HAND BOOK OF
DR-TB PRACTICE

National TB Control Program

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Ministry of National Health Services, Regulation and Coordination (MNHSRC)

website: www.ntp.gov.pk

Government of Pakistan

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Preface

This Hand Book for programmatic management of drug resistant tuberculosis (DR-TB) is intended to be a reference tool for use by clinicians, Senior Fellows, chest specialists, DR-TB Physicians, public health decision-makers and technical and implementing partners committed to the prevention, care, diagnosis and treatment of drug-resistant TB. It provides brief and to the point information on day to day management of DR-TB cases and associated matters.

Effective management of drug-resistant TB requires input from those responsible for activities related to prevention, case detection, care and treatment, surveillance, drug management, and monitoring and evaluation of a program performance. The coordination of all these activities at different levels of National TB Program, Provincial TB programs, DR-TB management sites and BMUs are referred to as the 'programmatic management of drug-resistant tuberculosis' (PMDT). The contents of the hand book have been aligned with National DR-TB guidelines and recent recommendations from WHO companion handbook 2014 & WHO updated DR TB guidelines 2016.

The introduction of new diagnostic, treatment tools and new medicine for the management of drug-resistant TB is making a significant contribution to enable earlier diagnosis of multi drug-resistant TB (MDR-TB), and more effective treatment in cases were therapeutic options are very limited.

MDR-TB unit at NTP is always keen to keep updated all colleagues and professionals who are involved in TB/DR-TB care and services delivery. We hope that this hand book of DR-TB practice will be a useful tool for all colleagues as a quick reference and should be used along with National DR-TB Guidelines and ambulatory model of care for DR-TB.

Dr Nasir Mehmood Khan
National Program Manager
National TB Control Program,
Islamabad, June 2017

Scope of Update of 2016 DR TB Desk Guide

National TB Control Program, Pakistan always vigilantly adopts the WHO published guidelines on DR TB. In that context NTP updated these guidelines keeping in view the country context. WHO 2016 guidelines for DR-TB aimed to update the previous evidence-informed policy recommendations from 2011.

The scope of the current 2016 guidelines is different from the one of the 2011 guidelines. In 2011, the scope of the guidelines was broader and included programmatic aspects such as rapid diagnostics, patient monitoring with culture and sputum microscopy during treatment, use of antiretroviral therapy, and ambulatory/inpatient models of care. Recommendations were made also on the intensive phase and total duration of conventional regimens. This updated desk guide is not covering other aspects of policy guidance on the programmatic management of drug-resistant TB for which no new evidence had been published since the 2011 revision.

The main changes in the 2016 recommendations are as follows:

1. Regardless if isoniazid resistance is confirmed or not in a patient, MDR-TB treatment is recommended for all patients with rifampicin-resistant tuberculosis.
2. Regrouping on medicine used in conventional DR TB treatment based upon current evidence on their effectiveness and safety.
3. WHO has recommended shorter MDR-TB treatment regimen under specific conditions.
4. Specific recommendations are made on the treatment of children with rifampicin-resistant or MDR-TB.
5. Clarithromycin is excluded from the group of medicine to be used for the treatment of MDR-TB.
6. Recommendations on the role of surgery in DR-TB Treatment.

While there is no change in the following parameters;

- Definitions used in DR TB management
- Duration of injectable will remain same as of minimum 8 months and can be modified according to response of treatment.

- Minimum 20 months of duration of treatment and can be modified according to response to treatment
- Monitoring of DR-TB treatment and model of care as ambulatory care is preferred method
- Dosages of drugs used in DR TB treatment

So for above mentioned parameters previous NTP guidelines will continue to apply until further guidelines are updated.

Chapter 1- Definitions

Classification based on drug resistance *(adopted from WHO 2014 DR-TB companion handbook)*

Cases are classified in different types based on drug susceptibility testing (DST) of clinical isolates confirmed to be *M. tuberculosis*:

Mono-resistance: resistance to one first-line anti-TB drug only.

Poly-resistance: resistance to more than one first-line anti-TB drug, other than both isoniazid and rifampicin together

Multidrug resistance (MDR): resistance to at least both isoniazid and rifampicin.

Extensive drug-resistance (XDR): resistance to any fluoroquinolone, and at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to multi drug-resistance.

Rifampicin Resistance (RR): resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, in the form of mono-resistance, poly-resistance, MDR or XDR.

- Poly-/mono-resistant TB without rifampicin resistance. Some of these cases may have second-line anti-TB drugs added to their treatment. These patients should be treated in the program registered in separate ENRS as per program protocols.
- XDR-TB (confirmed or presumptive). Patients may be started on XDR-TB treatment on the basis of a laboratory diagnosis or, in its absence, because of significant risk.
- Patient based on previous H/O treatment (registration group): New, previously treated, Relapse patients, Treatment after failure, Treatment after lost to follow up, other previously treated, patients with unknown previous TB treatment history. For further information on these registration groups please refer to NTP Guidelines on PMDT

Definitions of Conversion & Reversion: The terms “conversion” and “reversion” of Culture as used here are defined as follows:

- **Conversion (to negative):** culture is considered to have converted to negative when two consecutive cultures, taken at least 30 days apart, are found to be negative. In such a case, the specimen collection date of the first negative culture is used as the date of conversion.
- **Reversion (to positive):** Culture is considered to have reverted to positive when, after an initial conversion, two consecutive cultures, taken at least 30 days apart, are found to be positive.
  For the purpose of defining *Treatment failed*, reversion is considered only when it occurs in the continuation phase.

Treatment Outcomes for RR-TB/MDR-TB/XDR-TB patients treated using second-line treatment

Cured:

- Treatment completed as recommended by the national policy (minimum 20 months with 18 months past culture conversion) without evidence of failure AND 3 (three) or more consecutive cultures taken at least 30 days apart are negative after the intensive phase
- For the purpose of declaring cure, the patient should have three consecutive negative cultures reported by the end of treatment, ensuring that cultures are done as per national policy.
- If there is one positive culture by the end of treatments, this positive culture should be followed by 3 negative cultures

Treatment Completed: Treatment completed as recommended by the national policy (minimum 20 months 18 months past culture conversion) without evidence of failure BUT no record that three consecutive cultures taken at least 30 days apart are negative after the intensive phase.

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

- lack of conversion by the end of the intensive phase, *or*
- bacteriological reversion in the continuation phase after conversion to negative, *or*
- evidence of additional acquired resistance to

fluoroquinolones or second-line injectable drugs, *or*
- adverse drug reactions (ADRs).

NOTE:

- If an MDR-TB patient has 4 positive cultures and is on month 6 of treatment, it is suggested to repeat DST to SLDs and act accordingly as per result. Please note that there may be a delayed response to treatment in XDR-TB patients.
- In case of reversion in continuation phase repeat DST to SLDs, continue with treatment and decide as per further response to treatment and in the light of result of DST.
- On the basis of baseline DST results there is only adjustment in treatment as per DST pattern and not to be declared failure.

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

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

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

Treatment success: The sum of *cured* and *treatment completed*

- For *Treatment failed*, lack of conversion by the end of the intensive phase implies that the patient does not convert within the duration of intensive phase applied by the program.
- If no specific duration is defined, an 8-month cut-off is proposed.
- For regimens without a clear distinction between intensive and continuation phases, a cut-off 8 months after the start of treatment is suggested to determine when the criteria for *Cured*, *Treatment completed* and *Treatment failed* start to apply provided that the patient had at least 18 months of treatment past culture conversion.

The sum total of *Cured* and *Treatment completed* is commonly used as an indicator of favorable outcome, or *Treatment success*. The outcome *Cured* is restricted to pulmonary bacteriologically confirmed TB cases only.

Factors Contributing to poor Treatment Outcome

(Lambregts-vanetal 1995)

HEALTH-CARE PROVIDERS: INAPPROPRIATE TREATMENT	DRUGS: INADEQUATE SUPPLY/QUALITY	PATIENTS: INADEQUATE DRUG INTAKE OR TREATMENT RESPONSE
Inappropriate guidelines Non-compliance with guidelines Absence of guidelines Poor training Financial disincentives Poor patient education No monitoring of treatment. Poor management of adverse drug reactions. Poor treatment support Poorly organized or funded TB control programmes.	Poor quality medicines Unavailability of certain medicines (stock-outs or delivery disruptions) Poor storage conditions Wrong dose or combination Poor regulation of medicines.	Lack of information Lack of means to adhere to treatment (transportation, food, etc.) Adverse effects Social barriers HIV Diabetes mellitus Under nutrition Malabsorption Substance abuse/ dependency Psychiatric condition

Interventions to prevent drug-resistant TB

There are five principal ways to prevent drug-resistant TB:

1. Early detection and high quality treatment of drug-susceptible TB.
2. Early detection and high quality treatment of drug-resistant TB.
3. Effective implementation of infection control measures.
4. Strengthening and regulation of health systems.

Chapter 2: Diagnosis of MDR-TB

2.1 General definitions for laboratory and DST *(adopted from WHO 2014 DR TB companion handbook)*

Phenotypic DST (conventional DST): Phenotypic testing determines if an isolate is resistant to an anti-TB drug by evaluating growth (or metabolic activity) in the presence of the drug. LJ and MGIT are examples of phenotypic DST.

Genotypic DST (molecular DST): Genotypic testing detects mutations in the TB genome associated with specific drug resistance. (Note: genotypic testing is also used to identify *M. tuberculosis* by detecting the presence of TB-specific mycobacterial DNA). G.Xpert and Line Probe Assay(LPA) are examples of Genotypic DST.

Direct testing: Direct testing refers to testing directly from a clinical sample (most commonly a sputum specimen). In direct DST, processed clinical samples are directly inoculated onto media with and without drugs, or processed for molecular testing.

Indirect testing: Indirect testing refers to testing performed on cultured isolates of *M. tuberculosis.*

Cross resistance: Mutations that confer resistance to one anti-TB drug may also confer resistance to some or all of the members of the same drug family, and less commonly, to members of different drug families.

TABLE 2.2 Summary of known cross-resistance between anti-TB drugs (Menzies R 2012)

Rifamycins	All rifamycins (rifampicin and rifabutin) have high levels of cross-resistance.
Isoniazid	There is high cross-resistance between isoniazid and ethionamide if the *inhA* mutation is present.
Aminoglycosides and polypeptides	· Amikacin and kanamycin have (very) high cross-resistance. · Amikacin/kanamycin and capreomycin can have cross-resistance, which is associated with the *rrs* mutation (clinical implications are not clear). · Streptomycin has low cross-resistance with amikacin/kanamycin and capreomycin.
Fluoroquinolones	· Fluoroquinolones are believed to have variable cross-resistance between themselves, with in vitro data suggesting that later-generation fluoroquinolones (levofloxacin, gatifloxacin, moxifloxacin) remain effective when lower generation fluoroquinolones (ofloxacin) are demonstrating resistance. · When levofloxacin (a third generation fluoroquinolone) is demonstrating resistance, it is not known if fourth generation quinolones (moxifloxacin and gatifloxacin) remain effective. · It is not known if cross-resistance is complete between fourth generation fluoroquinolones (i.e. between moxifloxacin and gatifloxacin), but is generally considered complete in vitro studies.
Thiamides	Prothionamide and ethionamide have 100% cross-resistance.

TABLE 2.3. **Summary of TB diagnostic and DST methods (non WHO endorsed tests are not included) and turnaround time**

Test Name	Turnaround Time	Description and comment
Conventional light microscopy – Ziehl-Neelsen microscopy	2 hours	Less sensitive than fluorescent/LED microscopy.
Conventional fluorescence microscopy	As above	Sensitivity is improved over light microscopy, observation time is reduced, also expensive
Light emitting diode (LED) Fluorescence microscopy	As above	LED microscopes improve sensitivity by 10% over conventional light microscopy. Observation time is similar to conventional fluorescence microscopy.
Lowenstein–Jensen(LJ) Solid Culture: Middlebrook and Cohn 7H10	3 weeks smear Positive 4–8 weeks smear Negative	Egg-based medium, inexpensive. Agar based medium. Less prone to contamination than Lowenstein– Jensen but more expensive.
Automated Liquid Culture	8 days smear positive 2–6 weeks smear Negative	Liquid culture systems. Fully automated systems that uses either fluorimetric or colourimetric detection
Molecular Testing 1)Line probe assay (LPA) 1st line and 2nd line also called HAIN MDR TB and HAIN MDR TB plus. Recently endorsed by WHO	1–2 day (direct on smear positive specimen only).	Two LPA have been developed to detect *M. tuberculosis* resistant to R and H either directly or indirectly. DNA targets are amplified by PCR and hybridized to immobilized oligonucleotide targets. Results are visualized colourimetrically. If it is a smear negative specimen, culture must be grown first. Moreover, LPA 2nd line to check susceptibility of FQ & Inj is also now a good tool.
Molecular Testing 2)Xpert MTB/RIF	2 hours	A fully automated test working in a dedicated platform performing detection of MTB and R resistance, using real time PCR. Results are available in less than two hours.

2.4 Interpreting rifampicin resistance results from molecular testing

- It is necessary that patient details such as treatment history and risk factors for drug-resistant TB should always be taken into account when interpreting laboratory results.
- WHO-recommended molecular methods detect mutations in the *rpoB* region of *M. tuberculosis* DNA, which are responsible for >95% of rifampicin-resistant strains.
- Given the resultant high sensitivity of molecular methods, a negative result generally excludes rifampicin resistance and no further testing to confirm negative results is required. In rare instances, when a patient is strongly presumed to have RR-TB even after a negative molecular test, follow-up testing using phenotypic culture-based DST may be used to test for rifampicin resistance resulting from a small number of mutations occurring outside the *rpoB* region.
- It might be a decision of the clinician that xpert test may be repeated where there is strong suspicion of DR-TB or in cases where RR is reported with low risk of DR-TB (Van Deun A, Maug AKJ et al 2013).
- A recent study has shown that an epidemiologically-significant proportion (close to 10%) of rifampicin-resistant strains in first failure and relapsed patients are missed by phenotypic DST (http://www.who.int/hiv/pub/tb/pulmonary/en/index)
- Emerging data show that Xpert MTB/RIF detects some rifampicin-resistant strains that are susceptible on phenotypic DST. Sequencing of these discordant results usually resolves in favor of Xpert MTB/RIF(WHO 2014).
- Therefore, Xpert MTB/RIF may be repeated in cases with very low risk of DR-TB (never treated for TB and having no close contact history), otherwise the result of Xpert should be considered reliable regardless of DST results and MDR-TB treatment should be initiated.

2.5 High risk groups G.Xpert testing (DR-TB Case Finding)

1. All retreatment cases (failures of CAT-I, relapse, lost to follow up and patients treated in private sector with unknown regimens and quality of drugs).
2. Close contacts of DR TB cases who are symptomatic
3. New TB cases on treatment and remain smear positive at 1st or subsequent follow-up. Smear negative cases if reported as smear positive on follow-up.
4. Children and extra pulmonary cases if sample has been taken by all possible efforts
5. HIV patients and other immunosupressed

2.6 Case finding for pre XDR/XDR-TB

DST to SLD should be repeated in MDR-TB patients on treatment in following scenarios:

1. Patient is not responding to treatment by month 6 (having 4 positive cultures) of treatment
2. Patient is not responding to treatment by the end of intensive phase (8 months is cut off point)
3. Patient has reverted to positive during continuation phase

2.7 Drug-resistant TB case finding in Pediatric Patients

- Sputum induction with nebulized hypertonic saline may facilitate collection of tracheobronchial secretions, especially in children who have a dry cough or no cough.
- Nebulization may often also be unsuccessful in young children. In this situation, gastric lavage is the most common procedure for collecting specimens for Xpert MTB/RIF or culture and DST.
- Children (like adults) swallow their tracheobronchial secretions so gastric lavage specimens may contain respiratory secretions, especially early in the morning before the child has had anything to eat or drink. Gastric lavage should not be used if only smear microscopy is being done (because of the low yield, it is not worth

the distress caused to the child);

- Gastric lavage should be used for examination by Xpert MTB/RIF or culture (WHO 1998). In settings with appropriate facilities and technical expertise, fibre-optic bronchoscopy may be the best next step if gastric aspirates fail.

Chapter 3: Treatment strategies for DR-TB

Definitions of Terms used to describe treatment strategies are as following:

Standardized Treatment: DRS data from representative patient populations are used to base regimen design in the absence of individual DST. All patients in a defined group or category receive the same regimen. Suspected MDR-TB should be confirmed by DST.

Individualized Treatment: Each regimen is designed based on the patient's past history of TB treatment and individual DST results.

NTP has adopted combination of standardized and individualized approaches.

Empirical Treatment: The term "empiric" is referred to the initiation of treatment prior to determination of a firm diagnosis of drug-resistant TB. Empiric regimens can be used for both standardized and individualized treatment strategies. For example, an empiric XDR regimen refers to the use of a regimen designed to treat XDR-TB before the diagnosis of XDR-TB is made.

3.1 Patient Education

- Patient education is an essential component of any DR-TB control program and is possible when there is trusting interpersonal communication between patients and medical personnel.
- Provision of emotional & social support to DR-TB patients may increase the likelihood of adherence.
- The organization of patient education should be considered equally with the other components of the DR-TB program (such as detection and diagnostics, drug supply, etc.)
- The patient's knowledge and understanding of his/her role in achieving a successful treatment outcome is an essential.

Component for Treatment Selection

The following should be covered for patient and treatment supporter education and support:

Table 3.1: Components of health education and deliverable messages:

S. #	Component	Deliverable Messages for education of Patient and Treatment Supporter
1	**Patient knowledge and understanding of Disease**	What is TB and DR TB, difference between TB&DR TB ,treatment for DR TB ,duration of injecatbles and treatment, monthly follow ups and routine investigations ,benefits of regular treatment and harms of interruption of treatment.
2	**Prevention of Spread of DR TB**	What measures are to be taken to prevent spread of DR TB at household and community level, close contact screening, importance of regular intake of medicine
3	**Information about possible side effects**	What most common side effects patient may experience and how to report side effects for management, appropriate ways of drug intake, like FQs should not be taken with milk or calcium, aluminum, magnesium and iron containing products. PAS should be swallowed with acidic liquid. The constituted Injecatble dosages should be used within 24 hrs and kept refrigerated.
4	**Patients Rights and Responsibilities**	Explain patient role in treatment completion, what are patient rights and responsibilities during whole period of treatment.
5	**Role& Responsibilities of Treatment Supporter**	Clearly explain the role and responsibility of TS, daily supervised DOT provision, identifying side effects, emotional support to patient and family, accompanying patient on monthly follow ups to PMDT site and on weekly basis to nearest DOTS center, support in contact tracing benefits of supervised treatment and benefits of successful treatment completion, incentives for treatment supporter(like Fbs)
6	**Psycho-Social support throughout Treatment**	Psychologist should assess psycho-social issues and address accordingly, provide counseling and support, refer where necessary, explain that all drugs and investigations related to DR TB treatment are free of cost and delivery of social support in terms of travel allowances and food baskets.
7	**Maintaining confidentiality**	The PMDT health team should explore the need of the patient to maintain strict confidentiality regarding their disease and all aspects of ethical consideration should be applied.

Regrouping of Medicine used in Conventional DR-TB Treatment

There is major shift in the grouping of medicine as compare to 2011 WHO guidelines. The explanation of regrouping of medicine is given below.

- A **second-line TB medicine (or agent)** refers to one which is only used to treat drug-resistant TB
- The **core second-line TB medicines (or agents)** refer to those in Groups A, B or C below

Table 3.2 : Medicines recommended for the treatment of rifampicin-resistant and multi drug-resistant

Group	Drugs	Abbreviation	Comments
A.Fluoroquinolones	Levofloxacin Moxifloxacin Gatifloxacin	Lfx Mfx Gfx	atifloxaxcin is not available in Pakistan and is associated with dysglycemia. The order of preference of use of FQ is: high dose Lfx(750 mg or more), MfX
B. Second-line injectable agents	Amikacin Capreomycin Kanamycin (Streptomycin)	Am Cm Km (S)	Resistance to Streptomycine alone, does not fulfil the definition of XDR-TB. Streptomycine can be used as the injectable agent of the core MDR-TB regimen if none of the three other agents can be used and if the strain can be reliably shown not to be resistant. To note, however, that DST results to Spreptomycine are not considered accurate or reproducible (WHO 2015)
C. Other core second-line agents	Ethionamide / Prothionamide Cycloserine / Terizidone Linezolid Clofazimine	Eto / Pto Cs / Trd Lzd Cfz	Two or more of medicines are to be included in the regimen of RR/MDR: **ethionamide** (or **prothionamide**), **cycloserine**, **linezolid** and **clofazimine**, usually in this order of preference
D. Add-on agents			
D1	Pyrazinamide Ethambutol High-dose isoniazid	Z E H-inh	
D2	Bedaquiline Delamanid	Bdq Dlm	These drugs are currently being used at selected sites only and their use will be extended gradually
D3	*p-aminosalicylic acid* Imipenem-cilastatin Meropenem Amoxicillin-clavulanate (Thioacetazone)	PAS Ipm Mpm Amx-Clv (T)	Ipm , Mpm and T are not used in Pakistan and not part of MDR TB regimen

Important Considerations:

- Linezolid has shown a statistically-significant treatment benefit in both RCT and in cohort studies in adult patients, with this benefit being most pronounced in patients with additional resistance to fluoroquinolones and with XDR-TB(Tang S et al 2015)
- One of the meta analysis (adult individual patient data, aIPD), showed improved likelihood of success (vs. treatment failure, relapse or death combined) in patients who had **pyrazinamide** included in their regimens. Reliability of DST for pyrazinamide is still a concern in poor resource setting countries.
- Isoniazid is recommended to be used alongside a full MDR-TB regimen in patients with RR-TB strains confirmed or suspected to be susceptible to isoniazid. Strains bearing mutations in the promoter region of the inhA gene may have a minimum inhibitory concentration (MIC) to isoniazid which is low enough to be overcome by high-dose isoniazid; in such settings the drug may still add benefit (Niehaus AJ,et al 2015). Levels isoniazid resistance associated with katG mutations, high-dose isoniazid may be less effective and therefore its routine use may not be warranted.
- The aIPD, as well as the study-level meta-analysis conducted , found no significant effect of PAS on treatment success. PAS is thus reserved for situations when there is no option to use other drugs(Ahuja SD et al 2012)

Example of Standardized Drug Code to use Drug Regimen

Following is a standard code for writing TB treatment regimens; please see the abbreviations provided above.

8Am-Lfx-Eto-Cs-Z, Lzd,B6/ 12Lfx-Eto-Cs-Z, lzd, B6

The initial phase consists of five drugs and lasts for eight months in most patients. Amikacin is given six days a week and all other drugs are given seven days a week. In this example, the phase without the injectable continues all the oral agents for a minimum of 12 months, for a total minimum treatment of at least 20 months.

3.3 Role of drug susceptibility testing

- DST to isoniazid, rifampicin, the fluoroquinolones, and the second-line injectable agents are considered accurate and reproducible
- When DST results are from a quality-assured laboratory, individual regimens can be based on the DST results for these drugs.
- The reliability and clinical value of DST for some first-line and most second-line anti-TB drugs is not fully determined.
- DST for ethambutol, streptomycin, pyrazinamide,Eto, presents problems with accuracy and reproducibility in most settings.
- **Patients who are diagnosed by Xpert as RR**:

  Patients will be enrolled in DR-TB register and full MDR TB treatment regimen (RR patients are treated as MDR) is selected which can be adjusted once full DST pattern becomes available.

- **Patients who have been confirmed to have DR-TB by DST:**

  At least one pre-treatment culture was positive; the collection date of the sample on which the culture was performed was less than 30 days before, or 7 days after, initiation of DR-TB treatment.(Ref. National DR TB guidelines 2014)

3.4 Basic Principles for MDR-TB regimen and delivery of Treatment

2: Principles of Constructing the Regimen for treatment of RR/MDR-TB

Following major principles should be adopted as per WHO guidelines 2016 while constructing an effective regimen

- MDR-TB regimen should be composed of at least five drugs likely to be effective. The composition includes four core second-line drugs plus pyrazinamide
- As a matter of principle one drug is chosen from group A, one from Group B, at least two from group C agents are included to

bring the total of effective second-line TB medicines in the core regimen to at ***least four*** during the intensive phase of the regimen

- The addition of pyrazinamide to the core second-line MDR-TB regimen is recommended, unless there is confirmed resistance from reliable DST, or well-founded reasons to believe that the strain is resistant, or other contra-indications for its use, particularly risk of significant toxicity. If resistant to Z is reported by MGIT then this drug should not be considered clean.
- If pyrazinamide is compromised or cannot be used, the regimen may be strengthened with an additional agent from group C or D (preferably D2, or if not possible, from D3)
- If the minimum of effective TB medicines can not be composed as above, an agent from group D2 and other agents from D3 may be added to bring the total to five
- Agents from group D1 are added if they are considered to add benefit (e.g. high-dose isoniazid in patients without high-level isoniazid resistance) and Ethumbitol if no resistance is reported
- Due to high prevalence of FQ resistant in our country among enrolled DR TB patients (about 40%), Lzd should be added in the regimen from the start of the treatment. The continuity of Lzd will depend upon susceptibility of FQ/Injectables. If DST shows susceptibility to FQ/Injectables then Lzd should be taken out of regimen.
- The close contacts of DR TB patient should be treated as per DST pattern of the index case

3.5: Principles of Constructing the Regimen for treatment of Pre XDR/XDR-TB

- In RR-/MDR-TB patients with confirmed or well-founded belief of resistance to medications from group A (fluoroquinolones) or group B (second-line injectable), substitution of drugs from add

on agents is required. If any of the components of the regimen – the four core second-line medicines and pyrazinamide – is considered not to be effective, additional agents from groups D2 or D3 are added.

- If the minimum of effective TB medicines can not be composed as above, an agent from group D2 and other agents from D3 may be added to bring the total to five (WHO 2016)
- WHO has advised that this is almost always necessary to strengthen the regimen when resistance to both groups A and B drugs (i.e. XDR-TB) is present.
- Patients **with MDR-TB should be treated using mainly ambulatory care models and long hospitalizations should be avoided.**

EXAMPLE: How to build an MDR TB Treatment Regimen

A 40 years old patient comes to your clinic with clinical symptoms of weight loss, fever, shortness of breath and cough. History taking and available documents reveal that he is taking first line ATT (2HRZE/4HR) and continues to be smear positive after 3 months. Moreover, patient feels that his breathlessness is worsening and also feels lethargic.
Being on high risk of DR TB, you decided to do G.Xpert testing and result came out with Rif resistance. What should be done?

Answer:

- This Rif resistance is true positive because patient is on ATT and not responding to treatment. This patient should be started on MDR TB treatment. Culture & DST to 1st line TB drugs, injecatbles and fluoroquinolones should be requested. Moreover, other relevant baseline investigations should also be requested.
- If there is no previous H/O 2nd line drugs use of more than 30 days and there is no contraindication to any of MDR TB treatment dugs , following standard MDR TB regimen should be prescribed and patient should be counseled along with complete psychosocial assessment and adherence to treatment should be fully addressed.

8Am-Lfx-Eto-Cs-Z,Lzd,B6/ 12Lfx-Eto-Cs-Z,Lzd,B6

Later after two and half months, DST result has arrived and patient is resistant to HRZ and FQ. In the light of this result you will add PAS and switch to Mfx, while E will also be added to the regimen.

NOTE: For further details please refer to National DR TB guidelines

Examples of construction of Regimen for XDR TB and MDR TB failures

Example 1: A patient with RR was enrolled on MDR-TB treatment and after 10 weeks DST result shows patient is also resistant to HRZE, FQ and Am. How the treatment regimen will be adjusted in this case?

As per WHO guidelines we have to make sure that patient is on four essential (most likely effective) drugs. Due to FQ resistance lfx will be replaced with Mfx, AM will be replaced with Cm. There is still need of two drugs from group C drugs i.e Lzd and Cfz due to possible cross resistance between Am/Km and Cm(WHO 2014) because these two different groups share the same genetic markers. There is also likelihood of additional resistance between the time sample was taken and arrival of DST result as patient was not on functionally effective drugs. At sites where BdQ is available, it is recommended to add BdQ in the regimen.

The duration of injecatbles may be extended up to 12 months or more in XDR TB patients . Moreover, because patient i s on Mfx, Cfz and BdQ simultaneously and is at risk of QT prolongation, therefore, screening and monitoring with ECG to avoid sudden arrhythmias is mandatory.

EXAMPLE 2 : A patient failed the standardized regimen of Z -Am-Lfx-Eto-Cs and remained smear & culture positive after eight months of treatment. The DST was requested when patient was at 4th month of treatment and result revealed resistance to HRZE-S-Am/Km-Cm-Lfx . What treatment regimen is recommended?
Answer: Since the time DST was requested and result arrived, patient may have developed resistance to Eto and remained only on one or two effective drugs. In this case following regimen is suggested:

12 Z,Mfx,Cm,Eto,Cs,Lzd,Cfz,Amx/Clv,PAS, BdQ(6),B6/12 Z,Mfx,Cm,Eto,Cs,,Lzd,Cfz, Amx/Clv,PAS,B6

Cm is used because patient has never used it before. If patient is resistant to low level of H then high dose H may be considered . Consider hospitalization, adjuvant surgery if disease is localized, proper treatment of co-morbid conditions, palliative care for suffering from disease.

In XDR TB Patients all possible efforts should be ensured to improve outcome as there is no other chance to save the life is left.

3.6 Type of Resistance and constructing DR-TB regimens

NOTE:

1. Please refer to National DR-TB guidelines on PMDT and Desk Guide for MDR-TB Physicians for more information
2. Previous history of treatment should be carefully taken as this will have significant impact on selection of most appropriate regimen.
3. Vit B6 should be added to all MDR-TB regimens and adherence problems, side effects should be identified earlier
4. Treatment failure/non responders should be evaluated in a timely manner
5. PMDT site expert review panel approach is always recommended and encouraged.

Table 3: Type of resistance and suggested treatment regimen in patents with RR/MDR/XDR-TB

S. #	Type of Resistance	Suggested initial Treatment Regimen	Comments
1	R, RE,REZ with or without S	8Am-Lfx-Eto-Cs-Z,H,Lzd/ 12Lfx-Eto-Cs-Z,H, Lzd	Lzd will be part of each conventional MDR TB regimen and should be discontinued if DST shows susceptibility to FQ/inj. Follow NTP DR TB guidelines Request culture and DST at the start of treatment. Repeat DST to SLDs if culture positive by month 4
2	HRZS	8Am-Lfx-Eto-Cs-Z,Lzd/ 12Lfx-Eto-Cs-Z,Lzd	If previous exposure to SLDs for > 30 days, use Lzd, Cfz and add on drugs from group D2 and D3 as per guidelines. In cases with previous exposure > 30 days, the total duration of treatment will be minimum 24 months. Lzd will be part of each conventional MDR TB regimen and should be discontinued if DST shows susceptibility to FQ/inj.
3	HRZE+-S,FQ	8Am-MfX-Eto-Cs- Z,Lzd,/ 16Mfx-Eto-Cs-Lzd,Z	As above, If resistance to FQ is not documented and there is previous exposure to FQ > 1 month then use higher doses of Lfx. In cases with previous exposure of FQ > 30 days, the total duration of treatment will be minimum 24 months. At selected sites where BdQ is available, please add BdQ to the regimen
4	HRZE+-S, Am/KM	8Cm-Lfx-Eto-Cs-,Lzd, Z,/ 16Lfx-Eto-Cs-lzd,Z,	According to new guidelines in patients with resistant to any of the injectables a drug from group C need to be added to complete 4 core drugs
5	HRZ,+-S, Eto	8Am-Lfx-Cs,Z, E,Lzd/ 16Lfx-Cs,Z,E,Lzd	E can be added to regimen if DST shows susceptibility to it. If Eto is reported resistant then do not use it rather switch Eto to Lzd

6	HRZE+-S, FQ,	12Cm-Mfx-Eto-Cs-,Z,Lzd,Cfz,BdQ(6)/ 12Mfx-Eto-Cs-,Z, Lzd, Cfz	In XDR-TB Lzd and Cfz are preferred. If not available then Amx/Clv, high dose INH should also be considered. Admit the patient if possible. NTP has implemented the introduction of new drug at selected PMDT sites(Bedaquilline) and will expand in near future. But at selected sites where BdQ is available, this should be part of XDR-TB regimen
7	HRZE+-S,FQ, Am/Km/Cm	12Cm-Mfx-Eto-Cs,Z,Lzd,Cfz/ 12Mfx-Eto-Cs,Z, Lzd, Cfz	In such cases Cm is preferred as not being used widely in the community or choice could be the injectable patient may not have used before. In patients with resistant to Am/Km/CM , WHO has advised to use S if susceptibility is confirmed(though DST to S not reliable). BdQ can be used in patients where resistant to all three injectables is documented.
8	RR/MDR/XDR- TB treatment failures or previous exposure to SLDs >30 days	8 Cm-Mfx-Eto-Cs-, Z,Lzd,Cfz,BdQ,PAS, Amx/Clv/ 16Mfx-Eto-Cs-, Z, Lzd, Cfz, BdQ,PAS, Amx/Clv	BdQ is currently being used on selected sites and will be gradually expanded to other sites. The duration of intensive in XDR-TB patients will be 12 months.

3.7 The effectiveness and safety of standardized Short Course MDR TB Treatment (9-12 months)

WHO has recommended to use standard Short Course (lasting 9-12 months) in following patients;

- Adults or children with Rifampicin-resistant (RR) or multidrug-resistant TB (MDR-TB)
- Patients in whom resistance to fluoroquinolones and second-line injectable agents has been excluded
- Who have not exposed to 2nd line drugs > one month
- Resistant to FQ or Injectable is highly unlikely,

WHO has not recommended standard short course regimen in pregnancy and in extra pulmonary patients.

It is recommended that patients must be tested for susceptibility or resistance to fluoroquinolones and to the second-line injectable agent before being started on a shorter MDR-TB regimen. The use of rapid tests would be valuable to decide within a few days which patients would be eligible for shorter MDR-TB regimens. In patients with confirmed rifampicin-resistant TB or MDR-TB, the Genotype MTBDRsl line probe assay (http://www.hain lifescience.de) may be used as an initial direct test, over phenotypic culture-based DST, to detect resistance to fluoroquinolones and to the second-line injectable drugs.

The shorter MDR-TB treatment regimens is standardized in content and duration and divided into two distinct phases.

Firstly, an intensive phase of 4 months (extended to 6 months in case of lack of sputum smear conversion) with following drugs: moxifloxacin, **Amikacin, Ethionomide, clofazimine**, high-**dose isoniazid, pyrazinamide,** and **ethambutol.**

Followed by a continuation phase of 5 months with the following medicines:

moxifloxacin, clofazimine, ethambutol, and **pyrazinamide.**

NTP is planning to commence patients on short course MDR TB treatment by september 2017 at selected PMDT sites depending upon the availability of LPA 2nd line. NTP also plans to gradually expand short course MDR-TB treatment at all PMDT sites by 2020.

3.8 Enrolling/Registering patient on Treatment

The monitoring of treatment and the management of adverse effects may have to be more intensive in patients with pre-existing conditions or conditions identified at the initial evaluation. On the basis of evaluation necessary referrals should be made to get consultation on relevant co-morbid conditions.

Pretreatment Screening for Initial Medical Evaluation

1. HIV
2. Diabetes Mellitus
3. Hypertension
4. Renal insufficiency
5. Acute or chronic liver disease
6. Mental illness
7. Drug/alcohol dependency
8. Pregnancy -Breast feeding
9. Seizures
10. Malnutrition
11. Thyroid disease

Minimum Criteria to be considered before Initiation of Standard MDR-TB Treatment

- Is the patient pregnant?
- Is there jaundice or a known liver problem? Is there alcohol abuse or substance abuse?
- Is there chronic illness, such as HIV, diabetes mellitus, heart or kidney disease,
- Is the patient a household contact of a patient with confirmed extensively drug resistant TB?
- Has the patient ever taken second-line anti-TB drugs?

YES to any question? ➡Patient will need further evaluation and adjustments may be needed to the MDR-TB regimen and monitoring needs to be increased

NO to all? ➡No modifications to the MDR-TB regimen

Moreover, following should be ensured

- Follow protocols that who should be admitted to the hospital for the start of treatment versus who should be started as ambulatory patient
- Development of linkages with the BMU/DOTS center where patient can go for weekly follow up and get support for minor side effects
- Identification of the appropriate directly observed therapy (DOT) Provider/Treatment supporter (preferably a trained health worker)
- Teach the patient about treatment delivery and psycho-social support
- Educate the patient about infection control measures at home & in community

3.9 Duration of Treatment – Intensive and Continuation Phase

Duration of Treatment

- The recommended duration of treatment is minimum 20 months, with 18 months after culture conversion, with no evidence of failure.
- The treatment is divided into Intensive and Continuation phases.
- Extension of therapy to 24 months may be indicated in chronic cases with extensive pulmonary damage.

Completion of Injectable Agents-"Intensive Phase"

"The recommended duration of an injectable drug during the intensive phase is guided by the culture conversion. An injectable agent should be used for a minimum of eight months with at least four negative cultures and given that patient remains converted".

- Missing or contaminated results would not be counted.
- Once patient is converted and if there is one positive culture followed by at least two consecutive negative cultures and patient is clinically doing well, stable and improving, this positive culture may be ignored.
- If there are two positive cultures after conversion, then it should be followed by at least 4 negative cultures.
- In the case of XDR-TB the injectable should be used for at least 12 months with 6 negative cultures.

Example: MDR-TB patient has converted at month 5, as per national policy (5+18) month 23 is the end of treatment for this patient. To declare outcome of this patient (at month 23), MDR-TB Physician will have culture results of month 20, 18 and 16 available (bimonthly cultures). If these available results are negative and patient has no signs of failure then this patient may be declared cured. If one culture is positive, this must be followed by three negative cultures.

3.10 Extra-Pulmonary & Central Nervous System DR-TB

Extra-pulmonary drug-resistant TB is treated with the same strategy and duration as pulmonary drug-resistant TB.

In case of central nervous system involvement and is infected with drug-resistant TB, then the regimen should use drugs, which have adequate penetration into the central nervous system.

Following drugs have adequate penetration into the central nervous system:

- Isoniazid, pyrazinamide, prothionamide / ethionamide & cycloserine.
- Kanamycin, amikacin and streptomycin are effective only in the presence of meningeal inflammation. Additionally, the penetration of capreomycin is less studied and not well determined.
- PAS and ethambutol have poor or no penetration.
- The fluoroquinolones have variable cerebrospinal fluid

penetration, while moxifloxacin has slightly better penetration.

- For clofazimine or clarithromycin there is no data available.
- Linezolid is believed to penetrate the central nervous system, and has been used in meningitis treatment (Tuberculosis drug information guide. 2nd edition. California Department of Public Health; 2012..)

3.11 Recommendations of Surgical Intervention in the Treatment if Drug Resistant TB

- The role of pulmonary surgery is beneficial to reduce the amount of lung tissue with intractable pathology and to reduce bacterial load and thus improve prognosis.
- In patients with rifampicin-resistant or multi drug-resistant TB, elective partial lung resection (lobectomy or wedge resection) may be used alongside a recommended MDR-TB regimen
- It is considered an adjunct to chemotherapy and appears to be beneficial for improved outcome. It is not indicated in patients with extensive bilateral disease.
- Minimum two months of therapy should be given prior to resection surgery to decrease the bacterial infection in the surrounding lung tissue.
- Surgery should be performed by a trained thoracic surgeon in patients with localized disease and result may reduce morbidity and mortality. Prognosis could be better when partial lung resection is performed after culture conversion as compared to patients who underwent pneumonectomy

3.12 Corticosteroids

- Corticosteroids can be beneficial in conditions like severe central nervous system or pericardial involvement.
- Corticosteroids may also alleviate symptoms in patients with an exacerbation of obstructive pulmonary disease.
- Therefore corticosteroids should only be used if clearly indicated and if the patient is on an adequate effective regimen.

3.13 Treatment of Mono & Poly Drug Resistant Strain (other than RR & MDR-TB)

- Treatment of mono- and poly-resistance with WHO

standardized first-line anti-TB drug regimens has been shown to increase the risk of treatment failure and even worse, amplification (acquisition of additional resistance) to multidrug resistance *(Jacobson KR et al 2011).*

- The suggested treatment regimens for mono and PDR cases as per resistance pattren are discussed in table 3.5 and for more details refer to National DR TB guidelines.
- It is essential that always use Xpert MTB/RIF at month 0, 2, and 3 and if rifampicin resistance is found switch to full MDR-TB treatment.
- The basic principle is to add at least 3, ideally 4, likely effective drugs in the regimen.
- DST results at baseline and previous treatment history should be considered to design the appropriate regimen.
- It is imperative to perform Xpert in all mono and PDR cases, before enrolling them on treatment (this excludes cases with R, RZ, RZE as such cases require full MDR-TB treatment).

Table 4: Suggested Treatment Regimen in Patents with Mono and Poly DR-TB Cases (other than RR)

S. #	Type of Resistance	Suggested initial Treatment Regimen	Comments
1	H	RZE,Lfx(for new patients)	G.Xpert at month 0.Then smear culture and Xpert should be performed at month 2. For more information see section. In patients where InhA gene mutation is reported or low level resistant to INH is reported High dose INH should used.
2	H	3Am,Lfx,R,Z,E/7 Lfx, R,Z,E(for previously treated patients)	As above, Smear and culture monthly until patient is on Inj. For more information see section
3	HE or HES	3 Am, Lfx, R,Z/7 Lfx, R,Z.	G.Xpert at month 0, smear and culture monthly until patient is on Inj. Xpert at month 2. For more information see section???
4	HEZ+,-S	3Am,Lfx,Eto,R,Z/ 12 Lfx, Eto, R,Z	WHO has recently advised to use Inj for 6 months with extensive disease at the beginning. Perform Xpert Rif/MTB at month 0, 2 and 3. Perform smear and culture monthly during intensive phase while patient is on injectable and culture bimonthly (or otherwise as indicated) during continuation phase.

Treatment Outcomes for Mono or Poly Drug Resistant Cases

Outcome	Definition
Cured:	A mono or PDR-TB patient who has completed treatment and bacteriological follow up without evidence of failure and has been consistently culture negative with at least three results for the final 6 months of treatment.
Completed:	A mono or PDR-TB patient who has completed treatment and bacteriological follow up without evidence of failure , but does not meet the definition of cure due to lack of bacteriological result(fewer than 3 cultures were performed in the final 6 months of treatment).
Failure:	Need for treatment change (adding at least 2, 2nd line ATT because of any of the following · Lack of clinical improvement and culture conversion after 3 months of treatment, or · Amplification of resistance · Bacteriological reconversion (at least two positive cultures at least 30 days apart) after conversion, or · If a clinical decision has been made to terminate treatment early due to poor response or adverse events.
Lost to follow up, death and transferred out will be declared as per standard NTP MDR TB protocols	

3.14 Registration and Management of Mono & PDR Cases

These cases will require some of the 2nd line drugs follow up and monitoring by smear, culture and repeating Xpert. Therefore, such cases should be managed at PMDT sites as a separate cohort and should be reported on separate ENRS as per protocols.

3.15 Treatment of drug-resistant TB in Pregnancy, breast feeding and children

Below is the treatment outline of DR-TB in pregnancy, breast feeding and children. More information is available in management of adverse events chapter in National DR-TB guidelines.

Pregnancy

- Pregnancy is not a contraindication for treatment of active drug-resistant TB, but poses great risk to the lives of both the mother & fetus.

- All female patients of child bearing age should be tested for pregnancy upon initial evaluation.
- The risks and benefits of treatment should be carefully considered, with the primary goal to protect the health of the mother and child, both before and after birth.
- Most pregnant patients should be started on treatment as soon as the diagnosis is made
- Treatment may be delayed until the second trimester when the patient is very stable with minimum disease as majority of taratogenic effects occur during 1st trimester. Risks and benefits should be carefully evaluated
- Other family members, especially the father may need to be consulted depending on the relevant family, religious, cultural and social dynamics
- Treat with three or four oral second-line anti-TB drugs which are likely to be highly effective plus pyrazinamide and regimen should be reinforced with an Injectable agent and other drugs as needed immediately postpartum *(WHO 2014)*
- Despite limited data on safety and long-term use of fluoroquinolones (cycloserine, paraaminosalicylic acid (PAS) and amoxicillin/clavulanate) in pregnancy, they are considered the drug of choice for MDR-TB treatment during pregnancy
- Avoid Aminoglycosides as can be particularly toxic to the developing fetal ear and there is little experience or evidence of the use of capreomycin in pregnancy. The risks/benefits of its use should be discussed with the mother. The option of using capreomycin thrice weekly from the start can be considered to decrease drug exposure to the fetus (WHO 2014). The risks and benefits should be discussed with mother.
- Ethionamide may be avoided as can increase the risk of nausea and vomiting associated with pregnancy, and teratogenic effects have been observed in animal studies.
- The termination of pregnancy may be considered if would carry

a significant risk to her life

- If the injectable agents, ethionamide/prothionamide, or other drugs were withheld because of the pregnancy, they can be added back postpartum to make a more complete regimen (WHO 2014)
- The injectable agent can be given for three to six months postpartum even in the middle of treatment. Alternatively, if the patient is doing well and past the normal eight-month period for the injectable agent, it need not be added (WHO 2014)
- Please be informed of the principle of never adding single drug to failing regimen
- Total duration is same as for MDR-TB
- The child should receive Bacillus Calmette–Guérin (BCG) vaccination at birth as per WHO policy.

Group 5 drugs and Pregnancy (adopted from WHO 2014 companion handbook and PIH 2013 guidelines)

Clofazimine (CfZ) safety class C
Use in pregnancy/breastfeeding: Not recommended due to limited data (some reports of normal outcomes, some reports of neonatal deaths). Avoided with breast feeding due to pigmentation of the infant.

Linezolid(lzd) safety class C
Use in pregnancy/breastfeeding: Not recommended during pregnancy or breast feeding due to limited data.

Bedaquiline (Bdq) safety class C
Use in pregnancy/breastfeeding: Not recommended during pregnancy or breast feeding due to limited data. Reproduction studies performed in rats and rabbits have revealed no evidence of harm to the fetus.

Clarithromycine (Clr) safety class C- Avoid if possible, may be teratogenic

Breast feeding

- Most anti-TB drugs will be found in the breast milk in concentrations that would equal only a small fraction of the therapeutic dose used in an infant. Any effects on infants of such exposure during the full course of drug-resistant TB treatment have not been established (WHO 2014).
- If any adverse events have been observed due to breast feeding while on DR-TB treatment, feeding with formula milk may be considered
- A woman who is breast feeding and has active drug-resistant TB should receive a full course of anti-TB treatment (WHO 2014. Timely and properly applied chemotherapy is the best way to prevent transmission of tubercle bacilli to the baby.
- The mother and her baby should not be completely separated. However, if the mother is sputum smear positive, the care of the infant should be left to family members until she becomes sputum smear negative, if this is feasible
- When the mother and infant are together, this common time should be spent in well-ventilated areas or outdoors. The mother should use a surgical mask until she becomes sputum smear/culture negative.

Contraception

- There is no contraindication to the use of oral contraceptives with non rifamycin containing regimens
- Patients should be advised to take their contraceptives apart from times when they may experience vomiting caused by the anti-TB treatment medications.
- For patients with mono and poly-resistant TB but who are susceptible to rifampicin, the use of rifampicin interacts with the contraceptive drugs resulting in decreased efficacy of protection against pregnancy.
- While receiving riafampicin during treatment, contraceptive pills containing high dose of estrogen(50 microgram) should be recommended

- Patients should be aware that condom use is not as effective as contraceptive pills, especially when not used correctly.
- Patients should be referred to specialized center to discuss and opt the best, long term method of contraception as per suitability

Management of DR-TB in Children:

- Children with drug-resistant TB generally have initial resistance transmitted from a primary case with drug-resistant TB. The risks and benefits of each drug should be carefully considered while designing a regimen and family should be involved and counseled. Drug-resistant TB is life-threatening, and no anti-TB drugs are contraindicated in children. Children who have received treatment for drug-resistant TB have generally tolerated the second-line drugs well.
- In general, anti-TB drugs should be dosed according to body weight (See Annex for weight based dosing). Monthly monitoring of body weight is therefore especially important in paediatric cases, with adjustment of doses as children gain weight.
- Expert opinion is that all drugs, including fluoroquinolones, should be dosed at the higher end of the recommended ranges whenever possible. Levofloxacin is not recommended under 10 kg ,but risks and benefits should be discussed with mother and ¼ of 250 mg tab can be given twice a day .Ethambutol should be dosed at 15 mg/kg, and not at 25 mg/kg as sometimes used in adults with drug-resistant TB, as it is more difficult to monitor optic neuritis in children.
- Tablets can be given with food or something sweet to make the taste
- WHO on the basis of paediatric individual data analysis describes in guidelines 2016, that children with bacteriologically-confirmed MDR-TB as compare to clinically diagnosed were more likely to have severe disease, having statistically-significantly greater levels of malnutrition and severe disease on chest radiography.

- In children with mild forms of disease, the harms associated with the group B medications (second-line injectable agents) outweigh potential benefits and therefore group B medications may be excluded in this group of children.
- The use of group B (2nd line injectables) medicine in children may be excluded who are clinically diagnosed or with mild form of disease as the harms associated outweigh potential benefits.
- In case of additional resistance to fluoroquinolones, group B medication should be used
- The use of medicine from group D2 are not recommended by WHO so far

3.16 Management of Contacts of DR-TB:

Studies have shown that close contacts of MDR-TB patients who develop active TB almost always have MDR-TB, even if the exact pattern of resistance is not always the same *(*Becerra MC et al 2012*).* Therefore, Household contacts are excellent candidates for empiric MDR-TB treatment.

Following are details of management of close contacts of DR-TB based on WHO companion handbook DR-TB 2014.

Contacts with bacteriological confirmed TB, but without confirmation of MDR-TB:

- All the symptomatic close contacts of DR-B patients should be tested by Xpert, irrespective of smear microscopy results.
- Culture and DST should also be requested to further confirm pattren of resistance.
- If there is no Rif resistance on Xpert , these patients should be empirically treated with the same regimen as the index patient while DST is pending.
- Clinical judgment can be used to decide if isoniazid and rifampicin should be added while awaiting DST results.
- If the DST eventually shows pansuceptibility, the contact can be switched to a regimen of first-line drugs. But in the vast majority of cases, family members are infected with the same

MDR strain *(*Parr JB1, Mitnick CD et al 2014, Shah NS1 et al 2014*).* It is not recommended to under treat close contacts of DR TB patients until full pattren of DST is available.

Contacts with extra pulmonary TB

- Certain forms of extra pulmonary TB are often culture negative. Contacts with evidence of these forms of extra pulmonary TB should therefore be started empirically on MDR-TB treatment after collecting samples of pleural tissue, as well as peritoneal and cerebrospinal fluid for TB culture.
- Xpert MTB/RIF can be done on a number of body fluids and tissues.
- Close contacts with evidence of extra pulmonary TB should be started on empiric treatment with the same regimen as the index patient, with the possible addition of isoniazid and rifampicin.

Contacts with smear/ culture negative TB:

- It is often counter productive to insist on laboratory confirmation in all patients. This is particularly true for children, who are often unable to produce good sputum samples.
- Once a child contact of MDR-TB meets the criteria for diagnosis with active TB, he/she should be started empirically on DR TB treatment with the same regimen as the index patient. Isoniazid and rifampicin can be added to the regimen.

Management of Latent TB infection in close contacts of MDR-TB patients:

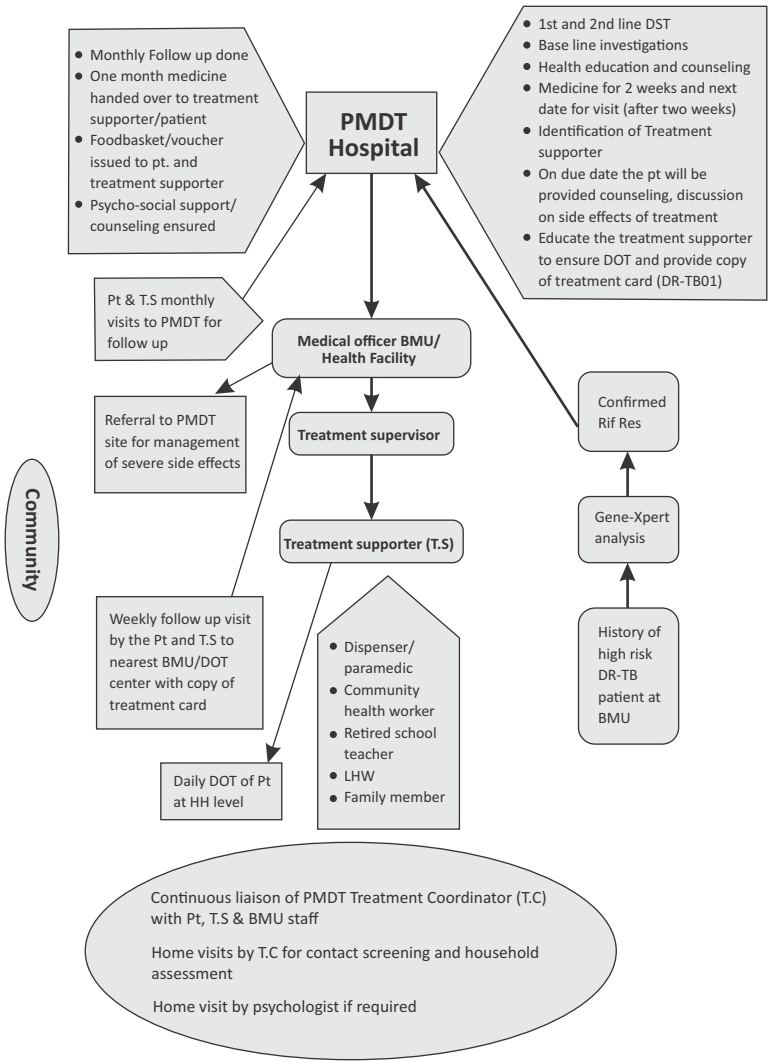
- Unfortunately, there have been very few studies of the use of second-line anti-TB drugs to prevent disease in MDR-TB contacts *(*van der Werf et all 2012*).*
- Due to lack of evidence, there is no consensus about whether close contacts of MDR-TB patients should be given preventive therapy, and if so, which drugs should be given.
- On the basis of the currently available evidence, the universal use of second-line anti-TB drugs for the treatment of latent TB

in MDR-TB contacts is not recommended.

Management of Mycobacterial Disease Other Than Tuberculosis (MOTT)

- There is no specific definition that describes MOTT.
- Diagnosis of MOTT is established by isolation of MOTT from a clinical specimen.
- In DR TB practice if a Rif resistant case on treatment is identified as MOTT by culture/DST, should be continued with treatment with addition of Clrarithromycin Tab to the regimen.
- It is important to sought expert opinion from chest specialist for management.
- The response to treatment in such cases is normally observed by clinical and radiological improvement as MOTT may grow on subsequent culture/DST for longer period.

MDR-TB Ambulatory Management Model –Flow Chart



Chapter 4 : Monitoring Treatment Response

- Monitoring the progress and response of SLD treatment and identifying failure of treatment that indicates the need for a change in treatment strategy is an important practice of MDR TB management. The response to second line anti-TB drugs is often slow with the median time to conversion being three months *(1)*. Initial culture conversion is not always maintained in some patients.
- *Molecular tests such as Xpert MTB/RIF and line probe assays should not be used to monitor response to treatment*.
- Patients should be monitored closely for signs of treatment failure. Monitoring response to treatment is done through regular history taking, physical examination, chest radiograph and laboratory monitoring (smear & culture). The classic symptoms of TB – cough, sputum production, and fever and weight loss – generally improve within the first few weeks. Cough and sputum production can persist after sputum conversion in patients with extensive lung damage, but even in those with extensive lung damage improvement is often seen within a month or two of effective treatment.
- The recurrence of TB symptoms after sputum conversion may be the first sign of treatment failure. For children, height and weight should be measured monthly to ensure that they are growing normally.
- Performing direct smear microscopy on monthly basis on at least two consecutive specimens (one collected on fasting and spot sample).
- Sputum smear and culture examinations are also dependent on the quality of the sputum produced, so care should be taken to obtain adequate specimens and transporting them to the laboratory according to standard procedures to maintain viability of the bacilli to get a valid culture result.
- Persistently positive sputum and cultures for acid-fast bacilli (AFB) should be assessed for non TB mycobacteria (NTM) as colonization or infection with NTM in a damaged lung secondary to TB is not uncommon. In such cases, though drug-resistant TB may be adequately treated, treatment may need to be directed towards the NTM as well (WHO 2014).

4.1 Monitoring and Evaluation Testing During DR TB Treatment

Health Education and Counseling	At the time of enrolment and on monthly follow up
Clinical Evaluation & weight	Monthly
Smear Microscopy	Monthly
Culture	Monthly Monthly during intensive phase, then every other month during continuation phase or as decided by the DR TB physician
DST	At baseline, then for patients who remain culture positive at month 4-6 or if reverted to positive culture any time during continuation phase
Chest Radiograph	Baseline ,then every 3-6 months or earlier as decided by DR TB physician
CBC	At baseline or later if indicated
S. Creatinine	Baseline then monthly while patient is on injectables ,specially for patients who have diabetes or renal disease
Electrolytes	Baseline ,then monthly while patient is on injectables
TSH	At baseline then every 3-6 months, especially when patient is taking Eto/Pto and PAS together. Monitor for signs and symptoms of hypothyroidism regularly.
Liver Enzymes	At Baseline then periodically in patient taking PZA for extended period
HIV	At baseline and repeat if indicated
Pregnancy Test	Initially for every female patient of child bearing age (married),then repeat if indicated. Family planning during treatment is important
Audiometry	Monthly during intensive phase, periodically afterwards
Visual Test	At baseline and Monthly if on E, otherwise use visual testing charts monthly , refer to opthlamologist where indicated
DOT & Treatment supporter assessment	Monthly, ensure that DOT provider is taking care of all aspects of daily DOT and assess the effectiveness and suitability of DOT provider/treatment supporter

Ethambutol or linezolid: in case of any complaint of visual impairment / visual changes (test all patients at baseline as a certain percentage of people have color blindness as a genetic variation; repeat if there is suspicion of a change in vision) refer patient to ophthalmologist.

4.2 Follow –up-Management of Treatment Interruption

Assess patient as following

- Fully evaluate the patient i.e take full history, review clinically, radilogically including review of regimen, symptoms, signs, other clinical indicators and adherence to treatment
- Exclude other illnesses leading to decreased absorption of drugs or immune suppression.
- Review the DOT and performance of treatment supporter
- Listen to the problems of patient, educate the patient and treatment supporter, informing about current status of response to treatment and offer any required support.

4.3 Follow–up-Management of Treatment Interruption

If interruption is more than two weeks but less than two months

Assess		Act	
Clinical	**Laboratory**	**Regimen**	**Other**
Assess for deterioration, and record Review the adherence supervision	Sputum for smear and culture Request for DST if Smear or culture positive on retrieval	Continue the same regimen	Educate on adherence ,listen and resolve the patient problem Consider changes in supervision arrangements

Comments:

If culture negative: Continue the same regimen**,** add the missed duration in the total duration of treatment

If Culture Positive: Continue the treatment**,** ask for DST if previously not requested due to patient being smear negative. Discuss case in review panel meeting, later review DST and decide to adjust accordingly.

Patient with Interruption of Treatment > two months:
If interruption is for more than two months, the patient should be declared as lost to follow up and managed according to National Guidelines.

4.4 Follow-up after successful completion of MDR-TB treatment

At a minimum schedule visits should be for the patient at three, six and 12 months post treatment (WHO 2014). Also, instruct the patient to return to the clinic if there is cough of more than two weeks, or persistent fever and weight loss or for any medical concerns. Check sputum culture at six and 12 months after treatment completion date to evaluate for possible recurrence or whenever relapse is suspected.

4.5 Pharmacovigilance in programmatic management of DR-TB

- Many of the second-line anti-TB drugs are more prone to cause toxic reactions in patients than first-line drugs, making pharmacovigilance more important in the programmatic management of drug-resistant TB.

- Pharmacovigilance is defined by WHO as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem".
- Three methods of pharmacovigilance are identified in the Pharmacovigilance handbook: (i) spontaneous reporting, (ii) targeted reporting, and (iii) cohort event monitoring (CEM). The first two methods are normally used into national program of routine Pharmacovigilance. CEM is best to use for introduction of new drug/regimen.
- It is therefore mandatory that all PMDT site should collect the data/information of any minor to major side effect/adverse event and record it properly as per national guidelines.

4.6 Palliative care after Termination of Treatment in M/XDR-TB Patients

- ü *Supportive care* is the only option left after suspension of treatment.
- ü Adequate nursing care , provision of ancillary medicine by BMU and symptomatic relief if patient is severely ill.
- ü Nutritional support (if budget available) or linking the patient to NGO support
- ü Psychosocial support and continuing health education by peer educators.
- ü Strict infection control measures must be appropriately applied to prevent spread of disease to contacts including health-care workers (
- ü **MDR-TB treatment termination is not abandonment of the patient.**

Chapter 5: Management of Adverse Effects

The initial evaluation serves to establish a baseline and may identify patients who are at increased risk for adverse effects. The monitoring of treatment and the management of adverse effects must be more intensive in patients with pre-existing conditions or conditions identified at the initial evaluation (diabetes mellitus, renal insufficiency, acute or chronic liver disease, thyroid disease, mental illness, drug or alcohol dependence, HIV infection, pregnancy, lactation and others).

Recording and reporting of minor to major side effects as per NTP guidelines is mandatory for all MDR TB Physicians

Table 5: Adverse Events and Management

Adverse Effect	Suspected Agent	Suggested Management	Comments
Rash, allergic reaction and anaphylaxis	Any drug	1. For serious allergic reactions, stop all therapy pending resolution of reaction. In the case of anaphylaxis manage with standard emergency protocols. 2. Eliminate other potential causes of allergic skin reaction (like scabies or other environmental agents). 3. For minor dermatologic reactions, various agents may be helpful and allow continuation of the medication. They include: Antihistamines Hydrocortisone cream for localized rash Prednisone in a low dose of 10 to 20 mg per day for several weeks can be tried if other measures are not helpful. Phototoxicity may respond to sunscreens, but these can also cause rash Dry skin may cause itching (especially in diabetics); liberal use of moisturizing lotion is recommended. Dry skin is a common and significant problem with clofazimine. 4. Once rash resolves, reintroduce remaining drugs one at a time, with the most likely culprit last. Consider not re-introducing in the challenge any drug that is highly likely to be the culprit. 5. Suspend permanently any drug identified to be the cause of a serious reaction.	1. History of previous drug allergies should be carefully reviewed. Any known drug allergies should be noted on the treatment card. 2. Flushing reaction to rifampicin or pyrazinamide is usually mild and resolves with time. Antihistamines can be used. Hot flashes, itching, palpitations can be caused with isoniazid .If this occurs advise patients to avoid foods that precipitate the reaction. 3. Hives (urticaria) can be caused by any drug. To identify the drug, introduce the drugs one at a time. In the case of hives a desensitization attempt can be made; methods are described elsewhere. 4. Any drug that resulted in anaphylaxis or Steven-Johnson syndrome should never be reintroduced to the patient, noteven as a challenge.

Nausea and vomiting	Eto, Pto, PAS,H, E, Z, Amx/ Clv,Cfz	1. Assess for danger signs including dehydration, electrolyte disturbances and hepatitis; initiate rehydration therapy if indicated and correct any electrolyte disturbances. If blood in the vomit, check haemoglobin and treat possible bleeding ulcers. 2. Initiate stepwise approach to nausea and vomiting. **Phase 1: Adjust medications and conditions** **without lowering overall dose:** Give the Eto/Pto at night Give Eto or PAS twice or thrice daily. Give a light snack (biscuits, bread, rice, tea) before the medications. Give PAS 2 hours after other anti-TB drugs **Phase 2: Start antiemetic(s):** Metoclopramide 10 mg 30 minutes before anti-TB medications. Ondansetron 8 mg 30 minutes before the anti-TB drugs and again 8 hours after. Ondansetron can either be used on its own or with metoclopramide. (If ondansetron is not available, promethazine can be used) For refractory nausea 24 mg 30 minutes before the dose can be tried. **Phase 3: Decrease dose of the suspected drug** by one weight class if this can be done without compromising regimen. Rarely is it necessary to suspend the drug completely.	1. Nausea and vomiting is universal in early weeks of therapy and usually abate with time on treatment and adjunctive therapy. Some nausea and even vomiting may need to be tolerated at least in the initial period and patient should be advised about this side effect. 2. Creatinine and electrolytes should be checked if vomiting is severe. Give IV fluids and replace electrolytes as needed. 3. Another strategy is to stop a responsible medicine for two or three days and then add it back, gradually increasing the dose (advise the patient the medicine will be increased back to a therapeutic dose in a manner that will be better tolerated). 4. Odansetron is serotonin 5-HT3 receptor antagonist and considered to have strong anti-emetic properties. It is on the WHO essential drug list. A number of other anti-emetics from this class of serotonin 5-HT3 receptor antagonists exist. Trying different antiemetics, even if from the same class, may be helpful for some patients. 5. For patients particularly anxious about the nausea (and who have "anticipatory nausea and vomiting"), a small dose of an anti-anxiety medicine (5 mg of diazepam) 30 minutes prior to the anti-TB drugs can help.
Diarrhoea and/or flatulence	PAS, Eto/Pto	1. Encourage patients to tolerate some degree of loose stools and flatulence. 2. Encourage fluid intake. 3. Treat uncomplicated diarrhoea (no blood in stool and no fever) with loperamide 4 mg by mouth initially followed by 2 mg after each loose stool to a maximum of 10 mg per 24 hours. 4. Check serum electrolytes (especially potassium) and dehydration status if diarrhea is severe.	1. Consider other causes of diarrhoea: Pseudo-membranous colitis related to broad-spectrum antibiotics such as the FQs is a serious and even life-threatening condition. Fever, bloody diarrhoea, intense abdominal pain and increased white blood cells are danger signs of possible pseudo-membranous colitis. Parasites and common water-borne pathogens in the area should

		5. Fever and diarrhoea and/or blood in the stools indicate the diarrhoea may be secondary to something other than a simple adverse effect of the anti-TB drugs.	be looked for in the patient and treated if present. Lactose intolerance, especially if patient has been exposed to new foods in a hospital not normally part of their diet. 2. Loperamide can be used in children over 2 years old.
Hepatitis	Z, H, R, Pto/Eto, and PAS	1. If enzymes are more than three times the upper limit of normal, stop all hepatotoxic drugs and continue with at least three nonhepatotoxic medications (an example of three non-hepatotoxic drugs are the injectable agent, fluoroquinolone and cycloserine). 2. Eliminate other potential causes of hepatitis(viral hepatitis and alcohol-induced hepatitis being the two most common causes) and treat any identified. 3. Consider suspending most likely agent permanently. Reintroduce remaining drugsone at a time, with the least hepatotoxic agents first, while monitoring liver function by testing the enzymes every three days, and if the most likely culprit is not essential, consider not re-introducing it.	1. History of previous drug hepatitis should be carefully analyzed to determine most likely causative agent(s); these drugs should be avoided in future regimens. 2. Viral serology should be done to rule out other etiologies of the hepatitis if available, especially to A, B, and C. 3. Alcohol use should be investigated and alcoholism addressed if found. 4. Generally, hepatitis due to medications resolves upon discontinuation of suspected drug.
Hypothyr-oidism	Eto/Pto, PAS	1. Most adults will require 100 to 150 mcg of Thyroxine/levothyroxine daily. Start in the following manner: Young healthy adults can be started on 75 to 100 mcg daily.Older patients should begin treatment with 50 mcg daily Patients with significant cardiovascular disease should start at 25 mcg daily. Thyroxine should be taken early in the morning 30 minutes before breakfast. 2. Monitor TSH every 1 to 2 months and increase dose by 12.5–25 mcg until TSH normalizes. Adjust dose more slowly in the elderly and patients with cardiac conditions.	1. Symptoms of hypothyroidism include fatigue, somnolence, cold intolerance, dry skin, coarse hair, and constipation, as well as occasional depression and inability to concentrate. 2. Do not start treatment unless TSH is above 1.5 to 2.0 times upper normal limit. 3. Completely reversible upon discontinuation of PAS and/or ethionamide/protionamide. 3. The combination of ethionamide/protionamide with PAS is more frequently associated with hypothyroidism than is the individual use of each drug.

Arthralgias	Z, Fluoroquinolones	1. Initiate therapy with non-steroidal anti-inflammatory drugs twice daily or ibuprofen 400–800 mg three times a day). 2. Lower dose of suspected agent (most commonly pyrazinamide), if this can be done without compromising regimen. 3. Discontinue suspected agent, if this can be done without compromising regimen.	1. Symptoms of arthralgia generally diminish over time, even without intervention. 2. Uric acid levels may be elevated in patients on pyrazinamide. There is little evidence to support the addition of allopurinol for arthralgias, although if gout is present it should be used. 3. If acute swelling, redness, and warmth are present in a joint, consider aspiration for diagnosis (gout, infection, autoimmune disease, etc).
Electrolyte disturbances (hypokalaemia and hypomagnesaemia)	Cm, Km, Am, S	1. Check potassium. 2. If potassium is low, also check magnesium and calcium (if unable to check for magnesium, consider empiric treatment with magnesium in all cases of hypokalemia). 3. Replace electrolytes as needed. Dose oral electrolytes apart from FQ as they can interfere with FQ absorption.	1. If severe hypokalaemia is present, consider hospitalization. 2. Amiloride 5–10 mg per day or spironolactone 25 mg per day may decrease potassium and magnesium wasting and is useful in refractory cases. 3. Oral potassium replacements can cause significant nausea and vomiting. Oral magnesium may cause diarrhea.
Nephrotoxicity (Renaltoxicity)	S, Km, Am, Cm	1. Discontinue suspected agent. 2. Consider using capreomycin if an aminoglycoside had been the prior injectable in regimen. 3. Consider other contributing etiologies (NSAIDs, diabetes, other medications, dehydration, congestive heart failure, urinary obstruction, etc.) and address as indicated. 4. Follow creatinine (and electrolytes) closely, every 1 to 2 weeks. 5. Consider dosing the injectable agent at 2-3 times a week if the drug is essential to the regimen and patient can tolerate (close monitoring of creatinine). If the creatinine continues to rise despite 2-3 times a week dosing, suspend the injectable agent. 5. Adjust all TB medications according to the creatinine clearance.	1. History of diabetes or renal disease is not a contraindication to the use of the agents listed here, although patients with these co-morbidities may be at increased risk for developing renal failure. 2. An example of how to calculate a creatine clearance based on the serum creatinine 3. Renal impairment may be permanent.

Vestibular Toxicity (tinnitus and dizziness)	S, Km, Am, Cm, Cs, FQs, H Eto, Lzd	1. If early symptoms of vestibular toxicity appear, change the dosing of the injectable agent to 2 or 3 times a week. Also, consider using capreomycin if an aminoglycoside had been the prior injectable in regimen. 3. If tinnitus and unsteadiness worsen with the above adjustment, stop the injectable agent. This is one of the few adverse reactions that cause permanent intolerable toxicity and necessitate discontinuation of a class of agents.	1. Ask the patient monthly about tinnitus and unsteadiness. 2. Fullness in the ears and intermittent ringing are early symptoms of vestibular toxicity. 3. A degree of disequilibrium can be caused by Cs, FQs, Eto/Pto, INH or Linezolid. Some clinicians will stop all drugs for several days to see if symptoms are attributed to these drugs. Symptoms of vestibular toxicity generally do not improve with withholding medications.
Hearing loss (also see vestibular toxicity above)	S, Km, Am, Cm, Clr	1. Document hearing loss and compare with baseline audiometry if available. (Some degree of hearing loss occurs with most patients, starting with high-frequency loss). 2. If early symptoms of hearing loss are documented, change the dosing of the injectable agent to 2 or 3 times a week. Also, consider using capreomycin if an aminoglycoside had been the prior injectable in regimen. 3. Discontinue the injectable agent if this can be done without compromising the regimen.	1. Patients with previous exposure to aminoglycosides may have baseline hearing loss. In such patients, audiometry may be helpful at the start of MDRTB therapy. 2. Hearing loss may be reversible or permanent (often permanent). 3. Some patients may choose to tolerate significant hearing loss to achieve a higher chance of cure. This should be discussed between a physician trained in MDR-TB and the patient. Continuing the injectable agent despite hearing loss almost always results in deafness. 4. While the benefit of hearing aids is minimal to moderate in auditory toxicity, consider a trial use to determine if a patient with hearing loss can benefit from their use.
Peripheral neuropathy	Cs, Lzd, H, S, Km, Cm, H, FQs, rarely Pto/Eto, E	1.Increase pyridoxine to maximum daily dose (200 mg per day). 2. Consider whether the dose of cycloserine can be reduced without compromising the regimen. (Lowering the dose of likely culprits can also be done – linezolid, isoniazid, ethionamide). If possible, switching the aminoglycoside to capreomycin may also be helpful. 3. Initiate medical therapy: NSAIDs or acetaminophen may help alleviate symptoms. Therapy with tricyclic antidepressants such as amitriptyline (start with 25 mg at bedtime; the dose may be increased to a maximum of 150 mg). Do not use tricyclic antidepressants with	1. Patients with co-morbid disease (e.g. diabetes, HIV, alcohol dependence) may be more likely to develop peripheral neuropathy, but these conditions are not contraindications to the use of the agents listed here. 2. Neuropathy may be irreversible but many patients experience improvement when offending agents are suspended. However, the neuropathy associated with linezolid is common after prolonged use and often permanent (for this reason suspension of this agent should be considered when neuropathy develops).

		selective serotonin reuptake inhibitors (SSRIs) antidepressant drugs. Carbamazepine, an anticonvulsant, at 100–400 mg twice daily can be tried. 4. Rarely, medication may be discontinued, but only if an alternative drug is available and the regimen is not compromised.	
Depression	Socioeconomic circumstances, chronic disease, Cs, fluoroquinolones, H, Eto/Pto	1. Assess and address underlying socioeconomic issues. 2. Assess patients for co-existing substance abuse and refer to treatment if appropriate. 3. Initiate individual counselling (or group counselling if the patient is smear- and culture-negative). 3. When depression is more significant, initiate antidepressant therapy (amitryptiline, fluoxetine or similar). Tricyclic antidepressants and SSRIs should not be given together and should not be given to patients on linezolid. 4. Lower dose of suspected agent if this can be done without compromising the regimen. (Reducing the dose of cycloserine and ethionamide to 500 mg daily to see if the depression is lessened is a common strategy). 5. Discontinue suspected agent if this can be done without compromising regimen.	1. Socioeconomic conditions and chronic illness should not be underestimated as contributing factors to depression. 2. Depressive symptoms may fluctuate during therapy and may improve as illness is successfully treated. 3. History of previous depression is not a contraindication to the use of the agents listed but may increase the likelihood of depression developing during treatment. If significant depression is present at the start of treatment, avoid a regimen with cycloserine if possible. 4. Question the patient regarding suicidal ideation any time the depression is judged to be more than mild.
Suicidal ideation	CS, H, Eto/Pto	1. Hospitalize the patient and put under 24- hour surveillance. 2. Discontinue cycloserine. 3. Request psychiatric consultation. 4. Initiate antidepressant therapy. 5. Lower the dose of Eto/Pto to 500 mg daily until the patient is stable.	1. Keep the patient in the hospital until risk of suicide has passed. 2. If no improvement occurs after holding cycloserine, hold H and/or Eto/Pto.
Psychotic symptoms	Cs, H, Fqs	1. Stop suspected agent for a short period of time (1–4 weeks) while psychotic symptoms are brought under control. The most likely drug is cycloserine followed by high-dose isoniazid.	1. Some patients will need to continue antipsychotic treatment throughout MDRTB therapy (and discontinue upon completion of MDR-TB therapy). 2. Previous history of psychiatric

		2. If moderate to severe, initiate antipsychotic therapy (haloperidol). 3. Hospitalize in a ward with psychiatric expertise if patient is at risk to himself/herself or others. 4. Increase pyridoxine to maximum daily dose (200 mg per day). 5. Lower dose of suspected agent (most commonly cycloserine to 500 mg a day) if this can be done without compromising regimen. 6. Discontinue suspected agent if this can be done without compromising regimen. 7. Once all symptoms resolve and patient is off cycloserine, anti-psychotic therapy can be tapered. If cycloserine is continued at a lower dose, anti-psychotic therapy may need to be continued and any attempts at tapering should be done with a psychiatrist trained in the adverse effects of second-line anti-TB drugs.	disease is not a contraindication to the use of cycloserine, but its use may increase the likelihood of psychotic symptoms developing during treatment. 3. Some patients will tolerate cycloserine with an antipsychotic drug, but this should be done in consultation with a psychiatrist as these patients will need special observation and this should only be done when there is no other alternative. 4. Psychotic symptoms are generally reversible upon completion of MDR-TB treatment or cessation of the offending agent. 5. Always check creatinine in patients with new-onset psychosis. A decrease in renal function can result in high blood levels of cycloserine, which can cause psychosis.
Seizures	Cs, H, fluoroquin-olones	1. Hold cycloserine, FQs and isoniazid pending resolution of seizures. 2. Initiate anticonvulsant therapy (carbamazepine, phenytoin, or valproic acid are most commonly used). 3. Increase pyridoxine to maximum daily dose (200 mg per day). 4. Check serum electrolytes including potassium (K+), sodium (Na+), bicarbonate (HCO3−), calcium (Ca2+), magnesium (Mg2+), chloride (Cl−). 5. When seizures have resolved, restart medications one at a time. Cycloserine should not be restarted unless it is absolutely essential to the regimen. If cycloserine is reinitiated, start a dose one weight band lower.	1. Anticonvulsant is generally continued until MDR-TB treatment is completed or suspected agent discontinued. 2. History of previous seizure disorder is not a contraindication to the use of agents listed here if a patient's seizures are well controlled and/or the patient is receiving anticonvulsant therapy. (Do not include cycloserine if an alternative drug is available). 3. Patients with history of previous seizures may be at increased risk for development of seizures during MDR-TB therapy. 5. Always check creatinine in patients with new-onset seizures. A decrease in renal function can result in high blood levels of cycloserine, which can cause seizures. Adjusting the dose of cycloserine in the presence of low creatinine may be all that is needed to control the seizures.
Optic neuritis	**E**, Eto/Pto, Lzd, Cfz, H, S	1. Stop ethambutol. Do not restart. 2. Refer patient to an ophthalmologist.	1. The most common drug responsible is ethambutol. 2. Usually reverses with cessation of ethambutol. 3. Improve diabetic control in diabetic patients

Metallic Taste	Eto/Pto, Clr, Fqs	1. Encourage the patient to tolerate this side effect. 2. Sucking hard candy or chewing gum can be helpful.	1. Normal taste returns when treatment is stopped.
Gynecom-astia	Eto/Pto	1. Breast enlargement can be a troublesome side-effect of Eto/Pto therapy, especially for male patients. Galactorrhoea has also been reported. 2. Encourage patients to tolerate this side effect.	1. Resolution occurs after treatment

Annexures: Weight-based dosing of anti-TB drugs (adopted from WHO 2015 Companion Handbook)

DRUGS	DAILY DOSE	30–35 KG	36–45 KG	46–55 KG	56–70 KG	>70 KG
Isoniazid	4–6 mg/kg once daily	150 mg	200 mg	300 mg	300 mg	300 mg
Rifampicin	8–12 mg/kg once daily	300 mg	450 mg	450 mg	600 mg	600 mg
Pyrazinamide	20–30 mg/kg once daily	800 mg	1000 mg	1200 mg	1600 mg	2000 mg
Ethambutol	15–25 mg/kg once daily	600 mg	800 mg	1000 mg	1200 mg	1200 mg
Rifabutin	5–10 mg/kg once daily	300 mg	300 mg	300 mg	300 mg	300 mg
Levofloxacin	750–1000 mg once daily	750 mg	750 mg	1000 mg	1000 mg	1000 mg
Moxifloxacin	400 mg once daily	400 mg	400 mg	400 mg	400 mg	400 mg
Ethionamide	500–750 mg/day in 2 divided doses	500 mg	500 mg	750 mg	750 mg	1000 mg
Prothionamide	500–750 mg/day in 2 divided doses	500 mg	500 mg	750 mg	750 mg	1000 mg
Cycloserine	500–750 mg/day in 2 divided doses	500 mg	500 mg	500 mg	750 mg	750 mg
p-aminosalicylic acid[a]	8 g/day in 2 divided doses	8g	8g	8g	8 g	8–12 g
Bedaquiline(N/A until NTP advice)	400 mg once daily for 2 weeks then 200 mg 3 times per week					
Delamanid (N/A until NTP advice)	100 mg twice daily (total daily dose = 200 mg)					
Clofazimine	200–300 mg daily (2 first months) then reduce to 100 mg daily (alternative dosing 100 mg daily)					
Linezolid	600 mg once daily	600 mg	600 mg	600 mg	600 mg	600 mg
Amoxicillin/clavulanic acid[b] 7/1	80 mg/kg/day in 2 divided doses	2600 mg	2600 mg	2600 mg	2600 mg	2600 mg
Amoxicillin/clavulanic acid[b] 8/1	80 mg/kg/day in 2 divided doses	3000 mg	3000 mg	3000 mg	3000 mg	3000 mg
High-dose isoniazid	16–20 mg/kg once daily	600–1000 mg	1000–	1500 mg	1500 mg	1500 mg
Imipenem/cilastatin	1000 imipenem/1000 mg cilastatin twice daily					
Meropenem	1000 mg three times daily (alternative dosing is 2000 mg twice daily)					

Weight-based injectable anti-TB daily dosing in adults >30 kg

DRUGS		30–33 KG	34–40 KG	41–45 KG	46–50 KG	51–70 KG	>70 KG
Streptomycin	12–18 mg/kg once daily	500 mg	600 mg	700 mg	800 mg	900 mg	1000 mg
Kanamycin	15–20 mg/kg once daily	500 mg	625 mg	750 mg	875 mg	1000 mg	1000 mg
Amikacin	15–20 mg/kg once daily	500 mg	625 mg	750 mg	875 mg	1000 mg	1000 mg
Capreomycin	15–20 mg/kg once daily	500 mg	600 mg	750 mg	800 mg	1000 mg	1000 mg

NOTE:

1. Amx/Clv: Provided by NTP is with the ratio of 7/1(625 mg), so the appropriate dosage is 2600 mg/day in two divided doses
2. PAS: NTP is providing sodium PAS granules, the dosage is(150 mg/kg) 18.4 gm daily in two divided doses , same as mentioned in National DR TB guidelines
3. Inj-Am: NTP is providing 500 mg vial, so for patients on > 500 mg or higher should be provided two vials. If pt is on 625 mg daily then remaining should be discarded, if not stored on recommended temperature.

Pediatric Dosing of Second-line Anti-Tuberculosis Medications

General considerations

Anti-TB drugs should be dosed according to weight and adjusted regularly as weight increases during treatment.

When a liquid formulation is available, it should be used for patients less than 15 kg.

Most second-line TB drugs do not have pediatric liquid or tablet formulations, so it may be necessary to split the pills in order to approximate the correct dose. To split tablets into 0.75, it is suggested to split the tablet in half and then split a half tablet in half. Discard the smaller quarter tablet and give the child a half tablet plus the remaining quarter tablet.

Doses of most anti-TB drugs have not been established for children below 5 kg, but often the potential benefit outweighs the risks. In such cases, the child should be dosed as close to the middle of the mg/kg range as possible.

Group	Drug	Daily Dose	Maximum Daily Dose
1	isoniazid (H)	If 100 mg tab For 5 kg .5 tab. From 6-9 kg 1 tab. From 10-12 kg 1.5 tab. From 16-30 kg 2 tab. 7-15 mg/kg for less than 30 kg.	If 300 mg Tab, 1 tab daily maximum dose. Children with malnutrition, peripheral neuropathy should also use pyridoxine 5-10 mg/day
	rifampicinpy(R)	10-20 mg/kg once daily for patients less than 30 kg. For 150 mg tablet: Body weight 5-7 kg .5 tab. From 8-12 kg -1 tab. From 13-15 kg -1.5 tab.From 16-30 kg -300 mg -1 tab	600 mg
	ethambutol	15-25 mg/kg once daily	1200 mg
	azinamide (Z)	30-40 mg/kg for less than 30 kg once daily For 400 mg tab. 5–6 kg - 0.25 tab 7–9kg- 0.50 tab 10–11kg- .75 tab 12–18 kg-1 tab 19–25 kg- 1.5 tab 26–30 kg- 2 tab15-30 mg/kg once daily	2000 mg
2	amikacin (Am)	15-30 mg/kg once daily	1000 mg
	kanamycin (Km)	15-30 mg/kg once daily	1000 mg
	capreomycin (Cm) Streptomycine	15-30 mg/kg once daily 20-40 mg/kg daily	1000 mg

Example: Injectable dose calculation for a child weighing 6.9 kg

Calculate the low and high doses for the child's weight. For kanamycin:

Low dose: 15 mg/kg x 6.9 kg = 103 mg

High dose: 30 mg/kg x 6.9 kg = 207 mg

Choose a convenient dose between the two numbers.

Select a dose between the two numbers and toward the higher number. In this case, 200 mg is a convenient dose.

Calculate the number of ml to draw up in the syringe based on the mg/ml concentration of the preparation.

3	levofloxacin (Lfx)	Less than 5 years 15-20 mg/kg twice daily. Over 5 years 10-15 mg/kg once daily.	–
	moxifloxacin (Mfx)	7.5-10 mg/kg once daily 400 mg Tab. 10–17 kg- 0.25 tab 18–30 kg 0.50 tab	–
4	ethionamide (Eto)/	15-20 mg/kg once daily	1000 mg
	cycloserine	10-20 mg/kg once daily	1000 mg
	(Cs)PAS (4 g sachet)	200-300 mg/kg two times daily	12 g
5	clofazimine (Cfz)	1 mg/kg once daily	200 mg
	co-amoxiclav (Amx/Clv)	80 mg/kg in 2 divided doses	4000 mg of Amx and 500 mg Clv
	Linezolid (Lzd)	10 mg/kg given three times daily (pyridoxine should also be given)	600 mg

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