What is new on HIV associated TB diagnosis?

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Stop TB Department
Recent autopsy studies among PLHIV (CROI 2013)

Proportion of cadavers with TB

- Adults died at home in South Africa (Martinson et al): 34%
- PLHIV died after median 10 months of ART (Some et al): 52%
- PLHIV died within 3 months of ART (Mutevedzi et al): 21%

Undiagnosed TB: a major cause/contributor to PLHIV deaths
Victims of TB

Nelson Mandela
Desmond Tutu
E. Roosevelt (US 1st Lady)
Rene Laennec (inventor of stethoscope)

Roberto Bettega
George Orwell (author)
Katherine Mansfield (author)
F. Chopin (musician)
“I had TB”

Pope Francis
Current status of TB diagnostics

- 7 new tools or methods since 2007
- 6 classes in development
- No point of care test envisaged
<table>
<thead>
<tr>
<th>Brazil</th>
<th>(Coimbra et al, 2012)</th>
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<tbody>
<tr>
<td>- Referral HIV/AIDS centers</td>
<td></td>
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<tr>
<td>- Study period: July 2007-June 2010</td>
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<tr>
<td>- Range: 1-552 days</td>
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<td>- Median: 41 (IQR: 19-85) days</td>
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<table>
<thead>
<tr>
<th>Brazil</th>
<th>(Silva et al, 2012)</th>
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<tbody>
<tr>
<td>- Tertiary, university-affiliated hospital</td>
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<tr>
<td>- Study period: Jan 2008-Jan 2011</td>
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<tr>
<td>- Median: 6 (IQR: 2-12) days</td>
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Delay in TB diagnosis among PLHIV (onset of symptoms to initiation of Rx)

- Malawi (van Lettow et al, 2012)
  - ART centers in 2 referral hospitals
  - Study period: Feb 2010-June 2011
  - Median for clinically diagnosed: 47 (IQR: 32-87) days
  - Median for lab diagnosed: 27 (IQR: 17-65) days
Mainstay of TB diagnosis: microscopy
Xpert MTB/RIF
Pooled sensitivity of Xpert MTB/RIF
(Steingart, 2013)
Sensitivity of Xpert MTB/RIF
(repeat sputum test increase smear negative sensitivity)

Boehme et al NEJM 2010
# Xpert and Extrapulmonary TB
(Sensitivity=53-97%)

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Country</th>
<th>TB gold standard diagnoses (n)</th>
<th>TB not diagnosed (n)</th>
<th>Main sample types testing positive for TB (n)</th>
<th>Gold standard for TB diagnosis</th>
<th>Xpert sensitivity, % (95% CI)</th>
<th>Xpert specificity, % (95% CI)</th>
</tr>
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<tbody>
<tr>
<td><strong>Index study</strong></td>
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<tr>
<td>Tortoli et al. (2012)</td>
<td>Italy</td>
<td>268</td>
<td>1206</td>
<td>Tissue biopsies/fine-needle aspirates (94); pleural fluid (18); gastric aspirates (61); pus (55); CSF (14); urine (16); peritoneal/synovial/pericardial fluid (10)</td>
<td>Culture (solid and liquid) or suggestive radiology/histology with documented positive response to TB treatment</td>
<td>81.3 (76.2–85.8)</td>
<td>99.8 (99.4–100)</td>
</tr>
<tr>
<td><strong>Other studies</strong></td>
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</tr>
<tr>
<td>Armand et al. (2011)</td>
<td>France</td>
<td>32</td>
<td>NA</td>
<td>LNs (16); pleural (7); bone (5)</td>
<td>Culture (solid and liquid media)</td>
<td>53.1 (34.7–70.9)</td>
<td>NA</td>
</tr>
<tr>
<td>Causse et al. (2011)</td>
<td>Spain</td>
<td>41</td>
<td>299</td>
<td>Tissue biopsies (18); CSF (6); gastric aspirates (8); pleural fluid (4); purulent exudates (5)</td>
<td>Culture (solid and liquid media)</td>
<td>95.1 (83.5–99.4)</td>
<td>100 (98.8–100)</td>
</tr>
<tr>
<td>Friedrich et al. (2011)</td>
<td>South Africa</td>
<td>20</td>
<td>5</td>
<td>Pleural fluid (25)</td>
<td>Culture (liquid media)</td>
<td>25.0 (8.7–49.1)</td>
<td>100 (47.8–100)</td>
</tr>
<tr>
<td>Hillemann et al. (2011)</td>
<td>Germany</td>
<td>45</td>
<td>476</td>
<td>Tissue (30); gastric aspirate (8); urine (5)</td>
<td>Culture (solid and liquid media)</td>
<td>77.3 (60.5–87.1)</td>
<td>98.2 (96.0–98.9)</td>
</tr>
<tr>
<td>Ligthelm et al. (2011)</td>
<td>South Africa</td>
<td>30</td>
<td>18</td>
<td>Fine-needle aspiration LN biopsy</td>
<td>Composite standard: positive cytology + AFB and/or culture of MTB</td>
<td>96.6 (86.6–100)</td>
<td>88.9 (69.6–100) (note: only 18 samples)</td>
</tr>
<tr>
<td>Moure et al. (2011)</td>
<td>Spain</td>
<td>108</td>
<td>41</td>
<td>All smear-negative. Pleural fluid (26); LNs (34); abscess aspirates (17); tissues (12)</td>
<td>Culture (solid and liquid media)</td>
<td>58.3 (48.5–67.8)</td>
<td>100 (91.4–100)</td>
</tr>
<tr>
<td>Vadwai et al. (2011)</td>
<td>India</td>
<td>283</td>
<td>250</td>
<td>Tissue biopsies (105); pus (98); body fluids (24)</td>
<td>Composite of smear, culture, clinical, radiology and histology</td>
<td>80.6 (75.5–85.0)</td>
<td>99.6 (97.8–100)</td>
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</table>

Lawn & Zumla, Exp Rev Anti-Infect Ther 2012
Sensitivity of Xpert MTB/RIF as a TB screening tool among PLHIV (Lawn et al, 2011)

<table>
<thead>
<tr>
<th>Samples</th>
<th>Microscopy</th>
<th>Xpert MTB/RIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>All samples</td>
<td>28</td>
<td>73</td>
</tr>
<tr>
<td>One sample</td>
<td>22</td>
<td>58</td>
</tr>
<tr>
<td>Two samples</td>
<td>26</td>
<td>72</td>
</tr>
</tbody>
</table>

- Gold standard used: liquid culture
- Sputum samples collected from 445 PLHIV regardless of symptoms
- Overall Xpert result 45% increase in case detection compared to microscopy
### Xpert MTB/RIF negatives cases
(Lawn et al, 2012)

<table>
<thead>
<tr>
<th>Samples</th>
<th>numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture positive TB</td>
<td>89</td>
</tr>
<tr>
<td>Xpert positive (1\textsuperscript{st} sample)</td>
<td>52</td>
</tr>
<tr>
<td>Xpert negative (1\textsuperscript{st} sample)</td>
<td>37</td>
</tr>
<tr>
<td>Xpert negative (2\textsuperscript{nd} sample)</td>
<td>25</td>
</tr>
</tbody>
</table>

**Characteristics of Xpert negative TB cases**
- High CD4 count
- Less advanced TB
- Smear negatives with longer culture grow time
- Less likely to die during follow up
Ambulatory patient with presumptive TB\textsuperscript{1}, HIV positive\textsuperscript{2} 
No danger signs\textsuperscript{3}

- Xpert MTB/RIF

1\textsuperscript{st} Visit

- Xpert MTB+/RIF+
  - Treat for MDR-TB
  - CPT\textsuperscript{4}
  - ART\textsuperscript{5}
  - DST FLD+SLD\textsuperscript{6}

- Xpert MTB+/RIF-
  - Treat for TB
  - CPT\textsuperscript{4}
  - ART\textsuperscript{5}

- Xpert MTB-/RIF- PTB unlikely

  - Clinical assessment for EPTB or other diseases 
  - Chest x-ray\textsuperscript{7}

  - EPTB likely
    - Refer to 2007 algorithms for Rx and management

  - EPTB unlikely
    - Treat for bacterial infection\textsuperscript{8}
    - HIV Rx assessment\textsuperscript{9}
    - CPT\textsuperscript{4}

- No or partial response
  - Reassess for TB 
  - Repeat Xpert MTB/RIF

2\textsuperscript{nd} Visit

- Response
  - Treat for PCP\textsuperscript{10}
  - CPT\textsuperscript{4}

3\textsuperscript{rd} Visit
Determine TB-LAM Antigen detection
Urine LAM (Dheda et al, 2013)

- Overall sensitivity: 50%
- Specificity: 50-100%
- Urinary excretion of LAM correlates with MTB burden and hence show prognosis
- Cross-reactivity with *Candida* spp and normal oral flora containing LAM-like molecules
- Poor sensitivity and specificity in pleural and pericardial and cerebrospinal fluid
Urine antigen (Lipoarabinomannan) detection for HIV positives
Among 101 confirmed TB patients with median CD4 count 60, Uganda, Shah et al, CROI 2013
Recent contrasting results on the use of Urine LAM (CROI 2013)

- Sensitivity of 25% among PLHIV in Uganda with a median CD4 count of 180 \((\text{Drain et al})\)

- Sensitivity of 69% among PLHIV in South Africa with a median CD4 count of 116 \((\text{van Rie et al})\)
Diagnostic and prognostic value of serum C-reactive protein for screening for HIV-associated tuberculosis

S. D. Lawn,* † A. D. Kerkhoff,** † M. Vogt, * R. Wood*

P < 0.001

![Box and whisker plot showing concentrations of CRP in serum from patients with TB (n = 81) or without TB (n = 415). Bars, box and whiskers indicate medians, 25th and 75th centiles and ranges, respectively. CRP = C-reactive protein; TB = tuberculosis.](image)

**Figure 1** Box and whisker plot showing concentrations of CRP in serum from patients with TB (n = 81) or without TB (n = 415). Bars, box and whiskers indicate medians, 25th and 75th centiles and ranges, respectively. CRP = C-reactive protein; TB = tuberculosis.

CRP lacked diagnostic utility as a screening tool but its high value indicate poor prognosis.
More on Xpert MTB/RIF scale-up
Almost 2 million cartridges procured by public sector
Cumulative number of GeneXpert modules and Xpert MTB/RIF cartridges procured under concessional pricing

Data: FIND

(public sector in eligible countries)
Cartridge Price dropped from 17 USD to 10 USD

- Dec 2010-August 2012: 16.86 USD for public sector buyers (including NGOs) in 145 eligible countries.

- August 2012: 9.98 USD due to a “buy-down” arrangement by PEPFAR, USAID, UNITAID and BMGF for 145 eligible countries.

- For-profit private sector does not benefit from the concessional pricing.
Remote calibration of modules is now possible

- Previous method of calibration:
  - Sites annually receive new modules from France
  - Old modules sent back to France
  - 1800 USD (including shipping)

- New option for calibration:
  - Sites receive “remote calibration cartridges” annually
  - Readings are provided to Cepheid remotely
  - Decision will be made if modules must be swapped
  - 450 USD for cartridges plus 450 USD per module needing calibration in France (including shipping)
Outstanding questions

- Can Xpert be used for routine screening of PLHIV at baseline evaluation regardless of symptoms?
- Should we bother about Xpert/MTB Rif negatives?
- Empiric TB treatment in seriously sick patients? Can novel diagnostics assist decision making?
- Algorithm for earlier TB diagnosis at homesteads, communities and facilities?
Summary

• Xpert MTB/RIF as a primary tool for PLHIV and in all ART services.

• Enhance TB diagnostic and treatment capacity in all ART facilities (Do not refer PLHIV for TB diagnosis and treatment).

• Revise WHO’s guidelines on diagnosis of TB among PLHIV including recommended Xpert algorithm.

• TB case finding algorithm for PLHIV in homesteads and communities needed.