COMMENTARY
TB prevention drugs for infants and children living with HIV: Challenges, prospects and key research gaps

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Paediatric Tuberculosis Prevention Therapy Disconnect

Annual estimated burden of TB among children aged 0–4 years

<table>
<thead>
<tr>
<th>Measure</th>
<th>Estimate</th>
<th>% of all pediatric TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB incidence</td>
<td>435,000</td>
<td>51.4%</td>
</tr>
<tr>
<td>Isoniazid-resistant TB</td>
<td>42,200(^{b})</td>
<td>50.2%</td>
</tr>
<tr>
<td>Multidrug-resistant TB</td>
<td>12,700(^{a})</td>
<td>51.2%</td>
</tr>
</tbody>
</table>

Dodd et al. 2016
Paediatric Tuberculosis Prevention Therapy Disconnect

Children Under 5 years

General Population

High Risk groups

Prevention Therapy

<table>
<thead>
<tr>
<th>Study setting</th>
<th>Year</th>
<th>Study population</th>
<th>HIV prevalence</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zambia</td>
<td>1994</td>
<td>Children with clinical TB diagnosis (n=120)</td>
<td>56%</td>
<td>Luo et al Tuberc Lung Dis 1994 [14]</td>
</tr>
<tr>
<td>Johannesburg, South Africa</td>
<td>2008</td>
<td>Cultured confirmed cases of TB in children aged years (n=1317)</td>
<td>52% in children with drug-susceptible TB; 33% in the 13 with MDR-TB</td>
<td>Fallier et al BMC Inf Dis 2014 [15]</td>
</tr>
<tr>
<td>Mumbai, India</td>
<td>2002</td>
<td>Children with disseminated TB (n=68)</td>
<td>16%</td>
<td>Karande et al J Pediatr 2002 [16]</td>
</tr>
<tr>
<td>Rio de Janeiro, Brazil</td>
<td>1999-2008</td>
<td>Children attending a reference hospital (n=473)</td>
<td>17% (but only 56% tested for HIV)</td>
<td>Matos et al J Pediatr 2012 [17]</td>
</tr>
<tr>
<td>Cape Town, South Africa</td>
<td>1999-2004</td>
<td>Children born in 1999 and diagnosed with TB in public health facilities up to 2004 (n=1461)</td>
<td>37% (but only 16% had HIV test results available)</td>
<td>Moyo et al Int J Tuberc Lung Dis 2010 [18]</td>
</tr>
<tr>
<td>Santo Domingo, Dominican Republic</td>
<td>1996</td>
<td>Children aged 18-59 months with clinical TB diagnosis (n=189)</td>
<td>5.8%</td>
<td>Espinal et al J Acquir Immune Defic Syndr Hum Retrovir 1996 [19]</td>
</tr>
<tr>
<td>Abidjan, Côte d’Ivoire</td>
<td>1994-1995</td>
<td>Children aged 0-5 years with newly diagnosed TB (out- and in-patients) (n=141)</td>
<td>19%</td>
<td>Masters et al AIDSS 1997 [21]</td>
</tr>
</tbody>
</table>

Venturini et al, 2014
Paediatric Tuberculosis Prevention Therapy Disconnect

General Population

High Risk groups

Children Under 5 years
- Higher TB incidence
- Higher TB related Mortality
- Higher incidence of Disseminated disease
- Higher incidence of TBM

HIV infected Children

Prevention Therapy
Conflicting Efficacy Data in Children (0-5yrs)

**P1041**

HIV Exposed uninfected and HIV Infected (early ART)

Summary of First End Point Met toward Primary Outcome Measures in Children Randomly Assigned to Isoniazid or Placebo.*

<table>
<thead>
<tr>
<th>End Point</th>
<th>Total (N = 547)</th>
<th>HIV-Infected Children</th>
<th>HIV-Uninfected Children</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Isoniazid Group (N = 273)</td>
<td>Placebo Group (N = 274)</td>
<td>P Value‡</td>
</tr>
<tr>
<td>Primary end point: tuberculosis disease or death</td>
<td>105 (19.2)</td>
<td>52 (19.0)</td>
<td>53 (19.3)</td>
</tr>
<tr>
<td>Specific end points</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol-defined tuberculosis§</td>
<td>69 (12.6)</td>
<td>31 (11.4)</td>
<td>38 (13.9)</td>
</tr>
<tr>
<td>Definite PTB</td>
<td>8 (1.5)</td>
<td>5 (1.8)</td>
<td>3 (1.1)</td>
</tr>
<tr>
<td>Probable PTB</td>
<td>8 (1.5)</td>
<td>5 (1.8)</td>
<td>3 (1.1)</td>
</tr>
<tr>
<td>Possible PTB§</td>
<td>48 (8.8)</td>
<td>21 (7.7)</td>
<td>27 (9.9)</td>
</tr>
<tr>
<td>Definite EPTB</td>
<td>3 (0.5)</td>
<td>0</td>
<td>3 (1.1)</td>
</tr>
<tr>
<td>Probable EPTB and possible PTB</td>
<td>2 (0.4)</td>
<td>0</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Death without prior tuberculosis</td>
<td>36 (6.6)</td>
<td>21 (7.7)</td>
<td>15 (5.5)</td>
</tr>
<tr>
<td>Latent tuberculosis§</td>
<td>21 (3.9)</td>
<td>9 (2.2)</td>
<td>12 (3.0)</td>
</tr>
</tbody>
</table>

Zar H et al, 2007

Madhi S et al, 2011
Lessons from P1041

• Lack of efficacy of TPT in HIV exposed and HIV infected children?

• Alternative

• Known: Paediatric TB is spread by contact with adult TB case

• TPT lacks efficacy in the context of an ideal research clinic with
  • TB screening and treatment of caregivers
  • Early HIV diagnosis and initiation of ART
  • Regular TB screening and early secondary INH prophylaxis
  • Nutritional supplementation/Regular immunization
In the real world TPT works
TB or Not TB

No TB contact

GeneXpert: Negative (Pleural Fluid and ETA)

Culture: E-Coli (Blood culture/ETA)

No TB contact

GeneXpert: positive on induced sputum and lymph node aspirate
TB Diagnostic Uncertainty
RADIOLOGY

• Often non-specific so diagnosis should not be based on CXR alone

• CXR:
  • calcified Ghon focus + perihilar/hilar L/n
  • Broad mediastinum
  • Lobar collapse or atelectasis
  • Miliary infiltrates
  • Bronchopneumonia + pleural effusion
  • pericardial effusion
Tuberculin Skin test

>4 MM in HIV

Sensitivity related to immunosuppression, prior BCG exposure, Age, Disseminated disease

False (+) : MOTT’s
False (-) : Malnutrition / Fulminant infection / Immunosuppression
Interferon Gamma Release Assays (IGRA)

• T-spot assay
• Quantiferon-TB Gold

• Questions:
  • Usefulness in HIV positive children
  • Infection vs Disease
Microbiology

• Gold standard: culture for M. Tuberculosis
• Microbiological proof in 20-40% only
• Difficulties in HIV positive children
  • few organisms
  • transitory and late release
  • can’t produce sputum
  • collection errors
  • handling errors
Microbiology

• 3 early morning gastric aspirates,
  • early morning,
  • before breakfast
  • before child is out of bed
  • Add buffer or alkali immediately

• 1 induced sputum (Zar H, Lancet 2005)

• Only 47% smear positive

• Other samples: urine, bone marrow aspirates, CSF, stool
TB PCR (GeneXpert)

Sputum/Gastric Aspirates: Comparable performance in HIV positive and HIV negative children
Sensitivity of 70-90% on Sputum and 70% on Gastric aspirates.¹

Stool:
Decontaminated Stool sediment GeneXpert detected 75% of abdominal TB²
Direct stool GeneXpert detected 47% of culture-confirmed TB (80% in HIV positive children and 33% in HIV negative children)³

Nasopharyngeal Aspirates:
While sensitivity of the GeneXpert was comparable, culture was far superior with induced sputum (96.6% vs 70.1%)⁴

¹ Nicol MP et al Lancet Infect Dis 2011 (11), ² Walters et al Paediatr Infect Dis J 2012 (13), ³ Nicol et al CID 2013 (57), ⁴ Zar HJ et al CID 2013 (57)
Urinary LAM lacks the diagnostic accuracy for routine screening

In HIV-positive adults with advanced immunodeficiency – has demonstrated a high sensitivity and specificity\(^1\)

HIV/TB co-infected adult patients with a positive urine LAM have a higher mortality\(^2\)

In a recent paediatric study of HIV-infected children, mortality was 4.9 fold higher if LAM positive with an aHR 4.92 (95% CI 1.79-13.49)\(^3\)

? Very advanced disease
? Identifying undiagnosed TB where respiratory samples failed to diagnose

Histology

• Samples: lymph-node, liver, bone marrow, lung & joint
• FNAC, Trucut biopsy, open biopsy & trephine
• Findings: granuloma, caseous necrosis, epitheloid histiocytes and langerhans giant cells. Ziehl Nielsen stain for AFB should be performed
Pill (Syrup) burden

Need for FDC Antiretroviral treatment

Need for FDC Prophylaxis

Typical prescription of an HIV infected child

Combination of Cotrimoxazole/INH/VitB6
TB/ART Drug-Drug Interaction

- Boosted PIs – LPV/rtv, Atazanavir, Daurinavir
- Integase Inhibitors – Dolutegravir / Raltegravir / Bictegravir / Elvitegravir
- NRTI – TAF
- Rifampicin/Rifapentine

Rifampicin/Rifapentine
Prioritizing Paediatric Drug Development

• Paediatric drug development has traditionally followed a tortuous pathway from older to younger children

• Rifapentine FDA approvals:
  • 1998: Initially approved for treatment of pulmonary TB adults and children >12 years
  • 2014: Treatment of LTBI in adults and children > 10kgs
Conclusions

• Prioritizing research and implementation of TPT in Infants and Children esp in HIV-infected

  • New short course regimens
  • Drug development/formulation
  • Drug interaction
  • Screening/diagnostic algorithm