DRUG RESISTANT TUBERCULOSIS

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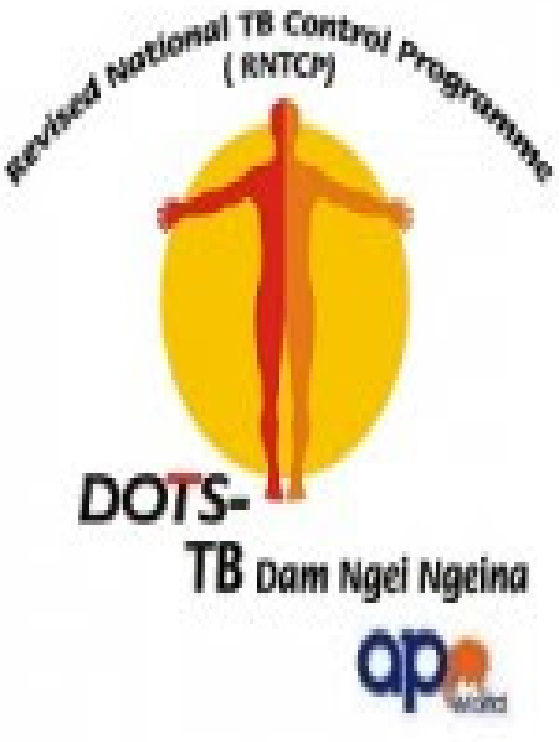


OBJECTIVES

To Familiarise the students with

- **Definition & classification of MDR & XDR**
- **Current scenario of drug resistance in tuberculosis.**
- **Mechanism of drug resistance.**
- **How to Diagnose drug resistance.**
- **Principles of MDR-TB & XDR case management.**
- **RNTCP response to drug resistance (PMDT).**

Definition

- Multidrug resistance TB-resistance to 2or more drugs which includes Rifampicin & Isoniazid .

  Most of the organism are resistant to rifampicin also resistant to isoniazid ,hence considered as MDR
- Extensive drug resistance TB- MDR plus resistance to fluoroquinolines & at least one of the 3 injectables (amikacin, kanamycin, capreomycin)

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"**

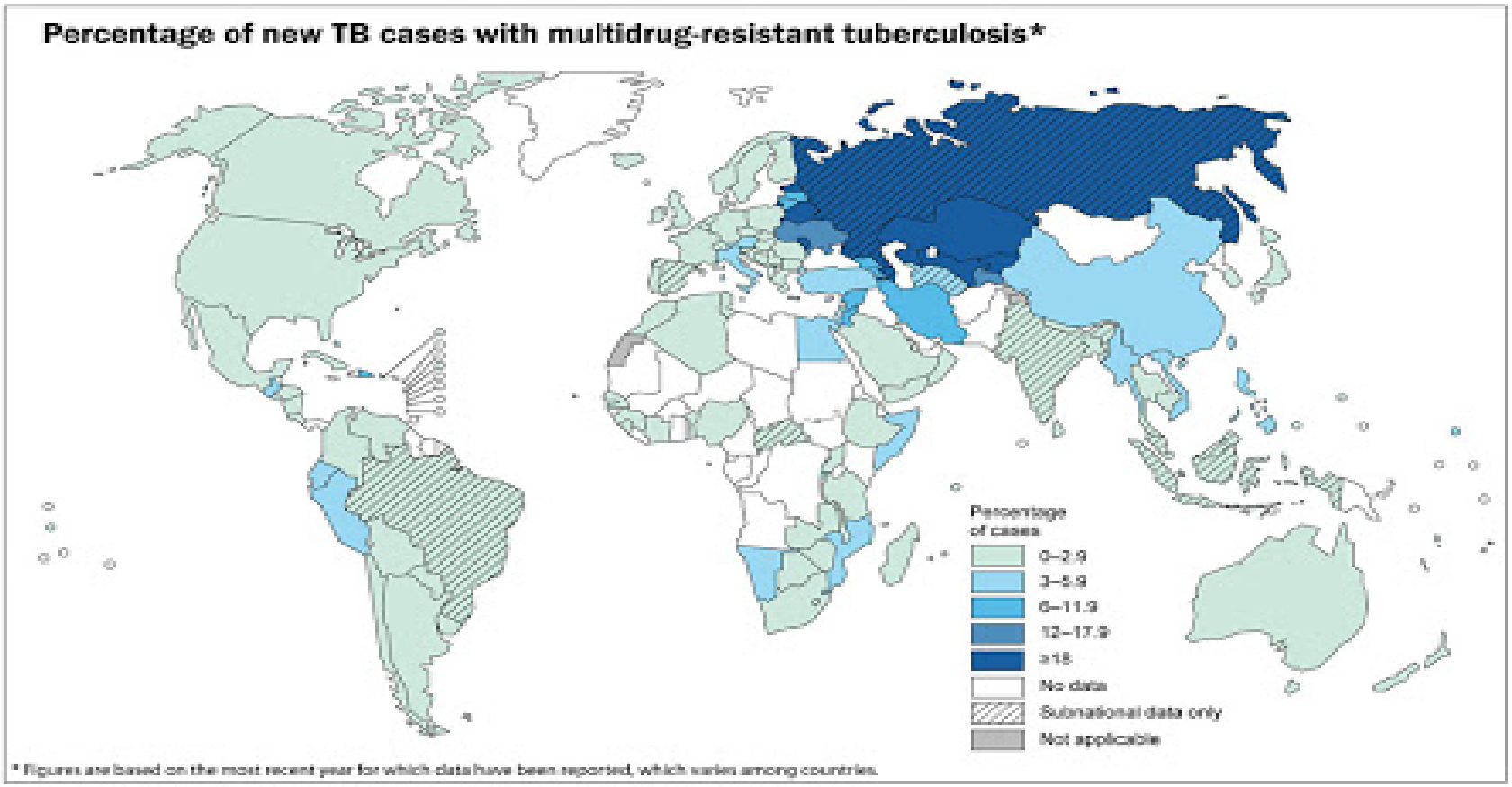
  Drug resistance in a patient who has received at least one month of anti-TB therapy

DRUG-RESISTANT TB: DEFINITIONS

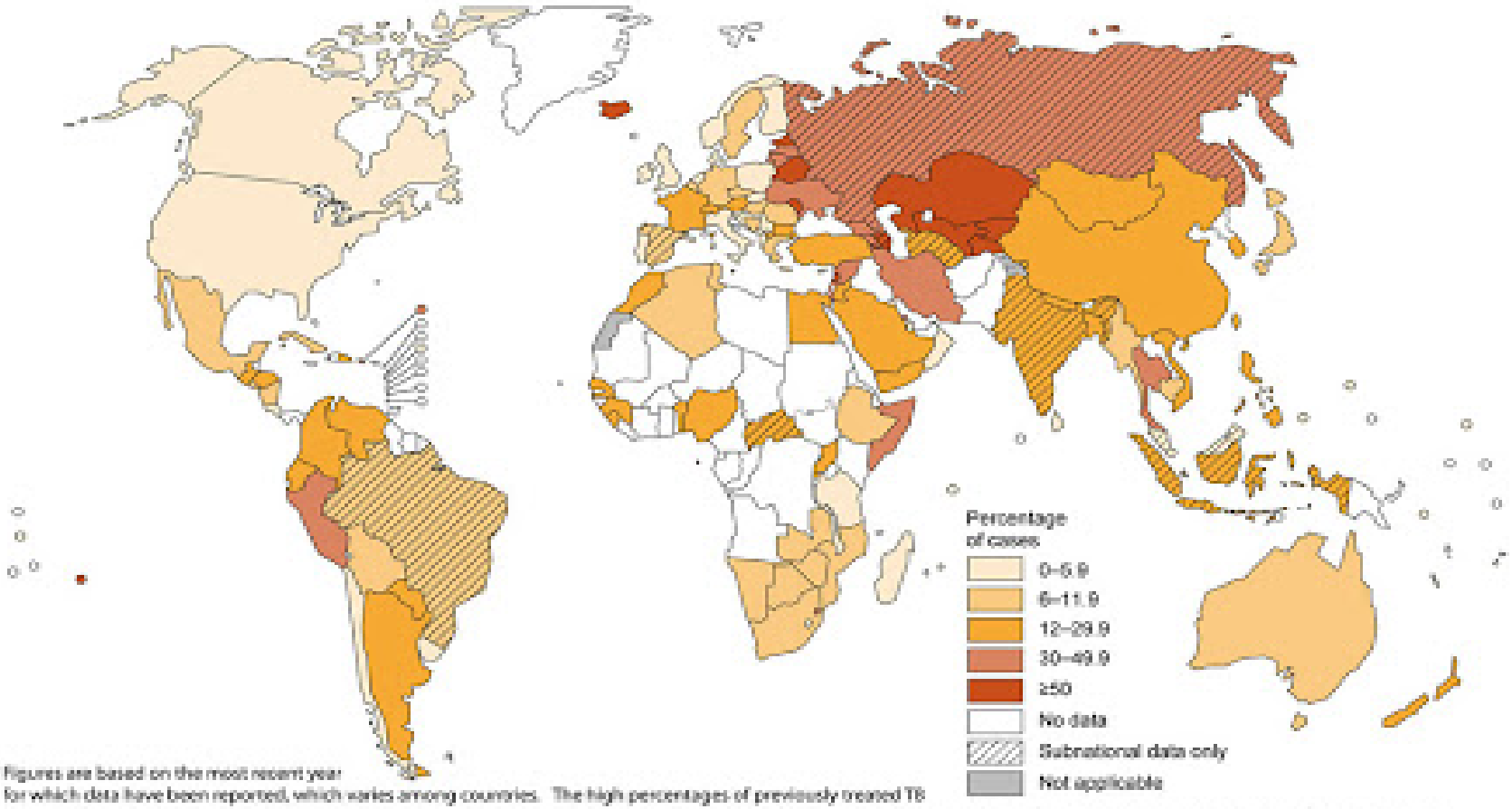
CLINICAL & LABORATORY

- **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)

CURRENT SCENARIO



Percentage of previously treated TB cases with multidrug-resistant tuberculosis*



* Figures are based on the most recent year for which data have been reported, which varies among countries. The high percentages of previously treated TB cases with MDR-TB in Bahrain, Bonaire – Saint Eustatius and Saba, Cook Islands, Iceland, Sao Tome and Principe, and Lebanon refer to only a small number of notified cases (< 10).

Data Source: *Global Tuberculosis Report 2013*. WHO, 2013.

World Health Organization

DRUG RESISTANCE

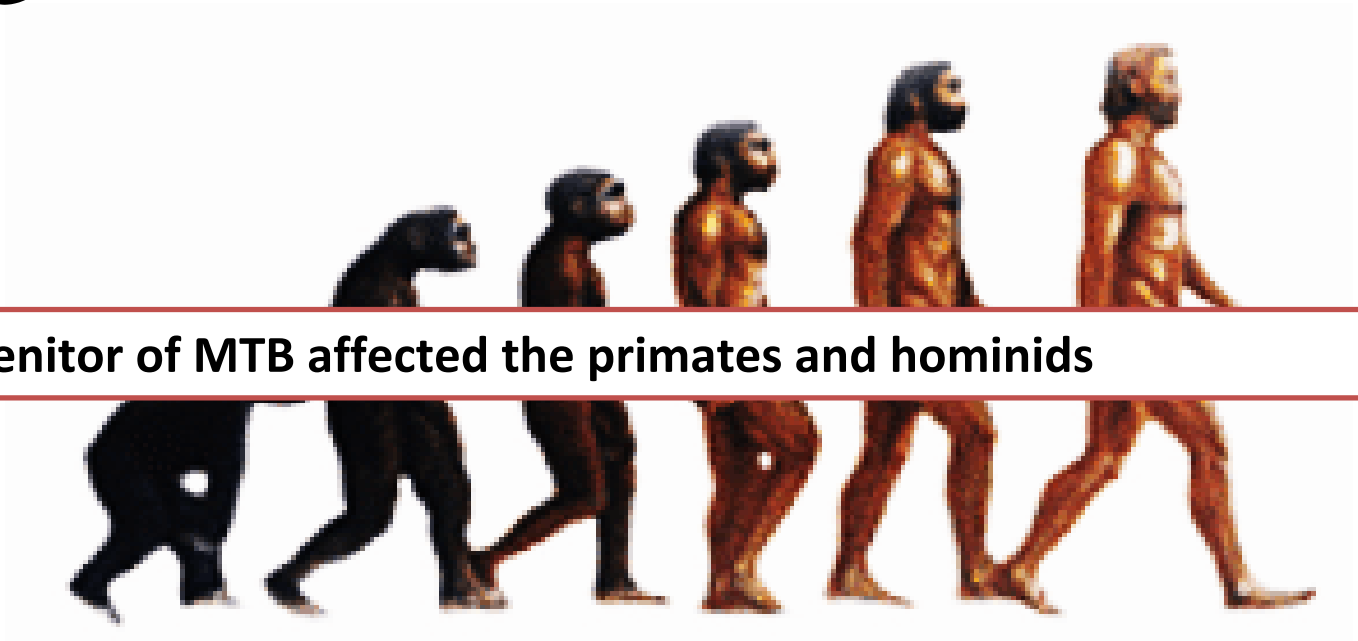
INDIAN SCENARIO...

- 2-3 % MDR in new smear positive cases.
- 15-20% MDR in previously treated cases.
- 6-9 % 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.**

3 million years ago

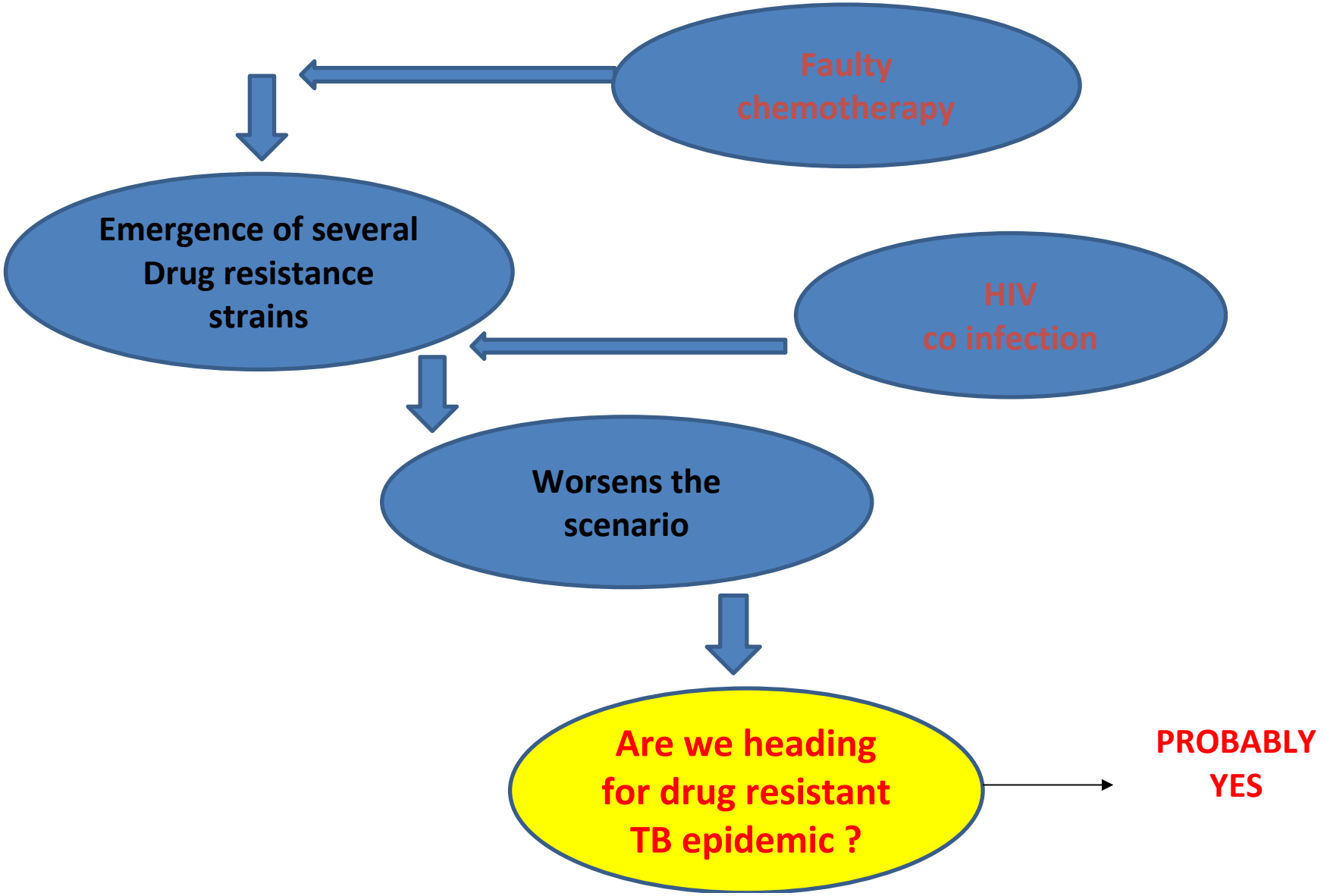


Progenitor of MTB affected the primates and hominids

Mutation continued….

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 : Variable 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 is a laboratory diagnosis .
- 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

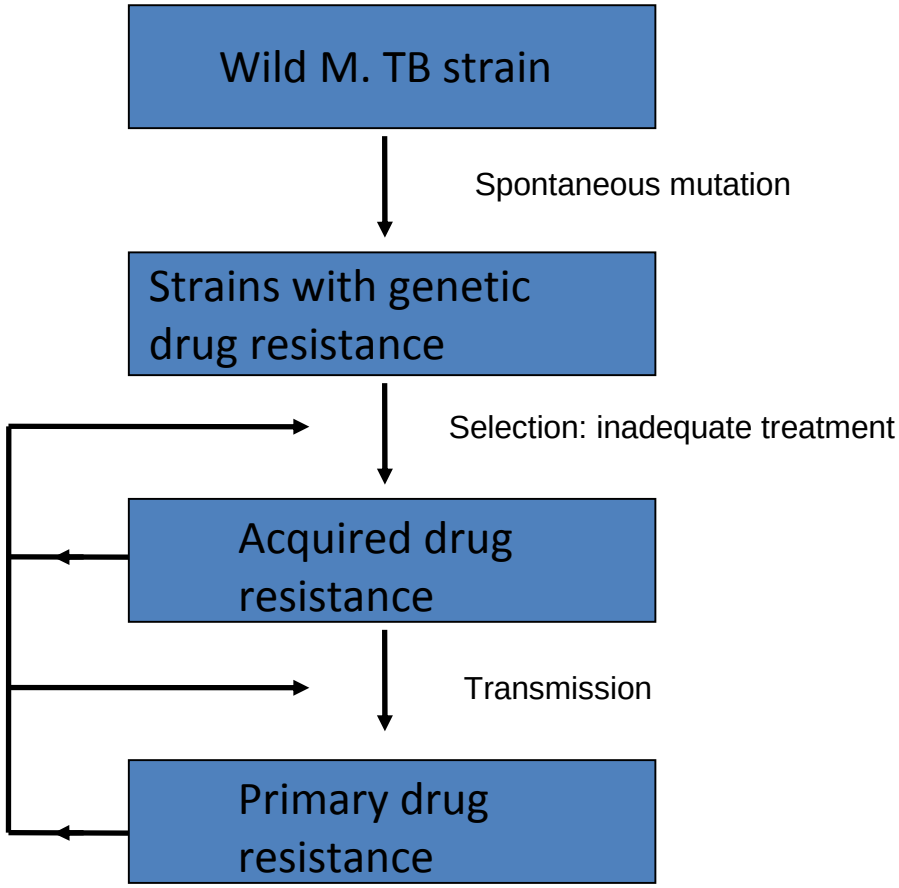
- **Think if there is history(MDR suspect)**
- Come from a country or region with high rates of drug resistance
- Had contact and significant exposure to MDR-TB in a household member or relative
- Are HIV positive. Acquired mono-rifampicin resistance is highly associated with HIV infection, especially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

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

Genesis of MDR TB

- Resistance is a man-made amplification of a natural phenomenon.
- Inadequate drug delivery is main cause of secondary drug resistance.
- Secondary drug resistance is the main cause of primary drug resistance due to transmission of resistant strains.
- MDR due to spontaneous mutations is not possible as the genes encoding resistance for anti TB are unlinked.

Development of anti-tuberculosis drug resistance



Pablos-Mendez et al. WHO, 1997

Clinical factors promoting resistance

- Delayed diagnosis and isolation
- Inappropriate drug regimen.
  - Inadequate initial therapy
  - Incomplete course of treatment
  - Inappropriate treatment modifications
  - Adding single drug to a failing regimen
  - Inappropriate use of chemoprophylaxis
- Poor adherence and incomplete F/U
- Failure to isolate MDR TB patients
- Failure to employ DOT
- Over the counter anti TB
- Faked drugs

Mechanism of resistance

- INH
- prodrug→ active form by catalase peroxidase
  - Chromosomally mediated
  - Mutation in the KAT G−Loss of catalase/peroxidase
  - Orf,inhA, ,Kas A
  - Mutation in mycolic acid synthesis
  - Regulators of peroxide response

  Resistance occur 1 in 10^6 replication.

Mechanism of resistance

- Rifampicin
- Rifampicin binds to the B subunit of RNApolymerase involved in the intiation & alongation of transcription.
  - Reduced binding to DNA dependent RNA polymerase by mutation in rpo B gene
    - •Clusters of mutations at "Rifampin Resistance Determining Region" (RRDR)
    - •Mutation in codon – 513,526,531–high level of drug resistance
    - •Mutation in the codon– 514,521,533 –low level of drug resistance
  - Reduced Cell wall permeability
  - Ripfampicin resistance occur 1 in 10^8 replications.

Drugs	Genes	Mechanism involved
INH	KatG, inhA	Cat peroxidase , enoyl reductase
Rifampicin	Rpo B	RNA polymerase
PZN	pncA ,rpsA	Pyrazinamidase,ribosomal protein1
Ethambutol	embB	arabinosyl transferase
Streptomycin	rpsL,rrs,gidB	16S Rrna,S12 RP
Quinolones	gyrA, gyr B,	DNA gyrase
Kanamycin/amikacin	rrs	16s rRNA
Ethionamide	ethA	Enoyl-ACP reductase
PAS	thyA,folA	Thymidylate synthase

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,

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

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 .**

TOTAL DURATION OF TREATMENT : MDR

- **18 months** after sputum conversion.
- **24 months** for chronic or extensive pulmonary damage.

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**

CATEGORY IV REGIMEN(XDR)

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

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

PREVENTION OF MDR

- **Effective implementation of DOTS.**
- **Strict counselling and monitoring of patients**
- **Ensure strict airborne infection control measures**
- **Nutritional support to the patients and society**
- **Effective implementation of immunization in new born's.**
- **Universal precautions.**

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.**

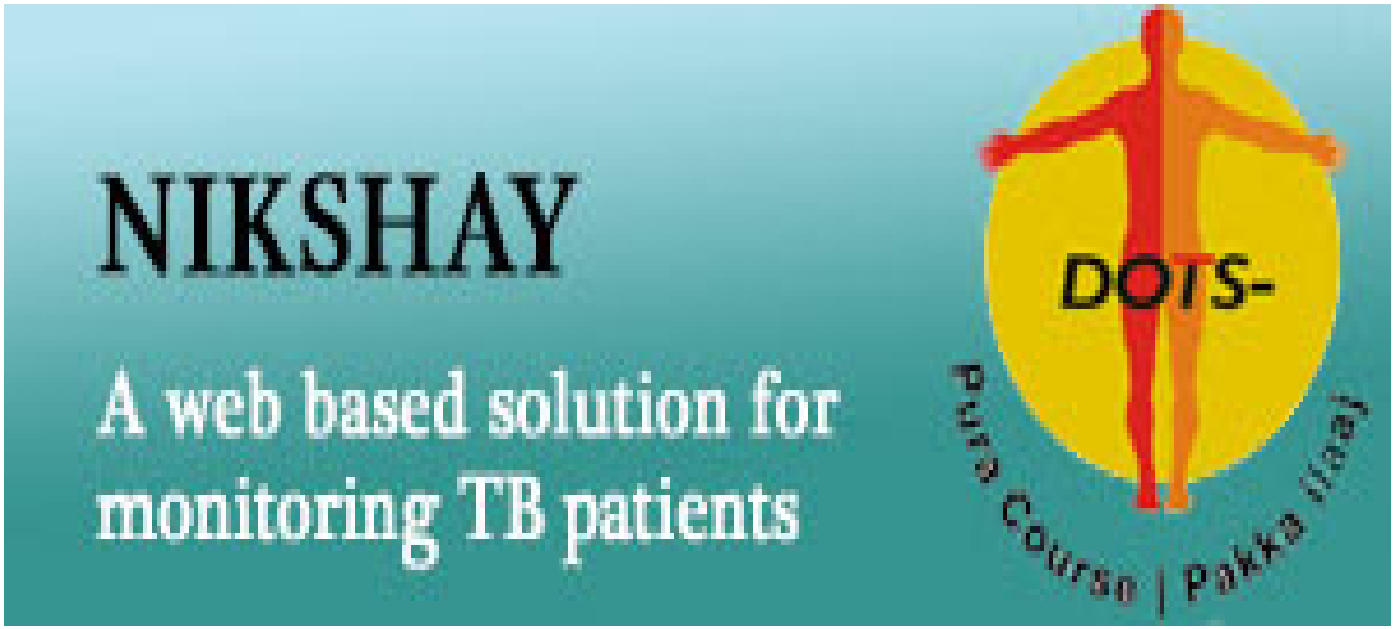
Summary....

- **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


NIKSHAY
A web based solution for
monitoring TB patients
DOTS-
Pura Course | Pakka Ilaj


THANK YOU
I
am
stopping
TB