
# Clinical Management : DR-TB

**Charoen Chuchottaworn MD.,**
**Senior Medical Advisor,**
**Central Chest Institute of Thailand,**
**Department of Medical Services, MoPH.**

# Tuberculosis Classification

- **Drug susceptible TB (DS-TB)**
- **Drug resistant TB (DR-TB**
  - **Mono-resistant**
  - **Poly-drug resistant**
  - **Multidrug resistant (MDR-TB)**
    - **+ Rifampicin resistant (RR-TB)**
  - **Pre-extensively drug resistant (Pre-XDR-TB)**
  - **Extensively drug resistant (XDR-TB)**

# Classification of Drug Resistant TB

- **Mono resistant : resist to one drug only**
- **Poly resistant : at least two drugs but not INH and RMP**
- **Multidrug resistant (MDR) : resist to INH and RMP ± other drugs**
- **Extensively drug resistant (XDR) : resist to INH and RMP and any fluoroquinolones and any aminoglycocide**
- **Extensively drug resistant (XDR) : resist to INH and RMP and either fluoroquinolones or any aminoglycocide**
- **Rifampicin resistant (RR-TB) : resist to RMP**

# Drug Resistant Tuberculosis Classification

## Primary resistant

- **Routine standard DST***
- **Routine molecular DST****

## Secondary resistant

- **Risk groups with rapid molecular DST**

* Recommended in every new TB patients if facilities are available (Thai Guideline 2017)

**If patient does not have risk of drug resistant, there is a high false positive resistant and need the second molecular test.

**Drug Resistant Tuberculosis is a "Man Made Phenomenon".**

**Drug Resistant Tuberculosis occurred from "Mis-management"**

**No Laboratory Result – No Diagnosis**

# Diagnosis of DR/MDR/XDR-TB

- Clinical signs and symptoms are not specific
- Chest X-ray is not specific
- Diagnosis of DR/MDR/XDR is based on result of drug susceptibility test
- Standard susceptibility test take time of 8-12 weeks to get result
- Rapid DST is recommended by WHO only for INH and RMP

# Risk Factors of Drug resistant TB

- Any history of treatment ( anti-TB drug exposure) : recurrent or treatment after default.
- Living in the same house with known case of drug resistant TB.
- Sputum smear positive after third month of treatment or beyond.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 9, 2010 VOL. 363 NO. 11

# Rapid Molecular Detection of Tuberculosis and Rifampin Resistance

Catharina C. Boehme, M.D., Pamela Nabeta, M.D., Doris Hillemann, Ph.D., Mark P. Nicol, Ph.D., Shubhada Shenai, Ph.D., Fiorella Krapp, M.D., Jenny Allen, B.Tech., Rasim Tahirli, M.D., Robert Blakemore, B.S., Roxana Rustomjee, M.D., Ph.D., Ana Milovic, M.S., Martin Jones, Ph.D., Sean M. O'Brien, Ph.D., David H. Persing, M.D., Ph.D., Sabine Ruesch-Gerdes, M.D., Eduardo Gotuzzo, M.D., Camilla Rodrigues, M.D., David Alland, M.D., and Mark D. Perkins, M.D.

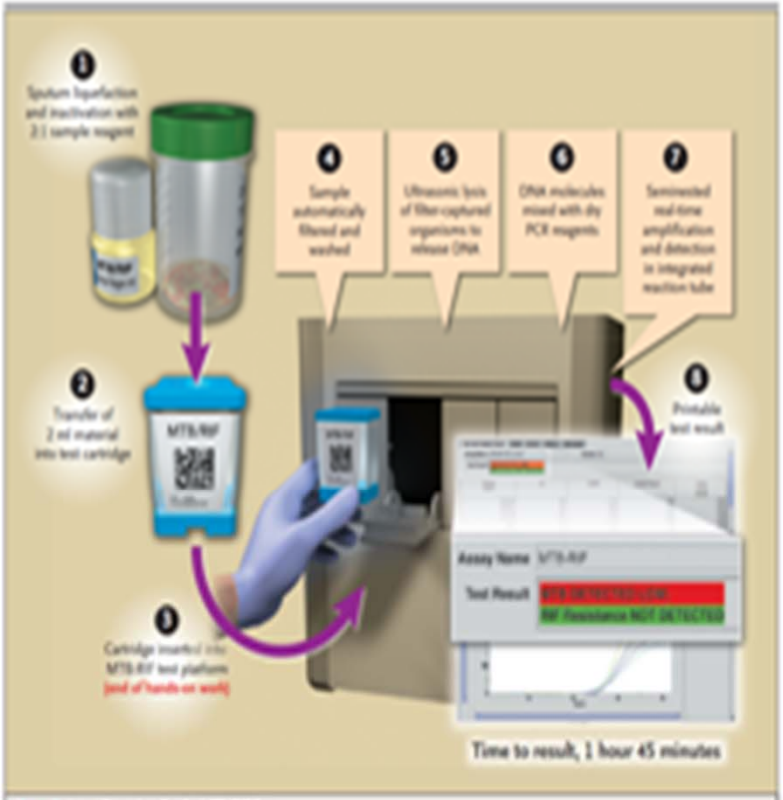



**Figure 2. Assay Procedure for the MTB/RIF Test.**

Two volumes of sample treatment reagent are added to each volume of sputum. The mixture is shaken, incubated at room temperature for 15 minutes, and shaken again. Next, a sample of 2 to 3 ml is transferred to the test cartridge, which is then loaded into the instrument. All subsequent steps occur automatically. The user is provided with a printable test result, such as "MTB detected, RIF resistance not detected." PCR denotes polymerase chain reaction.

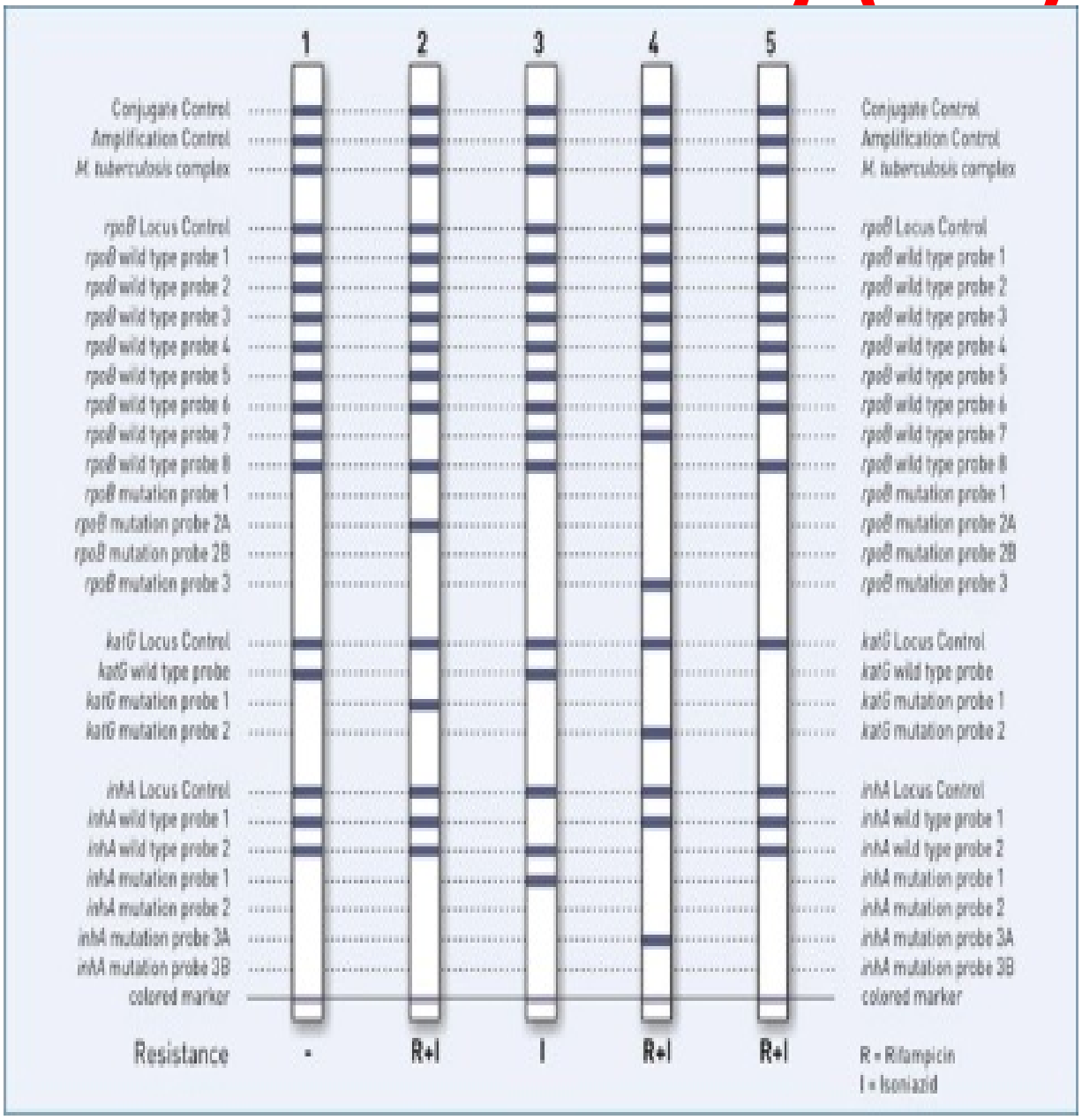
# Xpert MTB/RIF

- **Semi-automated technique**
- **Hemi-nested PCR of *rpoB* genes with 5 different color primers**
- **Result will be known in 2 hours**
- **Sensitivity of 96.7%, Specificity of 98.6% with PPV of 93.6% and NPV of 99.3%**
- เครื่องจะ รายงานเป็น **: M.tb detected or not detected**

  **: RMP resistant : detected or not detected**

  **: indetermined**

# Line Probe Assay (LPA)




TB or NTM

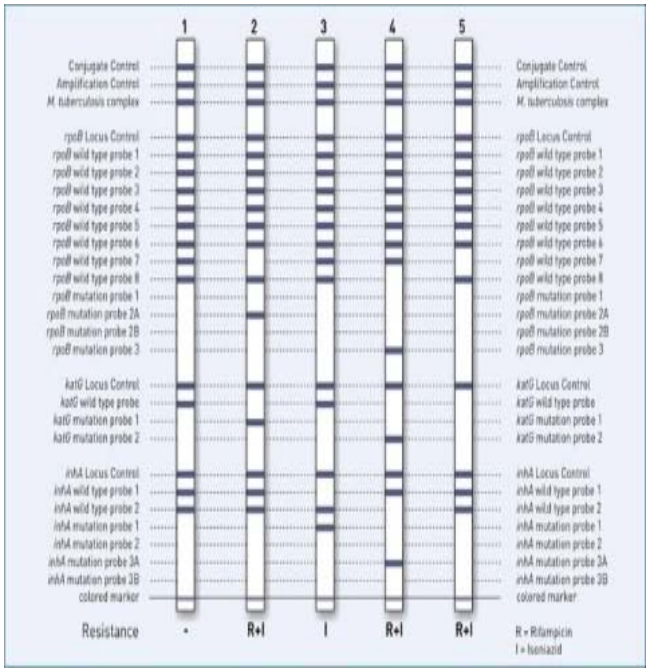
Wild type

Mutate type

## Xpert MTB/RIF


- Very sensitive for TB diagnosis
- Can tell only RMP resistant

## Line Probe Assay (LPA)




- Not sensitive for TB diagnosis
- Can tell INH + RMP resistant and also FQs + Ags resistant

# Causes of treatment failure

- Poor compliance
- Related to drugs
  - Poor quality
  - In-appropriated doses
  - Poor regimen
- Related to pharmacokinetics
  - Decreased absorption
  - Drugs are reaching the infection site
  - Drug-drug interaction
- Related to patient's condition
  - Poor general condition of patient
  - Adverse drug reaction
- Related to drug resistance

# Recommended Treatment of Mono- and Poly-drug Resistant

**Before changing regimen, Rapid DST should be done**

| Resist to | Recommended Regimen | Duration |
|---|---|---|
| INH | RMP + PZA + EMB | 9 months |
| INH + EMB (± S*M*) | RMP + PZA + LVX | 9 - 12 months |
| INH + EMB + PZA (± SM) | RMP + ETA +LVX + KM (2-3 months) | 18 months |
| RMP | Shorter MDR regimen | |

# New Classification of Second Line Drugs (2016)

- **Group A : Levofloxacin, Moxifloxacin**
- **Group B : Kanamycin, Amikacin, Capreomycin**
- **Group C : Ethionamide, Prothionamide**
  **: Cycloserine, Terazidone**
  **: Linezolid, Clofazimine**
- **Group D**
  **D1 : Pyrazinamide, Ethambutol, INH high dose**
  **D2 : Bedaquiline, Delamanid**
  **D3 : PAS, Imipenem/Cilastatin, Meropenem**
  **: Amoxicillin/Clavulanate**

# Principle of MDR-TB Treatment

- Number of drug used to treatment MDR : at least 4 drugs that are likely to sensitive
- Duration of using aminoglycoside injection : 6 months and 4 months after culture conversion
- Duration of treatment : 18 months after culture negative
- Any case with known MDR from DST , treatment must be changed to MDR regimen

# Proposed Treatment Regimen

- **Kanamycin or Amikacin for 6 months because less likely to resist**
- **Levofloxacin is the recommended fluoroquinolone ( listed in the essential drug list)**
- **Ethionamide**
- **Cycloserine**
- **± PAS**

ถ้ามียา **first line drugs** ที่เชื้อยังไวต่อยา สามารถจะนำมาแทนได้

# Monitor and Evaluation of Treatment

- **Smear and culture should be done every month for the first 6 months or until negative and then every 2 months**
- **Chest X-ray should be done very 6 months**
- **Body weight is an good indicator of clinical response, symptoms and signs are insensitive**
- **Don't forget to treat co-morbidities**
- **Consider surgical intervention in every case if patient has unilateral lung lesion and general condition is suitable for operation.**

# WHO RECOMMENDATIONS

## ON THE USE OF THE SHORTER MDR-TB REGIMEN

In May 2016, WHO issued a conditional recommendation on the use of the shorter MDR-TB regimen. A flow chart outlining selection of patients on the shorter MDR-TB regimen is presented below.

**Intensive Phase 4-6 months**

- Moxifloxacin
- Clofazimine
- Pyrazinamide
- Ethambutol
- Ethionamide
- High-dose INH
- Kanamycin

**Continuation phase 5 months**

- Moxifloxacin
- Clofazimine
- Pyrazinamide
- Ethambutol

**Treatment of 9-11 months instead of conventional 20 - 24 months**

# The Standardised Treatment Regimen of Anti-TB Drugs for Patients with MDR-Tb (STREAM) Trial

- The first randomised control trial in the world for MDR-TB.
- Nine month regimen vs Standard 20 month regimen for MDR-TB.

| | favourable outcome |
|---|---|
| Nine month regimen | 78.1 % |
| 20-24 months regimen | 80.6 % !!!! |

- EKG monitoring was useful and required throughout treatment.
- Nine month regimen reduces pill burden, costs to both the health system and patients.

# WHO RECOMMENDATIONS

## ON THE USE OF THE SHORTER MDR-TB REGIMEN

### CHOOSING THE MDR-TB TREATMENT REGIMEN IN PATIENTS WITH CONFIRMED RIFAMPICIN-RESISTANT OR MDR-TB

**CRITERIA:** Do any of the following apply ?

- ✓ Confirmed resistance or suspected ineffectiveness to a medicine in the shorter MDR-TB regimen (except isoniazid resistance)
- ✓ Exposure to ≥1 second-line medicines in the shorter MDR-TB regimen for >1 month
- ✓ Intolerance to ≥1 medicines in the shorter MDR-TB regimen or risk of toxicity (e.g. drug-drug interactions)
- ✓ Pregnancy
- ✓ Extrapulmonary disease
- ✓ At least one medicine in the shorter MDR-TB regimen not available in the programme

**NO**

**Shorter MDR-TB regimen**

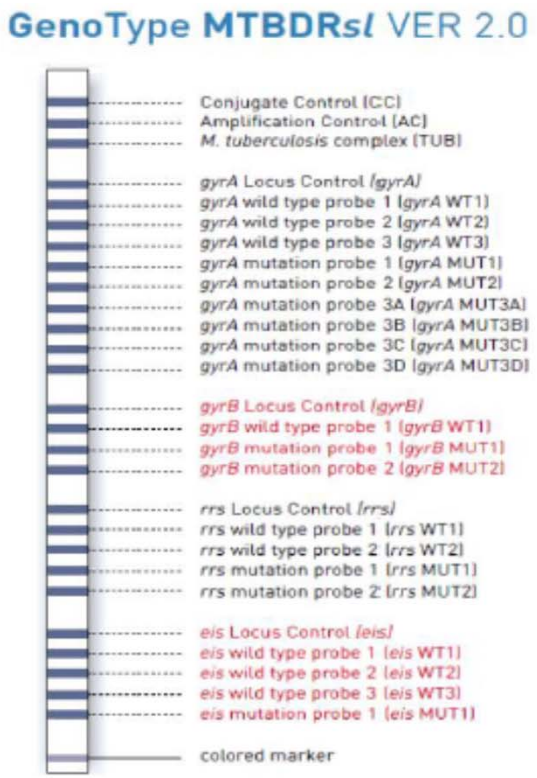
**FAILING REGIMEN, DRUG INTOLERANCE, RETURN AFTER INTERRUPTION >2 MONTHS, EMERGENCE OF ANY EXCLUSION CRITERION**

**YES**

**Individualised ("conventional") MDR/RR-TB regimens**

**TUBERCULOSIS DIAGNOSTICS**

# MOLECULAR LINE-PROBE ASSAY FOR THE DETECTION OF RESISTANCE TO SECOND-LINE ANTI-TB DRUGS (SL-LPA)




**Assay results pattern**

## POLICY RECOMMENDATION

WHO recommends the use of the SL-LPA for patients with confirmed rifampicin-resistant TB or MDR-TB as the initial test to detect resistance to fluoroquinolones and the second-line injectable drugs, instead of phenotypic culture-based drug-susceptibility testing (DST).

# New Classification of Second Line Drugs (2016)

- **Group A :** ~~Levofloxacin, Moxifloxacin~~
- **Group B :** ~~Kanamycin, Amikacin~~, **Capreomycin**
- **Group C :** ~~Ethionamide, Prothionamide~~
  : ~~Cycloserine, Terazidone~~
  : **Linezolid, Clofazimine**
- **Group D**
  - **D1 :** Pyrazinamide, Ethambutol, INH high dose
  - **D2 :** Bedaquiline, Delamanid
  - **D3 :** PAS, Imipenem/Cilastatin, Meropenem
    : Amoxicillin/Clavulanate

# Conclusions :

- Drug resistant TB has became a serious public health problem because resistant compromised outcomes of standard 6 month regimen.
- Diagnosis of drug resistant TB is based on laboratory test and availability of laboratory facilities is issue to consider.
- Treatment of DR-TB is based on recommended regimen in National Guideline which was considered from survey of susceptibility pattern of second line drugs in Thailand.
- Shorter MDR regimen is a recommended regimen and proved by RCT.