WHO Guidelines for IPT and ICF

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Outline

• Background
• Evidence
• Recommendations
  • Adults and adolescents
  • Children
• Conclusions
A. Establish NTP-NACP collaborative mechanisms
- Set up coordinating bodies for effective TB/HIV activities at all levels
- Conduct surveillance of HIV prevalence among TB cases
- Carry out joint TB/HIV planning
- Monitor and evaluate collaborative TB/HIV activities

B. Decrease burden of TB among PLHIV (the "Three I's")
- Establish intensified TB case finding
- Introduce INH preventive therapy
- Ensure TB infection control in health care and congregate settings

C. Decrease burden of HIV among TB patients
- Provide HIV testing and counselling
- Introduce HIV prevention methods
- Introduce co-trimoxazole preventive therapy
- Ensure HIV/AIDS care and support
- Introduce ARVs
PT is recommended for PPD+ HIV-infected individuals who do not have active tuberculosis. In some settings it may not be feasible to perform PPD testing. Under these circumstances the following individuals may still be considered for preventive therapy if they are infected with HIV:

- Those living in populations with a high prevalence of tuberculous infection (estimated to be >30%)
- Health care workers
- Household contacts of TB patients
- Prisoners
- Miners
- Other selected groups at high risk of acquisition or transmission of TB

Isoniazid is the recommended drug. 5mg/kg (max. 300mg) may be given as daily, self-administered therapy for six months. Individuals should be seen monthly and given only one month supply of medication at each visit.
Key IPT recommendations (1993-2009)

• IPT should be provided to TST positives

• If TST is not feasible IPT should be given to:
  • PLHIV in areas >30% MTB infection in population
  • Health workers, prisoners, contacts, miners

• Mandatory CXR to exclude active TB

• Self administered for 6 months
Implementation progress
ICF among people living with HIV, 2005-2009

* Data as per June 2010

* Numbers under years show the number of countries reporting data followed by the percentage of total estimated HIV-positive people accounted for by reporting countries.
IPT provision for people living with HIV, 2005-2009

* Data as per June 2010

Numbers under years show the number of countries reporting data followed by the percentage of total estimated HIV-positive people without active TB accounted for by reporting countries.

* Data as per June 2010
People living with HIV receiving IPT 2009

* Data as per October 2010
IPT policy in Country X, 2006

Eligibility criteria for a facility to offer IPT

Minimum requirements to offer IPT

**Human resource:**
- Medical Officer
- Laboratory assistant
- Trained counselor
- Pharmacy technician
- Adherence supporters

**Infrastructure:**
- Functional Laboratory
- X-ray or access to x-ray services
- Counseling room/space
- Consultation room

**Equipment and logistics:**
- Facilities for TB microscopy
- Facilities for skin testing (mantoux)
- Cold chain system
- Facilities for HIV testing
- Sustainable supply of anti-TB drugs including Isoniazid
- Sustainable supply of HIV test kits

**Other key issues:**
- If an organization has a TB default rate of greater than 5% it will not be eligible to provide IPT
Conclusion: reconceptualised IPT as part of TB screening and requested WHO to revise the IPT policy
# WHO GRC recommended policy development: quality of evidence

## Table 2: GRADE quality assessment criteria

<table>
<thead>
<tr>
<th>Quality of evidence</th>
<th>Study design</th>
<th>Lower if *</th>
<th>Higher if *</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Randomized trial</td>
<td><strong>Study quality:</strong>&lt;br&gt;-1 Serious limitations&lt;br&gt;-2 Very serious limitations</td>
<td><strong>Strong association:</strong>&lt;br&gt;+1 Strong, no plausible confounders, consistent and direct evidence**&lt;br&gt;+2 Very strong, no major threats to validity and direct evidence***</td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
<td>-1 Important <strong>inconsistency</strong></td>
<td><strong>Dose response</strong> gradient</td>
</tr>
<tr>
<td>Low</td>
<td>Observational study</td>
<td><strong>Directness:</strong>&lt;br&gt;-1 Some uncertainty&lt;br&gt;-2 Major uncertainty</td>
<td><strong>All plausible confounders would have reduced the effect</strong></td>
</tr>
<tr>
<td>Very low</td>
<td>Any other evidence</td>
<td><strong>-1 Sparse data</strong>&lt;br&gt;-1 High probability of <strong>Reporting bias</strong></td>
<td></td>
</tr>
</tbody>
</table>

* 1 = move up or down one grade (for example from high to intermediate)<br>2 = move up or down two grades (for example from high to low)<br>** A statistically significant relative risk of >2 (< 0.5), based on consistent evidence from two or more observational studies, with no plausible confounders.<br>*** A statistically significant relative risk of > 5 (< 0.2) based on direct evidence with no major threats to validity.
### Judgments on strength of recommendation: criteria to consider for WHO

<table>
<thead>
<tr>
<th>Factors</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of the evidence</td>
<td>Higher the quality of the evidence the more likely a strong recommendation can be made</td>
</tr>
<tr>
<td>Balance between desirable and undesirable effects</td>
<td>Larger the gap or gradient between these then more likely a strong recommendation will be made</td>
</tr>
<tr>
<td>Values and preferences</td>
<td>If there is a great deal of variability or strong reasons that the recommended course of action is unlikely to be accepted then it is more likely a weak recommendation will be made.</td>
</tr>
<tr>
<td>Costs/financial implications (resource use)</td>
<td>Higher the cost both financial and in terms of infrastructure, equipment or requirements, and more resource intensive requirements, then less likely to make a strong recommendation</td>
</tr>
<tr>
<td>Feasibility</td>
<td>Is the intervention possible and practical in the settings where greatest impact is likely to be attained or is being sought</td>
</tr>
</tbody>
</table>
**Strength of recommendations**

- **Strong**: the desirable effects of a recommendation outweigh the undesirable effects.

- **Conditional**: the desirable effects probably outweigh the undesirable effects. However,
  - Data are scant or
  - Only applicable to specific group/population or setting or
  - New evidence may change risk to benefit balance or
  - Benefits may not warrant the cost or resources required
Risk and benefit summary

Table 10: Summary of risk and benefits assessment discussed by the TRS working groups

<table>
<thead>
<tr>
<th>Factor</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of evidence</td>
<td>Strong</td>
</tr>
<tr>
<td>Benefits or desired effects</td>
<td>Decrease in early mortality</td>
</tr>
<tr>
<td></td>
<td>Decrease in morbidity and disease progression especially reduction in CD4 impairment and hospitalizations and possible HIV kenmata increase in growth and development Reduction in cost to follow up better retention Less intense pre-ART follow up required With better PMTCT at national policy level</td>
</tr>
<tr>
<td>Morse or undesired effects</td>
<td>May result in early switch to 2nd line previous ART exposure in PMTCT, Pk issues, without long term adherence Greater time on ART Longer term toxicity Unnecessary exposure to treatment in long term non-progression Need to establish viral diagnosis may lead to less emphasis being placed on clinical algorithms</td>
</tr>
<tr>
<td>Values and preferences</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>Families concern about treating infants Health care worker fears about managing infants Implications for disclosure of maternal status</td>
</tr>
<tr>
<td></td>
<td>Weak...</td>
</tr>
<tr>
<td></td>
<td>Strong ethical obligation Care givers will like immediate ART</td>
</tr>
<tr>
<td></td>
<td>Allows a new focus on reaching and managing infants</td>
</tr>
<tr>
<td>Costs</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>Mortality reduces Morbidity related costs (hospitalizations, Ots diagnosis, treatment and prevention etc) Lab monitoring pre-ART no longer necessary to start ART Changes in PMTCT site and activities Parental cost (less hospitalization, less stick, parents can work and earn money) Life long savings if child survives to adulthood Increased by</td>
</tr>
<tr>
<td></td>
<td>Greater need for Viriological tests ART No long costs related to choice of starting regimen Strengthening of infrastructure to deliver care Additional man power (HCT specifically trained within labs and clinics) Increased drug pharmacy costs (delivery and storage of infant formulations)</td>
</tr>
<tr>
<td>Possibility</td>
<td>Conditional to country setting</td>
</tr>
<tr>
<td></td>
<td>Easier to start if no requirement for CD4 Access to infant diagnosis still limited in many countries scale up is challenging PID programs need more capacity on the ground</td>
</tr>
<tr>
<td></td>
<td>Delays in getting results of Viriological tests Need for increased human resources (exp, lab staff) Need for strong linkage between PMTCT and ART clinics May become feasible if less MTCT transmission Availability of infant formulations Need infrastructure to do quick counselling for mothers Need for integration of services (family based care)</td>
</tr>
</tbody>
</table>

Overall ranking of recommendation: **STRONG**
WHO 2010 IPT/ICF Recommendations

- Use four symptom screen to rule in for IPT
- No need for TST or chest radiography
- Simplified algorithm
- HIV program leadership
Rationale

• Ruling out TB is major barrier to implementing IPT

• Chronic cough more than 2 or 3 wks alone is insensitive predictor of TB in people living with HIV

• TB screening tools are not standardised and vary from country to country

• Role of CXR is not clear and inconsistent

• Demand from countries for evidence-based TB screening algorithm
IPT/ICF Guidelines Preparation Process:
HIV/AIDS & Stop TB Departments

1. Scoping the document: reasons for choosing the topic, problems with existing guidelines, variations and gaps,

2. Group composition

3. Conflict of interest

4. Formulations of the questions and choice of the relevant outcomes

5. Evidence retrieval, evaluation and synthesis (balance sheet, evidence table)

6. Benefit/risk profile: integrating evidence with values and preferences, equity and costs

   Benefit/risk profile: affected community

7. Formulation of the recommendations

8. Committee review/finalization (January 25th 2010)

9. Submission to GRC for approval

10. Dissemination

 Reporting standard and process

Standards for evidence: GRADE system

Reporting standard and process
Individual patient meta-analysis (12 studies)

Total patients in the 12 datasets (n=29,523)

- HIV-uninfected patients or those with unknown HIV status (n=19,466)
- HIV-infected patients (n=10,057)
  - Patients receiving TB disease or TB infection treatment at screening (n=187)
  - Patients not receiving TB treatment (n=9,870)
    - Unknown smear results or sputum smear positive with no culture or negative culture or culture grew NTM (n=160)
    - Patients with sputum smear results (n=9,710)
      - Patients with unknown TB status (n=84)
        - Patients with known TB status (n=9,626)

- Patients with known TB status (n=9,626)
  - Patients with TB (n=557)
  - Patients without TB (n=9,069)

Numbers:
- 29,523
- 10,057
- 9,626
## Top 5 Best Performing Rules (1 of m) in all Subjects (n = 8173)

<table>
<thead>
<tr>
<th>Combination Rule</th>
<th>Sen (%)</th>
<th>Spe (%)</th>
<th>LR-Spe</th>
<th>NPV (95% CI) 5% TB Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC, F, NS, WL</td>
<td>85</td>
<td>53</td>
<td>0.29</td>
<td>98.5 (98.1 - 98.8)</td>
</tr>
<tr>
<td>H, F, NS, WL</td>
<td>82</td>
<td>56</td>
<td>0.32</td>
<td>98.4 (97.9 - 98.7)</td>
</tr>
<tr>
<td>CC, F, WL</td>
<td>81</td>
<td>57</td>
<td>0.33</td>
<td>98.3 (97.9 - 98.6)</td>
</tr>
<tr>
<td>CC, NS, WL</td>
<td>81</td>
<td>57</td>
<td>0.34</td>
<td>98.3 (97.9 - 98.6)</td>
</tr>
<tr>
<td>H, F, NS, WL</td>
<td>81</td>
<td>62</td>
<td>0.31</td>
<td>97.4 (98 - 98.7)</td>
</tr>
</tbody>
</table>

**Combination Rule**
- CC: Cough in the last 24 hours; F: Fever; H: Haemoptysis; NS: Night sweats; WL: Weight loss
Performance of the Best Rule
(one of the current cough, fever, night sweats or weight loss)

<table>
<thead>
<tr>
<th>Setting</th>
<th>Sen (%)</th>
<th>Spe (%)</th>
<th>LR- (%)</th>
<th>NPV (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community</td>
<td>76</td>
<td>61</td>
<td>0.39</td>
<td>98.0 (97.4 - 98.4)</td>
</tr>
<tr>
<td>Clinical</td>
<td>89</td>
<td>38</td>
<td>0.50</td>
<td>97.4 (96.7 - 98.8)</td>
</tr>
<tr>
<td>CD4 &lt; 200</td>
<td>94</td>
<td>27</td>
<td>0.45</td>
<td>97.7 (95.8 - 99.5)</td>
</tr>
<tr>
<td>CD4&gt; 200</td>
<td>83</td>
<td>34</td>
<td>0.49</td>
<td>97.6 (95.3 - 98.7)</td>
</tr>
</tbody>
</table>

CC: cough in the last 24 hours; F: Fever; H: Haemoptysis; NS: Night sweats; WL: Weight loss
## Top 5 Best Performing Rules (1 of m) in all subjects with abnormal CXR (n = 2805)

<table>
<thead>
<tr>
<th>Combination Rule</th>
<th>Sen (%)</th>
<th>Spe (%)</th>
<th>LR-Spe</th>
<th>NPV (95% CI) 5% TB prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC, F, NS, WL, X</td>
<td>93</td>
<td>40</td>
<td>0.17</td>
<td>99.1 (98.4 - 99.5)</td>
</tr>
<tr>
<td>CC, F, NS, X</td>
<td>92</td>
<td>50</td>
<td>0.16</td>
<td>99.2 (98.5 - 99.5)</td>
</tr>
<tr>
<td>H, F, NS, WL, X</td>
<td>92</td>
<td>43</td>
<td>0.2</td>
<td>99.0 (98.2 - 99.4)</td>
</tr>
<tr>
<td>H, F, NS, WL, X</td>
<td>91</td>
<td>44</td>
<td>0.2</td>
<td>99.0 (98.2 - 99.4)</td>
</tr>
<tr>
<td>CC, NS, W, LX</td>
<td>91</td>
<td>45</td>
<td>0.2</td>
<td>99.0 (98.2 – 99.4)</td>
</tr>
</tbody>
</table>

CC: cough in the last 24 hours; F: Fever; H: Haemoptysis; NS: Night sweats; WL: Weight loss.
### TB prevalence and the number of diagnostic Evaluations required to yield one TB case

<table>
<thead>
<tr>
<th>Setting</th>
<th>TB Prevalence 1%</th>
<th>TB Prevalence 5%</th>
<th>TB Prevalence 20%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No CXR</td>
<td>CXR</td>
<td>No CXR</td>
</tr>
<tr>
<td>All study subjects*</td>
<td>56</td>
<td>63</td>
<td>11</td>
</tr>
<tr>
<td>Community</td>
<td>51</td>
<td>75</td>
<td>10</td>
</tr>
<tr>
<td>Clinical</td>
<td>75</td>
<td>83</td>
<td>14</td>
</tr>
<tr>
<td>CD4 &lt; 200</td>
<td>82</td>
<td>70</td>
<td>16</td>
</tr>
<tr>
<td>CD4&gt; 200</td>
<td>76</td>
<td>75</td>
<td>15</td>
</tr>
</tbody>
</table>

*Number of PLHIV TB suspects that need to be investigated to get one TB case (FP/TP)
### Evidence for efficacy of different drug regimens

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Comparator</th>
<th>RR (95% CI)</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>Rifampicin and pyrazinamide</td>
<td>1.03 (0.75–1.4)</td>
<td>Moderate</td>
</tr>
<tr>
<td>INH</td>
<td>INH and rifampicin</td>
<td>0.97 (0.52–1.83)</td>
<td>Moderate</td>
</tr>
<tr>
<td>INH</td>
<td>INH, rifampicin and pyrazinamide</td>
<td>0.69 (0.23–1.57)</td>
<td>Low</td>
</tr>
<tr>
<td>INH and rifampicin</td>
<td>INH, rifampicin and pyrazinamide</td>
<td>0.75 (0.21–1.82)</td>
<td>Moderate</td>
</tr>
<tr>
<td>INH and rifapentine</td>
<td>INH</td>
<td>1.05 (0.56–1.97)</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
### IPT for people living with HIV: Evidence for recommendations 3, 4 and 5

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies</th>
<th>Patients</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable, confirmed or possible TB</td>
<td>8</td>
<td>4136</td>
<td>0.67 (0.51,0.87)</td>
</tr>
<tr>
<td>- TST positive</td>
<td>4</td>
<td>1311</td>
<td>0.36 (0.22,0.61)</td>
</tr>
<tr>
<td>- TST negative</td>
<td>7</td>
<td>2490</td>
<td>0.86 (0.59,1.26)</td>
</tr>
<tr>
<td>- TST unknown</td>
<td>2</td>
<td>335</td>
<td>0.86 (0.48,1.52)</td>
</tr>
<tr>
<td>Confirmed TB</td>
<td>4</td>
<td>2063</td>
<td>0.72 (0.47,1.11)</td>
</tr>
<tr>
<td>- TST positive</td>
<td>1</td>
<td>112</td>
<td>0.13 (0.01, 2.32)</td>
</tr>
<tr>
<td>- TST negative</td>
<td>3</td>
<td>1021</td>
<td>0.76 (0.36,1.61)</td>
</tr>
<tr>
<td>- TST unknown</td>
<td>2</td>
<td>930</td>
<td>0.79 (0.46,1.36)</td>
</tr>
</tbody>
</table>

The effect of IPT is more in TST positives than TST negatives and unknowns

*(Akolo et al 2010 Cochrane Review)*
### GRADE analysis table: 36 months vs. 6 month IPT

<table>
<thead>
<tr>
<th></th>
<th>RR for Probable TB (95% CI) = 0.50 (0.29 to 0.84)</th>
<th>RR for Confirmed TB (95% CI) = 0.48 (0.26 to 0.9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Samanadari <em>et al</em>, unpublished, 2010</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martinson <em>et al</em>, unpublished, 2010</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Settings for 36 months should be determined by national guidelines
- Local context (feasibility, resources, safety and relevance)
- Higher TB prevalence and transmission
IPT and drug resistance
RR 95% CI 1.45 (0.85-2.47)

(Balcell's et al, 2006)
### GRADE analysis table: IPT and drug resistance

**GRADE profile table 10: Drug resistance and use of preventive therapy**


<table>
<thead>
<tr>
<th></th>
<th>Quality assessment</th>
<th>Summary of findings</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mono-resistance to IPT vs. Placebo (IPT vs. placebo)</td>
<td>No of patients: 11/1255 (0.9%)</td>
<td>Effect: RR 1.87 (0.65 to 5.38)</td>
<td>Critical</td>
</tr>
<tr>
<td></td>
<td>No of medications: 5/1059 (0.5%)</td>
<td>Absolute: 4 more per 1000 (from 2 fewer to 20 more)</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Anti-TB medications: None</td>
<td>Relative (95% CI): 1.87 (0.65 to 5.38)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No medications: None</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other considerations: None</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quality: MODERATE</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Importance: Critical</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Mono-resistance to IPT vs. Rifampin (IPT intervention vs. Rifampin as control) | No of patients: 3/1469 (0.2%) | Effect: RR 2 (0.13 to 22.03) | Less critical |
|                                                                           | No of medications: 1/1469 (0.1%) | Absolute: 1 more per 1000 (from 1 fewer to 14 fewer) | |
|                                                                           | Anti-TB medications: None | Relative (95% CI): 2 (0.13 to 22.03) | |
|                                                                           | No medications: None | | |
|                                                                           | Other considerations: None | | |
|                                                                           | Quality: VERY LOW | | |
|                                                                           | Importance: Less critical | | |

1. Incomplete accounting of patients and outcomes
2. Low number of cases and patients
3. Low number of patients

**RR 95% CI = 1.87 (0.65 - 5.38)**
Prevalence of INH resistance among IPT exposed is similar to background population

Fig. 1. Percentages of tuberculosis episodes with any isoniazid resistance (bars show 95% confidence intervals).

Van Halsema et al, 2010
Concomitant use of IPT with ART (Strong recommendation, low quality evidence)

• No study directly address the issue

• Contrasting results on immune status and IPT effect
  • No difference by HIV stage at baseline (Gordin, 1997)
  • Greater effect when TLC >2/L (Mwinga, 1998)
  • Not affected by CD4 count (Churchyard, 2003)

• IPT+ART= TB IRR 0.20 (0.09–0.91) (Golub, 2007-Brazil)
• IPT+ART= TB IRR 0.15 (0.004–0.85) (Golub, 2009-SA)
Recommendation 1: TB screening for adults and adolescents

Adults and adolescents living with HIV should be screened with a clinical algorithm and those who do not report any one of;

- current cough,
- fever,
- weight loss or
- night sweats

are unlikely to have active TB and should be offered IPT.

*(Strong recommendation, moderate quality evidence)*
Recommendation 2: TB screening for adults and adolescents

Adults and adolescents living with HIV screened with a clinical algorithm and reported one of the following:

- current cough,
- fever,
- weight loss or
- night sweats

may have active TB and should be evaluated to TB and other diseases.

(Strong recommendation, moderate quality evidence)
Recommendation 3: IPT 6 months for adults and adolescents

Adults and adolescents who are living with HIV and:
- have unknown or positive TST status and;
- unlikely to have active TB

should receive IPT for at least 6 months

IPT should be given to such individuals irrespective of the degree of immunosuppression, and also to those on ART, those who have previously been treated for TB and pregnant women

(Strong recommendation, high quality evidence)
Recommendation 4: IPT 36 months for adults and adolescents

Adults and adolescents who are living with HIV in settings with higher TB transmission and:
• have unknown or positive TST status and;
• unlikely to have active TB
should receive IPT for at least 36 months

IPT should be given to such individuals irrespective of the degree of immunosuppression, and also to those on ART, those who have previously been treated for TB and pregnant women

(Conditional recommendation, low quality evidence)
Recommendation 5: TST

- Tuberculin skin test is not a requirement for initiating IPT for people living with HIV
  
  (Strong recommendation, moderate quality evidence)

- People living with HIV who have a positive TST benefit more from IPT; TST can be used where feasible to identify such individuals

  (Strong recommendation, high quality of evidence)
Recommendation 6: INH resistance

• Providing IPT to people living with HIV does not increase the risk of developing INH resistant TB. Therefore concerns regarding the development of INH resistance should not be a barrier to providing IPT.

(Strong recommendation, moderate quality evidence)
Screen for TB with any one of the following:**
- Current cough
- Fever
- Weight loss
- Night Sweats

Person living with HIV

Yes

Investigate for TB & other disease

Not TB
- Follow up & consider IPT
- Treat for TB

TB
- Appropriate treatment & consider IPT

Other diagnosis

No

Assess IPT contraindications

No
- Give IPT

Yes
- Defer IPT

Screen for TB regularly
Search criteria:
PubMed Search ("Child"[Mesh] OR "Child, Preschool"[Mesh]) OR "Infant"[Mesh]) AND "Tuberculosis"[Mesh]) AND "HIV Infections"[Mesh]) AND "Diagnosis"[Mesh]) OR (TB screening, Children, HIV)

546

Limits: Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Review, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Controlled Clinical Trial, Evaluation Studies, Multicenter Study, MEDLINE, PubMed Central, All Infant: birth-23 months, Newborn: birth-1 month, Infant: 1-23 months, Preschool Child: 2-5 years, Child: 6-12 years

161

By title
57 (+ 17 added)

By abstract
20 (+10 added from references)

Of interest
15

International conferences (CROI, IAS, International AIDS conference):
CROI 2008, 2009: 0
IAS 2009: 2
IAC 2008: 2

Abstracts of Interest: 1
16

Studies of interest:
A total of 16 articles/abstracts provided information about clinical presentation of tuberculosis among HIV-infected children or utility of TB scoring system in HIV-infected children or combination of signs and symptoms or diagnostic tests among HIV-infected children.
TB screening for IPT for children

<table>
<thead>
<tr>
<th>No. of studies</th>
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**Negative predictive value 0.99**

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**Sensitivity 0.90**

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**Specificity 0.65**

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**Positive predictive value 0.15**

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A combination of culture and radiological appearance was used as a gold standard, which is not a perfect gold standard. The study did not qualify for the highest quality of evidence since it was an observational study and did not have a well-defined gold standard.

* The reference standard used is unlikely to correctly classify all the children with disease as having the disease. Moreover, sputum was collected only from children having signs and symptoms suggestive of TB or abnormal chest X-ray findings.

# Confidence intervals for sensitivity and specificity were not reported.

Bibliography: Song et al. 2009
Recommendations for children: TB screening

Strong recommendation, low quality evidence

Children living with HIV who do not have poor weight gain*, fever or current cough are unlikely to have active tuberculosis TB.

Strong recommendation, low quality of evidence

Children living with HIV who have any one of the following symptoms – poor weight gain, fever, current cough or contact history with a TB case – may have TB and should be evaluated for TB and other conditions. If the evaluation shows no TB, such children should be offered IPT regardless of their age.

*Poor weight gain is defined as reported weight loss, or very low weight (weight-for-age less than -3 z-score), or underweight (weight-for-age less than -2 z-score), or confirmed weight loss (>5%) since the last visit, or growth curve flattening
Recommendations for children: IPT

**Strong recommendation, moderate quality of evidence**
- Children living with HIV who are more than 12 months of age and who are unlikely to have active TB on symptom-based screening, and have no contact with a TB case should receive six months of IPT (10 mg/kg) as part of a comprehensive package of HIV prevention and care services.

**Strong recommendation, low quality of evidence**
- In children living with HIV who are less than 12 months of age, only those children who have contact with a TB case and who are evaluated for TB (using investigations) should receive six months of IPT if the evaluation shows no TB disease.

**Conditional recommendation, low quality of evidence**
- All children living with HIV who have successfully completed treatment for TB disease should receive INH for an additional six months.
Secondary prophylaxis

• No evidence on the use of IPT in children living with HIV after successful completion of TB treatment

• Children living with HIV are exposed to reinfection and recurrence of TB

Conditional recommendation

All children living with HIV who have been successfully treated for TB and are living in settings with a high TB prevalence and transmission should receive IPT for an additional six months.

(IPT can be started after the last dose of anti-TB therapy or at a later date)
Role of TST and IGRA: Children

• TST is not required to initiate IPT in children and should not be routinely used as part of the process to determine eligibility for IPT.

• TST may provide important additional information in assessing a child with suspected TB, especially if there is no positive contact history.

• The main limitation of TST in the diagnosis of TB in HIV-infected children is its variable sensitivity.

• In settings where it is available, TST may be used for the diagnosis of active TB in children and may also have a role in screening for LTBI.

• No role for IGRA.
IPT and ART: Children

- No data regarding the efficacy of IPT for children stratified by degree of immunosuppression.
- Biological plausibility in extrapolating what is known for adults and adolescents to children

Conditionally recommended the combined use of IPT with ART for all children (ART priority).
Algorithm for TB screening in children more than one year of age and living with HIV

Child more than 12 months of age and living with HIV*

Screen for TB with any one of the following symptoms:
- Poor weight gain
- Fever
- Current cough
- Contact with a TB case

No | Yes
---|---
Assess for contraindications to IPT*** | Investigate for TB and other diseases****

No | Yes
---|---
No | Other diagnosis
Give IPT | Defer IPT

Yes | Not TB | TB
---|---|---
Give appropriate treatment and consider IPT | Follow up and consider IPT | Treat for TB

Screen regularly for TB
Summary: what is new in 2010?

• Screening for TB only by using symptom based algorithm is sufficient to start IPT for PLHIV

• No mandatory CXR and TST requirement for IPT

• Regular screening of those on IPT at every visit

• Pregnant women, children, those on ART and those who completed TB treatment should receive IPT

• Conditional recommendation of 36 months IPT for settings with high TB transmission among PLHIV
Conclusions

• The analysis represent the best available evidence from Asia and Africa

• The recommended rule perform consistently across different settings, populations and CD4 count

• The rule entail replacement of longer duration cough with current cough among PLHIV

• CXR improves the sensitivity of the rule by 13-16%

• The trade offs to the health system are similar to the expected practice at 5% TB prevalence

• The ultimate solution lies in the better point of care TB diagnostics (TB dipstick test). RESEARCH
Conclusions

• Screening rule is applicable to those living with HIV in resource limited settings
• The screening rule can be effectively used among people living with HIV, including during HIV testing campaigns
• The rule is not practical for TB screening among those without HIV as the numbers of false positives would be very high
• Further research in children is needed to build evidence base
Laws, like sausages, cease to inspire respect in proportion as we know how they are made.

Otto von Bismarck 1930
Thank you

**Review Team:**
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Date, Anand (CDC/CCID/NCHHSTP)
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Martina Penazatto

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Andrew Doupe (HIV/AIDS)
Christian Gunneberg (STOP TB)
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Malgorzata Grzemska (STOP TB)
Reuben Granich (HIV/AIDS)
Siobhan Crowley (HIV/AIDS)
Caoimhe Smyth (HIV/AIDS)
Evidence for TB screening recommendations (1 and 2)

**Individual patient data meta-analysis**

What is the most sensitive clinical algorithm to screen for culture-confirmed TB in people living with HIV?

**Inclusion criteria for studies**

- Collected sputum specimens from PLHIV regardless of signs or symptoms;
- Used mycobacterial culture of at least one specimen to diagnose TB and;
- Collected data about signs and symptoms.
Methods

• Clinical symptoms that can be assessed at any level of the health system

• Analysis of common variables across studies:
  • Cough (4 wks, 2 wks and last 24 hours)
  • Night sweats
  • Fever
  • Weight loss
  • Hemoptysis

• Only observations with no missing data included

• Impact of adding CXR was also examined
Systematic search of studies

Database searching (n=2352)

Other sources (n=18)

Records (n=2119)

Screened (n=53)

Excluded (n=32)

Full text articles (n=21)

Full text excluded (n=9)

Studies included (n=12)
WHO Guidelines for National TB Programmes on the Management of Children

Figure 1

Approach to contact management when chest X-ray and tuberculin skin test are not readily available

Child in close contact with source case of smear-positive pulmonary TB

- Under 5 years of age
  - Well
  - Symptomatic

- Aged 5 years or over
  - Well
  - Symptomatic

If becomes symptomatic

Evaluate for TB

If becomes symptomatic

No treatment

---

1 If TB is suspected, refer to Section 1.
2 Isoniazid 5 mg/kg daily for 6 months.
3 Unless the child is HIV-infected (in which case isoniazid 5 mg/kg daily for 6 months is indicated).
## Pediatric dosing chart

<table>
<thead>
<tr>
<th>Weight range (kg)</th>
<th>Number of 100 mg tablets of INH to be administered per dose (total dose 10 mg/kg/day)</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>½ tablet</td>
<td>50</td>
</tr>
<tr>
<td>5.1–9.9</td>
<td>1 tablet</td>
<td>100</td>
</tr>
<tr>
<td>10–13.9</td>
<td>1 ½ tablet</td>
<td>150</td>
</tr>
<tr>
<td>14–19.9</td>
<td>2 tablets</td>
<td>200</td>
</tr>
<tr>
<td>20–24.9</td>
<td>2 ½ tablets</td>
<td>250</td>
</tr>
<tr>
<td>&gt;25</td>
<td>3 tablets or one adult tablet</td>
<td>300</td>
</tr>
</tbody>
</table>
Call for Rigor and Transparency

BMJ Grading quality of evidence and strength of recommendations

BMJ 2004;328:1490-
doi:10.1136/bmj.328.7454.1490

GRADE: grading quality of evidence and strength of recommendations for diagnostic tests and strategies

The GRADE system can be used to grade the quality of evidence and strength of recommendations for diagnostic tests or strategies. This article explains how patient-important outcomes are taken into account in this process.
Ideal recommendations
• Screening algorithm for IPT and further TB evaluation
• Recommendations regarding diagnostic methods for ruling out TB
• Preferred regimen for adults and children
• Answer questions regarding duration, toxicity, cost, and resistance

Populations being considered
• HIV+ adults, adolescents and children
• HIV+ pregnant women

Relevant outcomes
• Mortality
• Disease progression (morbidity)
• Severe or regimen limiting adverse events
• Adherence and retention on IPT
• Durability of IPT regimen effect
• Cost effectiveness
1. What are the best combination of signs, symptoms and diagnostic procedures (e.g., smear microscopy, radiography, serum-based tests such as IGRA, etc.) as screening tools to determine eligibility for treatment for latent TB infection?

2. What is the optimal duration and drug regimen (e.g., INH, RIF, etc.) for treatment of LTBI to reduce the risk of developing Tuberculosis among PLHIV?

3. What is the optimal time to start considering IPT? (i.e., should immune status be considered and should IPT be started with ART)?

4. Should secondary treatment of LTBI be provided for people living with HIV to prevent re-infection or recurrence of tuberculosis after successful completion of TB treatment?

5. Does treatment for LTBI among people living with HIV lead to significant developments of mono-resistance against the drug(s) used for LTBI treatment?

6. Will low adherence rates to LTBI treatment be a barrier to implementation of LTBI treatment among PLHIV?

7. Is provision of treatment for LTBI cost-effective?

8. Is the use of tuberculin skin test feasible in resource limited settings?
Children living with HIV without poor weight gain*, fever, current cough are unlikely to have active tuberculosis and should be offered IPT

Children living with HIV who are over 12 months of age who are unlikely to have active TB should receive 6 months of INH preventive therapy (10mg/kg) as part of a comprehensive package of HIV care.

After successful completion of treatment for TB disease, all children living with HIV who are over 12 months of age should receive INH for an additional 6 months.

All children with a history of contact with a TB case should receive 6 months IPT.

<table>
<thead>
<tr>
<th>Population: Children living with HIV</th>
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<tr>
<td>Intervention: Careful history taking, and clinical assessment</td>
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<table>
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<tr>
<th>Factor</th>
<th>Decision</th>
<th>Explanation</th>
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<td>Quality of evidence</td>
<td>Low</td>
<td>The quality of evidence comes from one study by Song et al is low.</td>
</tr>
<tr>
<td>Benefits or desired effects</td>
<td>Strong</td>
<td>Simplifies screening and limits the numbers of radiologic and laboratory investigations. Identifies children that can benefit from IPT (and thus reduce TB morbidity/mortality)</td>
</tr>
</tbody>
</table>
| Risks or undesired effects | Strong   | • Small number of children with active tuberculosis might be given mono-therapy  
• Increase in time spent by health care workers for screening for TB |
| Values and preferences     | Strong   | • Parents would like their children to be protected from TB due to IPT especially in high TB burden setting |
| Costs                      | Weak/conditional | Increased by:  
• Training of clinicians and nurses to perform clinical assessment and correctly determine poor weight gain  
Additional staff due to increase in time spent by existing staff for screening  
Reduced by:  
• Limited resources needed for symptom screening among children already regularly attending clinical services for HIV  
• Avoiding costs of additional diagnostic tests including chest x-ray  
Avoiding costs that would have been associated with treatment of TB (if latent TB infection is effectively treated) |
| Feasibility                | Weak     | History taking and clinical assessment would be feasible but would require additional training and time for already overburdened staff. |
| Overall ranking of recommendation | Strength of recommendation | Strong (initial IPT for 6 months)  
Conditional (post TB treatment) |
Children living with HIV with any one of the following: poor weight gain, fever of current cough may have active tuberculosis and should be evaluated for TB and other diseases.

| Population: | Children living with HIV |
| Intervention: | Careful history taking, and clinical assessment |

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<td>Benefits or desired effects</td>
<td>Weak</td>
<td>Early identification of TB suspects followed by appropriate treatment of identified TB cases can reduce TB-associated morbidity and mortality among children living with HIV.</td>
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<td>Risks or undesired effects</td>
<td>Weak</td>
<td>Increased demand for clinical and laboratory investigations. This approach would result in a larger number of children undergoing diagnostic testing, including possible risks (generally not high danger) associated with sample collection (e.g. from lymph nodes or gastric aspirates).</td>
</tr>
<tr>
<td>Values and preferences</td>
<td></td>
<td>Patients/parents generally desire accurate diagnosis of disease and may be willing to undergo diagnostic evaluation or treatment in effort to prevent morbidity/mortality</td>
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<td>Costs</td>
<td>Weak/Weak</td>
<td>Increased by: Increase in number of children requiring diagnostic evaluation for TB will require resources (staff, reagents, transport, lab capacity). Increased need for quality assurance of diagnostic services. Need for additional drugs to increase in number of cases. Decreased by: Decreased costs of managing more severely ill or dying children if TB is recognized.</td>
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<td>Feasibility</td>
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<td>May require some additional training and time from overburdened health care workers, laboratory workers and families of affected children.</td>
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