Intensive case finding – does symptom screening cut it?

Gary Maartens
Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings
Why intensified case finding?

- Undiagnosed TB is common in HIV+
- Earlier treatment reduces transmission
- Earlier treatment reduces morbidity & mortality
- Select people eligible for IPT
All people living with HIV should be regularly screened for TB….at every visit to a health facility or contact with a health worker. Screening for TB is important, regardless of whether they have received or are receiving IPT or ART.
ICF yield in HIV+ in SA

Antenatal clinic  0.7%  Only women with symptoms cultured
Community        5%
Gold mines       4.9%
VCT               7.4%
Pre-ART           31.5%

Int J Tuberc Lung Dis 2006;10:523
AIDS 2010;24:1323
Am J Respir Crit Care Med 2007;175:87
Effect of ART on ICF yield

<table>
<thead>
<tr>
<th>Study</th>
<th>Pre-ART</th>
<th>On ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jo’burg</td>
<td>8.4%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Cape Town</td>
<td>13%</td>
<td>5.4%</td>
</tr>
</tbody>
</table>

JAIDS 2012;60:e22
Rangaka Clin Infect Dis 2012
For IPT essential to **rule out** active TB

Ideal test: neg. predictive value \( \sim 100\% \)

neg. likelihood ratio <0.1
Development of a Standardized Screening Rule for Tuberculosis in People Living with HIV in Resource-Constrained Settings: Individual Participant Data Meta-analysis of Observational Studies

Haileyesus Getahun¹, Wanitchaya Kittikraisak², Charles M. Heilig³, Elizabeth L. Corbett⁴, Helen Ayles⁴,⁵, Kevin P. Cain³, Alison D. Grant⁴, Gavin J. Churchyard⁶, Michael Kimerling⁷, Sarita Shah⁸, Stephen D. Lawn⁴,⁹, Robin Wood⁹, Gary Maartens¹⁰, Reuben Granich¹, Anand A. Date³, Jay K. Varma²,³

N=8,148
From 9 studies
Sputum cultures done
TB screening algorithm

Best symptom screen for TB – any one of:

• Cough – active *(any duration)*
• Fever >2 weeks
• Night sweats
• Weight loss

Overall diagnostic performance

• Sensitivity 78.9%
• Specificity 49.6%
• Likelihood ratio negative (LR-) 0.426
<table>
<thead>
<tr>
<th>Predictors</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study level</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Setting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Community</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td>4.45 (1.02, 19.46)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.25 (0.06–1.01)</td>
</tr>
<tr>
<td>Miners</td>
<td>0.25 (0.02–2.51)</td>
<td>4.07 (0.44–37.68)</td>
</tr>
<tr>
<td>Screening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prescreened for TB</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Not screened for TB</td>
<td>10.82 (2.45–47.78)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.08 (0.06–0.12)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Culture medium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solid</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Liquid</td>
<td>3.41 (0.57–20.30)</td>
<td>0.33 (0.06–1.97)</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>4.03 (0.65–24.84)</td>
<td>0.20 (0.04–1.00)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
TB symptom screen performance in clinic by TB prevalence

<table>
<thead>
<tr>
<th>TB prevalence</th>
<th>1%</th>
<th>5%</th>
<th>20%</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPV</td>
<td>99.7%</td>
<td>98.3%</td>
<td>92.3%</td>
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</tbody>
</table>
Effect of ART on WHO symptom screening (clinic regularly does TB screening)

<table>
<thead>
<tr>
<th>ART status</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>NPV</th>
<th>LR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre ART (n=657)</td>
<td>47.6%</td>
<td>79.8%</td>
<td>91.2%</td>
<td>0.66</td>
</tr>
<tr>
<td>On ART (n=772)</td>
<td>23.8%</td>
<td>94.4%</td>
<td>95.6%</td>
<td>0.81</td>
</tr>
</tbody>
</table>

Pre ART  
On ART  

prior prob. 13%  
prior prob. 5%  
post. prob. 9%  
post prob. 4%

Rangaka Clin Infect Dis 2012
BMI <18.5 & CD4 count <200 contribute to screening for TB
What about CXR? - WHO

Abnormal CXR increased sensitivity of symptoms by 11.7%, but reduced specificity by 10.7%
What about CXR? - BOTUSA

‘Symptom+CXR’ vs ‘Symptoms only’: 98 excess cases of TB, 15 excess deaths.

‘Symptom+CXR’ policy reduced deaths only if attrition were close to zero, but the cost would be US$2.8 million per death averted.
Does tuberculin skin test help?

• TST+ benefit from IPT (Tom Boyles)

• TST+ group have more TB in ICF studies
  – aOR 3.5 (95%CI 1.9-6.7)
  – aOR 4.8 (95%CI 1.6-14.4)

IJTLD 2004 ;8:792
Eur Resp J 2012;39:163
Microbiological screening

• Xpert MTB/RIF had sensitivity of 73.3% in an ICF study in a Cape Town pre-ART clinic – similar to passive case finding

CRP screening?

- Passive case finding study in Pietermaritzburg
  - Sensitivity 98%
  - Likelihood ratio negative 0.04
- No data in ICF
- Point of care CRP test available
Conclusions

- There is a lot of HIV-associated TB when you look
- Symptom screening reasonable yield if no prior screening & done in a clinic pre-ART
- Need better rule out tests in other settings
- High prevalence argues for routine culture or PCR in some settings, especially pre-ART