TB & HIV CO-INFECTION IN CHILDREN

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Introduction

TB & HIV are two of the leading causes of morbidity & mortality in children in South Africa

- HIV infection enhances susceptibility to TB
- TB hastens progression of HIV disease
- 6 times higher mortality in children co-infected compared to those with HIV infection alone
Global summary of the AIDS epidemic 2010

- **Number of people living with HIV in 2010**
  - Total: 34.0 million [31.6 million–35.2 million]
  - Adults: 30.1 million [28.4 million–31.5 million]
  - Children <15 yrs: 3.4 million [3.0 million–3.8 million]

- **People newly infected with HIV in 2010**
  - Total: 2.7 million [2.4 million–2.9 million]
  - Adults: 2.3 million [2.1 million–2.5 million]
  - Children <15 yrs: **390 000** [340 000–450 000]

- **AIDS-related deaths in 2010**
  - Total: 1.8 million [1.6 million–1.9 million]
  - Adults: 1.5 million [1.4 million–1.6 million]
  - Children < 15 yrs: **250 000** [150 000–290 000]
Children (<15 years) estimated to be living with HIV | 2010

Total: 3.4 million [3.0 million – 3.8 million]
Incidence worldwide

- 8.8 million new cases of TB in 2010
  
  (128 per 100,000 population)

- 1 million of these in children <15 yrs
  
  Underestimated – most childhood TB is culture negative

- Of 22 identified countries with the highest burden of TB, world-wide, South Africa is the only one with increasing TB incidence rates
## Epidemiology of TB

- Top 5 countries with the highest number of incident cases of TB in 2010

<table>
<thead>
<tr>
<th>Country</th>
<th>Population (thousands)</th>
<th>Incidence of TB per 100,000 per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>1,341,335</td>
<td>78</td>
</tr>
<tr>
<td>India</td>
<td>1,224,614</td>
<td>185</td>
</tr>
<tr>
<td>Indonesia</td>
<td>239,871</td>
<td>189</td>
</tr>
<tr>
<td>Pakistan</td>
<td>173,593</td>
<td>231</td>
</tr>
<tr>
<td>South Africa</td>
<td>50,133</td>
<td>981</td>
</tr>
</tbody>
</table>

[WHO GLOBAL TB CONTROL 2011]
The spread of HIV has contributed to the rise of TB around the globe.

Of the 8.8 million incident cases of TB in 2010, an estimated 1.1 million occurred in people living with HIV infection.

The proportion of TB cases co-infected with HIV is highest in Africa.
Pathogenesis of disease

- Protective immunity is critically dependent on CD4 cells
- HIV infected patients are at a significantly higher risk of disease progression

*Nature Reviews Microbiology* 6, 520-528 (July 2008)
### Age Specific Risk For Disease Development Following Primary Infection

<table>
<thead>
<tr>
<th>Age at primary infection</th>
<th>Risk of pulmonary disease</th>
<th>Risk of TBM/Miliary disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 year</td>
<td>30 – 40%</td>
<td>10 -20%</td>
</tr>
<tr>
<td>1 – 2 years</td>
<td>10 – 20%</td>
<td>2 – 5%</td>
</tr>
<tr>
<td>2 – 5 years</td>
<td>5%</td>
<td>0.5%</td>
</tr>
<tr>
<td>5 – 10 years</td>
<td>2%</td>
<td>&lt; 0.5%</td>
</tr>
<tr>
<td>&gt; 10 years</td>
<td>10 -20% Adult-type disease</td>
<td>&lt;0.5%</td>
</tr>
</tbody>
</table>


- Children with HIV experience a similar risk as those under 2 years of age
- Young age and HIV infection are the most important risk factors for severe or disseminated disease
Diagnosis of TB in Children

- Accurate diagnosis of TB is a major challenge in children.

- Few cases are confirmed by positive smear or culture samples:
  - Pauci-bacillairy disease in children
  - Non-cavitatory disease

- Diagnosis often relies on the triad:
Clinical Symptoms of TB

- Chronic cough > 14-21 days
- Fever >38°C for > 14 days
- Weight loss / Failure to thrive

- Reduced sensitivity of symptom-based diagnosis in HIV infected children
- Many other opportunistic infections and HIV itself may present with similar symptoms
Clinical signs of TB

- No pathognomonic signs confirm diagnosis

- Some suggestive signs:
  - Pneumonia unresponsive to antibiotic therapy
  - Non-painful lymphadenopathy
  - Pleural or pericardial effusion
  - Distended abdomen with ascites
  - Gibbus of the spine

- Less sensitive in HIV infected children
**Tuberculin skin test**

- Indicates infection & not disease

  - **TST is positive if:**
    - > 5mm in high risk children (HIV+ or malnourished)
    - > 10mm in all other children

- Main limitation – low sensitivity especially in HIV infected children

- Reasons for false negative TST:
  - **HIV infection**
  - Disseminated (miliary) TB
  - Severe malnutrition
  - Recent TB exposure – 2-3 mo delay in conversion
  - Incorrect administration
Chest X-Ray

- Commonly relied upon to make a diagnosis

- Limitations:
  - Wide observer variation in interpretation
  - May not be available in poorly-resourced settings
  - Overlap with other HIV-related lung diseases
    - Lymphocytic interstitial pneumonitis
    - Recurrent pneumonia
    - Bronchiectasis
Parenchymal disease
Widened mediastinum
Hilar lymphadenopathy
Bacteriological confirmation

CHALLENGES:

- Paucibacillary disease in children
- Cavitatory disease rare in children
- Difficult specimen collection in children
  - Gastric washings
  - Induced sputum
  - Nasopharyngeal aspirate
  - Fine needle aspiration of lymph nodes
  - Bronchoalveolar lavage
Specimen Collection

Gastric Washings

- Generally requires hospitalization
- Performed early in the morning before a meal or after 3-4 hours of fasting
- Requires 3 specimens for optimum yield

Induced sputum

- Safe & effective even in infants
- Performed in outpatient setting
  - 3 induced sputums = 87%
  - 3 gastric washings = 64%
  - 1 induced sputum = 66%
Under-utilized as a diagnostic tool for TB

<table>
<thead>
<tr>
<th>Specimen type</th>
<th>Culture positive (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FNAB (1)</td>
<td>54%</td>
</tr>
<tr>
<td>Gastric aspirates (3)</td>
<td>27%</td>
</tr>
<tr>
<td>Induced sputum (1-2)</td>
<td>40%</td>
</tr>
<tr>
<td>Expectorated sputum (2-3)</td>
<td>45%</td>
</tr>
</tbody>
</table>

Wright et al. FNAB: A First line diagnostic procedure in paediatric TB suspects with peripheral lymphadenopathy. 2009 Int J Tuberc Lung Dis
Bacteriological confirmation

- TB microscopy:
  - Requires organism load of 5000 – 10000 bacilli/mL
  - Rapid detection
  - BUT only positive in 10-15% of culture-proven TB cases
Bacteriological confirmation

- **TB culture:**
  - Gold standard for TB diagnosis
  - Requires organism load of 10 bacilli/mL – more sensitive than microscopy
  - Requires 6-8 weeks for incubation
  - Valuable if any concerns for drug resistance

- **Nucleic acid amplification tests**
  - PCR line probe assay
  - Can rapidly identify commonly occurring mutations that confer resistance to INH & Rifampicin
Real-Time PCR

- **GeneXpert/Rif System (Cepheid & FIND)**
  - Closed system to detect MTB complex & identify the rpoB gene for Rifampicin resistance
  - Performed *directly* on sputum sample

- **Hemi-nested PCR**
  - When performed on children with 2 induced sputum specimens:
    - **Sensitivity**
      - 100% (Smear + & Culture +)
      - 61.1% (Smear - & Culture +)
    - **Specificity**
      - 98.8%

Treatment of TB

- Basic principles for TB treatment are the same for HIV infected and uninfected children
  - Directly observed therapy
  - Fixed dose combinations enhance adherence
  - 6 month duration of therapy in all children except in cases with drug resistant TB
# Treatment regimens

<table>
<thead>
<tr>
<th>TB Case</th>
<th>Intensive phase 2 months</th>
<th>Continuation phase 4 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>• New smear negative PTB</td>
<td>RHZ</td>
<td>RH</td>
</tr>
<tr>
<td>• TB lymphadenitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• New smear positive TB</td>
<td>RHZE</td>
<td>RH</td>
</tr>
<tr>
<td>• Extensive parenchymal disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Extrapulmonary TB (except TBM/miliary TB)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• TB meningitis</td>
<td></td>
<td>RHZEo</td>
</tr>
<tr>
<td>• Miliary TB</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## TB Drug Dosing Chart for Children <8 years of age (2010)

### Dosing for Isoniazid Preventive Therapy (IPT) in Children

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>Daily isoniazid (INH)</th>
<th>RHZ dissolvable tablets 60/30/150mg (scored)</th>
<th>RHZ dissolvable tablets 60/30mg (scored)</th>
<th>E tablets 400mg (un-scored)</th>
<th>RHZ dissolvable tablets 60/30mg (scored)</th>
<th>TB meningitis or miliary TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.2 - 2.9</td>
<td>1/2</td>
<td>1/2</td>
<td>Use Eto 1/4</td>
<td>1/2</td>
<td>Use RHZ (60/30/150) 1/2 + H 1/4</td>
<td>1/4</td>
</tr>
<tr>
<td>3.3 - 3.9</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>Use RHZ (60/30/150) 1 + H 1/2</td>
<td>1/2</td>
</tr>
<tr>
<td>4.4 - 4.9</td>
<td>3/4</td>
<td>3/4</td>
<td>3/4</td>
<td>2</td>
<td>2/2</td>
<td>3/4</td>
</tr>
<tr>
<td>5.5 - 5.9</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1/2</td>
</tr>
<tr>
<td>6.6 - 6.9</td>
<td>3/4</td>
<td>3/4</td>
<td>3/4</td>
<td>3</td>
<td>3/4</td>
<td>3/4</td>
</tr>
<tr>
<td>7.7 - 7.9</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3/4</td>
</tr>
<tr>
<td>8.8 - 8.9</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1/2</td>
</tr>
<tr>
<td>9.9 - 9.9</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3/4</td>
</tr>
<tr>
<td>10.1 - 10.9</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3/4</td>
</tr>
<tr>
<td>11.2 - 11.9</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4/4</td>
</tr>
<tr>
<td>12.3 - 12.9</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5/4</td>
</tr>
<tr>
<td>13.4 - 13.9</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6/4</td>
</tr>
<tr>
<td>14.1 - 14.9</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7/4</td>
</tr>
<tr>
<td>15.2 - 15.9</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8/4</td>
</tr>
<tr>
<td>16.3 - 16.9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9/4</td>
</tr>
<tr>
<td>17.4 - 17.9</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10/4</td>
</tr>
<tr>
<td>18.5 - 18.9</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>11/4</td>
</tr>
<tr>
<td>19.6 - 19.9</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12/4</td>
</tr>
<tr>
<td>20.7 - 20.9</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13/4</td>
</tr>
</tbody>
</table>

**H** = Isoniazid, **R** = Rifampicin, **Z** = Pyrazinamide, **E** = Ethambutol, **Eto** = Ethionamide

Uncomplicated TB disease in children = new smear negative pulmonary TB, or mild forms of extrapulmonary TB e.g. lymphadenitis, pleural effusion.

Complicated TB disease in children = new smear positive pulmonary TB, or extensive parenchymal/cavitatory lung disease, or extrapulmonary TB (excl. TB meningitis or miliary TB), or patients with severe immunosuppression from HIV disease.
TB treatment in relation to ART

- TB treatment is the priority

- Optimal timing for ART initiation:
  - Approximately 2 weeks after starting TB treatment
  - Concerns:
    - IRIS
    - Drug interactions
    - Shared toxicities
Complications of HAART: TB IRIS

- **Definition**
  - Unmasking/rapid progression of new disease or
  - Paradoxical worsening of established disease

- **Clinical Features**
  - Usually in the first 3-6 months of starting HAART
  - Presentation
    - Fever
    - Expanding peripheral or hilar lymphadenopathy
    - Worsening pulmonary infiltrates
    - New or enlarging pleural effusions

- **Treatment**
  - Expectant
  - Corticosteroids
Drug Interactions

- Rifampicin is a potent p450 enzyme inducer
  - Decreases serum levels of nevirapine & lopinavir
    - Lopinavir/Ritonavir based regimens require addition of additional Ritonavir
    - Nevirapine requires a switch to Efavirenz

- Both TB treatment & HAART can be hepatotoxic
  - Clinically monitor for jaundice
  - Monitor transaminases
  - Pyridoxine is protective for INH-induced peripheral neuropathy but not for hepatotoxicity
# Impact of HAART on risk of TB

## Incidence of TB (per 100 person-years) before HAART and when on HAART in South African children

<table>
<thead>
<tr>
<th></th>
<th>Not treated with HAART (95%CI)</th>
<th>On HAART (95%CI)</th>
<th>Incidence rate ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All children</td>
<td>16.4 (14.3–18.7)</td>
<td>6.3 (4.9–8.2)</td>
<td>0.4 (0.3–0.5)</td>
</tr>
</tbody>
</table>

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Prevention of TB

- If documented TB contact, provide INH prophylaxis for 6 months for the following children:

  - All children under age 5 years
  - HIV infected children irrespective of age
  - Dose of 10mg/kg/day
THANK YOU