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
WHO 2012 Global Report on TB

- Incidence worldwide

  - 8.7 million new cases of TB in 2011
    (125 cases per 100 000 population)

  - 490,000 of these in children <15 years
    - Estimated TB incidence in children
    - 327,000 children were notified from countries that collect age-disaggregated data
    - Underestimation – most childhood TB is culture negative
WHO 2012 Global Report on TB

22 HIGH TB-BURDEN COUNTRIES

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

Top 5 countries with the highest number of incident cases of TB in 2011

<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>India</td>
<td>1 241 492</td>
<td>181</td>
</tr>
<tr>
<td>China</td>
<td>1 347 565</td>
<td>75</td>
</tr>
<tr>
<td>South Africa</td>
<td>50 460</td>
<td>993</td>
</tr>
<tr>
<td>Indonesia</td>
<td>242 326</td>
<td>187</td>
</tr>
<tr>
<td>Pakistan</td>
<td>176 745</td>
<td>231</td>
</tr>
</tbody>
</table>
WHO 2012 Global Report on TB

Graphs showing trends in tuberculosis cases in various countries:
- Mozambique
- South Africa
- Kenya
- DR Congo
- Ethiopia
- Zimbabwe
- Uganda
Children (<15 years) estimated to be living with HIV | 2010

- **Western & Central Europe**: 1400 (<1000 – 1800)
- **Eastern Europe & Central Asia**: 17 000 [14 000 – 23 000]
- **Middle East & North Africa**: 40 000 [27 000 – 52 000]
- **South & South-East Asia**: 160 000 [110 000 – 210 000]
- **Eastern Europe**: 14 000 – 23 000
- **North America**: 4500 [4000 – 5800]
- **Caribbean**: 16 000 [12 000 – 19 000]
- **Latin America**: 42 000 [30 000 – 54 000]
- **Oceania**: 4600 [3600 – 5800]
- **Sub-Saharan Africa**: 3.1 million [2.8 million – 3.5 million]

**Total**: 3.4 million [3.0 million – 3.8 million]
• The spread of HIV has contributed to the rise of TB around the globe

• Of the 8.7 million incident cases of TB in 2011, 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 (39%)
HIV & TB Mortality in Children (SA)

Figure 1. Main cause of death in children under 5 years: 2005-2009

Figure 6. HIV status and cause of death: 2005-2009
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

<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%</td>
<td>&lt;0.5%</td>
</tr>
<tr>
<td></td>
<td>Adult-type disease</td>
<td></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
Impact of ART on risk of TB in Children

### 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>

Diagnosis of TB in HIV-positive Children

- Accurate diagnosis of TB is a major challenge in both HIV infected and un-infected children

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

- Diagnosis often relies on the triad:

  - Symptom Screening & History of TB contact
  - Positive tuberculin skin test
  - CXR with abnormalities suggestive of TB
Clinical Symptoms of TB in children with HIV

Cough > 14 days

Fever > 14 days

Weight loss or 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 in children with HIV

- Non-painful lymphadenopathy
- Pleural effusion
- Distended abdomen with ascites
- Gibbus of the spine

Signs may not be as definitive in HIV infected children. Other opportunistic infections can present in similar ways.
Tuberculin skin test in HIV-positive 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
  • Incorrect administration

• TST is positive if:
  • > 5mm in high risk children (HIV+ or malnourished)
  • > 10mm in all other children
Chest X-Ray Interpretation

• Commonly relied upon to make a diagnosis in children

• Limitations in HIV-infected children:
  
  • Overlap with other HIV-related lung diseases
    
    • Lymphocytic interstitial pneumonitis
    
    • Recurrent pneumonia
    
    • Bronchiectasis
Bacteriological confirmation

CHALLENGES:

• Paucibacillary disease in children

• Cavitative disease rare in children

• Difficult specimen collection in children
  • Gastric washings
  • Induced sputum
  • Nasopharyngeal aspirate
  • Fine needle aspiration of lymph nodes
  • Bronchoalveolar lavage

Obtaining a specimen is critical for all children especially for those who are HIV-positive
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 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: Gene Xpert

• When performed on children with 2 induced sputum specimens
  - Sensitivity
    • 100% Smear + & Culture + specimens (100% in HIV positive children)
    • 61.1% Smear - & Culture + specimens (100% in HIV positive children)
  - Specificity 98.8%
  - 24% of children in this study were HIV-positive

• When performed on gastric lavage specimens from children
  - Sensitivity 68.8% overall (62.5% in HIV-positive children)
  - Specificity 99.3% overall (99.1% in HIV-positive children)
  - No difference in assay performance when stratified by HIV status of child

1 Nicol MP et al. Accuracy of the Xpert MTB/RIF test for the diagnosis of pulmonary tuberculosis in children admitted to hospital in Cape Town, South Africa: a descriptive study, Lancet 2011
Treatment of TB in HIV-positive children

- 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 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>RHZEo</td>
<td></td>
</tr>
<tr>
<td>• Miliary TB</td>
<td></td>
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</tr>
</tbody>
</table>
TB treatment in relation to ART

- TB treatment is ALWAYS the priority

- Optimal timing for ART initiation:
  
  - Approximately 2 weeks after starting TB treatment

- Paediatric Literature:
  
  - Delaying ART for ≥ 2 months in children diagnosed with TB was associated with significantly increased mortality in a South African cohort (Yotebieng M et al. AIDS 2010)
    
    - Hazard ratio of death for initiating ART within 15 days 0.82 (95% CI:0.48;1.41)
    - Hazard ratio of death for initiating ART within 30 days 0.86 (95% CI:0.46;1.60)
    - Hazard ratio of death for initiating ART within 60 days 1.32 (95% CI: 0.55;3.16)

  - Starting ART within the first 2 months of tuberculosis therapy significantly improved survival in a cohort of Indian children (Pensi T et al. Trop Med and Int. Health 2012)

- Concerns:
  
  - IRIS
  - Drug interactions
  - Shared toxicities
Complications of ART: TB IRIS

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

• Clinical Features
  • Usually in the first 2-6 months of starting ART
  • Presentation
    • Fever
    • Expanding peripheral or hilar lymphadenopathy
    • Worsening pulmonary infiltrates
    • New or enlarging pleural effusions
    • Worsening neurological symptoms in patients with CNS TB

• Treatment
  • Expectant
  • Corticosteroids
Drug Interactions: LPV/r and Rifampicin

- Rifampicin is a potent p450 enzyme inducer - decreases serum levels of lopinavir
  - Lopinavir/Ritonavir based regimens require addition of additional Ritonavir
  - Raises the question of double-dose LPV/r vs. Ritonavir boosted LPV/r:
Drug Interactions: LPV/r and Rifampicin

• Pharmacokinetics:

  • Several pharmacokinetic studies have demonstrated that simply
doubling the dose of LPV/r provides *inadequate LPV exposure* in
children specifically

  • Zhang C et al. 2012. Population pharmacokinetics of lopinavir and ritonavir in
    combination with antitubercular treatment in HIV-infected children
  • McIlerson H et al. 2011. Lopinavir exposure is insufficient in children given double
doses of LPV/r during rifampicin –based treatment for tuberculosis
  • Elsherbiny D et al. 2010. Population pharmacokinetics of lopinavir in combination
    with rifampicin-based antitubercular treatment in HIV-infected South African
    children.
Drug Interactions: LPV/r and Rifampicin

- Clinical effect:

  - Virological suppression was similar in children with ritonavir boosted LPV/r compared to children without TB (69.2% vs. 74.8%) after 6 months of therapy.

  - Children given double-dose LPV/r were significantly less likely to be virologically suppressed (53.1% vs. 74.8%) after 6 months of therapy. After 12 months on ART, however, viral suppression rates were similar in both groups.
Drug Interactions: Shared toxicity

• Both TB treatment & ART can be hepatotoxic

  • Clinically monitor for jaundice

  • Monitor transaminases for ALT elevation

• Pyridoxine is protective for INH-induced peripheral neuropathy but not for hepatotoxicity
BCG Vaccination

- First introduced into South Africa in 1973

- Contains live attenuated *Mycobacterium bovis* strain

- Administration:
  - Initially administered percutaneously (Tokoyo strain)
  - Since 2000, changed to intradermal administration (Danish strain)

- Does not prevent the development of TB disease but is protective against developing complicated TB disease e.g. TB meningitis; miliary TB

- Can be associated with injection-site complications, suppurative adenitis, and very rarely with disseminated disease

- Frequency of disseminated BCG disease is extremely low (0.19–2 cases/1 million vaccinated infants) worldwide but occurs to a greater extent in immunocompromised children e.g. HIV-infected
BCG Vaccine in HIV-positive Children

- HIV infected children are at greater risk of:
  - BCG adenitis (IRIS)
  - Disseminated BCG disease

- WHO (2007)
  - HIV infection is a contraindication to BCG immunization
  - BCG vaccination should be delayed in infants until HIV-infection is excluded

- South African Policy
  - Risks of delaying vaccination in a country with a high prevalence of TB outweighs the risks to HIV-infected children

  - If HIV infection must first be excluded before BCG vaccination, this would delay BCG until 10-14 weeks of age
  - Risk of developing complicated TB in infants is highest in the first year of life

All South African children currently require BCG vaccine at birth regardless of HIV status unless symptomatic at birth
Complications of ART: BCG IRIS

- Local or regional BCG disease occurring usually within 3 months of initiating ART due to immune reconstitution

- Conservative management with observation alone is usually sufficient

- Limited role for anti-TB medication – reserved for disseminated disease
  - Rifampicin, High-dose INH, Ethambutol, Ofloxacin

- If any signs of super-infection, may require I&D but healing is very slow

- CHER study illustrated that early ART initiation at 7 weeks in infants decreases the risk of BCG IRIS
Prevention of TB in HIV-positive children

- Preventing TB in HIV-positive children is the ultimate goal

- HIV-positive children often have greater exposure to TB within their households

- Enquire about TB contacts at every clinic visit

- If documented TB contact, provide INH prophylaxis for 6 months to
  - All children under age 5 years
  - HIV infected children irrespective of age
Questions