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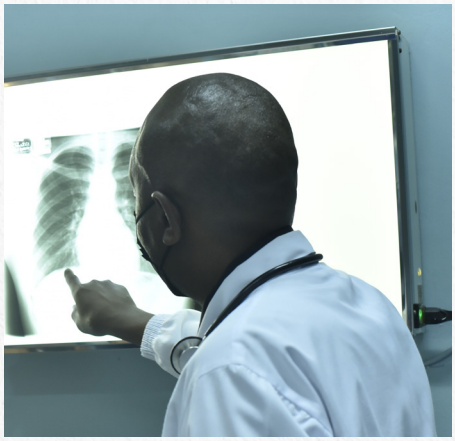

DRUG RESISTANT TUBERCULOSIS

By Oliver Angom, MBChB; Dorothy Gingo, MBChB, MMed Pediatrics; Paul Buyego, MBChB, MMed Internal Medicine; Ibrahim Magezi Kumbu, MBChB; Henry Byabajungu, Bsc. Laboratory Biomedical Science, Msc. Biomedical Laboratory Sciences and Management; Susan Akello Adakun, MBChB, MMed Internal Medicine

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EDITOR'S NOTE

Greetings and welcome to this edition of the ATIC newsletter! We at IDI hope that you are well, and using your knowledge and skills to manage your patients better.

Over the last year, the ATIC Call Centre received lots of questions on Drug Resistant Tuberculosis (DR-TB) both in adults and in children. So, we decided to focus this year's newsletter on DR-TB so that we can equip you with the knowledge and skills you need to manage your clients who may be suffering from DR-TB.

You will read about the epidemiology of DR-TB, clinical presentation, risk factors, causes, diagnosis, culture and susceptibility testing, treatment in adults, children and in special conditions and situations. You will also read about infection control measures at health facility, community and home levels. As always, we answer all your other questions in the ASK ATIC column.

We welcome all your health-related questions to our toll-free Call Centre which can be reached on: 0800200055 or WhatsApp: +256787311883 or on email: training@idi.co.ug.

Stay safe, healthy, and informed!

Lydia Caroline Nalule,
E-Learning Specialist - ATIC

BACKGROUND

Tuberculosis (TB) is a communicable disease that is a major cause of ill health and one of the leading causes of death worldwide. (27) TB is caused by the bacillus Mycobacterium tuberculosis, which is spread when people who are sick with TB expel bacteria into the air when they talk, sing, sneeze or cough. Without treatment, the death rate from TB disease is high (about 50%) (4).

With the currently-recommended treatments (a 4–6 months course of anti-TB drugs), about 85% of people can be cured. Some who do not cure may be explained by Drug resistant tuberculosis (DR-TB) among others. DR-TB is defined as a case of TB bacilli resistant to one or more anti-TB drugs. (5) DR-TB is a classification of TB based on Drug susceptibility to anti-TB medicines. DR-TB exists in various forms: mono drug-resistant TB (mono DR-TB), polydrug-resistant TB (poly-DR-TB), rifampicin-resistant TB (RR-TB), multidrug-resistant TB (MDR-TB), and extensively drug-resistant TB (XDR-TB) (6,4,7). This document provides information on the choice of regimens for the treatment of drug-resistant TB (DR-TB), including multidrug- or rifampicin-resistant TB (MDR/RR-TB), and confirmed rifampicin-susceptible, isoniazid-resistant TB (Hr-TB). (1)

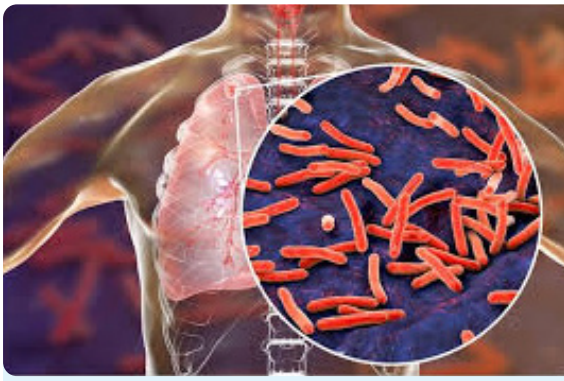
DR-TB is a major global health risk, driving the ongoing TB epidemic and increasing the morbidity and mortality of TB worldwide (26). It is a growing public health problem globally. The misuse of the first line regimens for drug susceptible TB among others, has led to the emergence of resistant strains and increasing cases of DR-TB. (2) Uganda is considered one of the 30 high burden TB countries (3,4) where TB presents a public health problem with a number of MDR TB cases notified to NTLP every year.

EPIDEMIOLOGY OF DR-TB

According to WHO, there was an estimate of about half a million new cases of multidrug- or rifampicin-resistant TB (MDR/RR-TB) in 2018. (10). In 2021 globally, 71% of people (2.4/3.4 million) diagnosed with bacteriologically confirmed pulmonary TB were tested for rifampicin resistance, the same level of coverage as in 2020 (2.1/3.0 million) and up from 61% (2.2/3.6 million) in 2019 (4). Among those tested, 141,953 cases of MDR/RR-TB and 25,038 cases of pre-XDR-TB or XDR-TB were detected, giving a combined total of 166,991 (4). This was an increase (6.4%) from the combined total of 156,982 in 2020, but less than the 9.7% increase in the overall number of people diagnosed and reported with TB between 2020 and 2021. (4)

In Africa, the prevalence of drug-resistant TB is estimated to be 2.5% among new cases and 12% among previously treated patients (25). In Uganda, results of a national RR-TB survey carried out in 2010 (limited to smear-positive samples) showed an MDR-TB prevalence of 1.4% and 12.1% among new and retreatment cases, respectively. The emergence of MDR-TB is a threat to populations in Sub-Saharan Africa due to high prevalence of infectious diseases, especially HIV infection, limited access to well-equipped healthcare facilities in the most resource-poor settings, and the high costs of treatment, thus worsening the effect of MDR-TB. In the year 2022 in Uganda, of the estimated 1,400 drug-resistant TB (DR-TB) cases, only 761 were diagnosed. Despite the detection gap of 46%, all these 761 cases were notified to the NTLP and started on treatment (World Health Organization. Global Tuberculosis Report, 2022.)

Sub-Saharan Africa (SSA) is majorly affected by tuberculosis, with an estimate of about 36% of child TB deaths. (9) The global burden of multi drug resistant tuberculosis in children has never been quantified and due to diagnostic challenges multiple cases are missed. (11).



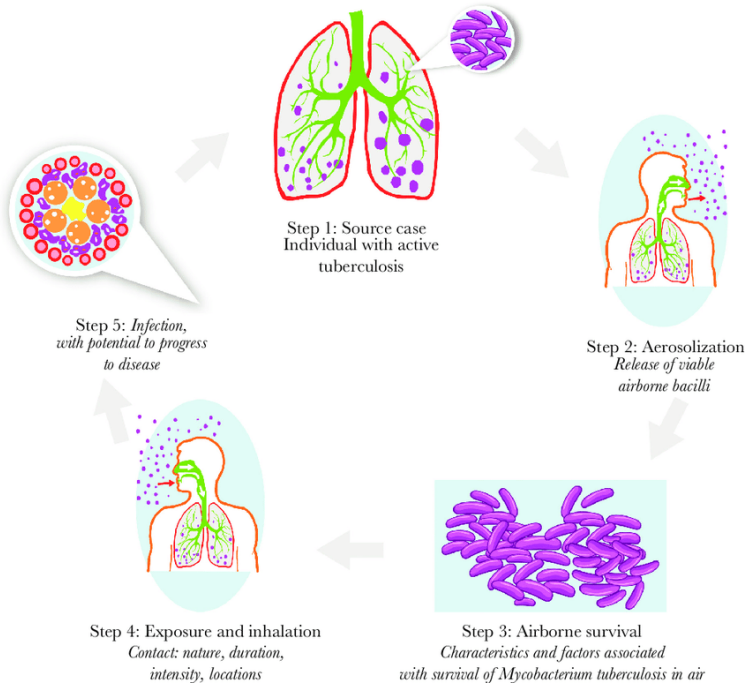
NATURAL HISTORY

The transmission of DR-TB is like drug susceptible TB. (12) TB is transmitted via inhalation of aerosols into the lungs. However, in some instances, the macrophages can localize the tubercle bacilli and form a granuloma.

When the immune system is weakened by HIV, immune suppressive drugs, etc., the granuloma is broken down and mycobacterium is released and spread throughout the system. The tubercle bacilli are then transmitted hematogenous and spread to other parts of the body.

TRANSMISSION

Transmission is greater among people with a smear positive sputum and in high burden countries. There is a high susceptibility in children less than 5 years, people living with HIV, smokers and in silica miners. (13)



Cascade of tuberculosis transmission (Source: The Aurum Institute) (13)

CLINICAL PRESENTATION

Individuals with DR-TB present with same signs and symptoms as drug susceptible TB. Signs and Symptoms can range from fever, cough, night sweats, weight loss among others, making diagnosis difficult. (5)

However, patients with DR TB tend to develop more complications and are often associated with significant morbidity and mortality than the drug sensitive TB (25).

Significantly DR-TB in HIV coinfection has been associated with increased mortality and severe disease complications because of interconnected challenges related to the complexity of DR-TB treatment and to clinical management of HIV coinfection (25)

CLASSIFICATION OF TUBERCULOSIS ACCORDING TO DRUG SUSCEPTIBILITY (14)

Table 1 Definitions of Drug-susceptible and drug-resistant tuberculosis (TB)

- Pan (Totally)-susceptible TB Tuberculosis caused by Mycobacterium tuberculosis strains susceptible to all first-line anti-TB drugs.
- INH Mono-resistant TB (Hr-TB) Tuberculosis caused by M. tuberculosis strains resistant only to Isoniazid
- Rifampicin resistant TB (RR-TB) Tuberculosis caused by strains resistant only to Rifampicin
- Multidrug-resistant tuberculosis (MDR-TB) Tuberculosis caused by M. tuberculosis strains resistant to at least two first-line anti-TB drugs isoniazid and rifampicin
- Extensively drug-resistant tuberculosis (XDR-TB) Tuberculosis caused by M. tuberculosis resistant to Rifampicin and isoniazid plus 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). (4)
- Pre-XDR-TB is TB caused by Mycobacterium tuberculosis (M. tuberculosis) strains that fulfil the definition of multidrug resistant and rifampicin-resistant TB (MDR/RR-TB) and which are also resistant to any fluoroquinolone (4)
- (Totally)-resistant TB Tuberculosis caused by M. tuberculosis resistant to all first and second-line anti-TB drugs

RISK FACTORS OF DRUG RESISTANT TUBERCULOSIS

Inadequate anti-TB treatment is the most important among the factors that can lead to drug-resistant TB; It leads to mutations in drug-susceptibility bacilli making them drug-resistant or overgrowth of initially drug-resistant bacilli.

Inadequate TB treatment can be caused by;

- Suboptimal drug regimen
- Inadequate duration of treatment
- Non-adherence to drugs by the patient
- Use of poor-quality drugs

HEALTHCARE PROVIDER	PATIENT	HEALTH SYSTEMS
• Non-compliance with guidelines • Absence of guidelines • Poor training • No monitoring of treatment • Wrong dose combination • Poor patient education • Poor patient support • Poor management of adverse events	• Inadequate intake • Poor adherence • Lack of transportation • Adverse effects • Social barriers • Malabsorption • Diabetes Mellitus • Alcohol and substance abuse	• Inadequate supply • Poor quality medicines • Unavailability of certain drugs (stock-outs or delivery disruptions) • Poor storage conditions • Poor regulation of medicines

CAUSES OF DRUG RESISTANCE IN TB

According to WHO, there are primarily two pathways that lead to development of drug resistant tuberculosis. (12). These are primary drug resistance and acquired drug resistance.

Pathways for drug resistance

Most patients that develop MDR tuberculosis have primary resistance rather than acquired resistance. Primary resistance is the acquisition of infectious agents from an individual diagnosed with MDR tuberculosis whereas acquired resistance is due to acquisition of mutant strains. This occurs due to inadequate drug concentration, incomplete or poor treatment quality and premature treatment interruption that creates a selection pressure leading to generation of drug resistant tuberculosis. The drug resistant strains then multiply and becomes the dominant strain. (5,12).

Other factors include:

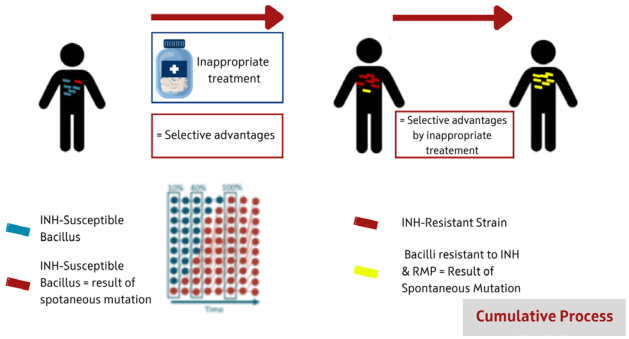
- Metabolism of bacillus shifted to dormancy
- Impaired or decreased drug uptake by M. tuberculosis cells
- Differential penetration of drugs to various body sites.
- Suboptimal concentration of drugs at some sites.
- Impaired drug absorption due to underlying host conditions like HIV/AIDS

WHEN TO SUSPECT DR-TB

- Drug resistant TB should be suspected under the following circumstances:
- When a patient presents with history of contact with known index case of drug-resistance Tuberculosis
- In cases of relapses
- Return after loss to follow up
- History of frequent interruption of drug treatment
- Failure of treatment for drug susceptible TB
- Health care workers presenting with signs and symptoms of TB
- Patients from prisons or other congregate settings

Health care workers and prisoners are at an increased risk due to DR-TB outbreaks and high DR-TB prevalence in these institutions

Acquisition of Resistance during Innappropriate Treatment



DIAGNOSIS

The diagnosis of drug resistant tuberculosis is based on clinical diagnosis, laboratory and radiological investigations. A high index of suspicion is required for the diagnosis of drug resistant tuberculosis; therefore a "presumptive case of MDR-TB" is defined as a TB patient who fails new treatment regimen or retreatment regimens with first-line anti-TB drugs. One who is sputum smear positive at the end of the 4th month of treatment or later and close contacts of drug-resistant TB cases (5). WHO recommends the universal access to drug susceptibility testing for at least rifampicin and isoniazid using the WHO recommended rapid diagnostic (WRDs) as the initial test for individuals with presumptive TB.

These are identified through active and passive case finding, to increase detection of bacteriologically confirmed cases, drug resistance, and to reduce the time to diagnosis (24). Uganda's TB diagnostic network is currently composed of 3 WRDs for the rapid detection of TB and MDR TB, these include: Xpert MTB/RIF Ultra & Xpert MTB/XDR (Genexpert), TruenatMTB plus &-RIF Dx and Looplamp MTBC detection. The National TB Reference Laboratory can also detect MDR TB using Line Probe Assays (LPA), culture, phenotypic drug susceptibility testing (DST) as well as targeted or whole genome sequencing.

The following methods are used for diagnosis of drug resistant tuberculosis in Uganda.

- GeneXpert MTB/RIF Ultra & MTB/ XDR assay
- Line Probe Assay
- Truenat Assay
- Culture and Drug Susceptibility Testing
- Next Generation Sequencing

Xpert MTB/RIF & Ultra

Truenat MTB, MTB Plus & RIF DX

Genexpert: Xpert MTB/RIF Ultra and Xpert MTB/XDR

This method uses semi-quantitative nested real time PCR to amplify a fragment to detect Mycobacterium tuberculosis complex DNA and drug resistance. Xpert MTB/RIF Ultra can detect only RIFAMPICIN resistance while Xpert MTB/XDR can detect resistance to ISONIAZID, FLUOROQUINOLES, INJECTABLES (amikacin, kanamycin, capreomycin) and ETHIONAMIDE. Xpert MTB/RIF ultra-assay is the initial test for diagnosis of TB and RR TB in Uganda while Xpert MTB/ XDR assay used as a reflex test for all positive Xpert MTB/RIF assay in order to detect INH monoresistance or fluoroquinolone resistance for the confirmed RR TB cases.

The results turnaround time for these assays are about 90 minutes implying that the client can easily initiate either susceptible TB or drug resistant TB treatment the same soon after diagnosis. Uganda has a sample referral network through the integrated specimen referral system that enables universal access to TB GeneXpert testing for the health facilities without a GeneXpert machine by referring of the samples to the GeneXpert testing site.

Loopamp – MTB C resistance

XPERT MTB/RIF ULTRA ASSAY

GeneXpert results interpretation:

MTB DETECTION	MTB GRADING	RIFAMPICIN STATUS	CLINICAL IMPLICATION
MTB NOT DETECTION			No TB, continue other investigations
MTB DETECTION	TRACE	INDETERMINATE	Repeat test with another morning sample: if same outcome or now MTB NOT DETECTED-do refer the sample to the NTRL for TB culture. Manage as susceptible TB pending outcome of culture results from NTRL
	LOW, MODERATE, HIGH	RESSISTANCE NOT DETECTED	Manage as susceptible TB
	LOW, MODERATE, HIGH	RESISTANCE DETECTED	Manage as MDR TB. Collect a 2nd sample for MTB/XDR assay. Send a baseline sample to the NTRL for culture and DST.
ERROR OR INVALID			Repeat test with another sample

XPERT MTB/XDR ASSAY

MTB DETECTION	DRUG STATUS	CLINICAL IMPLICATION
MTB NOT DETECTION		Insufficient TB bacilli load for the amplification and detection of DNA. Manage as susceptible to 2nd line anti-TB drugs pending outcome of culture results.
MTB DETECTION	*INDETERMINATE	Inadequate TB DNA to attain the minimum threshold for determination of resistance or no resistance to a specific drug (s). Manage as susceptible to that specific drug (s) pending outcome of culture results and DST from NTRL
	RESSISTANCE NOT DETECTED	Manage as susceptible to that specific drug (s)
	**RESISTANCE DETECTED	Manage as pre-XDR or specific drug resistance detected Initiate on individualized regimen pending outcome of the baseline culture and DST results from NTRL.
ERROR OR INVALID		Repeat test with another sample

*One or more drugs might be indeterminate, yet other drugs have interpretable results

** Resistance to isoniazid and fluoroquinolones can either be low level or high-level resistance. Low level resistance would imply the probable effective of that resistant drug at a higher dose.

Truenat MTB plus & RIF Dx

Truenat™ MTB Plus is a chip-based Real Time Polymerase Chain Reaction (PCR) test for the semiquantitative detection and diagnosis of Mycobacterium tuberculosis (MTB) in human pulmonary (sputum/non-sputum) and extra pulmonary TB specimen. Truenat™ MTB Plus runs on the Truelab™ Real Time Quantitative micro PCR analyzers. Truenat MTB-RIF Dx is a Chip-based Real Time Polymerase Chain Reaction (PCR) test for the detection of Rifampicin resistance in Mycobacterium tuberculosis ®(MTB) in Truenat MTB/MTB Plus positive human specimen and aids in the diagnosis of MDR-TB. This test detects the presence of major mutations in the MTB genome that are known to cause resistance to rifampicin. This is a follow-on test, to be performed only on the extracted DNA from Truenat MTB/MTB ®Plus positive sample.

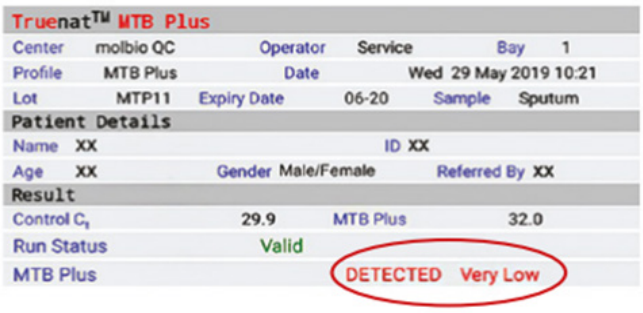
TRUENAT RESULTS INTERPRETATION

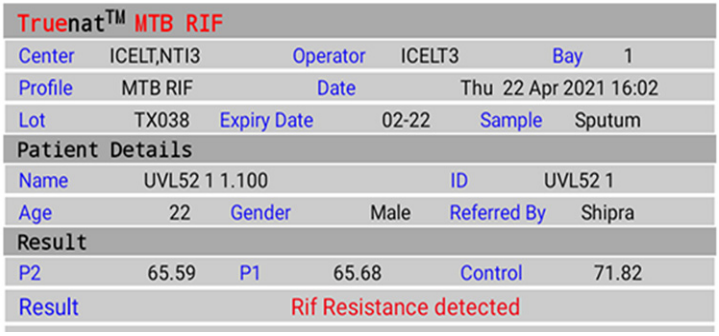
Truenat MTB plus results

MTB DETECTION	CLINICAL IMPLICATION
MTB NOT DETECTED	No TB, continue other investigations
MTB DETECTED: very low, low, medium and high	TB infection present: test already extracted DNA for Truenat RIF Dx

Truenat RIF Dx results

RIFAMPICIN STATUS	CLINICAL IMPLICATION
RESISTANCE NOT DETECTED	Manage as susceptible TB
RESISTANCE DETECTED	Manage as MDR TB Send a baseline sample to the NTRL for baseline culture and DST.
INDETERMINATE	Repeat test with another morning sample: if same outcome or now MTB NOT DETECTED-do refer the sample to the NTRL for TB culture. Manage as susceptible TB pending outcome of culture results from NTRL
ERROR OR INVALID	Repeat test with another sample





Appearance of Truenat MTB plus (L) and Truenat MTB RIF (R) result display

Line probe assays (LPAs):

These are basically DNA–DNA hybridization assays that allow the simultaneous detection of different mutations by using multiple probes. LPAs have been developed, most of them focus only on the hotspot regions of drug-resistance and different assays target different genes. (19).

In Uganda the LPAs are available at the NTRL and are used for the detection MDR TB or fluoroquinolone resistance using 1st and 2nd line LPA respectively. Resistance is identified by presence of specific mutations: for isoniazid and fluoroquinolones it is possible to identify low- or high-level resistances such that appropriate clinical management is given to the patients. The deployment of the GeneXpert and truenat assays at the lower-level health facilities has greatly reduced the role of LPAs that are mainly centralized at the NTRL.

INTERPRETATION OF 1ST LINE LPA RESULTS

DRUG	RESISTANCE STATUS	CLINICAL IMPLICATION
ISONIAZID/ RIFAMPICIN	RESISTANCE NOT DETECTED TO BOTH	Manage as susceptible TB
ISONIAZID/ RIFAMPICIN	RESISTANCE DETECTED/ RESISTANCE NOT DETECTED	Manage as Isoniazid-mono resistant TB.
ISONIAZID/ RIFAMPICIN	RESISTANCE DETECTED TO BOTH	Manage as MDR TB.
ISONIAZID/ RIFAMPICIN	RESISTANCE NOT DETECTED / RESISTANCE DETECTED	Manage as MDR TB.
ISONIAZID/ RI-FAMPICIN	Indeterminate to any or both	Manage as susceptible to indeterminate drug pending outcome of culture for repeat LPA and phenotypic DST.

INTERPRETATION FOR 2ND LINE LPA RESULTS

DRUG	RESISTANCE STATUS	CLINICAL IMPLICATION
MOXIFLOXACIN/ LEVOFLOXACIN	RESISTANCE NOT DETECTED TO BOTH	Manage as susceptible to fluoroquinolones
MOXIFLOXACIN/ LEVOFLOXACIN	RESISTANCE DETECTED TO ONE OR BOTH	Exclude use of the specific drug to which resistance is detected but if to both then exclude us of the fluoroquinolones and start on individualized regimen
MOXIFLOXACIN	LOW LEVEL RESISTANCE DETECTED	Moxifloxacin can be effectively used by increasing the daily dose (800mg/kg daily)
AMIKACIN	RESISTANCE NOT DETECTED	Amikacin might be used if desired in certain circumstances.
AMIKACIN	RESISTANCE DETECTED	Amikacin should not be used under any circumstances.

NB: Molecular assays mentioned above e.g. GeneXpert, Truenat and LPA have limitations of sensitivity to determine resistance because some mutations that confer resistance are outside the regions covered by the test hence phenotypic DST must always accompany these assays to rule out any resistances.

CULTURE AND DRUG SUSCEPTIBILITY TESTING:

Culture

The culture of Mycobacterium tuberculosis in the laboratory requires extra safety precautions since it involves the multiplication of highly infectious aerosolized organisms. All manipulations involving viable TB organisms should be carried out in a functional and certified biological safety cabinet with personnel having appropriate personal protective equipment like N95 respirators.

Two different culture methods are available at the NTRL for the culturing of TB organisms: Liquid Culture-Mycobacterium Growth Indicator Tube (MGIT) and solid culture-Lowenstein Jensen (LJ) media. TB grows slowly in the laboratory due its slow replication taking up to 42 days (6 weeks) and 56 days (8 weeks) with MGIT and LJ culture media respectively. Each of those media types have their own pros and cons: MGIT medium is more sensitive compared to LJ while the LJ medium is less susceptible to contaminants as compared to MGIT. MGIT medium is a commercial method leading to stock outs at times due to the complex supply chain mechanisms while LJ media is a more sustainable and dependable medium since it is locally prepared.

TB culture is very important during the monitoring of the DR TB patients on treatment to assess their infectiousness as well as confirm the effectiveness of treatment by evidence of conversion of positive to negative cultures.

Medium	Solid	Liquid
Example	Lowenstein-Jensen Middlebrook agar	MGIT
Equipment	Incubator (5-10% CO2)	Automated Incubator(MGIT960)
Growth detection	Visible colonies; manual reading	Metabolic activity; automated reading 02 results in fluorescence
DST duration	4-6 weeks	Control = 400 growth units (GU) (up to 13 days)

INTERPRETATION OF CULTURE RESULTS

RESULT	CLINICAL IMPLICATION
NEGATIVE OR NO GROWTH	TB drugs have cleared off the viable germs, i.e. patient is responding well to treatment.
POSITIVE FOR MYCOBACTERIUM TB COMPLEX (MTBC)	TB germs are still viable: continue treatment as desired as well as encouraging infection prevention and control measures since patient is still infectious.
POSITIVE FOR NON-TUBERCULOSIS MYCOBACTERIUM (NTM) or MYCOBACTERIUM OTHER THAN TUBERCULOSIS (MOTT)	Monitor patient for subsequent NTM/MOTT culture results. If no subsequent NTM/MOTT culture results, then ignore the result since the body self-cleared the NTM or it might have been a false culture result from the laboratory. But if persistent NTM/MOTT culture result then notify the laboratory to identify the specific NTM/MOTT if possible as well as perform drug susceptibility testing for all anti-TB drugs at its disposal (both 1st and 2nd line drugs).
CONTAMINATED	Other flora other than Mycobacterium tuberculosis complex were isolated. Await another result from the laboratory following the re-decontamination of the residual sample (pellet or sediment) available at the laboratory. If necessary send another sputum sample for repeat TB culture testing.

Drug susceptibility testing-DST

DST determines if a population of M. tuberculosis bacilli will respond to anti-tuberculosis drugs and indicate if the strain is susceptible to a specific drug therefore if treatment with those agents will be successful, and a result indicating that a strain is resistant means that there is a high possibility that treatment with those agents will fail and, therefore, other agents should be used. (18). The NTRL performs phenotypic DST either using solid-LJ or liquid-MGIT media, the choice of use the specific media is dependent on the availability of supplies as well as the drug compatibility for testing with specific media.

The table below identifies the compatibility of the different DST drugs to the different media.

Drug	DST media used
Rifampicin, Isoniazid, Ethambutol, Levofloxacin, Moxifloxacin, Amikacin	LJ or MGIT
Pyrazinamide, bedaquiline, clofazimine, linezolid, ethionamide	MGIT

DST results interpretation

DST results are either interpreted as sensitive or resistant. Sensitive for a specific drug implies that the TB germs will be cleared or killed by that specific drug while resistant results to a specific drug imply that the drug should not be used or be withdrawn from the TB treatment since it has no therapeutic value in curing or killing off the TB germs.

Clinical breakpoint (CB) for isoniazid and moxifloxacin

Isoniazid and Moxifloxacin phenotypic DST in the laboratory can be tested at critical concentration (lower dose) and at the clinical breakpoint (higher dose). TB germs that are resistant at the lower dose e.g. low-level resistance detected by the molecular assays like Xpert MTB/ XDR and LPA can be treated with high dose isoniazid or moxifloxacin following the outcome of DST at the clinical breakpoint.

Next Generation Sequencing

The NTRL can perform either whole genome sequencing-WGS or targeted Next Generation Sequencing-NGS. Targeted NGS is generally focused on sequencing a select set of genes or gene regions that have known or suspected associations with a specific pathogen (e.g. Mycobacterium tuberculosis) or a specific phenotype (e.g. drug resistance). While WGS is the process of determining the complete genome sequence for a given organism at one time through NGS. This method can determine the order of all nucleotides in each genome and detect any variations relative to a reference genome using bioinformatics analysis.

Role of sequencing in DR TB management

- Aimed for all 2nd line resistances to determine clinically relevant mutations such that appropriate treatment can be selected.
- Useful in identification of re-infection of DR TB with either a new strain or the previous strain for patients that are on DR TB retreatment.
- Can be used in surveillance to determine the epicentre or source of DR TB infection in cases of high surges of DR TB cases.

MONITORING RESPONSE TO TREATMENT

The mainstays for testing patient response to treatment are sputum smear microscopy and culture. (21)

DRUG RESISTANT TUBERCULOSIS IN CHILDREN

The diagnosis of drug resistant tuberculosis in children is challenging with less than 15% with a positive sputum detection. (3,9,22) However, it is still recommended to attempt to retrieve samples for testing. (3) The various methods for TB diagnosis in young children traditionally require invasive sampling techniques such as gastric aspiration, nasopharyngeal aspirates, or sputum induction.

Even after the acquisition of an adequate specimen, sensitivity is still low. (22) Therefore, TB diagnosis in children is based on clinical assessment, history of exposure to infectious TB, non-specific signs and symptoms, and use of imaging techniques e.g. chest radiography and tests such as tuberculin skin testing or interferon-gamma release assays. (3,22)

A practical approach is to treat children with suggestive symptoms or signs and chest radiograph abnormalities with a course of broad-spectrum (non-fluoroquinolone) antibiotics and to strongly consider the diagnosis of TB in those with minimal or no improvement. (9)

SECOND LINE TREATMENT

In 2019, Uganda adapted the oral treatment for drug resistant tuberculosis. (3)

2019 to 2024

1. Modified fully oral shorter regimen (mSTR(9-11 (BDQ, LFX, LZD, CFZ, CS)
2. Oral Longer regimen, individualized to age, resistance pattern, treatment history, site/ severity of disease
3. Salvage regimens with Group C drugs for treatment failures/intolerance XDR TB

Jan 2025

1. 6 months BPaLM regimen (Bdq-Pa-Lzd-Mfx) New 4 drug 6 months all oral regimen
2. 9-month all oral regiment (Bdq,Lfx, Lzd,Cfz,Cs)
3. Longer individualized regimens

Duration of treatment with mSTR

The total duration of treatment is between 9-11 months. Sputum cultures and will be done every month and a DST will be done whenever there is a positive sputum culture. Sputum culture results will determine the patient will receive treatment between 9-11 months. If the patient is still culture positive at month 4, treatment should be extended to 11 months; if culture positive at month 5, the patient will have failed treatment and will be referred to the National DR-TB Panel to switch to individualised longer regimen. (3)

Longer, individualized treatment regimens

Persons who do not qualify for the mSTR regimen will receive an 18-20-month treatment regimen; core drugs in the regimen include BDQ, LZD, LFX, CFZ, and CS. All three Group A agents and at least one Group B agent should be included, where possible; if only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it;

For persons ages 6 years and above, the longer regimen will consist of 4-5 drugs given for a period of 6 months followed by 12 months of LFX, CFZ, and 1-2. (3) In RR-TB patients on longer regimens, a total treatment duration of 18–20 months or 15 months after culture conversion is suggested for most patients; the duration may be modified according to the patient's response to therapy.(3) In RR/MDR-TB patients on longer regimens that contain amikacin, an intensive phase of 6–7 months is suggested for most patients; the duration may be modified according to the patient's response to therapy.(3)

Group and Steps	Medicine	Abbreviation
Group A: Include all three medicines	Levofloxacin OR	(Lfx)
	Moxifloxacin	(Mfx)
	Bedaquiline	(Bdq)
	Linezolid	(Lzd)
Group B: Add one or both medicines	Clofazimine	(Cfz)
	Cycloserine	(Cs)
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	(Eto)
	Delamanid	(Dlm)
	Pyrazinamide	(Z)
	Imipenem–cilastatin OR	(Ipm–Cln)
	Meropenem	(Mpm)
	Amikacin	(Am)
	Ethionamide	(E)
	p-aminosalicylic acid	(PAS)

Updated WHO grouping of anti-TB medicines

Salvage regimens after RR-TB treatment failure

Patients on either the longer or shorter regimen who have a positive culture at month 4 are likely to be failed by treatment and possibly need a salvage regimen, especially persons with a history of previous treatment with second-line drugs, including BDQ, LZD, or CFZ. (3) The future, WHO DR TB treatment 2022 update: Exciting BPaLM regimen: 4 drugs for only 6 months to start enrollment Jan 2025 expected to improve treatment outcomes because of shortened treatment duration. Currently, Uganda is in the process of reviewing PMDT guidelines to adopt these regimens.

Regimen options in the treatment of DR-TB

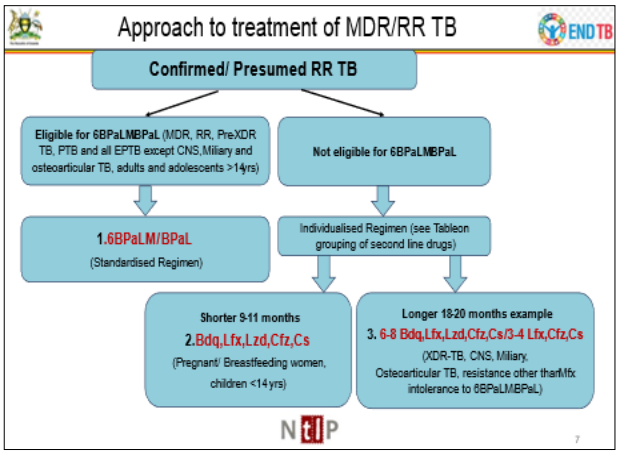
In patients with MDR/RR-TB, there are several regimens that can be used based on current WHO policy. The key factors that define treatment regimen choice include:

- Drug-resistance profile
- Prior exposure to TB medicines and patient history
- Drug-resistance profile of close contacts
- The patient's age
- Extent of pulmonary TB disease
- Localization of extrapulmonary TB lesions

• BPaLM regimen (6 Bdq-Pa-Lzd-Mfx1): is used in patients with MDR/RR-TB where fluoroquinolone susceptibility is presumed or documented. This 6-month all-oral treatment regimen comprises bedaquiline, pretomanid, linezolid and moxifloxacin. It is possible to omit moxifloxacin and continue with the BPaL regimen for MDR/RR-TB patients with confirmed fluoroquinolone resistance.

• Longer individualized regimens: for patients with MDR/RR-TB who are not eligible for or had no favourable treatment outcome using the above 6-month regimens, have TB disease caused by M. tuberculosis strains with extensive drug resistance (e.g. extensively drug-resistant TB [XDR-TB]) or have intolerance to key components of the above-mentioned regimens. These regimens have a duration of at least 9-18 months and are individually designed based on a hierarchical grouping of second-line TB medicines, the drug-resistance profile and the patient's medical history. Based on the review of the latest available evidence, the 6-month BPaLM regimen is the preferred option for most patients with MDR/RR-TB.

BPaLM is the regimen of choice for patients with MDR/RR-TB with absent or unknown fluoroquinolone resistance



MODELS OF DR-TB CARE

We have Hospitalisation and Ambulatory care. Treatment may be directly initiated using either model:

Hospitalization

Under this model of care, patients are initiated on treatment under admission by a DR-TB hospital. This is specifically for very sick patients, patients with adherence challenges and patients referred to ambulatory care but are unstable.

Ambulatory Care

Under this model, care is provided by a follow up DOT facility within patient's home community. This category is for medically stable patients and provided by a follow up DOT facility within patient's home community.

In both models:

- Treatment is initiated by a DR-TB initiation and treatment facility
- Patients are clinically reviewed by the treatment initiating facility monthly and during clinical reviews routine investigations are done to monitor treatment and recovery.

TREATMENT OF DR-TB IN SPECIAL CONDITIONS AND SITUATIONS

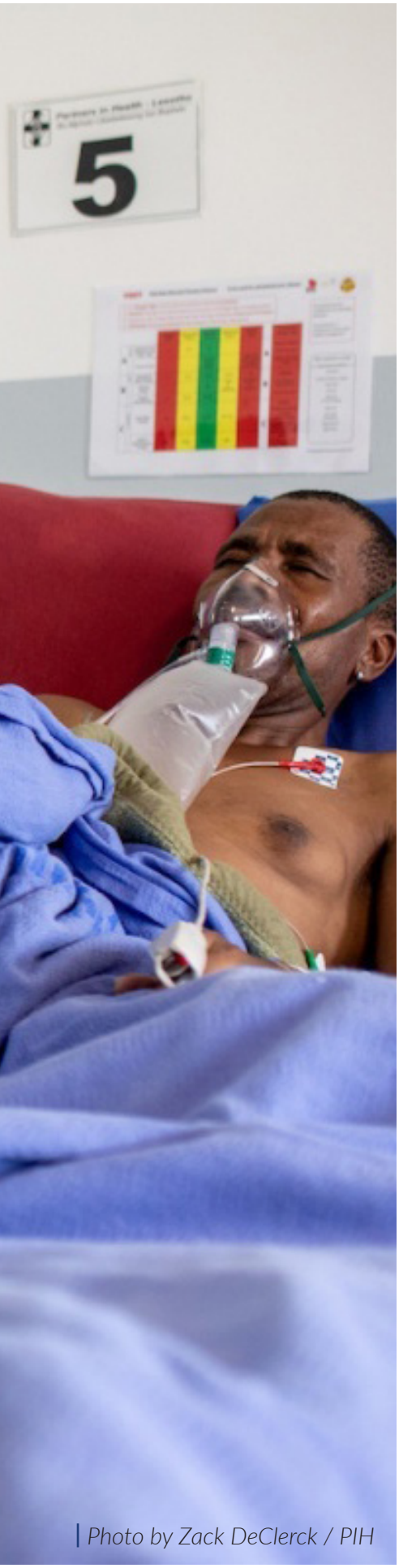


Photo by Zack DeClerck / PIH

PREGNANCY

In pregnancy, all oral modified Short Treatment Regimen (mSTR) is safe. Pregnant and breastfeeding women with pulmonary RR-TB and/or uncomplicated EPTB, regardless of HIV status; medications used in the treatment of RR-TB are not a contraindication to breastfeeding, although appropriate infection control measures should be followed.

Avoid:
- Injectables because they are teratogenic
- Ethionamide because it worsens nausea and vomiting during pregnancy

RENAL INSUFFICIENCY

Can be due to:
- Longstanding TB Infection
- Previous use of aminoglycosides

The dosing of second-line drugs is based on the patient's creatinine clearance

DIABETES MELLITUS

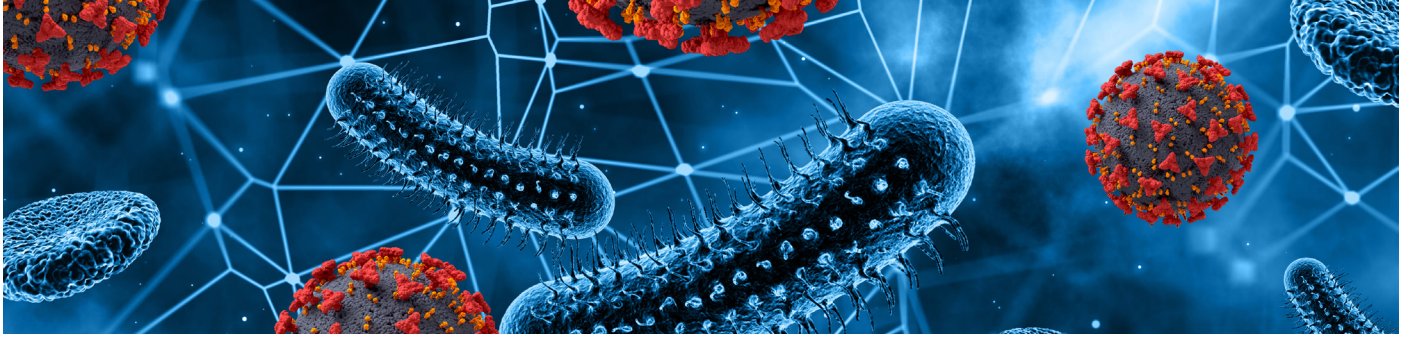
All patients with DR-TB should be screened for diabetes. Patients with both diabetes and MDR-TB are at risk of poor outcomes and diabetic care must be managed closely throughout the treatment of DR-TB. Some experts recommend the use of insulin for tight blood glucose control in all patients with diabetes and TB, they should have their blood sugar and HbA1C levels followed closely to ensure good glucose control. It is important to note that there are drug-drug interactions between metformin and DTG and thus the maximum recommended dose for metformin is 500mg twice daily when given with DTG.

Persons with diabetes may be at increased risk of developing adverse events, including peripheral neuropathy, optic neuropathy, and renal failure. Thus, while on treatment for RR-TB they should have more frequent monitoring so that early management can be pursued.
- Use of Ethionamide or Prothionamide may be associated with hypoglycaemia and difficulties in glucose control.
- An Angiotensin-Converting-Enzyme (ACE) inhibitor to prevent progression of diabetic nephropathy

HEPATITIS B AND C

Persons with hepatitis B and/or C now have treatment options for their liver disease. Hepatitis B treatment with TDF and 3TC can be initiated at any time, as there are limited drug-drug interactions or overlapping toxicities with RR-TB treatment. The limited data that exist on hepatitis C suggest that co-administration of treatment for hepatitis C during treatment for RR-TB may be safe; many providers, however, feel that treatment for hepatitis C be delayed until completion of treatment for RR-TB.

RR-TB treatment is associated with hepatic adverse events and if there is unstable or worsening liver disease while on RR-TB treatment, it is reasonable to initiate hepatitis C therapy. Patients with co-morbid viral hepatitis and RR-TB could be discussed with the National DR TB panel



TREATMENT OF ISONIAZID RESISTANT TB (HR-TB)

In patients with confirmed rifampicin-susceptible and isoniazid-resistant tuberculosis, treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months; if individual drugs are not available, the FDC of RHZE may be given until individual drugs are available.

PREVENTION OF DRUG-RESISTANT TB

- Well-administered first-line treatment: Using the most effective regimen and high-quality DOT for drug-susceptible cases
- Timely identification of DR-TB and adequate DR-TB treatment regimens administered early in the course of the disease are essential to stop primary transmission
- Infection control measures to stop/reduce transmission of MDR TB

DR-TB TREATMENT ADHERENCE CHALLENGES

- Pill burden (multiple drugs)
- Many side effects
- Long treatment duration (9-11 months for mSTR and 18-20 months for longer regimen)
- Co-infection with HIV
- Cultural/religious belief system and living circumstances
- Patient in denial (not accepting the diagnosis)
- Other social and/or medical conditions (e.g. homelessness, alcoholism, substance abuse, mental illness, etc.)

ADHERENCE INCENTIVES AND ENABLERS

- Provide money for transport and food
- Support patients to attend the daily DOT at a nearby health facility
- Support patients to attend the monthly MDR-TB clinical review at the treatment initiation facility
- Contribute to improvement of the nutritional status of patients
- Mitigate:
    - Initial “loss to follow up” of diagnosed RR patients
    - Treatment interruption

INFECTION CONTROL (IC) MEASURES

- Attend to MDR-TB patients early morning and first (triage) to reduce time in facility
- Attend in a well-ventilated place
- Have a separate waiting area (use outdoors if needed)
- Ensure 100% DOT
- Always ensure patients are given surgical masks to wear while still infectious or if coughing or have other TB symptoms
- Wear N95 respirators while attending to any DR-TB patient
- Educate on cough hygiene and etiquette

INFECTION CONTROL MEASURES FOR HOME AND COMMUNITY CARE

- To prevent the spread of MDR-TB, patients should be isolated until 3 consecutive sputa AFB smears are negative (or documented culture conversion in some circumstances) and there has been a good response to treatment. [Same criteria should apply for patients on home isolation.]
- Until Sputum culture becomes negative, advise the patient to:
- Sleep in a separate room if possible
- Spend most hours outdoor during daytime in fresh air
- Open windows and doors to allow fresh air into the house
- In the household, avoid contact with children less than 5 years, HIV positive and pregnant women) patient should wear surgical mask if he/she must have contact)
- Avoid social gatherings
- Avoid use of taxi if possible (or if no other option, sit by window and use mask)
- Avoid work situations and travel

ASK ATIC

01 **Dear Doctor, I have a 23/F who I diagnosed with severe malaria and completed IV artesunate and coartem on continuation phase but has not responded to treatment. How do I manage this patient?**

The first line treatment for complicated malaria is IV artesunate at 0, 12, 24 hours and if stable continuation on oral dihydroartimesinin and piperaquine. However, if the patient doesn't improve after 24hours, the patient should be started on IV quinine according to weight in 3 divided doses. (1)

02 **Dear Doctor, I have a patient who has completed coartem and has returned and reports persistent fever and joint pains but no signs of severe malaria. How do I manage this patient?**

Kindly repeat a blood smear to obtain parasitological evidence of treatment failure and restart on 2nd line treatment of malaria which is dihydroartemesinin and piperaquine. If dihydroartemesinin piperaqine is not available kindly use the alternative option which is pyoranidine artesunate. (1)

03 **I have a three-year-old with mumps. I am calling to inquire about the management of mumps.**

Mumps is viral illness caused by mumps virus. It presents with unilateral mandibular swelling, fever, headache and throat pain. Mumps has no cure; it is a self-limited viral infection. Mumps can present as mild or severe disease. Mild disease typically presents as fever, unilateral or bilateral parotid swelling. The main management of mumps is supportive care. This category can be managed as outpatients with analgesics, hydration, bed rest and icepacks if available.

However, according to WHO pediatric handbook, children with emergency signs should be admitted and handled accordingly. Severe disease can present in various forms as meningitis, encephalitis, pancreatitis and these need to be managed in the inpatient setting. Mumps infection can also lead to otitis media and epididymoorchitis that results in reduced fertility. Please note home remedies for mumps are discouraged, because the child needs to be assessed and managed by clinicians for the stated complications.

The prevention of mumps is through the Mumps Measles Rubella Vaccine. (2) There are two doses of MMR vaccine between 12-15months, then after 4 years of age. Infants below 1 year are protected by maternal antibodies.

04 **Dear Doctor, I have a patient who has completed intensive phase of tuberculosis treatment but has not improved on treatment, she reports persistent productive cough despite taking her medicine. How do I manage this patient?**

A sample should be taken off for a sputum analysis using ziehiel nelsen stain and gene x-pert to rule out rifampicin resistance and gram stain for other causes of pneumonia.
Depending on the results:

- If positive smear with no Rifampicin resistance, restart patient on the intensive phase with counselling and identify and address barriers to adherence.
- If positive smear and Rifampicin resistance, kindly refer the patient to the nearest DR TB sites where DR TB is managed.
- If negative proceed to the continuation phase and identify alternative causes of persistent productive cough.

05 **Dear Doctor, I was diagnosed with Hepatitis B and told my viral load is low and I do need not treatment. However, I am breastfeeding, is it possible to transmit to my child?**

Yes, it is possible. MOH guidance; All pregnant mothers should be screened for Hepatitis B, those found positive should have a viral load. If found > 200,000IU/ml, Start Tenofovir prophylaxis from 24 weeks or at earliest contact and continue 3 months post-delivery. Monitor for Viral load at 6months and 12 months. New born infants should have Hepatitis B birth dose vaccine followed by doses vaccine. If available give infant Hepatis B Immunoglobulin.

06 **Dear Doctor, I have a 22/M was previously diagnosed with tuberculosis and was co-infected with HIV. However, he dropped out of care for one year and returns with productive cough, fever night, sweats, and neck stiffness.**

According to the Uganda tuberculosis treatment guidelines, patients that interrupt care for 2 months should be traced. Secondly after finding the patient, re-educate the patient about tuberculosis. This includes risk of treatment failure andprogression to severe disease. Thirdly, support the patient to identify solutions to the problems to avoid future interruptions. According to MOH, the interruption of care for more than two months requires reassessment with Acid fast stain and gene x-pert to rule out rifampicin resistant tuberculosis. Kindly hold treatment while awaiting results as there is a possibility for drug resistant tuberculosis.

The patient possibly has Meningitis. All baseline investigations should be done, these include CD4, TB LAM, Serum CRAG and CSF analysis including Acid fast stain. If Serum CRAG is positive, also add CSF CRAG and culture and sensitivity.

Depending on the results, take a decision as shown in the table below:

Sputum results	Decision
Negative	Clinical decision to start or continue is on individual basis
Positive	If rifampicin resistant, refer for 2nd line treatment.
	If rifampicin sensitive, restart first-line treatment.

07 **Dear doctor, I have a 37/M known ISS virologically suppressed on third line of ART, current regimen Tenofovir/Lamivudine Dolutegravir/ Darunavir boosted with ritonavir and came in complaints of productive cough x 1/12, associated with weight-loss (13kg in 5months), drenching night sweats and poor appetite. He was previously treated for Tuberculosis in 2018. Kindly guide with management.**

Patient is a presumptive case of tuberculosis. Please investigate for tuberculosis using a gene x pert. Other point of care tests that can assist in diagnosis include a chest x-ray or urine LAM.
CD4 should also be done for all patients with advanced HIV disease and if CD4 is less than 200, screen for Cryptococcal Disease with a serum CRAG. If Gene x-pert shows rifampicin sensitive, substitute Rifampicin with rifabutin due to drug-drug interactions with Darunavir. However, continue with isoniazid, pyrazinamide and ethambutol and add the patient should be given pyridoxine and cotrimoxazole. If rifampicin resistant, please refer to MDR treatment unit for DST.

UPDATES IN HIV MANAGEMENT FROM CONSOLIDATED HIV GUIDELINES 2022(3)

HIVST
- Consent now 15 years and above.
- Target populations to include adolescent girls, Adolescent Girls, Youths and Women
- Blood based HIVST now in use

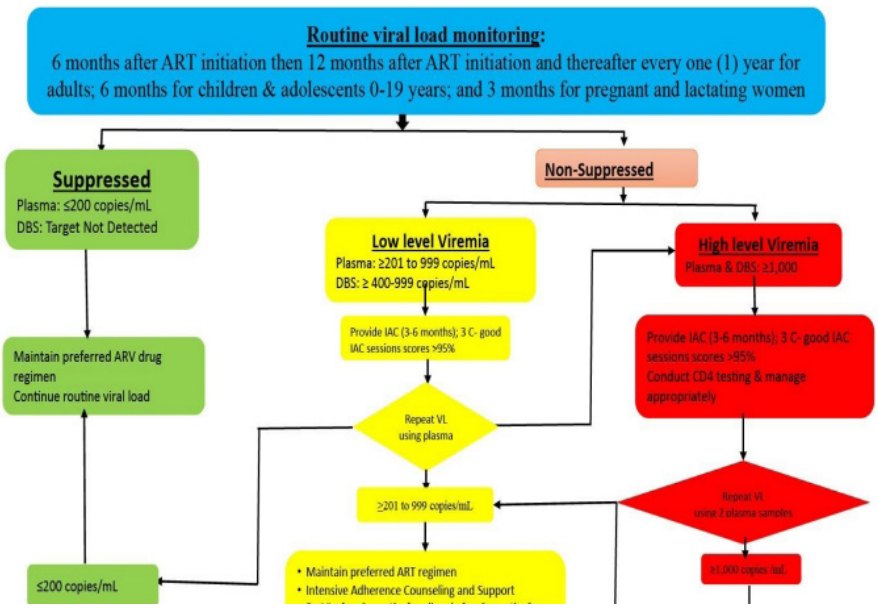
Index testing
- Biological Children recommended aged between 18 months to 19 years
- If using Caregiver-assisted oral screening to conduct index testing for biological children, then recommended ages are 2 years to 14 years

Dapivirine vaginal ring and Injectable Carbotegravir may be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination prevention approaches

PLHIV should be systematically screened for TB disease at each visit to a health facility with a combination of.
- Intensified Case finding (ICF)- form
- C-Reactive Protein (CRP) and or CXR

ART should be started at two weeks of initiating TB treatment, regardless of CD4 cell count, among people living with HIV with drug sensitive TB (Except when signs and symptoms of meningitis are present)

All people with HIV and drug-resistant TB, requiring second-line anti-TB drugs irrespective of CD4 cell count, should start ART as early as possible (within the first eight weeks) following initiation of anti-TB treatment
- For all patients diagnosed with CCM, ART should be stopped and restarted after 4-6 weeks.
- HIV-positive pregnant and breastfeeding women already on ART at ANC1 or MBCP: If HIV+ woman is already on ART at ANC1 or enrolled at MBCP, conduct a VL test at first ANC or MBCP visit.
- HIV positive pregnant and breastfeeding women: If newly initiated on ART at ANC, conduct a VL test at 3 months on ART. If VL supressed repeat VL every 3 months throughout pregnancy and until cessation of breastfeeding.
- All patients will have viral load resistance profile done prior to switching to alternative regimen.
- After every switch in treatment (after failure): The VL test should be done at 6 months after a switch to second- and third-line ART
- Third line ART patients: The VL test should be done every 6 months. If VL is un-suppressed, then genotype testing is recommended.
- A patient who has been on ART for more than 6 months and is responding to ART is considered virally suppressed at VL <200 copies/ml and 400 copies/ml in plasma and DBS respectively.
- The new changes to management of unsuppressed patients is illustrated below.



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