Mycobacterium tuberculosis infections

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Regarding tuberculosis

The world tuberculosis refers to:

1. M TB complex
2. What an individual with a + PPD has
3. Exposure to TB
4. Disease
5. Exposure, latency and disease
Tuberculosis

Communicable disease caused by *Mycobacterium tuberculosis*, or the acid-fast tubercle bacillus.
TB in History

- Identified in Stone Age skeletons
- Prevalent in Ancient Egypt
- Uprise in the Middle Ages after the Black death.
- Disease of poverty, crowding, war, famine, displacement, insalubrious life & work
Abreugraphy or chest photofluorography (mass miniature radiography) is a photo-fluorography for mass TB screening using miniature (50 to 100 mm) photograph of the screen of an x-ray fluoroscopy first developed in 1936 by Dr. Manoel Dias de Abreu, Brazil.

January 4- National Abreugraphy Day in Brazil
1/3 of the world’s population has been infected with TB
Countries with 80% of TB cases worldwide

Fonte: WHO 2004
Deaths in adults due to infectious diseases in developing countries 
(1997 a 2020*)

1997
- TB: 51.4%
- Inf. respiratórias: 10%
- Outras: 23.5%
- Malária: 6.4%
- HIV: 8.6%

2020
- TB: 54.7%
- Inf. respiratórias: 2.6%
- Malária: 1.3%
- Outras: 1.3%
- HIV: 37.1%

Fonte: Banco Mundial, 1997
* Estimativa
Epidemiology

In the mid-1980s, a resurgence of TB occurred in the US.

Since 1993, TB rates have been declining in the U.S.

However:

- TB cases continue to be reported in every state.
- **Drug-resistant TB** continues to be reported in nearly all states.
- An estimated 10 to 15 million are infected with *M tb* in the US.
- With no intervention, **10%** will develop TB throughout their lifetime.

25% of newly diagnosed cases are foreign-born.
TB Case Rates, United States, 2010

- ≤ 3.5 (year 2000 target)
- 3.6 - 5.6
- > 5.6 (national average)

Rate: cases per 100,000

D.C.
TB incidence coefficient per state, Brazil 2008

Overall incidence: 20.6/100,000

Porto Alegre

Fonte: MS / SVS / SINAN e IBGE
* Casos por 100.000 habitantes
Epidemiology

Higher risk groups for TB:
- First generation immigrants from high risk countries.
- Native Americans
- Alaskan natives
- Homeless individuals
- Individuals in correctional facilities
- Patients with diabetes mellitus, lymphoma, immunosuppression
- Patients with prolonged or high dose use of steroids.
- Individuals from urban/low income areas.
**Table 1. Persons at Increased Risk Who Should Be Tested for Latent Tuberculosis Infection.**

<table>
<thead>
<tr>
<th>Risk</th>
<th>Examples of Persons with Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased risk of exposure to infectious cases</td>
<td>Persons with recent close contact with persons known to have active tuberculosis*</td>
</tr>
<tr>
<td></td>
<td>Health care workers who work at facilities where patients with tuberculosis are treated</td>
</tr>
<tr>
<td>Increased risk of tuberculosis infection</td>
<td>Foreign-born persons from countries with a high prevalence of tuberculosis</td>
</tr>
<tr>
<td></td>
<td>Homeless persons</td>
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<tr>
<td></td>
<td>Persons living or working in facilities providing long-term care</td>
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<tr>
<td></td>
<td>HIV-infected persons</td>
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<tr>
<td></td>
<td>Persons with recent tuberculosis infection†</td>
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<tr>
<td></td>
<td>Injection-drug users</td>
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<tr>
<td></td>
<td>Patients with end-stage renal disease</td>
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<td></td>
<td>Patients with silicosis</td>
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<tr>
<td></td>
<td>Patients with diabetes mellitus</td>
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<td></td>
<td>Patients receiving immunosuppressive therapy</td>
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<tr>
<td></td>
<td>Patients with hematologic cancers</td>
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<tr>
<td></td>
<td>Malnourished persons or those with a recent weight loss of more than 10% of their ideal body weight</td>
</tr>
<tr>
<td></td>
<td>Persons who have undergone gastrectomy or jejunooideal bypass</td>
</tr>
</tbody>
</table>

*We define close contact as at least 12 hours of contact with a person with infectious tuberculosis, but there are no well-established criteria for such contact.

†Persons with recent infection include children less than four years of age and persons found to have tuberculin conversion, defined as an increase in induration of at least 10 mm on a tuberculin skin test within a two-year period.
Reported TB Cases by Race/Ethnicity
United States, 2005

- Hispanic (25%)
- Black, non-Hispanic (30%)
- White, non-Hispanic (21%)
- American Indian/Alaska Native (1%)
- Asian/Pacific Islander (22%)
Percentage of TB Cases Among Foreign-born Persons

1992

2010

- >50%
- 25%-49%
- <25%

CDC
Transmission and Pathogenesis
Mechanism of transmission:

- Primarily by droplet nuclei expelled by someone with infectious TB. Droplets with bacilli are inhaled and reach alveoli, being ingested by macrophages.
- Bacilli may spread via the bloodstream.
- In most cases, development of disease is contained by the immune system.
- About 10% of infected persons will develop disease; risk inversely proportional to immune function.
Majority of TB cases are pulmonary in all age groups. Children have more extra-pulmonary disease than adults.

May occur at any anatomical site or be disseminated

**Exposure**: Hx of contact; - skin test, CXR and PE

**Latent Tuberculous Infection (LTBI)**:
- + skin test, +/- - CXR, - PE

Infected individuals with no TB disease are asymptomatic, and non-infectious.

**Disease**: Symptoms, signs and radiological abnormalities are apparent.

Distinction between infection and disease in children is unclear.
Probability TB Will Be Transmitted

- Infectiousness of person with TB
- Environment in which exposure occurred
- Duration of exposure
- Virulence of the organism
Transmission

Primary Tuberculosis

Latent Tuberculosis

“Reactivation” Tuberculosis

Skin-test conversion in 6 to 8 weeks

Spontaneous healing in 6 months

Progression after 2 years, 5%

Progression within 2 years, 5%

Progression with concurrent HIV infection, 10% each year
Transmission

- Only *adults* and *adolescents* with TB are contagious.

- Number of organisms in sputum is critical for infectivity, and the frequency of cough.

- Infectivity lasts a few weeks after the initiation of effective therapy.

- When *3 sequential sputum* smears are negative, the patient is considered *non-contagious*.

- TB may rarely be transmitted *transplacentally* to the fetus.
Regarding TB in children...

Miliary TB or TB meningitis will occur
1. Only after a period of LTBI
2. Only after a positive PPD
3. Following exposure to an adult with active TB before skin test reactivity
4. By reactivation of primary pulmonary TB in young children
5. Only after establishment of Ghon’s complex
Burden of TB/HIV in women

**TB**
- 8.8 million new cases
- 14 million prevalent
- 59% Asia
- 26% Africa

**Women**
- 3.2 million (36% of total)
- Deaths 0.32 million

**HIV**
- 2.6 million new cases
- 33 million prevalent
- 16% Asia
- 68% Africa

**Women**
- 15.5 million (52% of total)
- Deaths 0.85 million

Highest burden in reproductive age 15-45 years of age

Incubation

- Tuberculin reactivity appears 2 to 12 weeks after initial infection. Median is 3 - 4 weeks.
- Exposed individuals by definition have no findings of TB, some may eventually develop disease.
- The risk of developing disease is highest during 6 months after infection and remains highest for 2 years.
- Infants and post-pubertal adolescents at highest risk of disease development.
<table>
<thead>
<tr>
<th>Appearance</th>
<th>Stage of Disease or Type of Dissemination</th>
</tr>
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<tbody>
<tr>
<td>Nodule</td>
<td>Tuberculoma</td>
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<tr>
<td>Cavity</td>
<td>Necrotic tuberculosis</td>
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<tr>
<td>Bronchial stenosis</td>
<td>Lymphangitic dissemination</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>Necrotizing bronchial inflammation</td>
</tr>
<tr>
<td>Pleural</td>
<td>Lymphangitic dissemination</td>
</tr>
<tr>
<td>Miliary</td>
<td>Blood-borne dissemination</td>
</tr>
<tr>
<td>Air space</td>
<td>Acinar nodose pneumonia (impaired immunity)</td>
</tr>
<tr>
<td>Air space</td>
<td>Diffuse alveolar damage (nonreactive)</td>
</tr>
</tbody>
</table>
Congenital Tuberculosis, Miliary lung lesions and hepatosplenomegaly.
Clinical Manifestations

- In children & adolescents, most TB infections are asymptomatic when the TST (tuberculin skin test) is +.
- CXR often does not demonstrate 1ary complex of infection.
- Most immunocompetent children with 1ary infection do not have rapid progression of disease.
- Early findings (1 to 6 mos after infection):
  - fever
  - weight loss
  - cough, night sweats, chills.
Clinical Evolution of Primary Pulmonary TB

- Droplet nuclei causes parenchymal lung disease.
- Child may have low grade fever, mild cough.
- Regional lymph nodes are involved.
- Enlarging granulomas cause obstruction of bronchioles leading to hyperaeration.
- Caseous material spills into airway, atelectasis ensues: fever, weight loss, night sweats, FTT
- There may be an initial response to antibiotics.
Primary Pulmonary TB,
right upper lobe, w/ atelectasis
Primary Pulmonary TB,
2 yr old
Clinical Manifestations

- Pulmonary radiographic findings:
  - Lymphadenopathy (hilar, mediastinal, cervical)
  - Involvement of a segment or lobe.
  - Atelectasis or infiltrates.
  - Pleural effusions
  - Cavitary lesions
  - Miliary disease

Meningitis is an early manifestation of disease.
Ghon Complex

Calcified focus of infection with an associated lymph node. Particularly common in children. Can retain viable bacteria and be source of reactivation.
Mycobacterium tuberculosis infection with paratracheal lymph nodes.
Primary pulmonary tuberculosis with pleural effusion (right lung).
Pulmonary tuberculosis with right-sided pleural effusion.
Progressive Primary Pulmonary Tuberculosis,
18 month old
Endobronchial tuberculosis, 1 yr old
Reactivation Pulmonary TB
Extrapulmonary TB (1/3 children)

- **Pleuritis**: Pleural effusion is very common;
  - Pleurisy is usually absent.
  - May be uni/ or bilateral
  - May be present up to 3 weeks after initiation of therapy.

- **Meningitis**: Due to lymphohematogenous spread.
  - Meningeal findings, fever, personality changes, irritability, listlessness, loss of developmental milestones.
  - Most severe at the base of the brain.
  - Very low glucose and monocytosis of CSF
  - Hydrocephalus and cranial nerve palsies are common.
Extrapulmonary TB

Miliary TB:
- common in young children;
- can develop within 9 months of infection, often accompanied by hepatosplenomegaly, ARDS, and generalized lymphadenopathy.

Adenitis:
- Firm, nontender lymphadenopathy.
- Supraclavicular, cervical, uni/bilateral, skin may be erythematous.
Miliary TB,
10 month old
Miliary tuberculosis with pulmonary cavitation (right lung).
Miliary TB, 29 yr old mother 4 months after delivery
Miliary TB,
29 yr old mother 4 months after delivery
Miliary TB
Miliary TB
Mycobacterial tuberculosis lymphadenitis with ulceration: Scrofula.
Atypical mycobacteria lymphadenitis with ulceration.
Atypical mycobacterial lymphadenitis.
Clinical Manifestations

Late extrapulmonary manifestations
(12 months after initial infection or later):

- Disease of the middle ear or mastoid: chronic draining ear
- Bones: collapse of vertebrae, gibbus formation.
- Joints/skin: granulomatous lesions
- Renal TB (hematuria, sterile pyuria) or adult-type pulmonary TB: more common in adolescents, rare in young children.

Clinical findings in patients with multi-drug resistant TB are indistinguishable from those of drug-susceptible disease.
Tuberculosis of the spine with paravertebral abscess (Potts disease).
Tuberculosis of the spine with paravertebral abscess (Pott’s Disease)
Diagnosis

- Hx of exposure to an adult with active disease.
- + TST
- + CXR
- + Physical exam
- Absence of other etiologies
- Response to TB medications
- > 50% of children are asymptomatic at diagnosis.
- Children < 1 year more likely to be symptomatic.
Diagnostic Tests

- **Isolation of** *M tuberculosis* **by culture**: gastric aspirates, sputum, pleural fluid, pleural biopsy, CSF, urine, other body fluids, or biopsy.

- Organism is a slow grower, will be identified in 2 - 6 weeks by radiometric method, 10 wks with solid media.

- **Smears**: Ziehl-Neelsen/ auramine-rhodamine staining. *M tb* not distinguished reliably from other mycobacteria with stain only.

- **Histology**: granuloma formation with giant cells.

- **PCR**: approved for smear positive/ respiratory tract specimens, pleural fluid.
Mycobacterium tuberculosis, or AFB

AFB (shown in red) are tubercle bacilli, Koch’s bacillus first identified in 1882.
Cultures

- Use to confirm diagnosis of TB
- Culture all specimens, even if smear negative
- Results in 4 to 14 days when liquid medium systems used

Colonies of *M. tuberculosis* growing on media
Histopathologic features of placenta thrombus with inflammatory cells and acid-fast bacilli of Mycobacterium tuberculosis (Ziehl-Neelsen stain).
Novel approaches to TB diagnosis

- Mycobacterium tuberculosis-specific immuno-dominant antigens identified leading to the development of interferon gamma-release assays (IGRAs) with high sensitivity and specificity for TB disease:
  - eg: Gold QuantiFERON-TB tests.

- Measure in vitro T cell release of interferon-gamma following stimulation by antigens unique to M. tuberculosis
  - Test-tube PPD: more specific for mTB than PPD antigens in IGRAs are not shared by non-TB mycobacteria.
  - No need to return for reading/ not sensitive < 4 years.
New TB diagnostics

Nucleic acid amplification testing (NAAT):
- Rapid diagnosis of MTB complex organisms
- Very effective in distinguishing TB organisms from non-tuberculous mycobacteria in AFB smear positive specimens.
- Can identify tuberculous mycobacteria in the presence of negative AFB smears in 50-80% of cases.
- Cannot replace culture, necessary for susceptibility determination
New TB diagnostics

**Gene Xpert MTB/RIF assay:**
- Automated nucleic assay amplification test that can simultaneously identify TB organisms and evaluate for rifampin resistance.
- Identifies 98% of individuals with AFB+ smears and 72% with AFB- smears
Promising new diagnostics

- Urinary lateral flow LAM TB tests for TB detection
  - *Alere Determine™ TB LAM Ag*
  - rapid test detects the LAM antigen (lipoarabinomannan) in urine samples

- TB detection in stool through:
  - PCR
  - Xpert MTB/ RIF testing in stool
  - Culture
Early Morning Gastric Aspirate

- Best diagnostic test in patients with non productive or absent cough.
- Should be obtained with a NG tube before child awakens and deambulates, with child NPO for at least 8 hours.
- Stomach contents should be aspirated first. 50 - 75 ml of sterile, distilled water should be added to stomach and included in first collection.
- Three aspirates should be submitted, and specimens should be sent for acid fast bacilli (AFB) smear and culture.
- Organisms isolated in < 50% of children & < 75% of infants with pulmonary TB.
TB source cases

- If there is an infected child there is a contagious adult or adolescent.

Identification of a source case should be pursued to:
- support presumptive diagnosis
- define drug susceptibility if organism is isolated from the source case
- identify all exposed who might have LTBI or disease.

Such activities should be coordinated with local health departments.

Reporting of suspected/confirmed cases is mandated by law.
Tuberculin Testing

- TST is the traditional TB diagnostic tool in asymptomatic individuals.
- Mantoux test: 5 tuberculin units of purified protein derivative (PPD) administered intradermally is the recommended TST.
- Other strengths of Mantoux should be avoided.
- Multiple puncture tests are not recommended, no specificity or sensitivity.
Tuberculin Testing

- PPD reactivity appears **2 to 12 weeks** after infection and is life long.
- TST should be used only in children who are at increased risk of acquiring TB infection. Routine testing of low risk populations should be avoided.
- Children without risk factors including infants under 1 yr of age should not be tested.
- May be administered with immunizations.
- Control skin tests are not indicated.
- BCG is not a contraindication for TST.
- Should be read in 48 to 72 hours.
Tuberculin Testing

- A negative PPD does not exclude disease.
- Technique: 0.1 ml of 5 TU of PPD intradermally into the volar aspect of the forearm using a 27-gauge needle.
- Administration and interpretation of results should be done by experienced personnel.
- The diameter of induration (by ballpoint pen technique) is measured transversely to the long axis of the forearm.
- TST reactivity may be decreased by a variety of host factors.
Positive Reaction to Purified Protein Derivative (PPD)
Interpretation of TST Results

- The cutoff induration for a + result varies depending on the person tested and background epidemiology.
- In US areas where non-tb mycobacteria are common, only 5% children w/ 5 - 9mm of induration are infected with M tb.
- Yet a child with equal reaction who had contact with a contagious adult has 50% chance of having tb infection.
Interpretation of TST Results

- **15 mm or > induration:**
  - + TST result.

- **10 mm or > induration:**
  - + in children < 4 years, presence of medical risk factors, born or travel to high prevalence regions, exposure to high risk individuals.

- **5 mm or > induration:**
  - + if contact with known or suspected cases of TB, + CXR, clinical evidence of TB, immunosuppression.
Follow-up of a + TST

- CXR for all children with a + TST are recommended, regardless of BCG status.
- If normal CXR, LTBI to be assumed and antituberculous therapy initiated.
- In selected cases: very recent BCG, multiple BCGs, and/or immigration from low prevalence area, treatment may not be indicated.
Airborne isolation is indicated for children with a **cough** and **smear + sputum**.

Children with TB may go to school if they are on therapy and sputum is negative.

Older children are not contagious after sputum smear turns negative (after 2 weeks of therapy).

Mother and newborn should be separated if mother’s **CXR** is + until therapy is initiated.
TB Treatment

TB drugs are bacteriostatic or bactericidal.

First line medications: INH, PZA, STP, RIF, ETH

- **INH**: Bactericidal, rapidly absorbed, penetrates well into body fluids, liver metabolized, kidney excreted.
  - Hepatotoxic effects rare.
  - Peripheral neuritis and seizures due to pyridoxine metabolism inhibition is rare in normal children, except for those on vegetarian or milk-sparing diets, nutritional deficiencies, with HIV or currently breastfed. Also recd for pregnant or lactating women.
TB Treatment

- **RIF**: Bactericidal, rapid absorption, good penetration into bodily fluids. Hepatic metabolism.
- Alters metabolism of several drugs.
- Hepatotoxicity is rare.
- Excreted in bile and urine, orange color to secretions.
- Blood dyscrasia with influenza like symptoms may occur if drug is taken sporadically.
- RIF resistance is rare in the US.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of studies</th>
<th>Patients</th>
<th>Clinical Hepatitis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>6</td>
<td>38,257</td>
<td>0.6</td>
</tr>
<tr>
<td>INH plus other drugs but not RIF</td>
<td>10</td>
<td>2,053</td>
<td>1.6</td>
</tr>
<tr>
<td>INH plus RIF</td>
<td>19</td>
<td>6,155</td>
<td>2.7</td>
</tr>
<tr>
<td>RIF plus other drugs but not INH</td>
<td>5</td>
<td>1,264</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Definition of abbreviations: INH = Isoniazid; RIF = rifampin.

**TB Treatment**

- **PZA:** Bactericidal, adequate CSF concentrations, detectable in macrophages, metabolized by the liver.
- Rarely hepatotoxic. In adults, may cause arthralgias due to inhibition of uric acid excretion.

- **STP:** Bactericidal, only available IM, renal excretion. Therapeutic CSF concentrations only in meningitis. Leads to vestibular and cochlear damage- not usually given > 12 wks.
- TB resistance to STP is common.
TB Treatment

**ETH:** Well absorbed, good tissue diffusion including CSF, excreted in urine.

Is bacteriostatic only at usual dose.

Primary role is prevention of emergence of drug resistance.

May lead to reversible optic neuritis: monitoring of visual acuity, visual fields, and red-green color discrimination warranted.

2nd line meds: ciprofloxacin, ethionamide, kanamycin, ofloxacin, capreomycin
New treatment approaches

- **Rifapentine**: Long acting rifamycin
- **Moxifloxacin**: In pediatric trials for MDR treatment
- **Bedaquiline**: First anti-TB drug approved in 40 years by the FDA (last day of 2012). Diarylquinoline (DARQ) antibiotic for MDR.
- **Nitroimidazoles** (same class as metronidazole)
- **Oxazilidiniones** (same class as linezolid)
Bactericidal activity of escalating doses of RPT

Data provided by E. Nuermberger
Drug resistance

- If there is a risk for INH resistance, STP or ETH should be added.
- For all cases of drug resistant TB, at least 2 meds to which organism is susceptible should be used.
- Longer treatment (12 to 18 months) should be used. Twice a week regimens not to be used.
- DOT (directly observed therapy) needed.
Therapy for LTBI

- All children with a + TST and no evidence of TB disease, who have never been treated should receive INH alone unless resistance is suspected.
- INH to adults with LTBI provides 54 to 88% protection against TB disease for at least 20 years. Efficacy in children nearly 100%.
- CXR should be obtained once, at baseline.
### Choosing the Most Effective LTBI Treatment Regimen

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Duration</th>
<th>Dose</th>
<th>Frequency</th>
<th>Total Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid (INH)</td>
<td>9 months</td>
<td>Adult: 5 mg/kg</td>
<td>Daily</td>
<td>270</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children: 10-20 mg/kg**</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maximum dose: 300 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adult: 15 mg/kg</td>
<td>Twice</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children: 20-40 mg/kg**</td>
<td>weekly†</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Maximum dose: 900 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid (INH) and Rifapentine (RPT)</td>
<td>6 months</td>
<td>Adult: 5 mg/kg</td>
<td>Daily</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children: Not recommended</td>
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<tr>
<td></td>
<td></td>
<td>Maximum dose: 300 mg</td>
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<tr>
<td></td>
<td></td>
<td>Adult: 15 mg/kg</td>
<td>Twice</td>
<td>52</td>
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<tr>
<td></td>
<td></td>
<td>Children: Not recommended</td>
<td>weekly†</td>
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<tr>
<td></td>
<td></td>
<td>Maximum dose: 900 mg</td>
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<td></td>
</tr>
<tr>
<td>Rifampin (RIF)</td>
<td>3 months</td>
<td>Adults and Children 12 and over:</td>
<td>Once weekly†</td>
<td>12</td>
</tr>
<tr>
<td></td>
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<td>INH*: 15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum</td>
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<td>RPT*: 10.0–14.0 kg 300 mg</td>
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<td></td>
<td></td>
<td>14.1–25.0 kg 450 mg</td>
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<td></td>
<td></td>
<td>25.1–32.0 kg 600 mg</td>
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<td>32.1–49.9 kg 750 mg ≥50.0 kg</td>
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<td></td>
<td>kg 900 mg maximum</td>
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<tr>
<td></td>
<td>4 months</td>
<td>Adult: 10 mg/kg***</td>
<td>Daily</td>
<td>120</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maximum dose: 600 mg</td>
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</tbody>
</table>
12-Dose (Isonaizid and Rifapentine [RPT]) Regimen

The directly observed 12-dose once-weekly regimen of INH and RPT is recommended as an option equal to the standard INH 9-month daily regimen for treating LTBI in otherwise healthy people, 12 years of age and older, who were recently in contact with infectious TB, or who had tuberculin skin test or blood test for TB infection conversions, or those with radiologic findings consistent with healed pulmonary TB.

The 12-dose regimen can be considered for other groups on a case by case basis when it offers practical advantages, such as completion within a limited timeframe. The regimen may be used in otherwise healthy HIV-infected persons, 12 years of age and older, who are not on antiretroviral medications. It may also be considered for children aged 2-11 years if completion of 9 months of INH is unlikely and hazard of TB disease is great.

The 12-dose regimen is NOT recommended for the following individuals:

- Children younger than 2 years of age
- People with HIV/AIDS who are taking antiretroviral therapy (ART)
- People presumed to be infected with INH or rifampin-resistant *M. tuberculosis*
- Pregnant women, or women expecting to become pregnant while taking this regimen

Rifampin (RIF) Regimen

A 4-month regimen of RIF can be considered for persons who cannot tolerate INH or who have been exposed to INH-resistant TB. It should not be used to treat HIV-infected persons taking some combinations of ART.

The choice between the 12-dose regimen and other recommended LTBI treatment regimens depends on several factors, including:

- Feasibility of DOT
- Resources for drug procurement and patient monitoring
- Considerations of medical and social circumstances that could affect patient adherence
- Preferences of the patient and prescribing health care provider
Therapy for LTBI

- For infants and children, recd duration of therapy is 9 months.
- If immunocompromised, 12 months.
- 10 mg/ kg, single dose, QD, not > 300 mg.
- If adherence a problem, 1 month of daily treatment, and 2 x week DOT thereafter, at 20 to 30 mg/ kg.
Preventive Therapy for Contacts

- INH recd for recent contacts of persons with contagious TB when clinical disease is excluded, even if TST results are negative.
- All young children and immunocompromised patients should be separated from the primary case and treated with INH for 3 mos, even if TST is -. Repeat testing after 3 mos.
  - IF - stop INH.
  - IF + treat for 9 months.
A Trial of Mass Isoniazid Preventive Therapy for Tuberculosis Control


In a cluster-randomized study, we designated 15 clusters with 78,744 miners as either intervention clusters (40,981 miners in 8 clusters) or control clusters (37,763 miners in 7 clusters). In the intervention clusters, all miners were offered tuberculosis screening. If active tuberculosis was diagnosed, they were referred for treatment; if not, they were offered 9 months of isoniazid preventive therapy. The primary outcome was the cluster-level incidence of tuberculosis during the 12 months after the intervention ended. Secondary outcomes included tuberculosis prevalence at study completion.

Nearly 80,000 SA miners evaluated: 89% of miners PPD+ at baseline.
Among employees on INH therapy, incidence of TB reduced by 58% during the 9 month treatment period.

Effect lost immediately after therapy was discontinued

No overall improvement of tuberculosis control in SA miners- additional problems increasing susceptibility to TB were HIV and silicosis.

**CONCLUSIONS**

Mass screening and treatment for latent tuberculosis had no significant effect on tuberculosis control in South African gold mines, despite the successful use of isoniazid in preventing tuberculosis during treatment. (Funded by the Consortium to Respond Effectively to the AIDS TB Epidemic and others; Thibela TB Current Controlled Trials number, ISRCTN63327174.)
Primary Isoniazid Prophylaxis against Tuberculosis in HIV-Exposed Children

Shabir A. Madhi, M.D., Ph.D., Sharon Nachman, M.D., Avy Violari, M.D., Soyeon Kim, Sc.D., Mark F. Cotton, M.D., Ph.D., Raziya Bobat, M.D., Patrick Jean-Philippe, M.D., George McSherry, M.D., and Charles Mitchell, M.D., for the P1041 Study Team

METHODS

We randomly assigned 548 HIV-infected and 804 HIV-uninfected infants (91 to 120 days of age) to isoniazid (10 to 20 mg per kilogram of body weight per day) or matching placebo for 96 weeks. All patients received bacille Calmette–Guérin (BCG) vaccination against tuberculosis within 30 days after birth. HIV-infected children had access to antiretroviral therapy. The primary outcome measures were tuberculosis disease and death in HIV-infected children and latent tuberculosis infection, tuberculosis disease, and death in HIV-uninfected children within 96 to 108 weeks after randomization.

**HIV+ children:** TB or death in 52 children INH group (19%) and 53 in the placebo group (19.3%); p = 0.93

**HIV-uninfected children:** TB infection, disease or death: INH group: 39 children (10%) vs. placebo: 45 children (11%), p = 0.44
CONCLUSIONS

Primary isoniazid prophylaxis did not improve tuberculosis-disease–free survival among HIV-infected children or tuberculosis-infection–free survival among HIV-uninfected children immunized with BCG vaccine. Despite access to antiretroviral therapy, the burden of tuberculosis remained high among HIV-infected children. (Funded by the National Institutes of Health and Secure the Future; ClinicalTrials.gov number, NCT00080119.)

Rate of TB:
HIV+ children: 121 cases per 1000 child-years
HIV-uninfected children: 41 cases per 1000 child-years
Treatment of Pulmonary Disease

- Goal: to achieve sterilization of the TB lesion in the shortest possible time.
- DOT is recommended in the US.
- **6 month regimen**: INH, RIF, PZA first 2 months, INH + RIF last 4 months.
- INH, RIF, PZA QD first 2 weeks to 2 months. Following, twice weekly DOT of INH and RIF acceptable.
- If resistance is suspected, a 4th drug is recd.
Extrapulmonary TB

- For bone, miliary TB and meningitis.

- **9 month regimen:** INH, RIF, PZA, STP first 1 to 2 months, followed by INH + RIF QD or twice weekly with DOT for 9 to 12 months.

- INH/ RIF may be given parenterally at the same dose if needed.

- PZA best for meningitis, good CSF penetration.
Monitoring of therapy

- DOT recommended.
- Repeat CXR after 2 - 3 months of therapy.
- It may take 2 - 3 years for hilar lymphadenopathy to resolve.
- A normal CXR is not criteria for discontinuation of therapy.
- If therapy is interrupted, extend duration.
- LFTs to be checked if concurrent hepatic disease, > doses of INH with PZA and RIF, pregnancy and postpartum period.
Role of Corticosteroids

- Controversial.
- Indicated in children with TB meningitis, and tuberculomas.
- May be considered in pleural and pericardial effusions, miliary disease or endobronchial disease.
- To be used for 6 to 8 weeks (if prednisone 1 to 2 mg/kg) with appropriate TB medications.
BCG Vaccination
Recommendations for BCG Vaccination

- Not recommended in immunization programs or TB control programs in the U.S.
- BCG vaccination undertaken after consultation with health department
Considered for an infant or child with negative skin-test result who

- Is continually exposed to untreated or to an ineffectively treated contact
- Will be continually exposed to multidrug-resistant TB
Recommendations for BCG Vaccination (cont.)

HCWs considered on individual basis in settings in which

- High percentage of MDR TB patients has been found
- Transmission of drug-resistant TB strains and subsequent infection are likely, and
- Comprehensive TB infection-control precautions implemented and not successful
BCG Contraindications

Contraindicated in persons with impaired immune response from

- HIV infection
- Congenital immunodeficiency
- Leukemia
- Lymphoma
- Generalized malignancy
- Receiving high-dose steroid therapy
- Receiving alkylating agents
- Receiving antimetabolites
- Receiving radiation therapy
BCG Vaccination and Tuberculin Skin Testing

- Tuberculin skin testing not contraindicated for BCG-vaccinated persons.

- LTBI diagnosis and treatment for LTBI considered for any BCG-vaccinated person whose skin test reaction is > 10 mm, if any of these circumstances are present:
  - Was contact of another person with infectious TB
  - Was born or has resided in a high TB prevalence country
  - Is continually exposed to populations where TB prevalence is high
Estimated TB/ HIV co-infection rates 2009

Range of rates (per 100 000)

- <1
- 1 – 9
- 10 – 99
- 100 – 999
- ≥1000
- no estimate

The designations employed and the presentation of material on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines represent approximate border lines for which there may not yet be full agreement.
## Comorbidity:
### Tuberculosis and ARV Therapy

<table>
<thead>
<tr>
<th>Status</th>
<th>Initiating ARV Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary TB and CD4 &lt; 50; extrapulmonary TB</td>
<td>Initiate TB therapy</td>
</tr>
<tr>
<td></td>
<td>Initiate ARVs when TB therapy is tolerated</td>
</tr>
<tr>
<td>Pulmonary TB+CD4 50 - 200 (in infants 1000-1200)</td>
<td>Initiate TB therapy</td>
</tr>
<tr>
<td></td>
<td>Initiate ARVs in 2-4 weeks.</td>
</tr>
<tr>
<td>Pulmonary TB+CD4 &gt;200 (infants &lt;1000)</td>
<td>Treat TB. Initiate ARV as per general guidelines</td>
</tr>
</tbody>
</table>
TB and HIV infection

- HIV testing recommended for all patients with TB.
- TST of 5 mm or > considered +, - PPD may occur.
- Yearly CXR recommended for patients with advanced HIV disease.
- Specimens for culture should be sent in HIV+ patients with suspected TB.
- At least 3 meds for a minimum of 12 months.
HIV infection

Moderate or severe immune suppression

Colonization caused by opportunistic organism

Initiation of HAART

Recovery of immunity against the organism

Paradoxical clinical deterioration due to dysregulated immune response

Improvement or progressive deterioration
Other new developments

- New vaccines (recombinant BCG/adenovirus vector vaccines in field studies)
- New indications for prophylaxis worldwide:
  - When to start treatment in HIV-infected individuals
  - Recognition of IRIS- Immune reconstitution syndrome in HIV-infected patients with advanced disease initiating antiretrovirals.
Crowded waiting rooms and TB transmission - a worldwide problem
TB infection in a guinea pig model was prevented by ionizers and UV light-70% protection against TB infection identified.
Inhaled Dry Powder Colistin:
A novel approach for reducing M/XDR-TB transmission in congregate settings and in the community

- No nebulizer or electricity
- No sterile saline or mixing
- No toxic by-products
- Inexpensive
- Pre-loaded, foil sealed
- Good storage without refrigeration
- Regulatory approval for use in SA obtained

Edward A. Nardell, MD, (PI)
Anton Stoltz, MD, PhD, (on-site PI)
Colistin mist and UV lights in waiting rooms…