DRUG RESISTANT TUBERCULOSIS guideline based approach

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OBJECTIVES

To Familiarise the students with

- **Current scenario of drug resistance in tuberculosis.**
- **Types of drug resistance.**
- **How to Diagnose drug resistance.**
- **Drugs available and their side effects.**
- **Principles of MDR-TB & XDR case management.**
- **RNTCP response to drug resistance (PMDT).**

DRUG RESISTANCE

INDIAN SCENARIO…

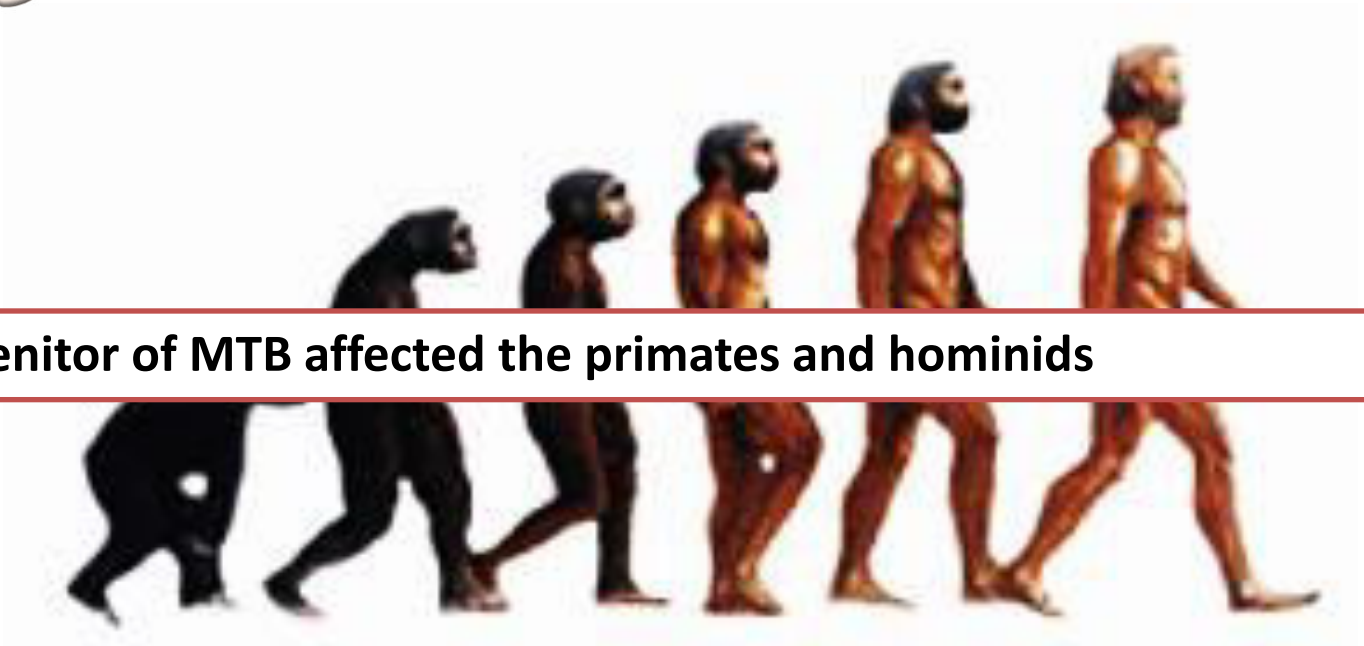
- **2-3 % MDR in new smear positive cases.**
- **12-17% MDR in previously treated cases.**
- **2-3 % MDR are already XDR-TB.**
- **40000 XDR - already reported across 49 countries.**
- **12 Cases of TDR reported in India**
- **The prevalence may be almost 3 times more than its incidence**

IS RESISTANCE A NEW MENACE??

- **All the available evidence shows that drug resistance occurs only by mutation.**
- **Mutation is not something new to MTB.**
- **Mycobacterium genus is characteristic of slow mutation.**
- **Present day MTB itself has originated by way of several mutations.**


150 million years – Jurassic period
Presence of mycobacterium ulcerans and mutation continued……

3 million years ago



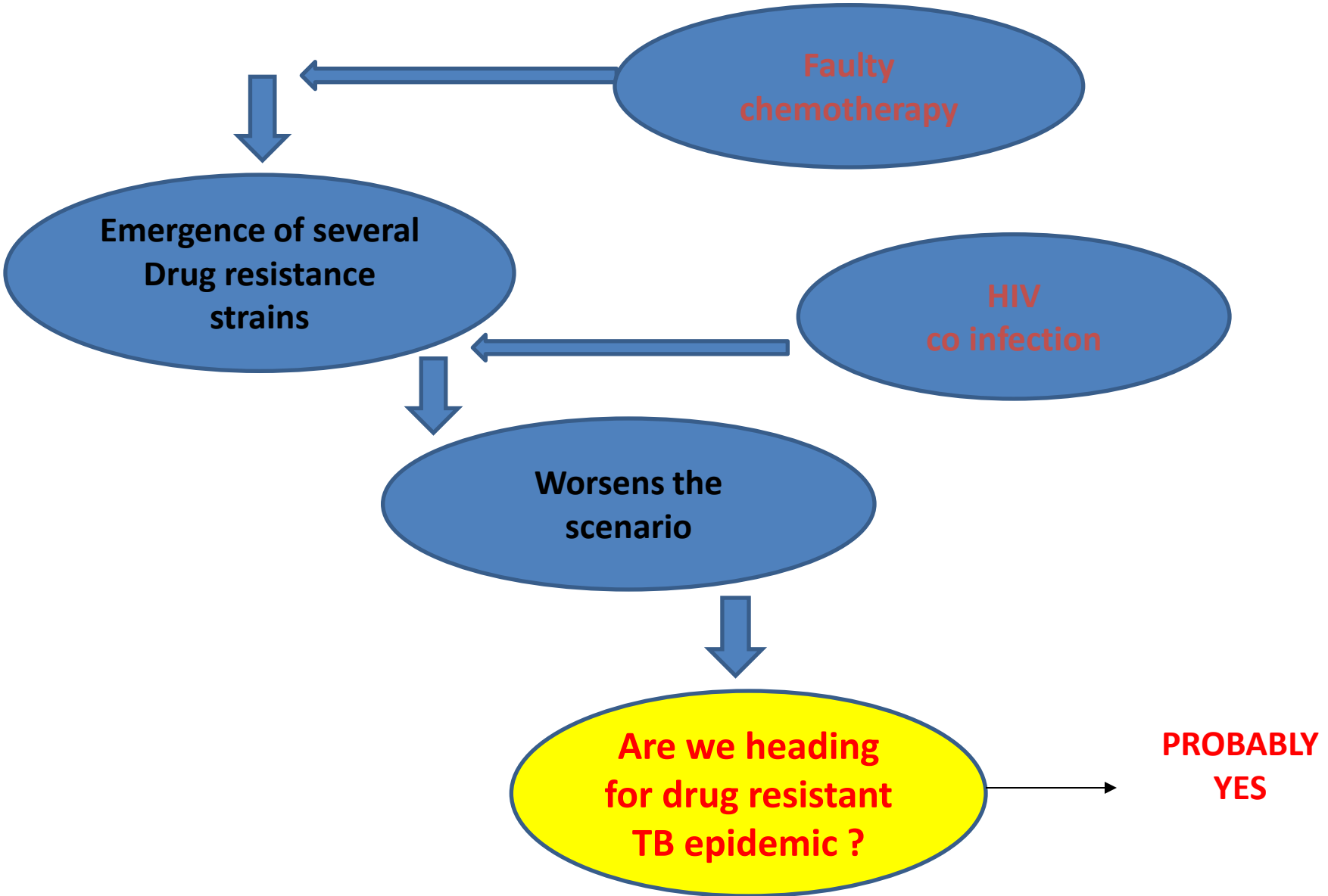
Progenitor of MTB affected the primates and hominids

Mutation continued….


15000 years ago
PRESENCE OF ANCESTERS OF MTB

PRESENT DAY MTB

250 -1000 years old, mutation continues...



When will you suspect drug resistance in Tuberculosis ?

While on treatment

Patient having unfavourable clinical, radiological or bacteriological response even after taking an appropriate chemotherapy for an adequate period of time.

Appropriate: Right regimen, right dosage and right duration .

Adequate : *Va*riable depending up on the regimen .

Is clinical worsening always due to drug resistance?

IT IS NOT ALWAYS !!

- **Check the regimen**
- **Review your diagnosis.**
- **Look for co morbidities.**
- **Repeat the sputum microscopy.**
- **Think of IRIS in extrapulmonary.**

Is radiological worsening always due to drug resistance?

IT IS NOT ALWAYS !!

- **Check the regimen**
- **Review your diagnosis.**
- **Look for co morbidities.**
- **Repeat the sputum.**
- **Think of IRIS in HIV Co-infection**

IS BACTERIOLOGICAL WORSENING-

Failure or delay in sputum conversion due to drug resistance ??

PROBABLY YES!!

Provided

- **On correct regimen**
- **co morbidities under control**

Still Confirm by DST

IS BACTERIOLOGICAL WORSENING-

Failure or delay in sputum conversion due to drug resistance ??

PROBABLY YES!!

Provided

- **On correct regimen**
- **co morbidities under control**

Still Confirm by DST

- Drug resistance -man-made ,consequence of suboptimal regimens and treatment interruption
- History of prior TB treatment, particularly if recent is the most common epidemiologic risk factor for MDR-TB
- H/o treatment interruption or patients with chronic tuberculosis (sputum positive after re-treatment) & those who fail treatment (sputum positive after 5 months of treatment) are at highest risk of having MDR tuberculosis, especially if rifampicin was used throughout the course of treatment

PREDICTORS OF DRUG-RESISTANT TB ON YOUR NEW PATIENT

- **Think if there is history**
- Come from a country or region with high rates of drug resistance
- Had contact and significant exposure to MDR-TB in a household member or relative
- Are HIV positive. Acquired mono-rifampicin resistance is highly associated with HIV infection, especially if treatment was not daily or breaks in treatment occurred.

If drug resistance is suspected, DST should be performed for at least INH &RIF

DRUG RESISTANCE - CLASSIFICATION

EPIDEMILOGICAL

- Primary
- Secondary or acquired

CLINICAL AND LABORATORY

- Mono resistance
- Poly resistance
- MDR
- XDR
- TDR - ?

DRUG-RESISTANT TB: DEFINITION

EPIDEMIOLOGICAL

- **Primary drug-resistance: "New Cases"**

  Drug resistance in a patient who has never been treated for tuberculosis or received less than one month of therapy

- **Secondary (acquired) drug-resistance: "Previously Treated Cases"**

  Drug resistance in a patient who has received at least one month of anti-TB therapy

DRUG-RESISTANT TB: DEFINITIONS

CLINICAL & LABORATORY

- **Mono-resistant:** Resistance to a single drug 1st line
- **Poly-resistant:** Resistance to more than one drug, but not the combination of isoniazid and rifampicin
- **Multidrug-resistant (MDR):** Resistance to isoniazid and rifampicin with or without resistance to other drugs
- **Extensively drug-resistant (XDR):** MDR plus resistance to fluoroquinolones and at least 1 of the 3 injectable drugs (amikacin, kanamycin, capreomycin)

AVAILABLE DRUG SUSCEPTIBILITY TESTS

1. Conventional (***LJ medium***):Gold standard

- egg based solid media
- R,H,E,S
- Proportion method

NEWER INVESTIGATIONS

- BACTEC 460 system (radiometric)-Liquid

  Direct: Inoculation of smear positive sputum in to drug containing and drug free medium.

  Indirect: Test performed with grown culture of MTB-reliable.

- BACTEC MGIT 960: MB /BACT- VERSA TREK (non radiometric)

  Performs better than BACTEC 460

MODS – MICROSCOPIC OBSERVATION DRUG SUSCEPTIBILITY

- Uses tissue culture plate

  - wells coated with different drugs in different concentration are used

  - *presence of growth with INH /RIF /SM/EMB can be detected.*

- Time taken 7 to 14 days

PHAGE BASED ASSAYS:

- Time taken 48 to 72 hrs
- Sensitivity and specificity -73 to 100 %

CALORIMETRIC METHODS :

- Simple for INH and Rif
- Viable mycobacteria –detected by change in colour 7 to 14 days
- Sensitivity and specificity – 98 %

MOLECULAR METHODS

Line probe assays :

- DNA strip based tests
- Nucliec acid amplification technique & reverse hybridation methods for rapid detection of mutation
- MDR TB-target genes-rpoB(R),Kat G&inh A(H)
- XDRTB-gyrA(FQ),rrs(aminoglycosides),emb B(Ethambutal)
- Rapid diagnosis with turn around time72 hours

Gene Xpert

"Game changer" in TB Diagnosis: targets rpoB gene

Advantage-

- Speed
- Unskilled persons
- Detects RIF resistance- 100 % sensitive
- No need for special labs

HOW RELIABLE ARE DRUG SUSCEPTIBILITY TESTS???

- **Conventional –** Gold standard
- **Newer tests-**

➢ **MGIT 960 (non radiometric) - faster, reliable but expensive.**

➢ **MODS – cost effective - laborious and risk of cross contamination.**

➢ **Molecular methods Line Probe Assay- faster , reliable , costly.**

➢ **Gene Xpert is it ultimate ?**

CONSEQUENCES OF INACCURATE DRUG SUSCEPTIBILITY TESTS

Misclassification of strains.

Unnecessary change of regimen & use of reserve drugs.

Higher toxicity & costs.

Less chance of cure.

DRUG RESISTANT TB -TREATMENT

- Drugs available
- General principles
- Treatment of individual resistance

CATEGORIES OF ANTITUBERCULOSIS DRUGS: WHO

- **Group 1 – First-line drugs:** Isoniazid, rifampicin, ethambutol, pyrazinamide
- **Group 2 - Injectable agents:** Kanamycin, amikacin, capreomycin, streptomycin
- **Group 3 - Fluoroquinolones:** Levofloxacin, moxifloxacin, ofloxacin
- **Group 4 - Oral bacteriostatic agents:** Ethionamide, cycloserine, para-aminosalicylic acid (PAS), prothionamide, terizadone
- **Group 5 – Unclear role:** Clofazamine, linezolid, amoxicillin/clavulanate, Imipenem/cilastatin, thioacetazone, high-dose isoniazid, clarithromycin,

Empiric Regimens for Drug-resistant non MDR

Predicted Resistance Pattern	Empiric Regimen (minimum duration)
INH	RIF, EMB, PZA (6-9 mo)
INH, EMB	RIF, PZA, Fluoroquinolone ± Injectable (9-12 mo)
RIF	INH, EMB ± PZA (18 mo minimum)
RIF, EMB	INH, Fluoroquinolone, PZA ± Injectable (18-month minimum)

INH = Isoniazid, RIF = Rifampicin, EMB = Ethambutol, PZA = Pyrazinamide

Note: PZA does not prevent acquired resistance to companion drugs. EMB prevents acquired drug resistance to companion drugs.

GENERAL PRINCIPLES MDR XDR TREATMENT

- **Use at least 4 drugs likely to be effective or not used earlier.**
- **Include drugs in group 1-5 in a hierarchical order based on potency**
- **Do not use drugs for which cross resistance is reported.**
- **Avoid drugs that are not safe for an individual.**
- **Be thorough with ADR of different drugs and to manage it effectively.**

ADDITIONAL IMPORTANT PRINCIPLES: WHO

- Use direct observation of treatment (DOT)
- Use daily administration, not intermittent.
- Treatment duration of a minimum of 18-24 months after culture conversion
- When possible, continue injectable for minimum six months (atleast 4 months post-culture conversion)
- Continue at least three oral drugs for full treatment duration

TREATMENT OF MDR

Condition of patients – **Is treatment urgent or can we wait ?**

- If urgent – empirical MDR regimen
- If we can wait – wait for culture sensitivity for AFB – to individualize the treatment. Till then continue the same treatment

BUILDING A REGIMEN FOR MDR-TB

STEP 1

Begin with any first-line agents to which the isolate is susceptible

Add a fluoroquinolone and an injectable drug based on susceptibilities

Use any available **PLUS** One of these **PLUS** One of these

First-line drugs	Fluoroquinolones	Injectable agents
Pyrazinamide	Levofloxacin	Amikacin
Ethambutol	Moxifloxacin	Capreomycin
	Ofloxacin	Streptomycin
		Kanamycin

BUILDING A REGIMEN FOR MDR-TB

STEP 2

If 4 drugs are not identified in Step 1:

Add second-line drugs until you have four to six drugs to which the isolate is susceptible

(and preferably which have not been used to treat the patient previously)

Pick one or more of these

Oral second-line drugs
Cycloserine
Ethionamide
PAS

BUILDING A REGIMEN FOR MDR-TB

STEP 3

If there are not four to six drugs available in the above categories, consider third-line drugs in consultation with an expert.

Consider use of these

Third-line drugs	
Clofazimine Linezolid Amoxicillin/ Clavulanate	Imipenem Clarithromycin

BUILDING A REGIMEN FOR XDR-TB

STEP 1

Begin with any first-line agents to which the isolate is susceptible

Add a fluoroquinolone and an injectable drug based on susceptibilities

Use any available **PLUS** One of these **PLUS** One of these

First-line drugs	Fluoroquinolones	Injectable agents
Pyrazinamide **Ethambutol**	**Levofloxacin** **✓ Moxifloxacin** **Ofloxacin**	**Amikacin ?** **Capreomycin ?** **Streptomycin ?** **Kanamycin ?**
Commonly not susceptible	**By definition fluoroquinolone Resistance** **Still use Moxifloxin**	**Select agent based on history and susceptibility testing**

BUILDING A REGIMEN FOR XDR-TB

STEP 2

Add second-line drugs until you have four to six drugs to which the isolate is susceptible (and preferably which have not been used to treat the patient previously)

Pick one or more of these

Oral second-line drugs
Cycloserine Ethionamide PAS
With XDR-TB, often all three of these agents are necessary

BUILDING A REGIMEN FOR XDR-TB

STEP 3

If there are not four–six drugs available in the above categories, consider third-line drugs in consultation with an expert.

Consider use of these

Third-line drugs	
Clofazimine Linezolid Amoxicillin+ Clavulanate	Imipenem Clarithromycin

MANAGEMENT GUIDELINES FOR XDR

- **Use any Group 1 agent that may be effective. (unlikely)**
- **Use an injectable (susceptible) for 12 months or through out treatment .**
- **If resistant to all injectable , still use the drug that patient has not used before.**
- **Use later generation fluoroquinolne – moxifloxacin (*even in quinolone resistance*)**

MANAGEMENT GUIDELINES FOR XDR

- **Use all group 4 agents that are not used extensively in the previous regimen.**
- **Use any 2 or 3 of group 5 drugs.**
- **High dose INH.**
- **Adjuvant surgical option.**
- **Ensure strict infection control .**

ADJUVANT THERAPIES

- **Nutritional support:** **Staple food and source protein**

- **B6 supplementation:** **for all patients on cycloserine & high dose INH.**

Remember

- **Zinc –iron-calcium interference with absorption of quinolones.**

- **Corticosteroids-In respiratory failure and CNS TB.**

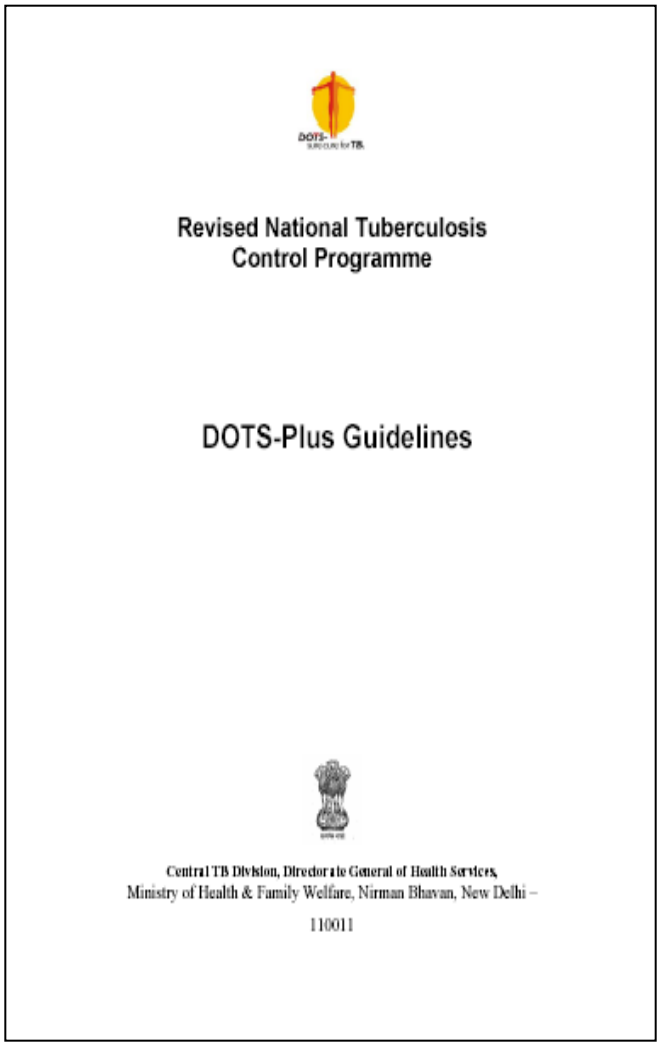
MDR/XDR-TB: MANAGEMENT PRINCIPLES

- Treat until 3 consecutive - Ve smears (or culture negative) and a good clinical Improvement

- Initiate MDR-TB treatment under close supervision and monitoring drug toxicity

- **Familiarity with RNTCP (PMDT) is a must**

DOTS PLUS (PMDT) UNDER RNTCP



- **DOTS-Plus activities approved under RNTCP Phase II PIP (2006-11)**
- **DRS in Gujarat and Maharashtra (2005-06)**
- **National DOTS-Plus Committee formed (2005)**
- **DOTS Plus Guidelines developed (2006)**
- **National Lab Scale-up Plan for establishment of a network of accredited labs for diagnosis**
- **Uninterrupted supply of quality assured second line anti-TB drugs**
- **Information systems and data management**
- **Special provisions for DOTS Plus under RNTCP Financial Norms (RCC)**

DOTS-Plus is an integral component of RNTCP to manage MDR-TB to be implemented through India's public health and programme infrastructure

MULTI-DRUG RESISTANT TUBERCULOSIS AND PMDT

- The standardized drug regimens used by RNTCP are highly effective, with low failure rates of around 2% and 6% amongst New (Cat I) and Previously Treated (PT) (Cat II) cases respectively.
- Although small in relation to percentages and proportions, these rates translate into large absolute numbers.
- Moreover, **MDR-TB patients often live a number of years before succumbing to the disease**.
- MDR-TB prevalence may be three times greater than its incidence.

FIVE COMPONENTS OF PMDT

1. **Sustained political and administrative commitment**
2. **Diagnosis of MDR-TB through quality-assured DST-National and Supra-National Reference Laboratories**
3. **Appropriate treatment strategies for the use of second-line drugs - Cat IV and V**
4. **Uninterrupted supply of quality assured Second line anti-TB drugs.**
5. **Recording and reporting system designed for PMDT programmes**

Suspecting MDR TB: RNTCP STYLE

- **Criteria A**

  All failures of new TB cases (CAT I), Sm+ve RT cases who remain Sm+ve at 4th month onwards in CAT II and *All PTB cases* who are contacts of known MDR TB case.

- **Criteria B**

  All Sm +ve Re-treatment PTB cases at diagnosis & any Sm+ve follow up in new or RT cases in addition to Criteria A

- **Criteria C**

  Sm -ve Re-treatment PTB cases at diagnosis, HIV TB co-infected cases, in addition to Criteria B

- In the larger states, all districts will introduce services with Criteria A and move to Criteria B as guided by the adequacy of laboratory capacity and availability of drugs. Small states like Goa, 7 North East states (except Assam) and all Union Territories will initiate services with Criteria B and move to Criteria C as soon as services are established on ground in these areas.

ORDER OF PREFERENCE FOR DIAGNOSIS & FOLLOW UP in PMDT

For Diagnosis:

1. Line Probe Assay is preferred diagnostic method
2. Liquid C-DST
3. Solid C-DST

For follow up:

1. Liquid C-DST
2. Solid C-DST

Pre-treatment Evaluation

1. Detailed history
2. Weight, Height
3. Complete Blood Count
4. Blood sugar
5. LFT & RFT
6. TSH
7. Pregnancy test (for all women in the child bearing age group)
8. Chest X-Ray
9. HIV & family counselling

CATEGORY IV REGIMEN

DRUGS	DURATION
INTENSIVE PHASE	
• Kanamycin(15-20mg/kg) • High dose ofloxacin(800mg) • Ethionamide(15-20mg/kg) • Ethambutol(25mg/kg) • Cycloserine(15-20mg/kg) • Pyrazinamide(30-40mg/kg)	6-9 months
CONTINUATION PHASE	
• High dose ofloxacin • Ethionamide • Ethambutol • Cycloserine	18 months

MONITORING PROGRESS DURING TREATMENT

1. Clinical monitoring:
   - monthly review for the first 6 months
   - every 3 months for subsequent period
2. Sputum AFB smear & Culture:
   0,3,4,5,6,7
   9, 12, 15, 18, 21, 24
2. CXR:
   - pretreatment
     end of IP and at the end of treatment
3. Sr. creatinine:
   monthly for first 3 months, every 3 months later

TREATMENT OUTCOMES

Cure:

5 consecutive negative culture in the last 12 to 15 months. If one culture is positive, at least subsequent 3 must be negative

Treatment failure :

if two or more of the five cultures recorded in the last 12-15 months or any one of the last 3 culture

Treatment completed :

An MDR-TB patient who has completed treatment according to guidelines but does not meet the definition for cure or treatment failure due to lack of bacteriological results.

Treatment default:

Treatment was interrupted for two or more consecutive months for any reasons.

Death :

Dies for any reason during the course of MDR-TB Treatment

TREATMENT OUTCOMES

Transfer out:

Transferred to another reporting unit

Treatment stopped due to adverse drug reactions:

On MDR-TB treatment who develops severe adverse reactions

Treatment stopped due to other reasons:

other medical reason (than adverse drug reactions)

Switched to Category V treatment:

A Category IV patient who during treatment is identified as an "XDR-TB suspect" and proved by an NRL

Still on treatment:

Continuing the treatment Beyond the duration

COMMON ADVERSE EFFECTS

G.I. complaints	Ethionamide Cycloserine PAS Fluoroquinolones Clofazimine Rifabutin
Hepatotoxicity (early symptoms are anorexia and malaise, then abdominal pain, vomiting, jaundice)	INH Rifampicin/rifabutin Ethionamide PZA PAS Fluoroquinolones

COMMON ADVERSE EFFECTS

Peripheral neuropathy	INH Ethionamide Cycloserine Linezolid Ethambutol
Rash	All
Headache	Fluoroquinolones Isoniazid Cycloserine Ethionamide Ethambutol
Seizures	Cycloserine INH

COMMON ADVERSE EFFECTS

Hypothyroidism	Ethionamide, PAS
Hearing loss, Vestibular toxicity	Aminoglycosides, Capreomycin
Behavioral changes	Cycloserine, Ethionamide, Isoniazid, Fluoroquinolones
Visual changes	Ethambutol, Rifabutin, Isoniazid, Linezolid
Renal failure Hypokalemia, Hypomagnesemia	Aminoglycosides, Capreomycin

Summary

- **Drug resistance is a real threat to the national TB Control program.**
- **MDR and XDR incidence reported are only tip of the iceberg as DST facility is not available freely.**
- **Always suspect drug resistance if no satisfactory improvement after 3- 4 months of ATT.**
- **Immediately ask for drug sensitivity testing.**

Summary….

- **Many available DST are too costly and unproven.**
- **Conventional culture is the GOLD standard.**
- **MGIT 960-(non radiometric) test, line probe assay and gene Xpert are promising.**
- **Treatment of MDR-TB is complex and costly. It is much easier to prevent than to treat. XDR-TB is even more difficult!**
- **Remember WHO classification of anti tubercular drugs.**

Summary….

- **Ideally the regimen should be guided by DST**
- **A patient-centered approach to DOT is an important element of successful care.**
- **Second-line drugs ADR are common and may be severe. Monitoring for these effects is essential.**
- **Be familiar with RNTCP & PMDT .**

Identify the following phrase

……. I will not cut for stones even for patients in whom disease is manifest, I will leave this operation to be performed by specialist in this art…..

Hippocratic oath

THANK YOU