Recent Advances in The Treatment of Mycobacterium Tuberculosis

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Who had TB?
Outline

• Case histories
• TB
  – Introduction and treatment
• LTBI
  – Definition and treatment
• Drug resistant TB
  – Definition and treatment
Case 1

• A 35 year old man presented with
  – Cough for 3/12
  – Fever on and off 3/12
  – LOA and LOW

• CXR – RUL consolidation

• Sputum AFB
  – Positive +++
Know your enemy!
National TB Strategy/Policies

- National Strategic Plan for Tuberculosis Control, 2011-2015 was launched in 2011
- It is in line with the 6 Strategies of TBC by WHO / Stop TB Org.
- Fund is allocated as proposed by National TB Coordinator under CDC, calculated on basis of planning as well as outcome of previous year
- Fund is solely by Ministry of Health, under jurisdiction of Finance Ministry

<table>
<thead>
<tr>
<th>TARGET</th>
</tr>
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<tbody>
<tr>
<td>1  To Reduce 50% Inc. Rate by the year 2015 Relative to 1990 Level</td>
</tr>
<tr>
<td>2  To Increase 95% Case Detection Rate by year 2015</td>
</tr>
<tr>
<td>3  To Achieve Beyond 85% Cure Rate by year 2015</td>
</tr>
<tr>
<td>4  To Achieve Beyond 85% Treatment Success Rate by year 2015</td>
</tr>
<tr>
<td>5  To Reduce 50% TB Death Rate By the year 2015 Relative to 1990 Level</td>
</tr>
</tbody>
</table>
# TB Indicators In 1990, 2013 and Target for 2015

<table>
<thead>
<tr>
<th>Indicator</th>
<th>1990</th>
<th>2013</th>
<th>Target 2015</th>
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<tbody>
<tr>
<td>Incidence of TB</td>
<td>127</td>
<td>81</td>
<td>63</td>
</tr>
<tr>
<td>(per 100,000) population</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case Detection Rate (%)</td>
<td></td>
<td>95%</td>
<td>95%</td>
</tr>
<tr>
<td>(％)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cure Rate (%)</td>
<td>-</td>
<td>77%</td>
<td>85%</td>
</tr>
<tr>
<td>Mortality Rate</td>
<td>8</td>
<td>5.4</td>
<td>3</td>
</tr>
<tr>
<td>(per 100,000) population</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Know your drugs!
Anti TB Medications

- Rifampicin
- Isoniazid
- Ethambutol
- Pyrazinamide
- Streptomycin
Anti TB Medications
# Fixed Dose Combinations

<table>
<thead>
<tr>
<th>Weight</th>
<th>Tablets</th>
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<tbody>
<tr>
<td>30 – 39 kg</td>
<td>2</td>
</tr>
<tr>
<td>40 – 54 kg</td>
<td>3</td>
</tr>
<tr>
<td>55 – 70 kg</td>
<td>4</td>
</tr>
<tr>
<td>&gt; 70 kg</td>
<td>5</td>
</tr>
</tbody>
</table>
Duration of treatment

- 2 months of intensive
  - EHRZ
- 4 months of maintenance
  - HR

- TB meningitis (12 months)
- TB joints and bones (9 – 12 months)
Four-Month Moxifloxacin-Based Regimens for Drug-Sensitive Tuberculosis


ABSTRACT

BACKGROUND

Early-phase and preclinical studies suggest that moxifloxacin-containing regimens could allow for effective 4-month treatment of uncomplicated, smear-positive pulmonary tuberculosis.
STAND Study - ongoing

• Phase 3 study
• Moxifloxacin 400mg/PA-824 100mg/Pyrazinamide 1500mg (4 months)
• or Moxifloxacin 400mg/PA – 824 200mg/Pyrazinamide 1500mg (4 months/6 months)
• versus EHRZ fixed dose combination
Case 2

• A 29 year old woman with underlying rheumatoid arthritis
• Failed DMARDS awaiting Infliximab infusion
• Clinically
  – asymptomatic
• CXR
  – normal
• Mantoux
  – 15mm
Latent TB Infection (LTBI)

LTBI is the presence of *M. tuberculosis* organisms (tubercle bacilli) **without signs and symptoms or radiographic or bacteriologic evidence of TB disease.**
IDENTIFYING RISK FACTORS THAT LEAD TO DEVELOPMENT OF TB DISEASE
Persons at high risk for developing TB disease fall into 2 categories:

- Those who have an increased likelihood of exposure to persons with TB disease
- Those with clinical conditions that increase their risk of progressing from LTBI to TB disease
Increased Likelihood of Exposure to Persons with TB Disease

Persons at risk for exposure to persons with TB disease include:

- Close contacts to person with infectious TB
- Residents and employees of high-risk congregate settings (e.g., correctional facilities, homeless shelters, health care facilities)
- Recent immigrants from TB-endemic regions of the world
Increased Risk for Progression to TB Disease

Persons more likely to progress from LTBI to TB disease include:

- HIV-infected persons
- Those with a history of prior, untreated TB or fibrotic lesions on chest radiograph
- Children $\leq 5$ years with a positive TST
Increased Risk for Progression to TB Disease - 2

Persons more likely to progress from LTBI to TB disease include:

- Underweight or malnourished persons
- Injection drug users
- Those receiving TNF-α antagonists for treatment of rheumatoid arthritis or Crohn’s disease
Increased Risk for Progression to TB Disease

Persons more likely to progress from LTBI to TB disease include:

- Those with certain medical conditions such as:
  - Silicosis
  - Diabetes mellitus
  - Chronic renal failure or on hemodialysis
  - Solid organ transplantation (e.g., heart, kidney)
  - Carcinoma of head or neck
  - Gastrectomy or jejunoilial bypass
Testing for *M. tuberculosis* Infection

- There are two testing methods available for the detection of *M. tuberculosis* infection:
  - Mantoux tuberculin skin test (TST)
  - Interferon-gamma release assays (IGRA)

- These tests do not exclude LTBI or TB disease.
- Decisions about medical and public health management should include other information, and not rely only on TST or IGRA results.
Mantoux Tuberculin Skin Test

Skin test that produces delayed-type hypersensitivity reaction in persons with *M. tuberculosis* infection

- TST is useful for:
  - Determining how many people in a group are infected (e.g., contact investigation)
  - Examining persons who have symptoms of TB disease
# TST Interpretation

<table>
<thead>
<tr>
<th>Positive TST Reaction (Measurement)</th>
<th>Type of Individual</th>
</tr>
</thead>
</table>
| ≥5 mm                              | • HIV-infected persons  
• Organ transplant recipients  
• Persons who are immunosuppressed for other reasons (such as those taking the equivalent of >15 mg/day prednisolone for ≥1 month or taking TNF-α antagonists) |
| ≥15 mm                             | • Individuals from countries with low incidence of TB |
| ≥10 mm                             | • All other high risk individuals |
Interferon-Gamma Release Assays (IGRAs)

- Whole-blood test used to detect *M. tuberculosis* infection
- Two U.S. Food and Drug Administration (FDA) approved IGRAs are commercially available in the U.S.:
  - QuantiFERON®-TB Gold-in-tube test (QFT-GIT)
  - T.SSPOT®.TB test (T-Spot)
# Interpretation of IGRA Test Results

<table>
<thead>
<tr>
<th>IGRA Test</th>
<th>Results Reported as</th>
</tr>
</thead>
<tbody>
<tr>
<td>QFT-GIT</td>
<td>Positive, negative, indeterminate</td>
</tr>
<tr>
<td>T-Spot</td>
<td>Positive, negative, indeterminate, borderline</td>
</tr>
</tbody>
</table>

Note: Laboratory should provide both quantitative and qualitative results
Treatment of LTBI – Milestones - 1

1965: American Thoracic Society (ATS) recommends treatment of LTBI for those with previously untreated TB, tuberculin skin test (TST) converters, and young children.

1967: Recommendations expanded to include all TST positive reactors (≥ 10 mm).
1974: CDC and ATS guidelines established for pretreatment screening to decrease risk of hepatitis associated with treatment

Treatment recommended for persons ≤ 35 years of age
1983: CDC recommends clinical and laboratory monitoring of persons ≥ 35 who require treatment for LTBI

1998: CDC recommends 2 months of rifampin (RIF) plus pyrazinamide (PZA) as an option for HIV-infected patients (later changed)
Treatment of LTBI – Milestones - 4

2000: CDC and ATS issue updated guidelines for targeted testing and LTBI treatment

9-month regimen of isoniazid (INH) is preferred

2-month regimen of RIF and PZA and a 4 month regimen of RIF recommended as options (later changed)

1 MMWR June 9, 2000; 49(No. RR-6)
http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4906a1.htm
Treatment of LTBI – Milestones -5

2001: Owing to liver injury and death associated with 2-month regimen of RIF and PZA, use of this option de-emphasised in favour of other regimens

2003: 2-month regimen of RIF and PZA generally not recommended — to be used only if the potential benefits outweigh the risk of severe liver injury and death

2 MMWR August 31, 2001; 50(34): 733-735 - http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5034a1.htm

3 MMWR August 8, 2003; 52(31): 735-739 - http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5231a4.htm
Treatment of LTBI – Milestones -6

2011: CDC recommends 12-doses (3 months) of isoniazid (INH) and rifapentine (RPT) as an option equal to the standard 9-month INH regimen for certain groups*

*MMWR. Recommendations for Use of an Isoniazid–Rifapentine Regimen with Direct Observation to Treat Latent Mycobacterium tuberculosis Infection
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?s_cid=mm6048a3_w
Evaluation of Persons with Positive TB Test Results

Person has a positive test for TB infection

TB disease ruled out

Consider for LTBI treatment

Person accepts and is able to receive treatment of LTBI

Develop a plan of treatment with patient to ensure adherence

If person refuses or is unable to receive treatment for LTBI, follow-up TST or IGRA and serial chest radiographs are unnecessary

Educate patient about the signs and symptoms of TB disease
## Treatment Regimens for Latent TB Infection

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Duration</th>
<th>Interval</th>
<th>Minimum Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>9 months</td>
<td>Daily</td>
<td>270</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice weekly</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>6 months</td>
<td>Daily</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice weekly</td>
<td>52</td>
</tr>
<tr>
<td>Isoniazid &amp; Rifapentine</td>
<td>3 months</td>
<td>Once weekly</td>
<td>12</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>4 months</td>
<td>Daily</td>
<td>120</td>
</tr>
</tbody>
</table>

**Note:** Rifampin (RIF) and Pyrazinamide (PZA) should not be offered to persons with LTBI. RIF and PZA should continue to be administered in multidrug regimens for the treatment of persons with TB disease.
Drug resistance TB

• Mono resistance
  – Resistance to one first line drug

• Poly resistance
  – Resistance to more than one first line drugs other than R and H

• Multi drug resistance (MDR)
  – Resistance to R and H

• Extensive drug resistance
  – MDR + Fluoroquinolones + second line injectables
Case 3

• A 45 year old man with previous history of TB interrupted treatment
• productive cough 3/12
• fever
• CXR
  – RUZ fibrosis and LUZ consolidation
• Sputum
  – AFB 3+
  – Culture resistant to INH and RIF
Drug resistance TB

Figure 1.1 Two pathways leading to drug-resistant TB

Acquired drug resistance

Primary drug resistance

Exposure to drug-susceptible TB

Infection with drug-susceptible TB

Active drug-susceptible TB

Exposure to anti-TB drug/s

Active drug-resistant TB

Factors that can prevent transmission or progression
1. Infection control and environmental interventions
2. Good host immunity
3. Latent TB treatment
4. High quality diagnosis, treatment, patient support and management of drug-resistant TB

Exposure to anti-TB drug/s

Further drug resistance

Note: Pathways to development of drug-resistant TB. Arrows represent progression along the two pathways. Numbers represent factors that can contribute to the prevention of progression.
MDR Drugs regime

**STEP 1**
Choose an injectable (Group 2)
- Kanamycin
- Amikacin
- Capreomycin

Choose a drug based on DST and treatment history. Streptomycin is generally not used because of high rates of resistance in patients with MDR-TB.

**STEP 2**
Choose a higher generation fluoroquinolone (Group 3)
- Levofloxacin
- Moxifloxacin

Use a later generation fluoroquinolone. If levofloxacin (or ofloxacin) resistance is documented, use moxifloxacin. Avoid moxifloxacin if possible when using bedaquiline or delamanid (see Annexes 4.1–4.2).

**STEP 3**
Add Group 4 drugs
- Cycloserine/terizidine
- Para-aminosalicylic acid (PAS)
- Ethionamide/prothionamide

Add two or more Group 4 drugs until there are at least four second-line anti-TB drugs likely to be effective. Ethionamide/prothionamide is considered the most effective Group 4 drug. Consider treatment history, side-effect profile, and cost.
**STEP 4**

**Add Group 1 drugs**

- Pyrazinamide
- Ethambutol

Pyrazinamide is routinely added in most regimens; ethambutol can be added if the criteria for an effective drug are met (see Section 5.7.1 for definition of “effective drug”). If isoniazid is unknown or pending it can be added to the regimen until DST results become available, see Section 5.8.

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**STEP 5**

**Add Group 5 drugs**

- Bedaquiline
- Delamanid
- Linezolid
- Clofazimine
- Amoxicillin/clavulanate
- Imipenem/cilastatin plus clavulanate
- Meropenem plus clavulanate
- High-dose isoniazid
- Clarithromycin
- Thioacetazone

Consider adding Group 5 drugs if four second-line anti-TB drugs are not likely to be effective from Groups 2–4. If drugs are needed from this group, it is recommended to add two or more. DST is not standardized for the drugs in this group. The drug–drug interactions between bedaquiline and delamanid have not been established and a recommendation about its combined use is not made in the WHO interim policy on these two drugs.
Global TB drug pipeline

Discovery*
- Lead Optimization
  - Nitroimidazoles
  - Mycobacterial Gyrase Inhibitors
  - Rimenophenazines
  - Diarylquinoline
  - Translocase-1 Inhibitor
  - MGyrX1 Inhibitor
  - InhA Inhibitor
  - GyrB Inhibitor
  - LeuRS Inhibitor
  - Pyrazinamide Anallogues
  - Spectinamides

Preclinical Development
- CPZEN-45
- SQ641
- SQ609
- DC-159a
- Q201
- BTZ043
- AZD5847

Phase 1
- Bedaquiline (TMC-207)
- PA-824
- Linezolid
- SQ-109
- Rifapentine
- Novel Regimens†
- PNU-100480

Phase 2
- Gatifloxacin
- Moxifloxacin
- Rifapentine
- Delamanid (OPC67683)

Phase 3

Stop TB Partnership
STREAM

The Evaluation of a Standardised Treatment Regimen of Anti-Tuberculosis Drugs for Patients with MDR-TB
STREAM study design

• STREAM is a randomised controlled trial of non-inferiority design currently being conducted in Ethiopia, South Africa and Vietnam

• The control regimen is the locally used WHO recommended regimen in the participating countries

• The study regimen is closely similar to the regimen used by Van Deun in Bangladesh with the exception that high dose moxifloxacin replaces high dose gatifloxacin
STREAM

• **Regimen C:** a 40-week all-oral regimen consisting of bedaquiline, clofazimine, ethambutol, levofloxacin, and pyrazinamide given for 40 weeks supplemented by isoniazid and prothionamide for the first 16 weeks (intensive phase).

• **Regimen D:** a 28-week regimen consisting of bedaquiline, clofazimine, levofloxacin, and pyrazinamide given for 28 weeks supplemented by isoniazid and kanamycin for the first 8 weeks (intensive phase).
Treatment phases of investigational regimens

Regimen A: Locally used WHO-approved MDR-TB regimen
- KM + INH + PTO +
- MFX + CFZ + EMB + PZA

Regimen B:
- KM + INH + PTO +
- MFX + CFZ + EMB + PZA

Regimen C:
- INH + PTO +
- BDQ + LFX + CFZ + EMB + PZA

Regimen D:
- KM + INH + BDQ +
- LFX + CFZ + PZA

Time:
- Week 0
- Week 8
- Week 16
- Week 28
- Week 40

First dose

- Intensive phase
- Continuation phase

Locally used WHO-approved MDR-TB regimen (treatment phases may vary)
Vaccines
<table>
<thead>
<tr>
<th>Target populations</th>
<th>Infection/Disease</th>
<th>Vaccine type</th>
<th>Advanced Candidates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant</td>
<td>Uninfected</td>
<td>Preexposure/Preventive BCG replacement</td>
<td>rBCG: VPM1002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>r-Mtb: MTBVac</td>
</tr>
<tr>
<td>Infant</td>
<td>Uninfected BCG</td>
<td>Preexposure/Preventive Prime-boost</td>
<td>Viral vectored: MVA85A/Aeras-485</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>Protein/adjuvant: H4:IC-31</td>
</tr>
<tr>
<td>Adolescent/Adult</td>
<td>LTBI/BCG (TST⁺)</td>
<td>Postexposure/Preventive Prime-boost</td>
<td>Viral vectored: MVA85A/Aeras-485</td>
</tr>
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<td></td>
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<td>Protein/adjuvant: M72:AS01E</td>
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<tr>
<td></td>
<td></td>
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<td>H56:IC-31</td>
</tr>
<tr>
<td></td>
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<td>ID93:GLA-SE</td>
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<tr>
<td>Adolescent/Adult</td>
<td>Active TB</td>
<td>Therapeutic</td>
<td>Killed mycobacteria: M. indicus pranii</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>M. vaccae</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RUTI</td>
</tr>
</tbody>
</table>

Weiner 3rd J, Kaufmann SHE JIM 2014
Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomised, placebo-controlled phase 2b trial

Michele D Tameris*, Mark Hatherill*, Bernard S Landry, Thomas J Scriba, Margaret Ann Snowden, Stephen Lockhart, Jacqueline E Shea, J Bruce McClain, Gregory D Hussey, Willem A Hanekom, Hassan Mahomed†, Helen McShane†, and the MVA85A 020 Trial Study Team

The primary study outcome was safety (incidence of adverse and serious adverse events) in all vaccinated participants.

Primary efficacy endpoint was incident tuberculosis.

No serious adverse events due to MVA85A.

Efficacy against incident tuberculosis was 17.3% (95% CI −31.9 to 48.2).
Summary

• Pulmonary TB is easy to treat
  – monitoring
  – adherence

• Not all LTBI need to be treated
  – high risk patient only

• MDR TB is avoidable
  – refer to specialist centre/pulmonologist
Ringo Starr
Thank You