INH Preventive Therapy in Children

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Prophylactic effect of INH on primary TB in children

RCT: INH vs. Placebo (4-6mg/kg/day)

2 Groups:
- <3y of age – TST 5TU ≥5mm
- >3y of age - TST 5TU ≥5mm + CXR evidence Primary TB

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<thead>
<tr>
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<th>INH N = 1394</th>
<th>Placebo N = 1356</th>
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<tbody>
<tr>
<td>Extra-pulmonary complications</td>
<td>5 (0.33%)</td>
<td>26 (1.91%)</td>
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80% cases prevented
P = 0.0002 Fishers Exact 2-tail test

INH reasonably effective for post-exposure prophylaxis

US Public Service TB prophylaxis trial – Am Rev TB 1957; 76: 942-63
How well is post-exposure prophylaxis given to TB-exposed children in public programs?

• Poor
    • Missed opportunities in 70% of 614 children with culture+ TB in Cape Town
  – Pothukuchi et al – Plos One 2011; 6: e225500
    • 56/172 (32%) children <6y of age in households od sputum+ve adults not screened for TB in South India
Post-exposure prophylaxis: INH X6m vs INH + RMP X3m

National TB Program
- Pre 1996
  - <2y: INH + RMP X3m
  - 2 – 5y: INH X6m
- Post 1996
  - <5y: INH X6m

Adherence %: 1996 – 2003
Retrospective study

OR: 4.97 (2.4-10.4)

Weekly rifapentine (RFP) + INH X 12 doses Latent TB infection in adults (vs. INH X 9m)

Intent to Treat

Rx Completion:
- RFP+INH – 82%
- INH: 69%

Role of HIV

• Low TB prevalence settings
• N = 8053
  – HIV - 205
• HIV and TB risk (multivariate analysis)
  – OR 4.1 (1.3 – 3.2)
Post exposure prophylaxis for TB

- After exposure to an adult source case
  - All children <6y
  - All HIV+ children
Post-exposure prophylaxis

INH daily X6m

• For
  – Simple
  – Long period
  – Less complicated if PI for HIV+

• Against
  – Not well implemented

INH + Rifampicin daily X3m
INH + Rifapentine weekly X 12 doses (3m)

• For
  – Shorter period
  – Adherence better
    • 70% vs 29%

• Against
  – Few randomized data
  – Rifapentine dosage & formulation issues in children (esp young children)
Post-exposure prophylaxis & HIV in children

• Drug interactions RMP & LPV/r / NVP
• No data on efficacy
• But - INH X6m may be less of a problem in integrated HIV/TB program, if seen monthly
Improving post-exposure prophylaxis for Children

- Separate Register
- Contact clinics
- Same healthcare worker to manage source case & contacts
- Add contact tracing to TB Rx card
- Each child to have own card

Control of TB in HIV+ endemic setting
The 3 I’s
WHO 2008

• IPT - all without active TB
• Intensified case-finding
• Infection Control
TB/death with IPT: 6m versus 36m in HIV+ adults, Botswana

But, benefit less obvious in multi-arm study from Soweto in HIV+ adults

Continuous IPT

- Increased
  - Toxicity
  - Temporary / Permanent discontinuation
IPT for HIV+ infants & children without active TB?

**Yes** – Zar et al BMJ 2007; 334: 36-43
5/131 vs 13/132 cases

**No** – Madhi et al N Engl J Med 2011; 365: 21 - 31

TB cases per 100 HIV+ children per year

Survival

TB free survival %

Fig 2: Survival in children on isoniazid (INH) or placebo
## Comparisons for HIV+ children

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<tr>
<td><strong>Strategy</strong></td>
<td>“All comers”</td>
<td>Pre-exposure prophylaxis</td>
</tr>
<tr>
<td><strong>INH Dosage mg/kg/day</strong></td>
<td>10</td>
<td>15 - 20</td>
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<tr>
<td><strong>Exclusions</strong></td>
<td>Known TB exposure requiring INH</td>
<td>Any current TB contact</td>
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<tr>
<td><strong>ART</strong></td>
<td></td>
<td></td>
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<tr>
<td>At baseline (%)</td>
<td>Unavailable</td>
<td>Available</td>
</tr>
<tr>
<td>During trial (%)</td>
<td>9</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>98.9</td>
</tr>
<tr>
<td><strong>Baseline Characteristics</strong></td>
<td></td>
<td></td>
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<tr>
<td>Median Age (m)</td>
<td>24.7</td>
<td>3-4</td>
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<tr>
<td>CDC N / A (%)</td>
<td>12</td>
<td>90</td>
</tr>
<tr>
<td>CD4%</td>
<td>20 (14-28)</td>
<td>28 (6-58)</td>
</tr>
<tr>
<td>&lt;20</td>
<td>21.5%</td>
<td>74%</td>
</tr>
<tr>
<td>WAZ</td>
<td>-1.6 (-2.5 – 0.4)</td>
<td>-0.58 (-4.3 - 3.1)</td>
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<tr>
<td>Prior TB treatment</td>
<td>17%</td>
<td>None</td>
</tr>
<tr>
<td>TST +ve</td>
<td>9%</td>
<td>N/A</td>
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# Differences in study conduct & outcome

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<thead>
<tr>
<th></th>
<th>Zar et al</th>
<th>Madhi et al (HIV+)</th>
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<tbody>
<tr>
<td><strong>Conduct</strong></td>
<td></td>
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<tr>
<td>Recruitment</td>
<td>44% recently hospitalized</td>
<td>Very rare</td>
</tr>
<tr>
<td>TB exposure on trial?</td>
<td>Open-label INH &amp; resume</td>
<td>Open-label INH &amp; Exit</td>
</tr>
<tr>
<td>TB diagnosis</td>
<td>Regular screening for contacts &amp; TB disease sx, TST</td>
<td>Same</td>
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<tr>
<td></td>
<td>CXR</td>
<td>CXR Algorithm &amp; Endpoint review committee (blinded)</td>
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<td></td>
<td>Single expert (HS Schaaf) - blinded</td>
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<tr>
<td><strong>Outcome</strong></td>
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<tr>
<td>Follow-up time (m)</td>
<td>5.7 (2 – 9.7)</td>
<td>18 (0.25 – 24)</td>
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<tr>
<td>Protocol-defined TB</td>
<td>18/263 (7%)</td>
<td>69/547 (12%)</td>
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<tr>
<td>TB incidence</td>
<td>Placebo: 23 per 100 children per year</td>
<td>12.1 per 100 child years</td>
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Continuation Zar study to Dec 2007 (495 person y / 5y)

Background
• Dec 2002: Study commenced
• May 2004: switch to open-label INH
• Majority started on ART
• Enrollment continued
• Adjusting for age, nutrition, ART, INH

HR for Reduction in TB incidence (95% CI)

Frigati L et al Thorax 2011;
Impact of early ART on TB

TB contact per 100,000 HIV-exposed infants 3-4 months of age, excluded from P1041

How easy is it to diagnose TB in HIV-infected young children?

Not very easy

- Often paucibacillary
- TST often –ve
- Culture yield 30 to 40% in the best circumstances

With delayed ART – 33% have abnormal CXR

Reasons why Zar IPT study showed effect?

• Higher prevalence of TB?

• INH may have treated paucibacillary TB? Mount et al N Engl J Med 1961; 265: 713-721

• Contact with source case often missed
  – 50% contacts not in the household
  – Household contacts not easily identified
    • Maritz E – P1041 data Union mtng 2012
At what point is source case identified in children diagnosed with TB? (P1041)

Why & when should IPT be given to HIV+ children?

- TB contact tracing program not working well?
- TB disease cannot be excluded in early phase (despite trying)?
- Absence of early diagnosis of HIV and initiation of ART by 12 weeks of age
- Also, whenever source case is identified.
When should pre-exposure IPT *not* be given?

- Mother identified antenatally & screened for TB
- No TB contacts in house
- Early diagnosis & initiation of ART <12 weeks of age
- Regular follow-up and screening for TB?
Scale-up of isoniazid preventive therapy in PEPFAR-assisted clinical sites in South Africa

C. C. Bristow,* E. Larson,† A. K. Vilakazi-Nhlapo,‡ M. Wilson,§ J. D. Klausner*


We reviewed the implementation of isoniazid preventive therapy (IPT) in South Africa from January 2010 to March 2011. The South African National Department of Health distributed revised IPT guidelines in May 2010 to increase IPT use in eligible human immunodeficiency virus (HIV) infected patients. We found a dramatic increase in the absolute numbers of patients reported to have been initiated on IPT (from 3309 in January–March 2010 to 49,130 in January–March 2011), representing an increase in the proportion (1.0–10.5%) of potentially eligible HIV-infected patients started on IPT.

KEY WORDS: IPT; tuberculosis; HIV; PEPFAR