Xpert MTB/RIF to diagnose TB in people living with HIV: patient management

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# TB diagnosis

<table>
<thead>
<tr>
<th>Location</th>
<th>Current practice</th>
<th>Delay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referral hospital</td>
<td>Physician, specialists, Culture, CXR, Microscopy</td>
<td>8 (0-45) days*</td>
</tr>
<tr>
<td>District hospital</td>
<td>Physician, Clinician, CXR, Microscopy</td>
<td>18 (0-191) days*</td>
</tr>
<tr>
<td>Health centres</td>
<td>Clinician, nurse, Microscopy</td>
<td>35 (21-56) days**</td>
</tr>
<tr>
<td>Health post/clinic</td>
<td>Clinician, nurse, HA, No diagnosis- referral</td>
<td>35(21-56) days**</td>
</tr>
<tr>
<td>Community/ home</td>
<td>CHW, Rx supporters, patients, No diagnosis - Referral</td>
<td>21 (7-49) days**</td>
</tr>
</tbody>
</table>

* IJTLD 2008 : 392-396  ** IJTLD 2006; 10:422-28
# Delayed diagnosis of smear-negative TB in PLHIV

<table>
<thead>
<tr>
<th>Smear samples: acid-fast bacilli before antibiotic treatment</th>
<th>Courses of antibiotics*</th>
<th>Smear samples: acid-fast bacilli after unsuccessful antibiotic treatment</th>
<th>Chest radiograph after unsuccessful antibiotic treatment</th>
<th>Clinical assessment after successful antibiotic treatment</th>
<th>Estimated time until diagnosis of SNP (days)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cambodia, (2003) 3x (1 set) 3 specimens</td>
<td>2 (1–2 weeks)</td>
<td>3x (1 set) 3 specimens</td>
<td>Yes</td>
<td>Yes</td>
<td>20</td>
</tr>
<tr>
<td>Côte d’Ivoire, (2003) 3x (1 set) 3 specimens</td>
<td>2 (7–10 days)</td>
<td>3x (1 set) 3 specimens</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Ethiopia, (2002) 3x (1 set), 2x (1 set) 5 specimens</td>
<td>1 (7–10 days)</td>
<td>3x (1 set) 3 specimens</td>
<td>Yes</td>
<td>Yes</td>
<td>18</td>
</tr>
<tr>
<td>India, (2005) 3x (1 set) 3 specimens</td>
<td>1 (10–14 days)</td>
<td>3x (1 set) 3 specimens</td>
<td>Yes</td>
<td>No</td>
<td>20</td>
</tr>
<tr>
<td>Kenya, (2003) 3x (1 set) 3 specimens</td>
<td>1 (5–7 days)</td>
<td>3x (1 set) 3 specimens</td>
<td>Yes†</td>
<td>No</td>
<td>11</td>
</tr>
<tr>
<td>Laos, (2004) 3x (1 set) 3 specimens</td>
<td>1 (7 weeks)</td>
<td>3x (1 set) 3 specimens</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Lesotho, (2005) 3x (1 set) 3 specimens</td>
<td>1 (10–14 days)</td>
<td>3x (1 set) 3 specimens</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Mozambique, (2004) 2x (1 set) 2 specimens</td>
<td>2 (7–15 days)</td>
<td>2x (1 set) 2 specimens</td>
<td>No§</td>
<td>Yes</td>
<td>21</td>
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<tr>
<td>Malawi, (2002) 2x (1 set) 2 specimens</td>
<td>1 (1 week)</td>
<td>None¶</td>
<td>Yes</td>
<td>No</td>
<td>11</td>
</tr>
<tr>
<td>Sri Lanka, (2005) 3x (1 set) 3 specimens</td>
<td>1 (1–2 weeks)</td>
<td>3x (1 set) 3 specimens</td>
<td>Yes</td>
<td>Yes</td>
<td>20</td>
</tr>
<tr>
<td>Sudan, (2000) 3x (1 set) 3 specimens</td>
<td>1 (1 week)</td>
<td>3x (1 set) 3 specimens</td>
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<td>No</td>
<td>13</td>
</tr>
<tr>
<td>Swaziland, (2004) 3x (1 set) 3 specimens</td>
<td>1 (1 week)</td>
<td>3x (1 set) 3 specimens</td>
<td>Yes</td>
<td>Yes</td>
<td>13</td>
</tr>
<tr>
<td>Tajikistan, (2003) 3x (1 set) 3 specimens</td>
<td>1 (7–14 days)</td>
<td>3x (1 set) 3 specimens</td>
<td>Yes</td>
<td>Yes</td>
<td>20</td>
</tr>
<tr>
<td>Tanzania, (2003) 3x (2 sets) 6 specimens</td>
<td>1 (14 days)</td>
<td>3x (1 set) 3 specimens</td>
<td>Yes</td>
<td>No</td>
<td>22</td>
</tr>
<tr>
<td>Uganda, (2002) 3x (1 set) 3 specimens</td>
<td>1 (1 week)</td>
<td>3x (1 set) 3 specimens</td>
<td>Yes</td>
<td>No</td>
<td>13</td>
</tr>
<tr>
<td>Zambia, (2001) 3x (1 set) 3 specimens</td>
<td>2 (3–4 weeks)</td>
<td>3x (1 set) 3 specimens</td>
<td>Yes</td>
<td>Yes</td>
<td>34</td>
</tr>
<tr>
<td>Zimbabwe, (1999) 3x (1 set) 3 specimens</td>
<td>2 II</td>
<td>3x (1 set) 3 specimens</td>
<td>Yes</td>
<td>Yes</td>
<td>13</td>
</tr>
</tbody>
</table>

SNP = smear-negative pulmonary tuberculosis. Best scenario assumption: 2 days to obtain one set (2–3 samples) sputum examination result, 2 days to obtain chest radiograph, 2 days for clinical peer review, plus the maximum duration for the antibiotic course specified. Sputum examinations, chest radiograph, and clinical consultations done in the same facility. * Duration of each treatment. † This scenario assumes the activities to be done sequentially, which might not always be the case. ‡ Timed with repeat smear samples. § Before antibiotic treatment. ¶ Direct to chest radiograph. ‖ Not specified, but for sufficient period.

Table 2: National tuberculosis control programme recommendations of selected countries for diagnosis of smear-negative pulmonary tuberculosis

Getahun et al Lancet 2007; 369: 2042-49
WHO recommendation for TB diagnosis in PLHIV, 2007
Key recommendations for TB diagnosis

- Recommendations for NAP and NTP
- Speed is important for PLHIV
- Microscopy, CXR and culture together and earlier
- Algorithms are tailored to clinical condition
- EP TB diagnosis should be part of routine programme activity (biopsy, ultrasound)
- Training of non classical staff is encouraged (e.g. nurses to read CXR)
WHO recommended 2007 algorithms

**Ambulatory patient**

Ambulatory patient with cough 2–3 weeks and no danger signs

- AFB HIV test
  - HIV+ or status unknown

1. **If VSN**
   - AFB-positive
     - Treat for TB CPT
     - HIV assessment
   - TB likely
   - CXR
     - Sputum AFB and culture
     - Clinical assessment
   - TB unlikely
   - Treat for PCP
     - HIV assessment
   - Response
     - No or partial response
     - Response
     - Reassess for TB

2. **If VSN**
   - AFB-negative
     - TB likely
     - CXR
     - Sputum AFB and culture
     - Clinical assessment
     - TB unlikely
     - Treat for bacterial infection
     - HIV assessment
     - Response
     - Reassessment for other HIV-related disease
     - TB unlikely
     - Reassess for tuberculosis
   - Start TB treatment
     - Complete antibiotics
     - Refer for HIV and tuberculosis care

3. **If No VSN**
   - Parenteral antibiotic treatment for bacterial infection
     - Sputum AFB and culture
     - HIV test
     - CXR
     - HIV+ or unknown

**Seriously ill patient**

Seriously ill patient with cough 2–3 weeks and danger signs

- Referral to higher level facility
  - Immediate referral not possible

- Parenteral antibiotic treatment for bacterial infection
  - Sputum AFB and culture
  - HIV test
  - CXR
  - HIV+ or unknown

- No tuberculosis
  - Treat tuberculosis

- AFB-positive
  - Improvement after 3–5 days
  - No improvement after 3–5 days

- AFB-negative
  - Reassess for tuberculosis

Not sufficient enough to prevent death of PLHIV!
TB screening and isoniazid preventive therapy (IPT)

None of current cough, fever, night sweats or weight loss = No TB = IPT

<table>
<thead>
<tr>
<th>Setting</th>
<th>Sen (%)</th>
<th>Spe (%)</th>
<th>Negative Predictive Value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community</td>
<td>76</td>
<td>61</td>
<td>97.3 (96.9-97.7)</td>
</tr>
<tr>
<td>Clinical</td>
<td>89</td>
<td>30</td>
<td>98.3 (97.5-98.8)</td>
</tr>
<tr>
<td>CD4 &lt; 200</td>
<td>94</td>
<td>22</td>
<td>98.9 (95.8-99.5)</td>
</tr>
<tr>
<td>CD4 ≥ 200</td>
<td>83</td>
<td>34</td>
<td>96.9 (95.1-98.0)</td>
</tr>
</tbody>
</table>

Getahun et al PLoS Medicine 2011

Symptom based TB screening is sufficient to exclude TB among PLHIV and provide at least 6 months IPT
TB screening and IPT algorithm

Person living with HIV

Screen for TB with any one of the following: Current cough; Fever Weight loss; Night Sweats

No

Assess IPT contraindications

No

Give IPT

Yes

Defer IPT

Yes

Investigate for TB and other Ds.

No

Other Dx

Appropriate rx & consider IPT

Follow up & consider IPT

TB

Not TB

Treat for TB

Screen for TB regularly
Guiding principles for Xpert use in PLHIV

- HIV prevalent setting
  - HIV prevalence among adults ≥1% or
  - HIV prevalence among TB patients ≥5%

- Target group:
  - PLHIV or those with unknown HIV status
  - Presumptive TB in adults and adolescents: (any one of current cough, fever, night sweats, weight loss)
  - Presumptive TB in children: (any one of poor weight gain, fever, current cough or contact history)

Speedier diagnosis and treatment to prevent death
Guiding principles for Xpert use in PLHIV

- **HIV testing**
  - Patients with TB and presumptive TB
  - Unknown status or refusal - clinical condition

- **Clinical condition**
  - Sound clinical judgement crucial
  - Seriously ill patients prioritised

- **Danger signs**
  - Unable to walk unaided
  - Respiratory rate >30/min
  - T° >39℃
  - Heart rate >120/min

*Speedier diagnosis and treatment to prevent death*
Seriously ill patients

Use of Xpert MTB/RIF in TB/HIV algorithm
**Ambulatory patients**

Use of Xpert MTB/RIF in TB/HIV algorithm

**Figure 1**

- Ambulatory TB suspect, HIV positive, No danger signs
  - Xpert MTB/RIF
    - Xpert MTB+/RIF+
      - Treat for MDR-TB
        - CPT
        - ART
        - DST FLD+SLD
    - Xpert MTB+/RIF-
      - Treat for TB
        - CPT
        - ART
    - Xpert MTB-/RIF-
      - PTB unlikely
        - Clinical assessment for EPTB or other diseases
          - Chest x-ray
      - EPTB likely
        - Refer to 2007 algorithms for Rx and management
      - EPTB unlikely
        - Treat for bacterial infection
          - HIV Rx assessment
          - CPT
          - No or partial response
            - Reassess for TB
            - Repeat Xpert MTB/RIF
          - Response

- AIDS
  - Xpert MTB/RIF
  - Xpert MTB+/RIF-
  - Xpert MTB-/RIF-
  - Xpert MTB-/RIF-
Operational considerations

- Diagnosis of EPTB particularly TB meningitis
- Use within HIV clinics or services
- Utility in TB and HIV mass campaigns
- Utility as a platform to diagnose other HIV related illnesses
Conclusions

• Revise algorithms that build on existing ones

• Use Xpert MTB/RIF when it is available

• Use all investigation at the same time when xpert is not available (WHO 2007)

• Expedite TB diagnostic process and thus prevent unnecessary death

• Empiric TB treatment in Xpert negative seriously ill patients not responding to antibiotics

• All TB patients should receive ART