Diagnosis of Tuberculosis in the HIV Patient

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Effect of HIV on Tuberculosis

Epidemiology
Estimated Incidence of TB per 100,000 Population in African Countries in 1990 and 2005


Newly reported cases of tuberculosis per 100 000 persons by year in the United States, 1980 to 1995

Estimated HIV Co-infection in Persons Reported with TB, United States, 1993–2008*

*Updated as of May 20, 2009.

Note: Minimum estimates based on reported HIV-positive status among all TB cases in the age group.

Fighting TB and HIV

“We can’t fight AIDS unless we do much more to fight TB. ”

Transmission of *M. tuberculosis*

Primary and Post-primary Disease
Outcomes of Exposure to *M. tuberculosis*

Inhalation of Droplet Nuclei

Regional replication in lungs, dissemination

Killing, clearance of organisms | Latent disease | Active disease

~90% | ~5% | ~5%

Outcomes of Exposure to *M. tuberculosis* in HIV-negative and HIV-positive patients

Inhalation of Droplet Nuclei

Regional replication in lungs, dissemination

Killing, clearance of organisms | Latent disease | Active disease

~90% | 10% reactivation per year | ~5% reactivation lifetime | Up to 36% active disease

~5%
Sites of TB Disease

- Lungs
  Extrapulmonary:
  - Larynx
  - Pleural effusion
  - Kidneys
  - Lymphatics
  - Bones & joints
  - Miliary (disseminated)

Extrapulmonary TB

- More of a diagnostic problem than pulmonary TB
- Involves inaccessible sites with fewer bacteria that can cause greater damage
- Bacteriologic confirmation more difficult
- Most forms represent reactivation TB
Evaluation for TB

- Medical history
- Physical examination
- Testing for TB infection
- Chest radiograph
- Bacteriologic or histologic exam
Signs & Symptoms - Pulmonary TB

Pulmonary Symptoms:
- Productive prolonged cough of over 3 weeks duration
- Chest pain
- Hemoptysis

Systemic Symptoms:
- Fever
- Chills
- Night sweats
- Appetite loss
- Weight loss
- Easy fatigability

An Algorithm for Tuberculosis Screening and Diagnosis in People with HIV

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Prevalence</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
<th>Likelihood Ratio+</th>
<th>Likelihood Ratio-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>In previous 4 wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>In previous 4 wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any</td>
<td>99/11</td>
<td>0.99</td>
<td>0.01</td>
<td>0.01</td>
<td>99.99</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>lasting 2 wk</td>
<td>18/12</td>
<td>0.92</td>
<td>0.78</td>
<td>0.22</td>
<td>7.33</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td>lasting 3 wk</td>
<td>26/20</td>
<td>0.96</td>
<td>0.75</td>
<td>0.25</td>
<td>4.44</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>lasting 4 wk</td>
<td>10/10</td>
<td>0.90</td>
<td>0.70</td>
<td>0.30</td>
<td>3.00</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td>with sputum production</td>
<td>12/10</td>
<td>0.92</td>
<td>0.78</td>
<td>0.22</td>
<td>7.33</td>
<td>0.22</td>
</tr>
<tr>
<td>Fever</td>
<td>In previous 4 wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>In previous 4 wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any</td>
<td>12/15</td>
<td>0.80</td>
<td>0.88</td>
<td>0.12</td>
<td>0.01</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>lasting 2 wk</td>
<td>25/18</td>
<td>0.83</td>
<td>0.67</td>
<td>0.33</td>
<td>1.56</td>
<td>0.33</td>
</tr>
<tr>
<td></td>
<td>lasting 3 wk</td>
<td>20/15</td>
<td>0.80</td>
<td>0.80</td>
<td>0.20</td>
<td>0.33</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>lasting 4 wk</td>
<td>11/11</td>
<td>1.00</td>
<td>0.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>hemoptysis in previous 4 wk</td>
<td>14/11</td>
<td>0.80</td>
<td>0.80</td>
<td>0.20</td>
<td>0.33</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>culture positive in previous 4 wk</td>
<td>15/15</td>
<td>1.00</td>
<td>0.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>smoking history</td>
<td>20/5</td>
<td>0.80</td>
<td>0.80</td>
<td>0.20</td>
<td>0.33</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>in previous 4 wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any</td>
<td>45/60</td>
<td>0.75</td>
<td>0.75</td>
<td>0.25</td>
<td>1.56</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>lasting 2 wk</td>
<td>55/55</td>
<td>1.00</td>
<td>0.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>lasting 3 wk</td>
<td>20/20</td>
<td>1.00</td>
<td>0.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>lasting 4 wk</td>
<td>15/15</td>
<td>1.00</td>
<td>0.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>weight loss in previous 4 wk</td>
<td>22/22</td>
<td>1.00</td>
<td>0.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>
Table 2. Performance Characteristics of Indicators in Predicting Tuberculosis in All 1,748 Patients.

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Prevalence</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Negative Predictive Value</th>
<th>Positive Predictive Value</th>
<th>Likelihood Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphadenopathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>222 (35)</td>
<td>30</td>
<td>90</td>
<td>88</td>
<td>36</td>
<td>0.77</td>
</tr>
<tr>
<td>Head and neck</td>
<td>175 (26)</td>
<td>27</td>
<td>93</td>
<td>88</td>
<td>42</td>
<td>0.78</td>
</tr>
<tr>
<td>CD4+ cells/mL ≤ 200/mm²</td>
<td>743 (43)</td>
<td>58</td>
<td>91</td>
<td>24</td>
<td>24</td>
<td>0.52</td>
</tr>
<tr>
<td>Either of first 2 sputum smears positive for acid-fast bacilli</td>
<td>129 (7)</td>
<td>38</td>
<td>95</td>
<td>84</td>
<td>84</td>
<td>0.63</td>
</tr>
<tr>
<td>Abnormal chest radiograph</td>
<td>390 (22)</td>
<td>65</td>
<td>85</td>
<td>93</td>
<td>44</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Table 3. Performance Characteristics of Combinations of Predictors.

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Negative Predictive Value</th>
<th>Positive Predictive Value</th>
<th>Likelihood Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination of 2 predictors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gauged on fever for ≤ 2 wk or chest x-ray for previous 4 wk</td>
<td>91</td>
<td>37</td>
<td>98</td>
<td>22</td>
<td>0.23</td>
</tr>
<tr>
<td>Gauged on fever for &gt; 2 wk or chest x-ray for previous 4 wk</td>
<td>84</td>
<td>40</td>
<td>96</td>
<td>22</td>
<td>0.27</td>
</tr>
<tr>
<td>Combination of 3 predictors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gauged on fever for ≤ 2 wk or chest x-ray for previous 4 wk</td>
<td>91</td>
<td>30</td>
<td>97</td>
<td>22</td>
<td>0.29</td>
</tr>
<tr>
<td>Gauged on fever for &gt; 2 wk or chest x-ray for previous 4 wk</td>
<td>91</td>
<td>25</td>
<td>97</td>
<td>21</td>
<td>0.29</td>
</tr>
<tr>
<td>Combination of 4 predictors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gauged on fever for ≤ 2 wk or chest x-ray for previous 4 wk</td>
<td>86</td>
<td>43</td>
<td>96</td>
<td>22</td>
<td>0.23</td>
</tr>
<tr>
<td>Gauged on fever for &gt; 2 wk or chest x-ray for previous 4 wk</td>
<td>86</td>
<td>44</td>
<td>96</td>
<td>22</td>
<td>0.24</td>
</tr>
</tbody>
</table>

2 The negative likelihood ratio is calculated as (1 - sensitivity) specificity, and the positive likelihood ratio as sensitivity / (1 - specificity).
Evaluation for TB

- Medical history
- Physical examination
- Testing for TB infection
- Chest radiograph
- Bacteriologic or histologic exam

Clinical Presentation

HIV-positive vs. HIV-negative patients

- Driven mostly by degree of immunity

- HIV-positive patients are more likely to have:
  - Isolated extrapulmonary localization (53-63% in some studies)
  - Primary infection
  - Pulmonary basilar involvement
  - Tuberculous pneumonia
  - Hilar or mediastinal lymphadenopathies
  - Miliary or disseminated TB
  - Normal CXR (8-20% in some studies)
Evaluation for TB

• Medical history
• Physical examination
• Testing for TB infection
  • Chest radiograph
  • Bacteriologic or histologic exam

Testing for TB Infection
- Principles

• Individuals who have a
  – + TST result,
  – a + IGRA result or
  – symptoms suggestive of TB (regardless of TST/IGRA results)
    should be evaluated with an chest x-ray

• Patients with HIV who may not react to testing by TST or IGRA
  should have a chest x-ray if TB is suspected or if exposed to an
  active TB case

• If abnormalities are noted, or the client has symptoms
  suggestive of extrapulmonary TB, additional diagnostic tests
  should be conducted
Testing for TB Infection - TST

• The tuberculin skin test (TST) may help differentiate infected from uninfected people with signs and symptoms

• A negative TST does not exclude the diagnosis of TB (especially for patient’s with severe TB illness or infection with HIV)

Classifying the Tuberculin Reaction

5 mm is classified as positive in

• HIV-positive persons

• Recent contacts of TB case

• Persons with fibrotic changes on chest radiograph consistent with old healed TB

• Patients with organ transplants and other immunosuppressed patients
IFN-γ (gamma) release assays (IGRAs)

Antigens for Gamma-Release Assays

<table>
<thead>
<tr>
<th>Tuberculosis complex</th>
<th>ESAT</th>
<th>CFP</th>
<th>Environmental strains</th>
<th>ESAT</th>
<th>CFP</th>
</tr>
</thead>
<tbody>
<tr>
<td>M tuberculosis</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>M africanum</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>M bovis</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>BCG substrate</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>gothenburg</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>moreau</td>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>tice</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>tokyo</td>
<td>-</td>
<td>-</td>
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<td>danish</td>
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<td>montreal</td>
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<td>-</td>
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</tr>
<tr>
<td>pasteur</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
FDA-approved IGRAs

- Quantiferon-Gold In-Tube (IT)
- T-SPOT. TB

Table 2. Distribution of QuantIFERON® TB Gold In-Tube results by CD4+ lymphocyte count, treatment period and TST result.

<table>
<thead>
<tr>
<th>CD4+ count (cells/µL)</th>
<th>Positive</th>
<th>Former</th>
<th>Indeterminate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4+ &lt; 200</td>
<td>200-399</td>
<td>400-499</td>
<td>500-699</td>
</tr>
<tr>
<td>&gt; 700</td>
<td>800-999</td>
<td>1000-1999</td>
<td>2000-2999</td>
</tr>
<tr>
<td>&gt; 3000</td>
<td>&gt; 4000</td>
<td>&gt; 5000</td>
<td>&gt; 6000</td>
</tr>
</tbody>
</table>

Figure 1. Distribution of QuantIFERON® TB Gold In-Tube results by CD4+ lymphocyte count. Proportion of both negative and indeterminate results increased with falling CD4+ lymphocyte count. QFT, QuantIFERON® TB Gold In-Tube. dx.doi.org/10.1016/S0924-0248(01)001

Chart showing data distribution.
Poor concordance between interferon-γ release assays and tuberculin skin tests in diagnosis of latent tuberculosis infection among HIV-infected individuals

*BMC Infectious Diseases 2009, 9:15*

- Cross sectional study in 2 HIV clinics in Atlanta, Georgia (n= 336), 85% black, 65% male, 91% US-born, 69% on HAART, 60% with a history of an OI.

- Median CD4 = 334, median viral load 400 copies/ml

- Conclusion:
  - We found a low prevalence of LTBI and poor concordance between all 3 diagnostic tests (TST, QF-IT, T-SPOT. TB).
Role of Interferon Gamma Release Assay in Active TB Diagnosis among HIV Infected Individuals

- 105 HIV/TB patients
- 50% were culture positive
- 31% were TST positive
  - Sensitivity decreased with declining CD4 count
- 65% were positive by Quantiferon-IT
  - More indeterminate results with CD4 <200

Role of interferon-gamma release assays in the diagnosis of pulmonary tuberculosis in patients with advanced HIV infection
Cattamanchi et al. BMC Infectious Diseases 2010, 10:75

![Diagram](attachment:image.png)

Number Enrolled: N=244
Number Included: N=206

- Positive TB Cultures: N=126 (52%)
- Negative TB Cultures: N=110 (47%)

**IGRA Results**
- Not Done: 14 (11%)
- Indeterminate: 38 (32%)
- Positive: 61 (48%)
- Negative: 23 (18%)

**IGRA Results**
- Not Done: 19 (9%)
- Indeterminate: 36 (34%)
- Positive: 34 (31%)
- Negative: 49 (38%)

Abbreviations: TB, tuberculosis; IGRA, interferon-gamma release assay

Figure 1 Study population: 244 patients eligible for the study. 159 (65%) were included. Pulmonary tuberculosis, defined as a 1 positive culture result, was diagnosed in 134 (55%) patients.
Evaluation for TB

- Medical history
- Physical examination
- Testing for TB infection
- Chest radiograph
- Bacteriologic or histologic exam

CXR – HIV infected persons

In HIV-infected persons, almost any abnormality on CXR may indicate TB

- May cause infiltrates without cavities in any lung zone
- May cause mediastinal or hilar lymphadenopathy with or without infiltrates or cavities
Primary Tuberculosis
Miliary Tuberculosis
CXR – Special Situations

- Pregnant women who are highly suspicious and being evaluated for active disease should undergo a CXR without delay, even during the first trimester.

- Patients suspected of extrapulmonary TB should have a CXR to rule out pulmonary TB.
CXR – old healed TB

Old healed TB nodules & fibrotic lesions have well-demarcated sharp margins

- Dense nodules, with or without visible calcification (hilar or ↑ lobes)
- Smaller nodules with or without fibrotic scars (↑ lobes, often with volume loss)

CXR – old healed TB

- Nodules & fibrotic lesions may contain slowly multiplying bacilli = potential for progression
- CXR consistent with old TB and + TST = high priority for LTBI treatment
Evaluation for TB

- Medical history
- Physical examination
- Testing for TB infection
- Chest radiograph
  - Bacteriologic or histologic exam
Bacteriologic or histologic exam

• Sputum
  – Three (8-24 hours apart, at least one first thing in the morning)

• Tissue
  – Lymph node biopsy
  – Bone marrow biopsy

• Other specimens
  – Urine
  – CSF
  – Peritoneal fluid
  – Pleural fluid (pleural biopsy)

Diagnosis

Table 1. Bacteriological and histological results observed during HIV-associated TB as a function of immune status

<table>
<thead>
<tr>
<th></th>
<th>CD4 &lt; 200/mm³</th>
<th>CD4 &gt; 200/mm³</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive tuberculin skin test reaction</td>
<td>30% *</td>
<td>50% *</td>
<td>[23]</td>
</tr>
<tr>
<td>Acid-fast bacilli on smear (≥ 5 mm without BCG)</td>
<td>56-60%</td>
<td>50-58%</td>
<td>[22,23,25]</td>
</tr>
<tr>
<td>Acid-fast bacilli on biopsy</td>
<td>60-65%</td>
<td>50-56%</td>
<td>[22]</td>
</tr>
<tr>
<td>Granuloma in biopsy</td>
<td>60-75%</td>
<td>67-100%</td>
<td>[23,31,32]</td>
</tr>
<tr>
<td>Mycobacteraemia</td>
<td>20-49%</td>
<td>0-7%</td>
<td>[22,30]</td>
</tr>
</tbody>
</table>
An Algorithm for Tuberculosis Screening and Diagnosis in People with HIV

Diagnosis – Summary

- Must have a high index of suspicion
- Must utilize many pieces of information in making the diagnosis
- TB can present very differently in HIV-infected patients when compared to HIV-negative patients

Appendix Table 1. Smear and culture results of patients with TB (N=267), stratified by symptoms and chest radiograph result.

<table>
<thead>
<tr>
<th>Symptoms*</th>
<th>Chest radiograph</th>
<th>Enrolled patients, n</th>
<th>TB diagnosed, n (% of enrolled patients)</th>
<th>Positive acid-fast cultures, n (% of smear, n)</th>
<th>Number of positive TB diagnosed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>Normal</td>
<td>493</td>
<td>7 (1)</td>
<td>0 (71)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>Present</td>
<td>Normal</td>
<td>865</td>
<td>87 (10)</td>
<td>26 (30)</td>
<td>40 (46)</td>
</tr>
<tr>
<td>Absent</td>
<td>Abnormal</td>
<td>56</td>
<td>11 (20)</td>
<td>3 (27)</td>
<td>2 (18)</td>
</tr>
<tr>
<td>Present</td>
<td>Abnormal</td>
<td>334</td>
<td>162 (49)</td>
<td>92 (57)</td>
<td>21 (13)</td>
</tr>
</tbody>
</table>

*Any one of: any cough in the past 4 weeks, any fever in the past 4 weeks, or night sweats for ≥3 weeks.
Thanks!!

Questions?
Lisa.Armitige@dshs.state.tx.us
Heartland National Tuberculosis Center
1-800-TEX-LUNG