The scale up of TB/HIV collaborative activities in Asia-Pacific

**TB/HIV Operational Research: Needs and Recent Advances**

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Operational Research: Definition

“Operational research is concerned with the day to day operations of programs. It is intended to provide managers, administrators, and policy-makers with the information that they need to improve service delivery activities and plan future ones. It seeks practical solutions to problem situations and viable alternatives to unsatisfactory operating methods.”
Operational Research should:

• Address country-specific TB/HIV control issues
• Be conducted rapidly, with involvement from programme managers
• Lead to specific recommended interventions, including changes in national policy and national strategies
Examples of Operational Research Questions for TB/HIV in Asia

• In HIV-infected patients diagnosed with TB, how do you reduce mortality?
• What is the best way to screen for and diagnose TB in people with HIV?
• Which TB infection control measures are most effective/cost-effective?
• What is the yield of contact-tracing among patients with pulmonary TB for TB case-finding? HIV case-finding?
• What is the cost-effectiveness of new diagnostic tests?
Need for intensified TB case finding among people with HIV

- Case-fatality rate for HIV-infected TB patients high (up to 25-50% during TB treatment)
- About half of deaths occur within 2 months
- Early diagnosis should decrease case-fatality
- Improve safety of ART initiation
- Improve uptake of IPT
- WHO recommendation
Difficulty of TB screening in HIV-infected persons

- HIV-infected TB patients often lack classic TB symptoms
- Up to 30% of HIV-infected TB patients with pulmonary TB have a normal chest radiograph
- Sputum smears may be negative in 50% or more
- Currently, no internationally accepted, evidence-based approach to screening
Improving the Diagnosis of TB in HIV-infected Persons in SE Asia

- Objectives are to:
  - Develop an evidence-based clinical algorithm with high sensitivity to rule-out TB in HIV-infected persons
  - Develop an algorithm with high specificity to diagnose TB in HIV-infected persons
- Algorithm based on all patients, i.e. no assumptions about importance of cough or other symptoms
- Enroll broad cross-section of HIV-infected persons from multiple settings
- Use a sensitive combination of microbiological tests as the gold-standard
Enrollment Sites & Sample Size

- Total planned enrollment: 2,050 across 3 countries
  - 600 in one site in Bangkok, Thailand
  - 1,000 in four sites in Cambodia
  - 450 in three sites in Ho Chi Minh City, Vietnam
Study procedures

• Informed consent
• Questionnaire administered by doctor/nurse
• Patient examined by doctor
• Chest radiograph
• Lab tests: Blood count, CD4
• Microbiology
  – Culture and smear of 3 sputum, 1 urine, 1 stool, and 1 blood specimen
  – Lymph node aspirate cx if enlarged peripheral node
• Optional tests (by site): TST, HIV viral load
Summary results: TB screening

• Chronic cough, or any other single symptom, is not sufficiently sensitive for TB screening in people with HIV

• Combination of symptoms achieves sensitivity >90%
  – Much better than standard methods
  – Achieving 100% not feasible
### Some candidate combinations

<table>
<thead>
<tr>
<th>Rule</th>
<th>Sens (%)</th>
<th>Spec (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 of 2 rules</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough, fever</td>
<td>91</td>
<td>37</td>
</tr>
<tr>
<td>Cough in past 24 hours, fever</td>
<td>88</td>
<td>44</td>
</tr>
<tr>
<td><strong>1 of 3 rules</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough, fever, drenching night sweats ≥3 weeks</td>
<td>93</td>
<td>36</td>
</tr>
<tr>
<td>Cough, drenching night sweats, loss of appetite</td>
<td>93</td>
<td>35</td>
</tr>
<tr>
<td>Cough in the past 24 hours, fever, drenching night sweats ≥3 weeks</td>
<td>90</td>
<td>43</td>
</tr>
</tbody>
</table>
Application of candidate approach to screening

All Patients (N=1,748)
267 (15%) MTB+

None of: night sweats >3 weeks, cough, fever (N=549)
18 (3%) MTB+

≥1 of symptoms (N=1,199)
249 (21%) MTB+
Diagnostic Algorithm

All Patients (N=1,199)
249 (21%) MTB+

2 sputum smears

Negative
151/1,086 (14%) MTB+

Positive
98/113 (87%) MTB+
Diagnostic Algorithm

All Patients (N=1,199)
249 (21%) MTB+

2 sputum smears

Negative
151/1,086 (14%) MTB+

Positive
98/113 (87%) MTB+

Chest radiography

Normal
68/836 (8%) MTB+

Abnormal
83/250 (33%) MTB+
Diagnostic Algorithm

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CD4

≥350
13/278 (5%) MTB+

<350
55/558 (10%) MTB+
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Comparison to other commonly used approaches

• We compared this algorithm to other commonly used approaches
  – WHO diagnosis of smear-negative TB, recommends initial screening for cough >2 or 3 weeks
  – Alternative: Sputum smears and chest radiography for every patient, TB ruled out if both negative

• Evaluated number of false negatives, resource utilization, and characteristics of false negatives
Comparison of approaches (N=1,748 patients)

<table>
<thead>
<tr>
<th></th>
<th>WHO</th>
<th>Smear/x-ray</th>
<th>Algorithm</th>
</tr>
</thead>
<tbody>
<tr>
<td># excluded by symptom screen</td>
<td>1,393</td>
<td>N/A</td>
<td>549</td>
</tr>
<tr>
<td># patients needing smears</td>
<td>355</td>
<td>1,748</td>
<td>1,199</td>
</tr>
<tr>
<td># x-rays</td>
<td>300</td>
<td>1,748</td>
<td>1,086</td>
</tr>
<tr>
<td># needing TB culture</td>
<td>300</td>
<td>N/A</td>
<td>808</td>
</tr>
<tr>
<td># False negatives</td>
<td>≥179</td>
<td>75</td>
<td>31</td>
</tr>
<tr>
<td>False negatives, median CD4</td>
<td>398</td>
<td>146</td>
<td>112</td>
</tr>
</tbody>
</table>
Conclusions: Screening

- Cough $\geq 2$ or 3 weeks insensitive (22-33% sensitivity), should not be used alone as initial screening
  - WHO algorithm for diagnosing smear-negative TB should be modified
- No other single symptom sufficiently sensitive
- Combination of symptoms (1 of 3)
  - Can be highly sensitive
  - Example – any 1 of: night sweats $\geq 3$ weeks, fever, cough
  - Simple, performs as well as or better than other approaches that we evaluated
Conclusions: Diagnosis

• Best approach based on available data
  – Symptom screen, then
  – Sputum smears, then chest radiograph, then CD4 testing
• It is ok if some steps occur at the same time, then this can be used as a decision tree
• Decreases smear and chest radiograph utilization
• Culture required for at least ~45% of people with HIV in order to diagnose TB
• Liquid culture much more sensitive than solid culture (data not shown)
Some next steps

Cambodia
- Cambodian Revised TB/HIV Framework/SOP drafted
- New guidelines to be implemented in next year
- Evaluation of new algorithm in field setting
  - Use new algorithm in selected sites; include IPT track for those eligible
  - Evaluate performance, acceptability, resources

International
- Meta-analysis including this and other studies → expert meeting Oct 2009 to revise WHO guidelines for ICF in PLHA
- Enhanced evaluation of algorithm (Thailand, Viet Nam, Kenya)
- Cost-effectiveness analysis (Thailand)
Summary

• Important new research findings on how to screen for TB among PLHA should reduce deaths
• Ongoing evaluation required to confirm algorithm performance
• High-quality operational research can address important programmatic questions and provide practical recommendations
• Requires:
  – Well-defined questions
  – Engagement of programme managers at all stages of planning, implementation, analysis (partnerships!)
  – Effective, rapid sharing of findings
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