monitoring: Monitor for peripheral neuropathy and optic neuritis. Monitor with a complete blood count (CBC) 2-weekly during the initial period, then monthly

Comments: Take with high fat meal will increase drug levels; avoid use of Efavirenz with Pretomanid

BPAL-L / BPAL Side Effects

	Adverse Drug Reaction	Medication	Nursing Management	MO / NIMDR Management
CNS	Seizures, tremors	FLQ, LZD	Pt safety – seizure precautions, increase B6; not permanent; inform MO	R/o other causes, anticonvulsants, d/c or lower drug doses
	Psychosis, anxiety, depression	FLQ	Psych assessment, assess verbal and nonverbal cues, patient communication, assess affect and sleep	Hold or decrease dose of offending med, B6 antipsychotics, antidepressants
	Peripheral neuropathy	LZD, FLQ, Pa	Nutrition, exercise, safety, DM control	Lower or d/c drug dose, add Lyrica (pregabalin), gabapentin
	Insomnia	Pa	Monitor sleep at each visit, avoid caffeine	Consider diphenhydramine 25mg as needed at bedtime
	Optic Neuritis	LZD, Pa	Visual acuity (Snellen) test every visit while on LZD, refer for ophthalmology eval	Ophthalmology evaluation; stop LZD if more than 2 line decrease in Snellen test
GI	Nausea, vomiting, diarrhea	LZD, Pa	Evening dosing, meds with food, bland diet, small freq meals, weekly weights, hydration	Anti-emetics 30 min prior, separate doses, rehydrate, lower doses, monitor electrolytes
	Gastritis / Abdominal Pain / GERD	BDQ (peds patients) Pa	Avoid caffeine, smoking, administer drugs with food, observe for GI bleeding in vomit or stool, monitor HB	Antacids, PPI (ancillary drugs given 6h before or 2h after TLD), lower doses, d/c offending drug
	Hepatitis	BDQ Pa (lipase elevation)	Stop treatment pending resolution, weights, observe for jaundice, N/V, abd pain, LFT's	Stop treatment pending resolution, observe for jaundice, N/V, abd pain, LFT's
MSK	Muscle aches/pain	Pa, LZD, FLQ	Assess pain level Hot or cold compress Massage Exercise regimen	anti-inflammatories
	Joint Pain	LZD, Pa, BDQ, FLQ	Assess pain level Provide B6 as ordered Hot or cold compress Exercise regimen	anti-inflammatories, aspirin, lower dose, may need to stop, uric acid levels of little relevance
DERM	Pruritis/Itching	Pa	Emollients, tepid baths, antihistamines	Antihistamines, treat through if possible
	Rash	LZD, Pa	Emollients, tepid baths, antihistamines	Antihistamines, treat through if possible, hold meds, drug challenge
	Severe – SJS, TEN	LZD	Stop drug, do not rechallenge; Observe for oral lesions; Notify MO	Stop drug, do not rechallenge
HAEM	Anaemia	LZD	Monitor HB at each visit	Close monitoring of HB, check FeSO4, Admit patients with HB <8, consider treatment interruption
	Thrombocytopenia	LZD	Monitor platelets at each visit	Close monitoring for bleeding
	Leukopenia	LZD	Monitor WBC at each visit	Close monitoring for infection

BOLD = most likely medication(s)

Abbreviations: abd, abdominal; BDQ, bedaquiline; d/c= discontinue; FLQ, fluoroquinolone; HB, haemoglobin; GERD, gastro-oesophageal reflux disease; LZD, linezolid; LFT, liver function tests; MO, medical officer; N/V, nausea and vomiting; Pa, pretomanid; PPI, proton pump inhibitor; r/o, rule out; SJS, Steven-Johnsons Syndrome; TEN, Toxic epidermal necrolysis; WBC, white blood cells

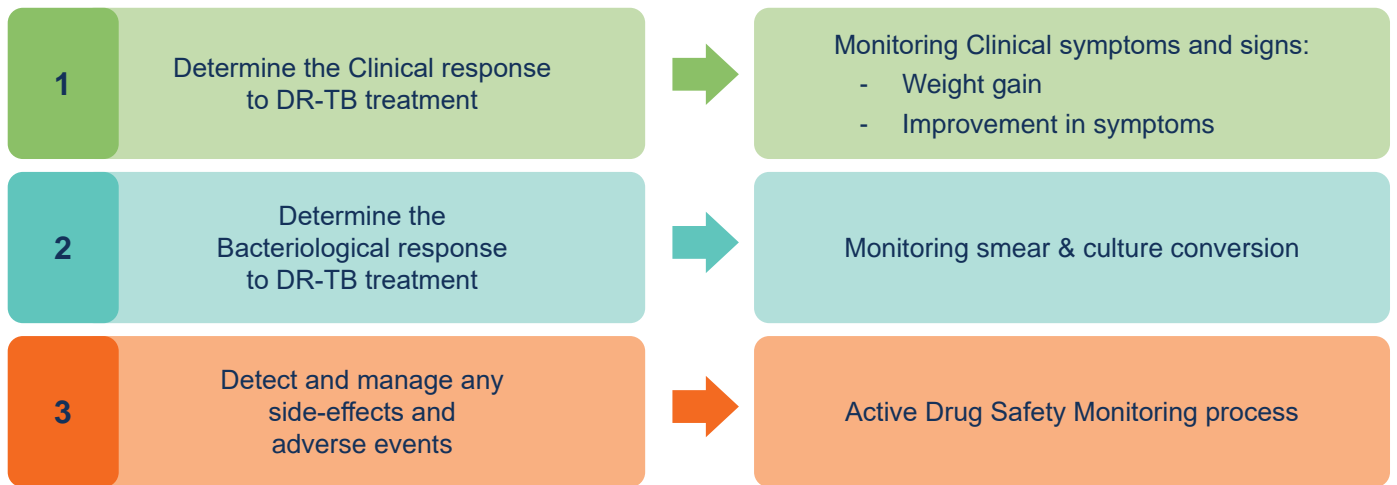
Module

Monitoring and Management on RR-TB Treatment



The Purpose of Monitoring for the RR-TB Client

Providing quality care at the follow-up visit is essential to promote adherence, achieve and sustain smear conversion, minimise side-effects and toxicities, and promote quality of life. A client on DR-TB treatment should be monitored to:



Nutritional Support

In addition to causing malnutrition, DR-TB can be exacerbated by poor nutritional status

A DR-TB assessment and management should contain integrated nutritional assessment, counselling, support for the duration of treatment

$$\text{BMI} = \frac{\text{Weight in kilograms}}{\text{Height in metres}^2}$$

Weight Category	BMI
Underweight	< 18.5
Normal Weight	18.5 - 24.9
Overweight	25 - 29.9
Obese	> 30

! When monitoring on DR-TB treatment, also integrate monitoring for other chronic conditions (HIV, HPT, DM, and mental health) and routinely offer reliable contraception and cervical cancer screening to female clients.

! Remember to check adherence at every clinical follow-up visit, in a non-judgemental way. Ask open ended questions e.g. “Is there anything that makes it difficult for you to take your treatment?”

Routine Monitoring Schedule for RR-TB Clients

Monitoring schedule for patients on BPaL-L/BPaL 6 month regimen

Examination	Baseline	2 weeks	Monthly	End of Treatment	6 & 12 months Post Treatment
Clinical Evaluation					
Clinical Assessment	X	X	X	X	X
Psychosocial Assessment	X	X	X	X	X
Weight/BMI	X	X	X	X	X
Performance Status*	X		X		
Peripheral Neuropathy Screening	X	X	X	X	
Visual Acuity and colour discrimination screening	X	X	X	X	
Assessment and follow-up of adverse events	X	X	X	X	X
Outcome consultation				X	X
Bacteriological evaluations					
Sputum Smear and Culture	X	X	X	X	X
Sputum Drug Susceptibility Testing (DST)	X		X	If smear or culture positive	
Other samples (smear/culture/DST)	X		X	If no documented response to treatment	
Radiology, ECG and Laboratory Evaluations					
Chest X-Ray	X			X	X
ECG	X	X	X	X	
Full Blood Count + Diff	X	X	X	X	
Liver Function Tests (AST, ALT and bilirubin)	X	X	X	X	
Serum Electrolytes	X				
Urea, Creatinine	X				
Pregnancy Test	X				
HIV/HBV/HCV tests	X				
BSL/HbA1c	X				

*Performance Status refers to activities of daily living

Monitoring Bacteriological Response and Determining Duration of Treatment

At baseline send DR-TB Reflex - If DST results have not returned at 1 month, submit a repeat sample for DR-TB Reflex

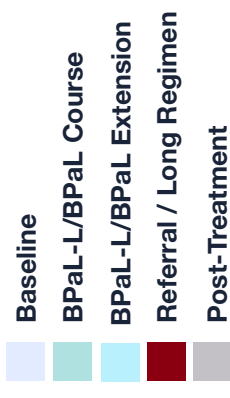
Monthly cultures are to be requested in addition to smear microscopy

Smear determines duration, culture determines treatment outcome

If smear **positive** at 2 months, enhance adherence counseling

If smear **positive** at 3 months, **REPEAT** the **DR-TB Reflex**

Adjust regimen in month 4, based on month 3 testing



	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 6 Months Post Rx	Month 12 Months Post Rx	
Baseline												
Smear ⊖	Sm ⊖	Sm ⊖	Sm ⊖	Sm ⊖	Sm ⊖	Sm ⊖	Sm ⊖	Sm ⊖	Sm ⊖	Sm ⊖	Sm ⊖	Sm ⊖
Smear ⊕	Sm ⊖	Sm ⊖	Sm ⊖	Sm ⊖	Sm ⊖	Sm ⊖	Sm ⊖	Sm ⊖	Sm ⊖	Sm ⊖	Sm ⊖	Sm ⊖
Smear ⊕	Sm ⊕	Sm ⊖	Sm ⊖	Sm ⊖	Sm ⊖	Sm ⊖	Sm ⊖	Sm ⊖	Sm ⊖	Sm ⊖	Sm ⊖	Sm ⊖
Smear ⊕	Sm ⊕	Sm ⊕ ^{**}	Sm ⊖	Sm ⊖	Sm ⊖	Sm ⊖	Sm ⊖	Sm ⊖	Sm ⊖	Sm ⊖	Sm ⊖	Sm ⊖
Smear ⊕	Sm ⊕	Sm ⊕ ^{**}	Sm ⊕ ^{**}	Sm ⊖	Sm ⊖	Sm ⊖	Sm ⊖	Sm ⊖	Sm ⊖	Sm ⊖	Sm ⊖	Sm ⊖

If smear is still ⊕ in Month 4, consider a Long Individualised Regimen

Smear ⊕	Sm ⊕	Sm ⊕ ^{**}	Sm ⊕ ^{**}	Sm ⊕	Sm ⊕	Sm ⊕	Sm ⊕	Sm ⊕	Sm ⊕	Sm ⊕	Sm ⊕	Sm ⊕
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** Refer to instructions above

Monitoring to Detect and Manage Adverse Event

An adverse event (AE) is any untoward medical occurrence that presents in a TB/ART patient during treatment with a pharmaceutical product

It is important to prevent, recognise, and manage adverse events timeously because AEs can:

Affect adherence which can lead to treatment failure

Interfere with clients normal functioning and quality of life

Cause permanent disability

Be life threatening

Result in death

Inadequate management of side effects and adverse events is the main reason patients discontinue medications and therefore one of the primary reasons for **treatment failure**

Anticipatory Guidance - Preparing the Patient

- Pre-treatment education regarding their disease and anticipated length of treatment
- Review potential side effects and management
- Instruct the patient on reporting adverse events
- Provide a supportive environment that facilitates communication between patients and staff
- Educate family members so that they can also be of support to the patient

Active Drug Safety Monitoring

Active Drug Safety Monitoring (aDSM)

is the active and systematic clinical and laboratory assessment of patients while on treatment to detect, manage and report suspected or confirmed drug toxicities

aDSM is important for the following reasons:

- Patient safety: aDSM reduces the risk to patients from drug-related harm
- aDSM provides drug safety surveillance data to inform policy changes

aDSM is applicable to:

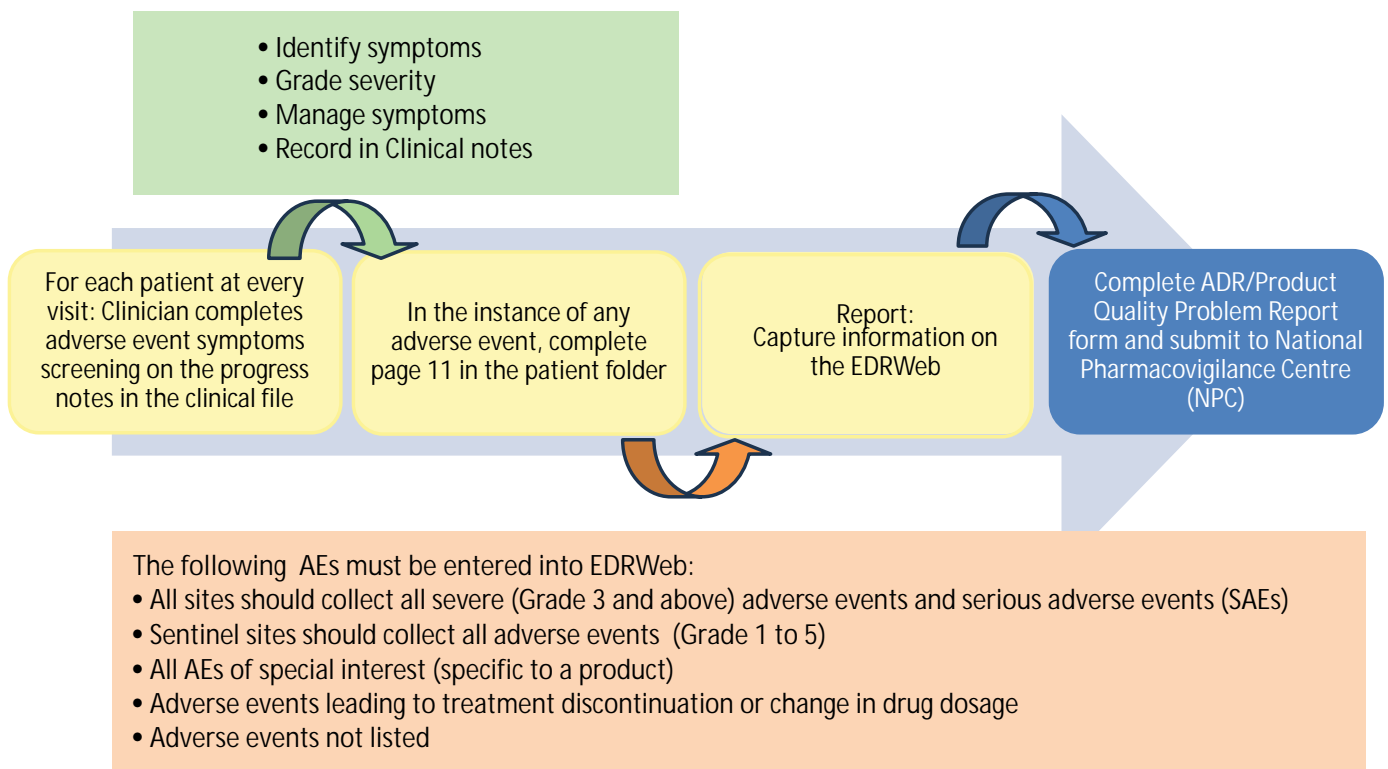
- New anti-TB drugs
- Novel MDR-TB regimens
- XDR-TB drugs
- Any other drugs given to TB clients (e.g., ART)

All persons with RR-TB need **baseline assessments** and **monthly monitoring** during treatment to **identify and grade** adverse events

Management of adverse events is essential for improving chances of treatment success, and medications to treat adverse events should be provided free of charge

Recording adverse events and their management in clinical records is crucial, as is **reporting** serious, severe, or unexpected adverse events

The aDSM Process



Identify symptoms using the Adverse Events Screening Questionnaire

Complete checklist at each follow-up visit for anyone receiving RR-TB treatment, regardless of the regimen:

- | | | |
|-------------------------|---------------------------------|----------------------------------|
| 1. Headache | 9. New cough | 17. Easy bruising/bleeding |
| 2. Anaemia | 10. Nausea/vomiting | 18. Changes in hearing |
| 3. Vision Changes | 11. Diarrhoea | 19. QTcF prolongation |
| 4. Depression/sadness | 12. Abdominal pain | 20. Renal failure/nephrotoxicity |
| 5. Rashes or sores | 13. Fainting | 21. Hepatotoxicity/Jaundice |
| 6. Chest pain | 14. Joint pain/swelling | 22. Lactic acidosis |
| 7. Coughing blood | 15. Burning/tingling hands/feet | 23. Other - |
| 8. Difficulty breathing | 16. Fatigue/tiredness | |

Grade severity using the Severity rating scale for adverse events

Mild (Grade 1)	Symptoms cause no or minimal interference with usual, age appropriate, social and functional activities (e.g. going to work, shopping, cooking, using transport, hobbies)
Moderate (Grade 2)	Symptoms cause greater than minimal interference with usual, age appropriate, social and functional activities (e.g. going to work, shopping, cooking, using transport, hobbies)
Severe (Grade 3)	Symptoms cause inability to perform usual, age appropriate, social and functional activities (e.g. going to work, shopping, cooking, using transport, hobbies)
Potentially life-threatening (Grade 4)	Symptoms cause inability to perform basic, age-appropriate, self-care functions (e.g. bathing, dressing, toileting, continence, feeding, movement); <i>OR</i> Medical or operative intervention required to prevent permanent impairment, persistent disability, or death
Death (Grade 5)	Death, regardless of cause or relationship to TB medications

Recording and Reporting Adverse Events

1. All adverse events of any grade must be screened for and recorded in the patient's clinical file
2. In addition, the following AEs must be entered into EDRWeb and reported to the national pharmacovigilance centre (NPC).
 - All severe (Grade 3 and above) adverse events and serious adverse events (SAEs)
 - All AEs of special interest (specific to a product)
 - Adverse events leading to treatment discontinuation or change in drug dosage
 - Adverse events not listed

Adverse events of Special Interest include:

- Peripheral neuropathy
- Psychiatric disorders and CNS toxicity
- Optic nerve disorder
- Ototoxicity
- Myelosuppression
- Prolonged ZT interval
- Lactic acidosis
- Hepatitis
- Hypothyroidism
- Hypokalemia
- Pancreatitis
- Phospholipidosis
- Acute kidney injury (acute renal failure)

Specific Adverse Events: Haematological

Hematological

Anaemia in TB patients is common. It is often due to the TB itself, but may be other contributing factors including nutritional deficiencies, blood loss from hemoptysis or other sources and HIV co-infection.

The greatest safety concern is anaemia due to myelosuppression, caused by Linezolid. This can be life-threatening - most cases of anaemia occur in the first 2 months of therapy.

	Monitor FBC *	Management
Prior to Starting Treatment	Baseline	<ul style="list-style-type: none"> If HB > 8 g/dL at baseline, start BPaL-L If Hb < 8g/dl: <ul style="list-style-type: none"> Treatment may need to be delayed until the anaemia is corrected Patients with severe anaemia and RR TB should be admitted to hospital A transfusion of packed cells should be considered
Weeks 2, 4 and 6	Every 2 weeks	<ul style="list-style-type: none"> If Hb < 8g/dl, the patient should be admitted to hospital for closer follow-up. A transfusion of packed cells should be considered Treatment interruption should be considered if the patient is symptomatic, <ul style="list-style-type: none"> LZD must be used for at least 2 months for the regimen to be considered effective. If LZD has to be interrupted, the NCAC or PCAC should be involved in the alternative regimen design
Weeks 8, 12, 16, 20, and 24	Every 4 weeks	If HB drops below 8g/dl, LZD can be stopped provided there has been a clinical response (reduction of symptoms, increase in weight, reduction in smear positivity)

*FBC and differential are preferred, but HB side room investigation can be done if FBC not available

Specific Adverse Events: Peripheral neuropathy

Peripheral Neuropathy

This adverse event tends to occur later in treatment, with peak time of onset around 16 weeks. The patient's experience of it is subjective. A grade 3 peripheral neuropathy by the DAIDS tables is one that causes severe symptoms - when there is an inability to perform usual social and functional activities without intervention or if hospitalisation is indicated.

Key to detection and management is patient and health care provider education and counselling, including symptoms to watch out for: pins and needles, pain, and numbness. The severity of the TB, clinical response and mycobacterial response needs to be considered. LZD remains a key drug in RR-TB treatment, and withdrawal too early may compromise the efficacy of the regimen. Consult DR-TB experienced clinician/NCAC to assist if unsure if to continue or stop LZD.

Management of Peripheral Neuropathy

	RR-TB / BPaL-L	Pre-XDR TB / BPaL
Weeks 1 to 8	Consider reduction of dose or change to an individualised longer regimen without LZD	Change to an individualised longer regimen without LZD
Weeks 8 to 16	Reduce dose of LZD. Consider permanent discontinuation if culture conversion has occurred	Reduce dose of LZD. Consider permanent discontinuation if culture conversion has occurred
Weeks 16+	Permanent discontinuation of LZD if culture conversion has occurred. Continue with BPaL.	Permanent discontinuation of LZD if culture conversion has occurred. Continue with BPa.

Specific Adverse Events: Optic Neuritis

Uncommon adverse event but if left can cause permanent disability. Optic neuritis is usually bilateral.

It is important to establish baseline for all patients to start the regimen, and prior visual history and problems obtained. Visual acuity (VA) should be measured using a Snellen test, and checked at every visit when the patient is on Linezolid. If the patient wears spectacles, the Snellen test should be done with them on. If there is more than a two line drop in VA, this requires action and referral to ophthalmology for an examination of the optic nerve.

Vision Testing

Use a Snellen chart to screen for visual acuity

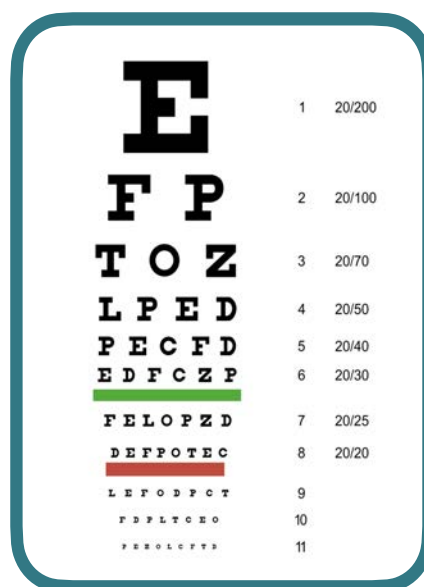
- Screen at baseline, week 2 and monthly whilst on LZD
- Repeat vision test if patient complains of decreased, blurry or double vision, redness or eye pain
- Floaters, field defects or sudden decrease in visual acuity may be associated with CMV

Management:

1. Withhold linezolid and refer patient to an ophthalmologist for further evaluation and management. Do not reintroduce without discussing with NCAC (or another RR-TB expert) and preferably with ophthalmologist.
2. If the patient has RR-TB with extensive disease or further resistance, and optic toxicity due to linezolid is ruled out by an ophthalmologist, reintroduction of linezolid may be considered with careful monitoring.

Other eye conditions that may affect a client with TB:

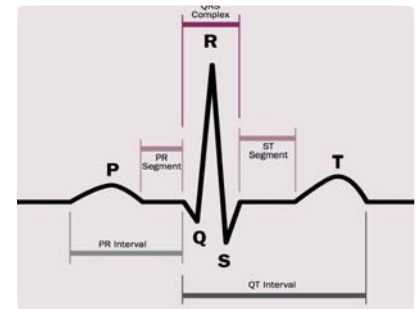
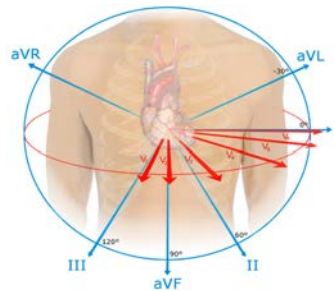
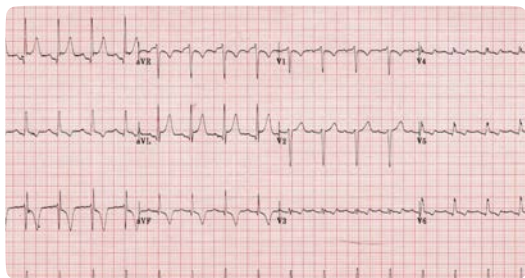
- Ethambutol toxicity
 - Generally color vision
- TB of the eye
 - Uveitis
- HIV-associated changes
 - CMV retinitis (CD4 < 50)
 - Kaposi sarcoma
 - Herpes zoster
- STI-associated uveitis
- Syphilis



Snellen chart

Electrocardiogram (ECG) 101

An electrocardiogram (ECG or EKG) records the electrical activity the heart and provides information about its structure and function



Bedaquiline, Clofazimine and Moxifloxacin can prolong the heart's QT interval, which is the duration of ventricular depolarisation (contraction) and repolarisation (relaxation). **When the QT interval is prolonged, it can result in ventricular arrhythmias (e.g. torsade de pointes) which can lead to sudden death**

QT Interval Monitoring

The calculation for the corrected QTcF interval using the Fridericia Formula is:

$$QTcF = QT / \sqrt[3]{RR}$$

$$RR = 60 / \text{Heart Rate}$$

QTc Prolongation			
Related Drugs	BDQ, CFZ, MFX		
Monitoring Tests	ECG - QTcF* interval (QT interval corrected using Frederica formula)		
Monitoring Schedule	Baseline, 2, 4, 8, 12, 16, 20 and 24 weeks after initiating BDQ treatment		
Grading	<p>Mild</p> <p>Asymptomatic QTc interval 450 – 470 msec</p> <p>OR</p> <p>increase in interval <30 msec</p>	<p>Moderate</p> <p>Asymptomatic QTc interval 471 – 500 msec</p> <p>OR</p> <p>increase in interval 30- 50 msec</p>	<p>Severe</p> <p>Asymptomatic QTc interval >500 msec</p> <p>OR</p> <p>increase in interval >50 msec</p> <p>OR</p> <p>Life-threatening consequence, e.g. Torsades or other associated serious ventricular dysrhythmia</p>
Indicated Actions	<p>Drug withdrawal for moderate and severe</p> <p>Consider rechallenge if moderate reaction resolves</p> <p>Mild reactions should be monitored</p>		

Assessing & Responding to Laboratory Values

FBC	Name of Test	Assessment	Normal Range
FBC	WBC White Blood Cells	Measures the amount of white blood cells in a volume of blood	4.0 – 10.0 x 10 ⁹ /L
	RBC Red Blood Cells	Measures the amount of red blood cells in a volume of blood	4.5 – 5.0 x 10 ¹² /L
	Hb Haemoglobin	Measures the amount of protein molecule in the blood that carries oxygen and gives blood its red color	13.0 – 17.0 (men) 11.0 – 15.0 (women)
	Hct Hematocrit	Ratio of the amount of red blood cells to the amount of whole blood	0.40 – 0.50 L/L (men) 0.36 – 0.46 L/L (women)
	PLT Platelets	Measure of how well a patient's blood will clot	150 – 400 x 10 ⁹ /L
U&E	Na Sodium	Hyper: Hypertension, Edema, Lethargy/Weakness, Seizures/Coma Hypo: Convulsions, Confusion/Irritability, Sedation, Muscle Weakness, Nausea/Vomiting	136 – 145 mmol/L
	K Potassium	Hyper: Severe Muscle Weakness, Paralysis, Chest pain, Palpitations Hypo: Severe Muscle Weakness, Paralysis, Chest pain, Palpitations	3.5 – 5.1 mmol/L
Lytes	Ca Calcium	Hyper: Dehydration, Fatigue, Thirst, Nausea Hypo: Severe Muscle Weakness, Cramping, Muscle Spasms, Fatigue	2.2 – 2.7 mmol/L
	Mg Magnesium	Hyper: Nausea/Vomiting, Slow Heart Rate, Slow Respiration Rate Hypo: Severe Muscle Weakness, Fast Irregular Heart Rate, Seizures, Drowsiness/Confusion, Insomnia	0.7 – 1.0 mmol/L
RBS	RBS Random Blood Glucose	Hyper: Excessive Thirst, Urination and Hunger, Peripheral Neuropathy, Problems with Vision, Dehydration, Confusion Hypo: Confusion, Seizures, Weakness	4 – 8 mmol/L
Cr	Cr Creatinine	A by-product of muscle breakdown that is excreted from the kidneys at a specific rate	64 – 104 µmol/L
	CrCl Creatinine Clearance	Calculation that takes into consideration the weight, sex and age of the person	97-137 ml/min (men) 88-128 ml/min (women)
	eGFR Estimated Glomerular Filtration Rate	A measure of overall renal function	> 60
LFT	ALT Alanine aminotransferase	Elevations may indicate liver damage	10 – 40 U/L
	AST Aspartate aminotransferase	Not as specific to liver as ALT	10-36 U/L
	Alk Phos (ALP) Alkaline phosphatase	Non-specific to liver, may be elevated with other disease states	53- 128 U/L
	GGT Gamma-glutamyl transferase	If elevated in conjunction with Alk Phos elevation, high probability of liver involvement	0 – 60 U/L
	T bili Total bilirubin	May indicate liver damage or certain types of anemia. Direct bilirubin is important to measure if drug toxicity is considered	5-21µmol/L

Chronic Kidney Disease

Stage	Description	GFR
1	Kidney damage with normal or high GFR	≥ 90
2	Kidney damage with mild GFR	60-89
3	Moderate GFR	30-59
4	Severe GFR	16-29
5	End Stage/Kidney Failure	<15

Module **10**

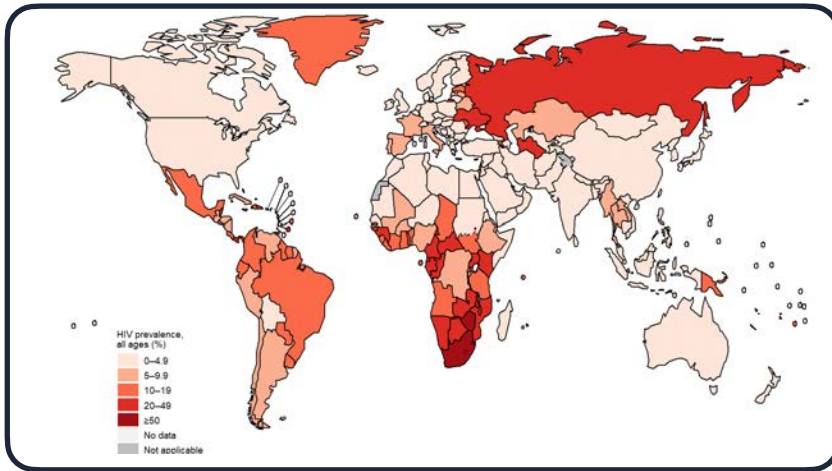
DR-TB in **Special Populations**



TB/HIV co-Infected Clients

The Impact of HIV on TB

Estimated HIV prevalence in new and relapse TB cases, 2021



World Health Organization: 2022 Global TB Report

▶ Active TB

1. Progression of TB disease
2. Extrapulmonary TB
3. Severity of TB disease
4. TB remains leading cause of death

▶ TB Diagnosis

1. Smear-negative disease

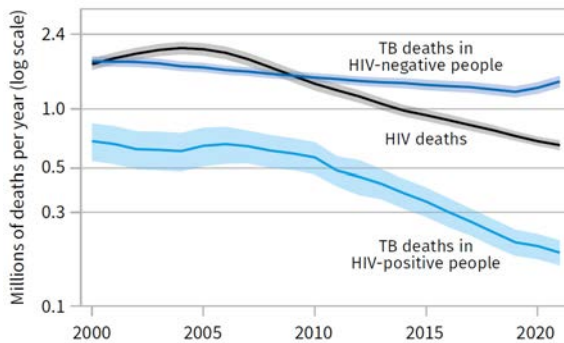
▶ Treatment Complexity

1. Treatment timing & IRIS
2. Overlapping toxicities
3. Drug-drug interactions

▶ Adherence

1. Pill burden`
2. Side effects
3. Multiple clinical visits
4. May prevent work
5. Stigma

Global trends in the estimated number of deaths caused by TB and HIV, 2000-2021



World Health Organization: 2022 Global TB Report

Key TB/HIV Integration Activities

For People Living with HIV to Reduce the Burden of TB (5 I's)



For Patients with Presumptive TB and Diagnosed TB to Reduce the Burden of HIV

- Provider Initiated Counselling and Testing
- For HIV negative TB patients
 - HIV prevention interventions, including Pre-Exposure Prophylaxis for HIV prevention (PrEP)
- For HIV positive TB patients
 - ART
 - Cotrimoxazole prophylaxis
 - Partner testing and HIV prevention interventions for sero-discordant partners

Considerations RR-TB/HIV co-infected clients

Key Principles

- The short and longer DR-TB regimens may both be offered to people with HIV, and HIV status alone does not mandate any changes in the DR-TB regimen composition.
- To improve the chances of RR-TB treatment success, all people co-infected with RR-TB and HIV should receive antiretroviral therapy (ART) to suppress their viral load (VL).

Dolutegravir (DTG) in combination with tenofovir (TDF) and lamivudine (3TC), in the fixed-dose combination known as TLD, is the optimized regimen of choice, provided the client has normal renal function

- Dolutegravir can be used concurrently with all currently recommended RR-TB medications
- TLD is well tolerated and minimizes the additional pill burden due to ART (TLD is one tablet once a day).
- ABC, 3TC and DTG (ALD) can be used in children < 10 years of age or weighing < 30 kg. Paediatric DTG 10 mg dispersible tablets are available for children weighing < 20 kg.
- For a client with an eGFR of < 50, TDF can be replaced with abacavir (ABC).
- Recommendations for routine VL, creatinine and eGFR, and CD4 count monitoring of clients on ART are still applicable, in addition to the routine monitoring investigations for the management of their RR-TB diagnosis.

Clinicians should provide integrated TB and ART management at clinical consultation visits. Failure to combine care leads to increased visits and significantly increases the risk of disengagement.

Indications to Defer ART Initiation

- TB symptoms (cough, fever, weight loss, night sweats)
- Diagnosis of DS-TB or RR-TB
 - ▶ If diagnosed with TB, start with TB treatment first, followed by ART within 8 weeks (as soon as the patient is tolerating their TB therapy)
 - ▶ If CD4 <50 cell/ μ l - start ART within 2 weeks of starting TB therapy
 - ▶ If CD4 count >50 cell/ μ l - Start ART after 2 to 8 weeks of starting TB therapy
- Signs/symptoms of meningitis or confirmed meningitis
 - ▶ Delay ART until 4-6 weeks after starting TB treatment
- Liver disease

* See **2023 ART Clinical Guidelines for additional reasons to defer ART**

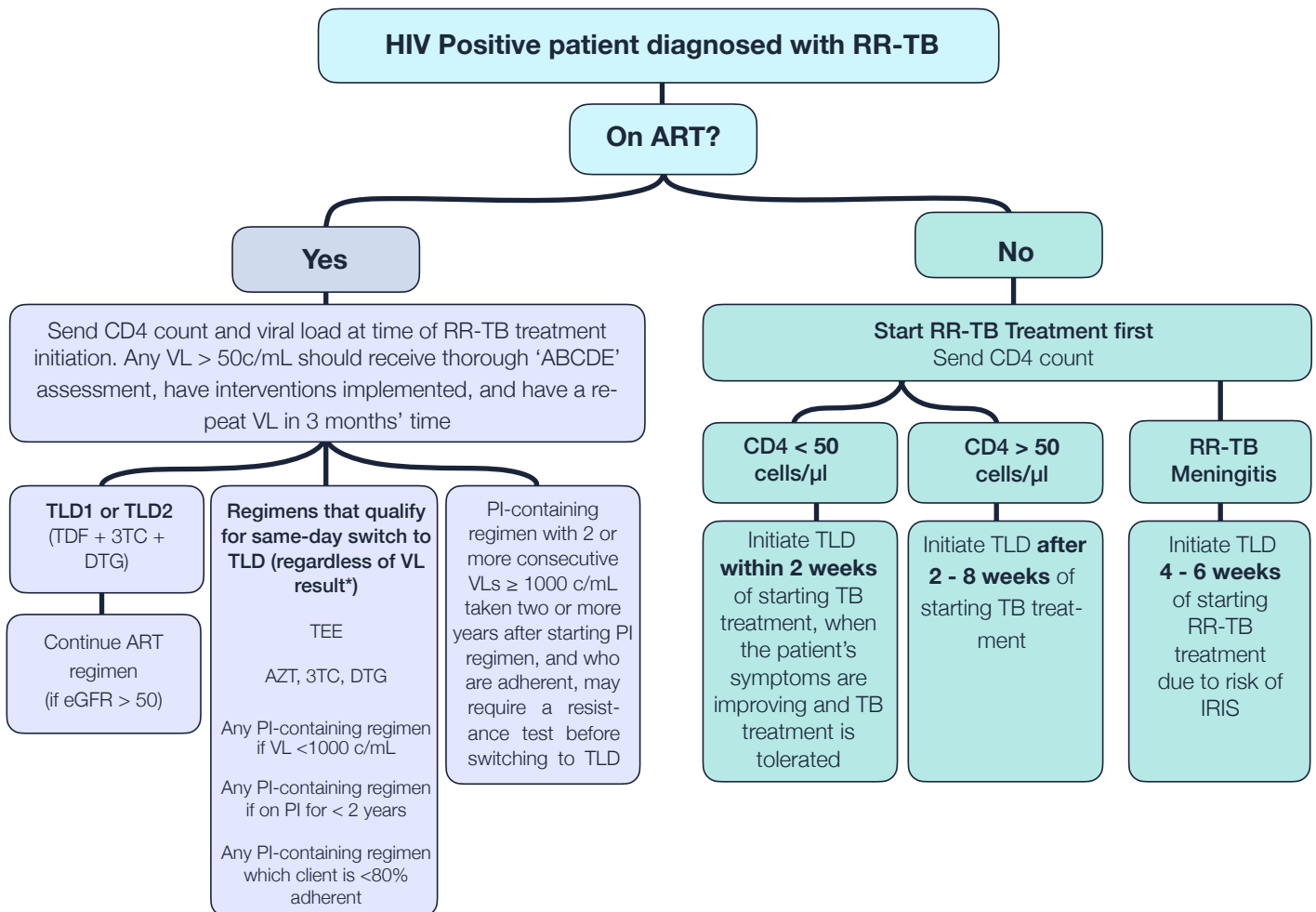


Drug Interactions with DTG and Rifampicin-containing TB Treatment for DS-TB

Rifampicin-containing TB treatment has significant drug interactions with all paediatric ART regimens, as well as with adult/adolescent regimens containing DTG:

ART while on RR-TB Treatment

TLD is the preferred regimen for all clients with normal renal function, including those on RR-TB treatment. All ART naïve clients and clients re-initiating ART after previously interrupting ART, should be initiated on TLD. Clients on ART who have not yet been transitioned to TLD should be evaluated and transitioned as a matter of urgency.



*Note: While the VL does not influence the decision to switch to TLD on the same day, the VL result in the last 12 months should still be checked. If the VL in the last 12 months was not suppressed, continue to switch same day, but do an ABCDE assessment and provide enhanced adherence counselling (EAC) if needed, as per the VL Monitoring and Management algorithm on page 21 of the 2023 ART Clinical Guideline. If the VL was not done in the last 12 months, do it at this visit, but do not wait for the result to switch.

All clients on PI regimen should be transitioned to a DTG-containing regimen. The timing of the transition will be dependent on the VL, the time the client has already been on the PI regimen, and the client's level of adherence. PIs will only be used in an ART regimen if DTG has been shown to be inactive based on a resistance test

Efavirenz induces hepatic metabolism of bedaquiline and decreases bedaquiline exposure; therefore, concomitant use of EFV and BDQ is contraindicated. EFV is no longer a preferred first-line antiretroviral agent, and all clients on TEE should be switched to TLD.

Zidovudine and linezolid should not be used concurrently, as both drugs can cause bone marrow suppression. AZT is no longer part of standard first and second-line regimens.

Routine Monitoring Schedule for RR-TB Clients on ART

Routine Monitoring tests for clients on ART					Additional tests at DR-TB diagnosis	Additional tests when clinically indicated
	At ART start	At 3 months on ART	At 10-12 months on ART*	Annually at 12-monthly intervals*		
CD4 count	X		X		X	X
Creatinine and eGFR	X	X	X	X		
Viral Load		X	X	X	X	X
HBVsAg	X					X
	* Aligned with 6-monthly scripting cycle					

Screening for TB at follow-up Visits

<p>At every routine follow-up visit:</p> <ul style="list-style-type: none"> Do a TB symptom screen. <p>If symptomatic, do a TB NAAT (e.g., Xpert MTB/RIF Ultra)</p>	<p>At every 10-12-monthly clinical review on ART (aligned with 12-monthly VL)</p> <ul style="list-style-type: none"> Routine TB NAAT (e.g., MTB/Rif Ultra (regardless of TB symptoms)) 	<p>For symptomatic PLHIV admitted to hospital [in addition to the TB NAAT]</p> <ul style="list-style-type: none"> Do a U-LAM test 	<p>For symptomatic PLHIV seen in an outpatient setting [in addition to the TB NAAT]</p> <ul style="list-style-type: none"> Do a U-LAM test if: <ul style="list-style-type: none"> CD4 count <200 within the last 6 months, or advanced HIV disease, or current serious illness.
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Overlap of Adverse Drug Reactions in DS-TB

ADR	TB Drugs	HIV Drugs
Rash/Skin Changes	Rifampicin, Isoniazid, Pyrazinamide, Ethambutol	Abacavir, Nevirapine, Efavirenz, Cotrimoxazole
Hepatotoxicity	Rifampicin, Isoniazid, Pyrazinamide, Ethambutol	Nevirapine, Efavirenz, Cotrimoxazole, PIs (especially when dose is increased to overcome rifampicin induction)
Joint pains	Ethambutol	Nevirapine, Efavirenz, Cotrimoxazole, PIs (especially when dose is increased to overcome rifampicin induction)
Nausea/Vomiting	Pyrazinamide, Isoniazid, Ethambutol, Pyrazinamide	Zidovudine, PIs, Ritonavir
CNS	Isoniazid	Efavirenz
Peripheral neuropathy	Isoniazid	None
Renal Toxicity	Rifampicin	Tenofovir

Overlap of Adverse Drug Reactions in RR-TB

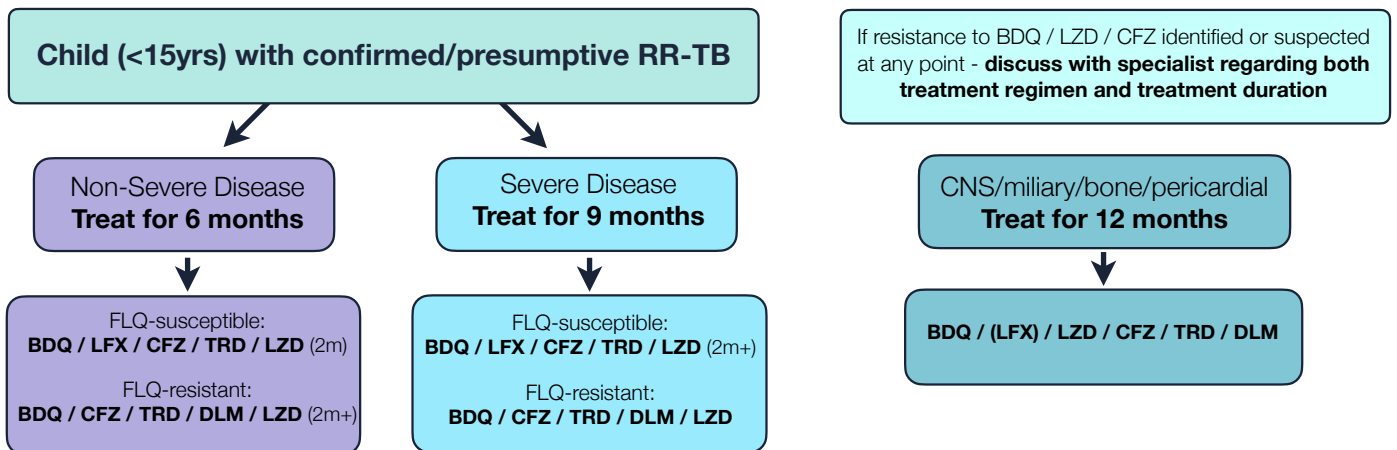
ADR	RR-TB Drugs	HIV Drugs
Rash/Skin Changes	Pretomanid, Linezolid, Quinolones	Abacavir, Nevirapine, Efavirenz, Cotrimoxazole
Bone Marrow Suppression	Linezolid	AZT
Hepatotoxicity, AST/ALT elevation	Bedaquiline, Pretomanid, Quinolones	Nevirapine, Efavirenz, Cotrimoxazole
Nausea/Vomiting	Linezolid, Pretomanid, Bedaquiline	Zidovudine, PIs, Ritonavir
QTc Prolongation	Bedaquiline, Quinolones	None
CNS	Quinolones, Linezolid, Pretomanid	Efavirenz
Optic Neuritis / Visual Changes	Linezolid	None
Headache	Bedaquiline, Ethambutol	AZT, Efavirenz
Peripheral Neuropathy	Linezolid, Quinolones, Pretomanid	None
Renal Impairment	Levofloxacin	Tenofovir
Mental Health Changes	Quinolones	Efavirenz
Arthralgia	Bedaquiline, Quinolones	None

Paediatrics

- ▶ Children with RR-TB generally have primary disease from an adult contact
- ▶ Children often have paucibacillary disease, (seldom culture-positive) but every effort should be made to confirm RR or XDR-TB
- ▶ Children under 15 years old do NOT qualify for BPaL or BPaL-L as pretomanid safety has not been established in children
- ▶ There is limited experience in the use of second-line medications for extended periods in children

Severe TB Disease in children <15 years	Non-Severe TB Disease in children <15 years
<ul style="list-style-type: none"> • CXR: bilateral disease (consolidation, infiltrates), or presence of cavities • Mediastinal lymph nodes causing airways compression • Extrapulmonary forms of disease other than peripheral LNs or simple pleural effusion 	<ul style="list-style-type: none"> • Peripheral lymphadenopathy • CXR: unilateral disease (consolidation, infiltrates in < 1 lobe in total) without cavities • Small/simple pleural effusions • Mediastinal lymph nodes without airways compression

Approach to treatment of RR-TB in children <15 years



Note that LZD is very toxic in children and often poorly tolerated, therefore will require close and regular monitoring for adverse effects including myelosuppression (FBC and diff WCC two-weekly in first month and then monthly; risk especially high in the first 2 months of exposure), peripheral neuropathy (especially beyond 2 months of exposure) and optic neuritis (any time during treatment). Drug substitution may be required if LZD is relied upon as one of the effective drugs in any regimen.

Pregnancy

- ▶ Advocate contraception in all RR-TB females
- ▶ All female patients of childbearing age should be tested for pregnancy before initiating treatment and throughout treatment
- ▶ Counselling and informed decision on treatment options for pregnant patient
- ▶ Pregnant women with RR-TB do NOT qualify for short BPaL-L regimen because pretomanid is contraindicated in pregnancy. They may benefit from a 6-month treatment regimen containing Group A and B drugs with delamanid
- ▶ BDQ is currently considered one of the safer drugs to use in pregnant women. There is limited data on the use of linezolid, levofloxacin, moxifloxacin, clofazimine, terizidone and delamanid during pregnancy
- ▶ Amikacin should not be used in pregnancy given associated foetal ear toxicity

The regimen for pregnant women is:

Bedaquiline - Delamanid - Linezolid and Levofloxacin for **6 months**.

Bedaquiline

+

Delamanid

+

Linezolid

+

Levofloxacin

Breastfeeding and RR-TB Treatment

- ▶ Breastfeeding should be encouraged in most women, and the medications used to treat RR-TB are not a contraindication to breastfeeding - however appropriate infection control measures must be followed
- ▶ Health and well-being of pregnant and breastfeeding women is in the best interests of their babies

Diabetes Mellitus

- ▶ Diabetic patients 3-5 times more likely to develop TB
- ▶ Patients with DM may be more difficult to diagnose with TB, presenting with atypical chest radiographs and extra pulmonary disease
- ▶ Patients with DM have worse outcomes from RR-TB treatment with as many as 25% dying of their disease
- ▶ Overlapping toxicity (e.g. neuropathy, renal failure)
- ▶ Patients with DM tend to be older than TB patients in general, further complicating their management
- ▶ Diabetes must be managed closely throughout treatment
 - Metformin is a preferred drug in patients with TB
 - Do not exceed a dose of 500mg twice daily when using metformin with dolutegravir

Seizure Disorder

- ▶ Terizidone should be avoided in patients with uncontrolled seizures
- ▶ When seizures present for the first time whilst patient is on RR-TB treatment they may need investigation (electrolytes, LP, CT Scan)
 - They may be due to second-line drugs
 - But clinically other causes like meningitis or electrolyte imbalances must be ruled out (more common in HIV patients)
- ▶ Fluoroquinolones may increase risk of seizure by lowering seizure threshold

Renal Insufficiency

- ▶ Great care should be taken in the administration of SLDs in patients with renal insufficiency
- ▶ If eGFR is < 60 mL/min, increase monitoring
- ▶ If eGFR is < 30 mL/min, decrease the frequency +/- dosages using the renal dosage chart in the guidelines

Renal dose adjustments for adults

Drug	Recommended dose and frequency for adults with creatinine clearance <30 ml/min or for patients receiving haemodialysis (unless otherwise indicated dose after dialysis)
Bedaquiline	No dosage adjustment is required in patients with mild to moderate renal impairment (dosing not established in severe renal impairment, use with caution)
Linezolid	No adjustment necessary
Levofloxacin	750-1000 mg per dose three times per week (not daily)
Moxifloxacin	No adjustment necessary
Clofazimine	No adjustment necessary
Terizidone	250 mg once daily or 500 mg three times per week (not daily)
Delamanid	No dosage adjustment is required in patients with mild to moderate renal impairment (dosing not established in severe renal impairment, use with caution)
Pretomanid	No dosage adjustment is required
Ethambutol	15-25 mg/kg per dose three times per week (not daily)
Pyrazinamide	25-35 mg/kg per dose three times per week (not daily)
Imipenem-cilastatin (given with amoxicillin-clavulanate)	Imipenem: for creatinine clearance 20-40 ml/min dose 500 mg every 8 hours; for creatinine clearance < 20 ml/min dose 500 mg every 12 hours Amoxicillin-clavulanate: 250 mg / 125 mg given 30 minutes prior to Imipenem
Meropenem (given with amoxicillin-clavulanate)	Meropenem: 1000 mg every 12 hours; for creatinine clearance < 10 ml/min dose 1000 mg once daily. Amoxicillin-clavulanate: 250 mg / 125 mg given 30 minutes prior to Imipenem
Ertapenem (given with amoxicillin-clavulanate)	Ertapenem: 500 mg once daily Amoxicillin-clavulanate: 250 mg / 125 mg given 30 minutes prior to Imipenem
Isoniazid	No adjustment necessary
Ethionamide	No adjustment necessary
Para-aminosalicylic acid	4 g/dose, twice daily maximum dose
Amikacin	Stop amikacin, or if considered essential to treatment administer only with therapeutic drug monitoring
Rifabutin	No adjustment necessary

Substance Abuse

- RR-TB treatment is not contraindicated in people who abuse alcohol or drugs
- Routine and non-judgmental screening with WHO Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)
- Brief counselling intervention with motivational interviewing
- Should initiate RR-TB treatment even if there is not complete sobriety
- Enhanced adherence support & harm reduction counseling
- Referral to substance use treatment center
- Pharmacotherapy-assisted treatment (i.e. naltrexone or acamprosate for alcohol use), opioid substitution therapy (methadone, suboxone) should be considered where appropriate

Liver Disease

If jaundice is present - STOP all treatment

- Stop all TB drugs and antiretrovirals and cotrimoxazole
- Rule out other causes (viral hepatitis, obstructive jaundice)
 - Delay treatment for hepatitis C until RR-TB is complete, unless patient has unstable liver disease or develops worsening liver function during RR-TB treatment
- Once jaundice settles, re-introduce the least hepatotoxic medicines (linezolid, delamanid and quinolone) all at once to provide a regimen backbone
- Then introduce potentially hepatotoxic medicines (clofazimine, bedaquiline, ethionamide, isoniazid) one by one every 5-7 days while monitoring LFTs.
- Pyrazinamide should not be reintroduced.
- Monitor LFTs closely

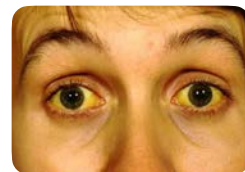
Stigmata of Chronic Liver Disease



Spider angioma



Scleral icterus



Jaundice



Gynecomastia



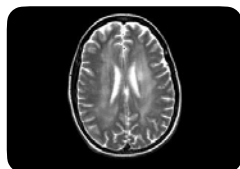
Esophageal varices



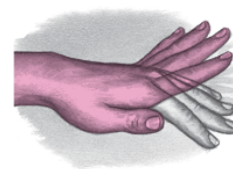
Ascites



Palmer erythema



Encephalopathy



Asterixis

Psychiatric Disorders

- ▶ There is a high baseline incidence of depression and anxiety in patients with RR-TB, related to:
 - chronicity of the disease
 - confinement in hospital
 - socioeconomic stressors
- ▶ Do a baseline mental state evaluation and evaluate for symptoms at each visit
- ▶ All RR-TB patients presenting with psychiatric episodes should be referred to a psychiatrist
- ▶ Treat the condition with the appropriate drugs, counselling, and group therapy
- ▶ Group therapy has been very successful in providing a supportive environment for RR-TB
- ▶ Psychiatric events are often due to terizidone/cycloserine
 - **Close monitoring** is recommended

Module **11**

Patient Centred Care in RR-TB

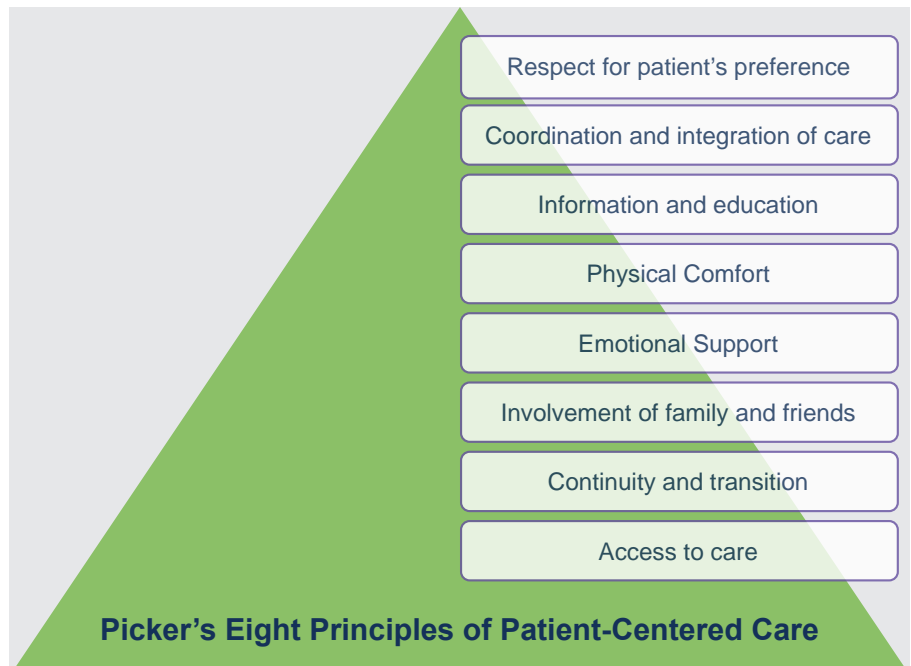


█ Patient Centred Care

Patient-centered care is the practice of caring for patients (and their families) in ways that are meaningful and valuable to the individual patient.

It includes:

- listening to, informing and involving patients in their care.
- respecting and responding to individual patient's care needs, preferences, and values in all clinical decision



Picker Institute, Harvard Medical School

█ Effective Communication

Effective communication between patients and healthcare providers is essential for the provision of patient centered care and recovery

- Good communication enhances the healthcare worker-patient relationship
- Good communication improves adherence
 - A study conducted by the MRC of South Africa has shown that “poor relation between the health care worker and the MDR-TB patients” is one of the major causes of poor adherence to MDR-TB treatment
- Good patient education results in
 - An informed patient
 - An empowered patient
 - A less fearful patient
 - Better treatment outcomes

The WHAT and HOW of Effective Communication

For effective communication, a healthcare provider needs to know:

What
content needs to be discussed

How
to communicate the information effectively

The WHAT of effective patient communication

Overview of elements to be included in counselling at every visit

- RR-TB disease, prevention and the treatment plan
- Knowledge and skills to support treatment adherence
- Importance of safety monitoring, hearing tests, sputum collection and evaluation of every laboratory result
- Management of adverse drug reaction
- Well-being of the patient and household
- Give words of encouragement, provide opportunities for questions and always re-assure patient of support

Specific content for counselling sessions

Session 1

- Detailed but focused history taking
- History of previous TB treatment used, and baseline blood results
- History of co-morbidities and medication use
- Take sputum for DR-TB reflex testing, do baseline hearing, blood tests and pregnancy test
- Decision on treatment regimen still provisional until DST results to be communicated to the patient
- Counsel on adherence, infection control practices and close contact tracing and management
- Discuss the consent form

Session 1

- Must be within 2 or 3 weeks after the first consultation
- Review culture and DST results and decide on regimen (short Vs long MDR-TB regimen); MDR or XDR-TB
- Review progress with treatment, counsel and re-assure patient on the decided regimen
- Discuss support structures available including disability grant/grant-in-Aid application
- Consider starting ARTs, family planning (if a female of childbearing age)

Subsequent monthly sessions

- Review the patient's clinical condition
- Check monthly sputum and safety monitoring blood results
- Screen for treatment side-effects and adverse events
- Record and report any adverse drug reaction accordingly
- Review treatment adherence
- Review contact tracing and management
- Review and re-enforce 1st and 2nd visit discussions
- and findings

The HOW of effective patient communication

Step 1 Assess receptive ability

- Assess the patient's ability to pay attention and understand your message
- Patient may feel sick, embarrassed, fearful or overwhelmed

Step 2 Use communication methods that promote understanding and builds positive relationships

1. Ask questions and listen
2. Demonstrate a caring, respectful attitude
3. Praise and encourage the patient
4. Speak clearly and simply
5. Encourage the patient to ask questions
6. Ask checking questions

Step 3 Support learning and understanding

Remember that

- Up to 80 % of patients forget what their doctor tells them as soon as they leave the consulting room
- Nearly 50 % of what they do remember is recalled incorrectly

Consider other additional communication methods to enhance verbal patient/provider interactions:

- Written: posters, pamphlets
- Video, DVD, audiotapes
- Computerized education e.g., mindset
- Role plays, storytelling
- Games

At every consultation, apply good communication skills

Defining Stigma

STIGMA is:

- Severe disapproval of or discontent with a person or group based on characteristics that separate them from other members of a group or community
- A belief or attitude
- Results in discrimination

Non-Clinical Impact of RR-TB Treatment

Financial

- ▶ Loss of Work
- ▶ Costs associated with accessing care

Social

- ▶ Loss of access to friends, family, social circles during hospitalization or because of diagnosis

Psychological

- ▶ Isolation
- ▶ "It can't happen to me"
- ▶ Internal Stigma

The Stigma Tree

CAUSES = Roots



Why do people stigmatise?

FORMS = Branches



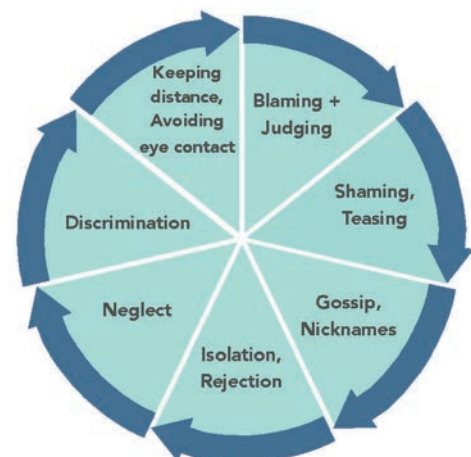
How do people stigmatise people with RR-TB?

EFFECTS = Leaves



What happens as a result of this stigma?

Causes of Stigma



Overcoming Stigma

Don't Stigmatize: **NORMALISE!**

- Be proactive - look for forms of stigma
- Listen to words used by yourself and others (actively listen)
- Challenge stigmatising words or opinions you hear
- Proactively address the patient, partner, family concerns, fears, misconceptions and lack of knowledge of RR-TB/HIV
- Encourage all health services not to stigmatise, and help patients access services in the face of stigma
- Invite back a speaker or client who completed treatment
- Treat clients with RR-TB as you would like to be treated

Adherence

Adherence vs Compliance

Adherence involves following the recommended course of treatment by taking all the medications prescribed, attending appointments and tests, and modifying lifestyle as needed for risk reduction. Adherence is taking an active role in one's own health care, whereas compliance is a passive act of following the will of the provider.

Improving adherence is arguably the single most important means of optimizing therapeutic outcomes

The following elements create an enabling environment for good adherence:



Non-adherence can lead to serious consequences such as drug resistance, an increase in the severity of illness, ongoing TB transmission, and even death. Non-adherence means:

- ▶ Not taking treatment regularly
- ▶ Stopping medicines before having finished the full course of treatment
- ▶ Missing clinic appointments

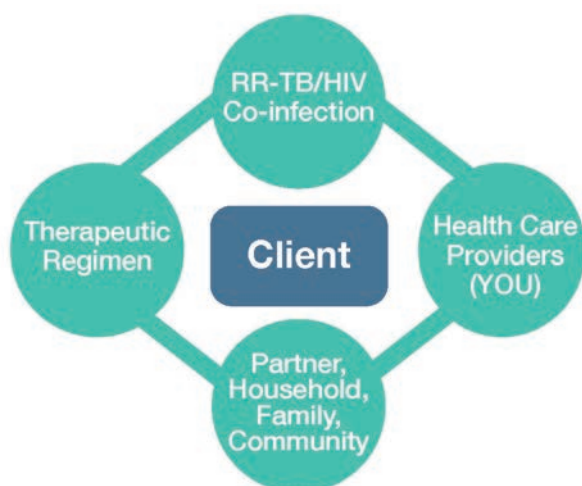
Predictors of GOOD Adherence

- ▶ Emotional, social and practical support systems
- ▶ Convenience of regimen
- ▶ Understanding of the importance of adherence
- ▶ Belief in efficacy of medications
- ▶ Feeling comfortable taking medications in front of others
- ▶ Keeping clinic appointments (TB/RR-TB, ARV)
- ▶ Severity of symptoms or illness
- ▶ Low stigma (perceived or enacted)
- ▶ Disclosure of health condition(s)

Predictors of LOW Adherence

- ▶ Complex treatment regimen and pill burden
- ▶ Low literacy level
- ▶ Active drug use or alcoholism
- ▶ Stigma
- ▶ Mental illness
- ▶ Cognitive impairment
- ▶ Lack of patient education
- ▶ Non-disclosure
- ▶ Low access to resources
- ▶ Treatment fatigue
- ▶ Negative Health care worker attitude

Factors Related to RR-TB Adherence



6 "A"s for Improving Adherence

- | | | |
|----------------------|-----------------------|---------------------|
| 01.
ASSESS | 02.
ADVISE | 03.
AGREE |
| 04.
ASSIST | 05.
ARRANGE | 06.
ASK |

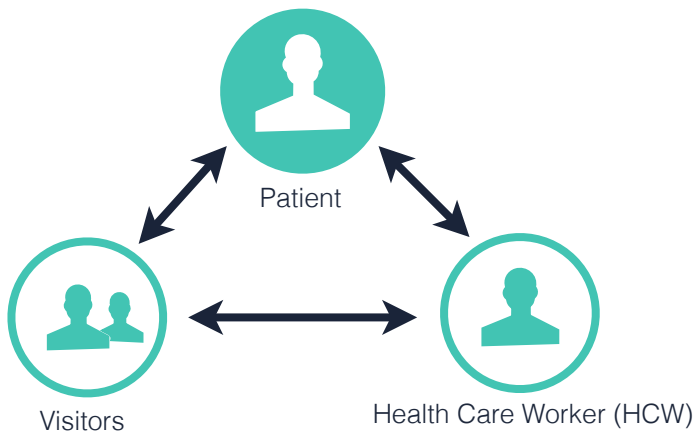
Module **12**

Tuberculosis **Infection Control**



Infection Control (IC)

Work practices and other measures designed to prevent transmission of infectious agents



Standard (Universal) Precautions
+
Transmission-Based Precautions

Why is Tuberculosis Infection Control (TBIC) so important?

TB is a communicable disease and is spread person to person

Most people with undiagnosed, untreated and potentially contagious TB are frequently seen in health care facilities but are missed

In areas with high HIV prevalence, infectious patients are a risk for HIV positive individuals and other immune suppressed persons (patients, visitors or staff) who are particularly vulnerable to TB

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

TBIC: Levels of Infection Protection & Control

Administrative

- Symptomatic screening
- Cough etiquette
- Separation/Fast tracking
- Prompt diagnosis/treatment
- Staff training
- Patient education

Environmental

- Natural ventilation
- Mechanical ventilation
- High Efficiency Particulate Air Filtration (HEPA)
- UV germicidal irradiation (UVGI)

Personal Protective

- Staff awareness on TB
- Personal respiratory protection
- Staff HIV Counselling and Testing
- TPT where indicated

Personal Protective Equipment (PPE)

Surgical Mask



Purpose:

To reduce transmission by capturing bacilli expelled by a coughing TB patient into the air before they get into the air

Who should wear it:

Patients with infectious PTB (sm+)
People with a chronic cough

Where Should It Be Used:

- In the waiting rooms, consulting rooms and when leaving the isolation ward for any reason
- During transportation i.e. ambulance, patient transport vehicles or other
- At home if isolation is not possible, ventilation inadequate and there are children <5years or people living with HIV in the household

Respirator



Purpose:

To reduce exposure to the bacilli in the air before the air is inhaled into the lungs

Who should wear it:

Health facility staff
Visitors to the TB isolation wards

Where Should It Be Used:

- TB isolation wards
- Sputum induction areas/ booth
- Other high risk areas based on the risk assessment
- During transportation especially when sharing the vehicle with a person who has infectious TB
- Community health workers/ visitor in the home of a patient with infectious TB

Respirators are disposable but can be re-used until it becomes damaged, breathing becomes difficult or it becomes contaminated with blood or other body fluids

- Respirators are to be inspected prior to each use to ensure proper fit and seal
- Store in a dry place
- Do NOT write on the respirator
- Do NOT bend the respirator
- Dispose of respirator if you question its performance

Determining Infectiousness

Patient Factors

Factors Associated with <i>More Infectiousness</i>	Factors Associated with <i>Less Infectiousness</i>
Presence of a cough	No cough
Cavity in the lung	No cavity in the lung
Acid-fast bacilli on sputum smear (based on grading)	No acid-fast bacilli on sputum smear
TB of the lungs, airway, or larynx	Most extra pulmonary (non-respiratory) TB
Patient not covering mouth or nose when coughing/sneezing	Patient covering mouth and nose when coughing
Not receiving adequate treatment or having prolonged illness	Receiving adequate treatment for 2 weeks or longer
Undergoing cough-inducing procedures	Not undergoing cough-inducing procedures
Positive sputum cultures	Negative sputum cultures

Environmental Factors

- Ventilation
- Duration of Exposure
- Concentration of the droplet nuclei
- Space
- Air circulation

Infection Control at Home and in the Community

TBIC measures at home and in the community:

- Ventilation/open windows
- Isolation of patient (ideally own bed room)
- Cough hygiene
- Refraining from close contact with children
- Maximising time in open-air environment (e.g., receive visitors outside)
- Minimising contact with known HIV-positive or other immune suppressed patients

Reforming TBIC:

A paradigm shift in traditional TBIC education and training is required:

- TBIC training for all levels of clinical staff is essential
- Training must be focused in **practical, hands-on training** with example patient-based case studies
- This training must also inform health care workers of ways to reduce their risk of contracting drug-resistant TB and methods to prevent infection within healthcare settings
- Comprehensive IC evaluations must include **direct observation of bedside practices** to avoid healthcare associated transmission
- **Adherence** to IC policies must be associated with some level of enforcement (e.g., annual performance reviews)

Module **13**

Recording & Reporting of RR-TB



Recording & Reporting of RR-TB



Recording: Process of capturing data or translating information to a specific format that is stored in a storage medium (e.g. paper or computer)



Reporting: Formal account of proceedings or transactions (from one level to another) through reports, meetings, workshops etc



Monitoring: Routine tracking of key elements of a programme through careful record-keeping and regular reporting (Quarterly reporting, Dashboard reporting, Supervisory visits by subdistrict, district & province)



Evaluation: Episodic, in-depth analysis of programme performance

Core Tools Used for Patient Management

Record	Completed by	Where is it kept?
RR-TB Treatment Record	Nurse/Doctor/Auxillary care workers e.g., social worker/dietician	RR-TB Treatment Facility
RR-TB Patient Identity Card (Blue)	Nurse/Doctor/Community Health	Patient
RR-TB Patient Consent Form	Worker	RR-TB Treatment Facility
TB Sputum Request Form	TB Sister and TB Clinician	Health Facilities
TB Patient Referral Form	Nurse/Doctor	Health Facilities
RR-TB Register (Paper Based)	Nurse/Doctor	Central RR-TB Unit Decentralised RR-TB Unit PHC facilities allowed to do so by NDOH & provinces
Electronic RR-TB Register (EDRWeb)	Data Capturer/Information officer/ Nurse/Doctor	Online

Purpose of the RR-TB Treatment Record

To record clinical information of patients diagnosed with RR-TB and started on treatment

- Details the patient's treatment and care on a day-to-day basis
- Used to monitor patient progress throughout the treatment period (including information regarding cultureconversion and treatment outcomes)

Purpose of the RR-TB Treatment Register

- ▶ To record all patient's on TB treatment and followed-up for final outcomes

RR-TB Patient Referral Form

- ▶ To facilitate follow-up of patients who are moved and/or transferred out from health facilities
- ▶ To provide confirmation that patients are continuing treatment and care at another health facility
- ▶ When to complete:
 - When patients are moved/transferred out of a health facility

Treatment Outcomes

Cured	<ol style="list-style-type: none"> 1. A pulmonary TB patient with bacteriologically confirmed DR-TB at the beginning of treatment who completed treatment as recommended by the national policy, with evidence of bacteriological response and no evidence of failure. 2. Bacteriological response refers to bacteriological conversion with no reversion. 3. Bacteriological conversion describes a situation where at least two consecutive cultures taken on different occasions <u>at least</u> 7 days apart, are negative. 4. Bacteriological reversion describes a situation where at least two consecutive cultures taken on different occasions at least 7 days apart, are positive either after the bacteriological conversion or in patients without bacteriological confirmation of TB. 5. That is at least 3 negative TB cultures during the entire duration of treatment. <p>TB smear microscopy and cultures must be taken at the beginning of treatment(baseline), 2 weeks later, 4 weeks later and monthly thereafter</p>
Treatment Completed	<ol style="list-style-type: none"> 1. A person who has less than 3 consecutive negative culture results during the entire duration of treatment. 2. Who completed treatment as recommended by the national policy 3. No evidence of clinical deterioration.
Treatment Success	The sum of treatment cured and completed
Lost to Follow Up	<p>A patient with treatment interrupted for:</p> <ul style="list-style-type: none"> - ≥ 2 consecutive months - Any reason without medical approval
Treatment Failure	<ol style="list-style-type: none"> 1. A patient's whose treatment regimen needed to be terminated or permanently changed to a new regimen or treatment strategy (change of 2 or more drugs) 2. Reasons for change of treatment include: <ul style="list-style-type: none"> - no clinical response and/or no bacteriological response - adverse drug reactions - or evidence of additional drug resistance to medicines in the regimen <p>When someone is started on shorter regimen and later it is picked up on the baseline sample that they had a condition that qualified them to be on the longer regimen, the patient may not be captured as a failure. They should be de-registered from the shorter regimen and registered in the new group</p>
Moved	<ol style="list-style-type: none"> 1. Referred from one facility to another facility within the same district to continue treatment. This is not an outcome but serves to match patient moving within the district in order to prevent double counting. 2. The treatment outcome is reported by the facility where the patient is newly registered
Transferred Out	<ol style="list-style-type: none"> 1. Referred from one facility to another reporting and recording facility in another district, province or country to continue treatment. 2. The treatment outcome is reported by the facility where the patient is newly registered
Died	Patient who dies for any reason during the course of treatment
Still on Treatment	Still on treatment after prescribed period
Not Evaluated	A patient recorded in the register and who does not have the necessary recorded data to enable classification of any outcome



Case Studies



Case Study 1: Tuberculosis

Vuyo Mayekiso

Vuyo Mayekiso, a 40-year-old man was suspected of having tuberculosis when he presented to the clinic on 15th September

[PRESENTATION]

His complaints were:

- Cough that has been there for more than 3 weeks
- Weight loss and not wanting to eat
- Sweating at night
- Hotness of the body
- Pressure across his chest
- Shortness of breath
- General body aches and feeling more tired

[PMH]

TB Hx: No history of previous TB treatment. No family members, co-workers, friends with TB or TB symptoms, has never worked in mines or jailed

Medical Hx: No Epilepsy, Hypertension, Diabetes Mellitus. Last HIV negative test 5 months ago

Social Hx: He is staying at 35 Yeoville Street, Hillbrow, KZN; but working in EC

[PHYSICAL EXAMINATION]

GENERAL: The patient is a well-developed, well-nourished male in no apparent distress. He is alert, oriented x 3

VITAL SIGNS: Temperature 38.4, pulse 112, respirations 18, blood pressure 146/78, and O₂ saturation 96% on room air. Height: 1.75m, Weight: 64kg

HEENT: Head is normocephalic and atraumatic. Extraocular muscles are intact. Pupils are equal, round, and reactive to light and accommodation. Mouth is well hydrated and without lesions. Posterior pharynx clear of any exudate or lesions

NECK: Supple. No carotid bruits. No lymphadenopathy or thyromegaly

LUNGS: Clear to auscultation

HEART: Regular rate and rhythm without murmur

ABDOMEN: Soft, nontender, and nondistended. Positive bowel sounds. No hepatosplenomegaly noted

EXTREMITIES: Without any cyanosis, clubbing, rash, lesions or edema

NEUROLOGIC: Cranial nerves II through XII are grossly intact

PSYCHIATRIC: Flat affect, but denies suicidal or homicidal ideations

SKIN: No ulceration or induration present

[INVESTIGATIONS]

A TB-NAAT was taken 15th September. The results came back on the same day showing:

Mycobacterium Tuberculosis Complex Detected, Rifampicin Susceptible

Case Study 2: Regimen Selection

Mrs. Jongile

[PRESENTATION]

Mrs. Betty Jongile is a 32 year old female, who came in as a referral from Central City clinic for initiation of RR -TB treatment. Her results of GeneXpert show *Mycobacterium tuberculosis* detected, *Rifampin Resistant*.

As provider of RR-TB services, you collect additional history and begin the counselling and consent process.

[HISTORY]


Betty: She has never had TB before and has never been treated for any respiratory infections. She does have a history of “abnormal heart rhythms” when she drinks too much coffee. She is HIV+ for 5 years. Her ART is TEE. She had an “undetectable” viral load 6 months ago. She reports taking her ART daily.

Based on this history, you collect the necessary baseline testing.

[REGIMEN SELECTION]

1. What RR-TB treatment would you start for Mrs. Jongile? Why are you starting her on that regimen today?

2. Describe your baseline diagnostic evaluation



3. After completing your baseline diagnostic list, show this to your facilitator... get your baseline results

4. Week 1 / Week 2 Visit: Based on your baseline results, what is your plan for today's visit? Describe 1) diagnostic evaluation; 2) medications changes, if any; 3) follow-up monitoring

5. Month 1 Visit: Mrs. Jongile complains of nausea and occasional vomiting, fatigue. Describe 1) diagnostic evaluation; 2) medications changes, if any; 3) follow-up monitoring

Case Study 3: RR-TB Management with Chronic Medical Issues Happiness

Happiness is a 32 year old woman who presents to your PHC for evaluation

[PRESENTATION]

- She reports a 3-week history of night sweats and cough
- She notes occasional discomfort in her chest associated with the coughing

[PMH]

Hypertension: She presently takes no medication, but notes headaches

Diabetes Mellitus: She is overweight and has been told she had type 2 DM. Reports she is trying to lose weight but notes that her daily exercises are more difficult due to cough. She notes she is happy she continues to lose weight despite her decrease in exercise. She takes no medication.

Tuberculosis: Reports she thinks she was treated with antibiotics for a couple of weeks for TB, not sure of when this was

HIV: Negative, one year ago

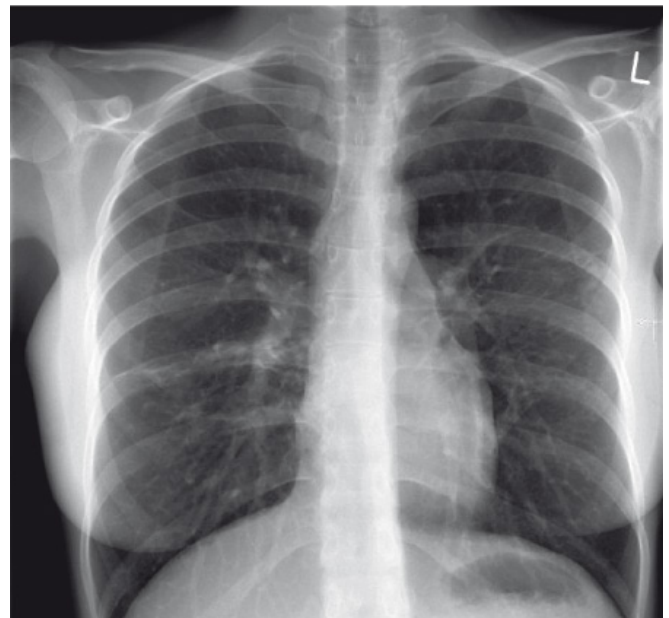
[SOCIAL HX]

She has 3 children ages 2, 4, and 7. Her husband is away working in the mines and her gogo has passed

Happiness also brings in two chests x-rays from another hospital:




CXR from 1 year ago



CXR from last week

[DISCUSSION]

1. Based on this basic history, what additional review of systems do you want to ask?



2. What would you expect the patient's physical exam to reveal? What should you focus on while examining Happiness?

3. How would you interpret these Chest X-Rays? What would your next steps be?

4. At this time what are appropriate differential diagnoses?

5. Outline your current plan for diagnosis:

6. List the reasons why you chose the differential and tests you have chosen to perform, below:



7. Based on your results (inquire with faculty for results), what RR-TB treatment regimen should Happiness be started on?

8. What additional baseline testing will need to be done? Any POC testing?

9. To optimize her health, what other chronic medical issues would you need to address?

10. Outline the anticipated treatment course and follow-up for Happiness:

Case Study 4: Putting It All Together

Thab'sile

Thab'sile is a 40 year old female, who presents today complaining of cough for “months”. She denies weight loss, but states “I have always been thin”. She has not checked her temperature, but might have had a cold “off and on”. She reports occasional fatigue, particularly when walking up stairs. Her other review of symptoms is negative.

[PMH]

HIV + for 10 years, currently taking TEE

- No VL in last 12 months in NHLS
- CD4 counts = 80 (3 months ago)
- She is currently taking Bactrim

Prior episode of TB, approximately 10 years ago

[SOCIAL HX]

Currently unemployed, but was previously a cleaner at a local clinic. She lives in a local township with her sister and her sister's two children. Her children are young adults and no longer live at home.

CHC name: _____ (insert your CHC name here)

Referring PHC name: _____ (insert the name of a referring PHC here)

Letter from Sister at PHC states:

“Please obtain a chest x-ray, we have ordered baseline TB screening results and viral load testing”. Urine LAM is positive for TB. GXP is pending. She denies weight loss, but her current BMI is 19.4, down from 20 three months ago. She reports adherence to her ART, but her CD4 count is low, at 80. She has no recent viral load and we drew that today in clinic.

[DISCUSSION]

1. At CHC, you check NHLS and note the following lab results and clinical notes from 7 days ago:

- a. VL = 57,543 copies/mL
- b. Urine LAM +
- c. TB-NAAT = error/inconclusive – NHLS recommends repeating specimen

2. Detail your plan for the patient today? List any investigations and orders.

3. When will your patient return for follow-up?

4. She returns to clinic at Day ____ (enter the date you suggested she follows-up).

- a) Ask your facility for her lab results based on your requested investigations in #2 above.
- b) Based on your results, detail your a) RR-TB plan; b) HIV plan; c) Follow-up plan – ensure you detail all baseline investigations for your RR-TB plan

5. How often should Thab'sile return to clinic after starting RR-TB treatment?

6. At your first follow-up visit after treatment initiation, you review your baseline testing results. Her BMI on today's visit is now 20.5 kg. She reports taking her pills daily and has mild nausea, but otherwise no other complaints.

- a) Ask your facility for her lab results based on your requested investigations in #4b above.
- b) What is your plan?

7. Month 1: She presents today complaining of increasing frequency of nausea and fatigue. She reports adherence to her HIV treatment. Her BMI has increased to 22.

- Her point of care HB is 10.
- Baseline smear was negative
- Baseline culture positive with DR-TB Reflex test demonstrating FQ resistance
- Her ECG shows normal sinus rhythm, pulse 104, QTc 400

a) What is your TB Plan?

b) What is your HIV plan?

c) Other / Follow-up plan?

8. Month 2: Visit – no new complaints. Continues to cough on occasion. Smear negative, culture negative; HIV RNA – lower than detectable limits; POC Hb 9.9. Taking her medication daily.

- Her point of care Hb is 9.9.
- M1 smear was negative
- M1 culture positive
- Her ECG shows normal sinus rhythm, pulse 110, QTc 410

a) What is your TB Plan?

b) What is your HIV plan?

c) Other / Follow-up plan?

12. Your adherence coaching was successful. She returned after only missing two weeks of BPAL. Her smear and culture both remain negative.

a) Do you extend her regimen? If no, why not? If yes, how long do you extend?

13. Final treatment visit: Thab'sile now has a BMI of 24. Her CXR is clear at this visit. Her labs indicate the following from the prior visit in clinic.

CD4 = 204 cells/mm³

Viral load = lower than detectable limits

Smear = negative

Culture = negative

Hb = 10.4

She continues to complain of heaviness with occasional tingling in her feet.

a) What is her RR-TB treatment outcome at treatment completion?

b) What is her follow-up plan for HIV care?

c) What is her follow-up plan for RR-TB care?

Question 4 lab result answers:

GXP Ultra – Positive for TB, Positive for RR-TB

DRTB-Reflex testing - Positive for FQ Resistance

CBC – normal, except for Hb of 11

CMP – normal, GFR is 68

ECG – Normal sinus rhythm – QTc 380

CXR – mild pleural effusion, left lower lobe

Question 6: Baseline results

Smear negative

Culture pending

Hb 11

eGFR 68

Preg – negative

HIV Resistance testing remains pending

Question 9 (b): Please address these questions about your patient

Do you stop the linezolid? Why or why not?

Has there been a clinical response?

If no, do you change your monitoring frequency?

Do you add any supportive medication?

Question 9 (d): Please complete this pharmacovigilance form for your patient

Question 10: Scenario - STOP LZD

You have decided to stop the patient's /LZD treatment. You ask her to return to clinic in 1 week, but she comes back in 2 weeks instead. Her Hb continue to fall, POC Hb 8.4

What are your next steps? Describe your plan in detail

Question 10: Scenario - CONTINUE LZD

You have decided to continue the patient's LZD treatment. You ask her to return to clinic in 1 week, but she comes back in 2 weeks instead. Her Hb continued to fall, POC Hb 7.9, patient has greater SOB and fatigue.

What are your next steps? Describe your plan in detail

References

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