Tuberculosis in the Setting of HIV Infection

Zelalem Temesgen, MD FIDSA AAHIVS
Professor of Medicine
Executive Director, Mayo Clinic Center for Tuberculosis
Director, HIV Program
Regional Training and Medical Consultation Centers

- Region 1, UCSF
- Region 2, University of Texas
- Region 3, Rutgers University
- Region 4, University of Florida
- Region 5, Mayo Clinic
Disclosures

No financial/industry conflicts
Learning Objectives

At the end of this talk, participants should be able to:

– Describe the overlapping epidemiology of TB and HIV globally

– Describe the impact of HIV on the various components of the natural history of TB

– Describe the challenges in the diagnosis and treatment of active tuberculosis in the setting of HIV infection
In 2015, there were an estimated 10.4 million new (incident) TB cases
- 5.9 million (56%) among men
- 3.5 million (34%) among women
- 1.0 million (10%) among children
- People living with HIV accounted for 1.2 million (11%) of all new TB cases.
TB

Cambodia
Sierra Leone

MDR-TB

Bangladesh
DPR Korea
Pakistan
Philippines
Russian Federation
Viet Nam

MDR-TB

Angola
China
DR Congo
Ethiopia
India
Indonesia
Kenya
Mozambique
Myanmar
Nigeria
Papua New Guinea
South Africa
Thailand
Zimbabwe

TB/HIV

Brazil
Central African Republic
Congo
Lesotho
Liberia
Namibia
UR Tanzania
Zambia

Botswana
Cameroon
Chad
Ghana
Guinea-Bissau
Malawi
Swaziland
Uganda
### Number of people living with HIV

<table>
<thead>
<tr>
<th>People newly infected with HIV in 2014</th>
<th>2 million [1.9 million–2.2 million]</th>
</tr>
</thead>
<tbody>
<tr>
<td>New HIV infections have fallen by 35% since 2000.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AIDS deaths in 2014</th>
<th>1.2 million [980 000–1.6 million]</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS-related deaths have fallen by 42% since the peak in 2004.</td>
<td></td>
</tr>
</tbody>
</table>
TB and HIV Co-Infection

• An estimated 11% of incident TB cases in 2015 were HIV positive.
• The African Region accounts for about four out of every five HIV-positive TB cases and TB deaths.
• > 50% in parts of southern Africa (Botswana 60%).
• Tuberculosis remains the leading cause of death among people living with HIV
  – 400,000 million deaths from TB among HIV-positive people in 2015.
Natural History
HIV Immune Deficiency

- Diminished T cell repertoire
- Reduced lymphocyte function
- Delayed hypersensitivity response to recall Ags
- Phagocytosis
- Chemotaxis
- Intracellular killing
- Natural killer cell-mediated killing
- Loss of specific antibody responses
- Increased immune activation
- disruption of immunoregulatory cytokine expression and production
- Decreased IL-2, γ interferon, and IL-12
- Increased IL-1, IL-6, TNFα
Natural History of TB Infection in Patients Without HIV

Exposure to TB

- No infection (70-90%)
- Infection (10-30%)

Infection

- Latent TB (90%)
- Active TB (5-10%)

Latent TB

- Never develop Active disease

Active TB

- Treated
  - Die/Relapse/Recurr
  - Cured
Tuberculous infection progressed to active disease within 106 days of acquiring the infection in 37 percent (11 of 30) of HIV-infected patients.

Tuberculosis did not develop in any of 28 staff members with exposures, although there were 6 with documented tuberculin conversions and 8 others had positive tuberculin reactions of unknown duration.
7 of 18 (39%) HIV-infected inpatients developed active tuberculosis within 60 days of diagnosis of the index case.
Natural History of TB Infection in Patients Without HIV

Exposure to TB

No infection (70-90%)

Infection (10-30%)

Latent TB (90%)

Active TB (5-10%)

Never develop Active disease

Treated

Die/Relapse/Recurr  Cured
A Prospective Study of the Risk of Tuberculosis among Intravenous Drug Users with Human Immunodeficiency Virus Infection

Peter A. Selwyn, M.D., M.P.H., Diana Hartel, M.P.H., Victor A. Lewis, M.D., Ellie E. Schoenbaum, M.D., Sten H. Vermund, M.D., Robert S. Klein, M.D., Angela T. Walker, M.D., and Gerald H. Friedland, M.D.


• Forty-nine HIV-seropositive subjects and 62 HIV-seronegative subjects had a positive TST response.
• 7/8 cases of TB occurred in HIV-seropositive subjects with a prior positive PPD test (7.9 cases per 100 person-years, vs. 0.3 case per 100 person-years in those without a prior positive PPD test; rate ratio, 24.0; P<0.0001).
Relative Risk of Reactivation Tuberculosis among Persons with Medical Conditions That Impair Immune Control of *M. tuberculosis*.

### Table 3. Relative Risk of Reactivation Tuberculosis among Persons with Medical Conditions That Impair Immune Control of *M. tuberculosis.*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced HIV infection</td>
<td>Pablos-Mendez et al.\textsuperscript{27}</td>
<td>9.9 (8.7–11.3) \textdagger</td>
</tr>
<tr>
<td></td>
<td>Moss et al.\textsuperscript{26}</td>
<td>9.4 (3.5–25.1)</td>
</tr>
<tr>
<td>Old, healed tuberculosis</td>
<td>Ferebee,\textsuperscript{13} Ferebee et al.\textsuperscript{20}</td>
<td>5.2 (3.4–8.0)</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>Pablos-Mendez et al.\textsuperscript{27}</td>
<td>2.4 (2.1–2.8) \textdagger</td>
</tr>
<tr>
<td>Infliximab therapy</td>
<td>Keane et al.\textsuperscript{28}</td>
<td>2.0 (0.7–5.5) \textdagger</td>
</tr>
<tr>
<td>Poorly controlled diabetes</td>
<td>Pablos-Mendez et al.\textsuperscript{27}</td>
<td>1.7 (1.5–2.2) \textdagger</td>
</tr>
<tr>
<td>Silicosis</td>
<td>Cowie\textsuperscript{29}</td>
<td>1.7 (1.3–2.1) \textdagger</td>
</tr>
<tr>
<td></td>
<td>Corbett et al.\textsuperscript{30}</td>
<td>1.3 (1.1–1.7) \textdagger</td>
</tr>
<tr>
<td></td>
<td>Kleinschmidt and Churchyard\textsuperscript{31}</td>
<td>1.2 (1.0–1.5) \textdagger</td>
</tr>
<tr>
<td>Underweight (≤10 percent below normal)</td>
<td>Palmer et al.,\textsuperscript{22} Edwards et al.\textsuperscript{23}</td>
<td>1.6 (1.1–2.2)</td>
</tr>
<tr>
<td>Gastrectomy</td>
<td>Thorn et al.\textsuperscript{32}</td>
<td>1.4 (1.1–1.9) \textdagger</td>
</tr>
<tr>
<td></td>
<td>Steiger et al.\textsuperscript{33}</td>
<td>1.3 (1.2–1.4) \textdagger</td>
</tr>
</tbody>
</table>

\* CI denotes confidence interval, and HIV human immunodeficiency virus.
\dagger The relative risk is estimated, as described in the Methods section.

Incidence of HIV-Associated Tuberculosis among Individuals Taking Combination Antiretroviral Therapy: A Systematic Review and Meta-Analysis

Tendesayi Kufa¹², Tonderai Mabuto¹, Evans Muchiri¹, Salome Charalambous¹², Dominique Rosillon³, Gavin Churchyard¹², Rebecca C. Harris⁴

• 42 studies describing 43 cohorts
  • 32 (74%) from high/intermediate burden
  • 11 (26%) from low burden

• Incidence rates in cohorts from high/intermediate burden settings are higher than rates in cohorts those from low burden settings
• HIV disease stage impacts TB incidence
• ART and duration of ART impacts TB incidence
HIV and Risk of Reactivation of TB

- Advanced HIV infection vs non HIV - Increased
- Untreated HIV infection that is less advanced vs. advanced - decreased risk of TB
- HIV infection on effective ART vs. untreated - decreased risk of TB
- HIV infection on effective ART vs. non HIV – increased risk
- ART failure - reversion to the higher level of risk.

Natural History of TB Infection in Patients Without HIV

Exposure to TB

- No infection (70-90%)
- Infection (10-30%)

Infection (10-30%)

- Latent TB (90%)
  - Never develop Active disease
- Active TB (5-10%)
  - Treated
    - Die/Relapse/Recur
    - Cured
• 23,517 culture-positive, pulmonary tuberculosis patients from the California tuberculosis case registry from 1993 to 2007 who completed anti-tuberculosis therapy.
• 148 (0.63%) had a late recurrence.
• Human immunodeficiency virus infection (adjusted hazard ratio, 1.81; p = 0.0149)
High Rates of Recurrence in HIV-Infected and HIV-Uninfected Patients with Tuberculosis

Judith R. Glynn,1 Jill Murray,2 Andre Bester,3 Gill Nelson,2,4 Stuart Shearer,5 and Pam Sonnenberg2

1Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, and 2Research Department of Infection and Population Health, University College London, London, United Kingdom; 3National Institute for Occupational Health, National Health Laboratory Service, 4School of Public Health, University of the Witwatersrand, and 5Gold Fields Limited, Johannesburg, South Africa

• Retrospective cohort study of South African gold miners, men with known dates of seroconversion to HIV (from 1991 to 1997) and HIV-negative men were followed up to 2004.
• 342 HIV-positive and 321 HIV-negative men who had had1 previous episode of tuberculosis,
• Rates of tuberculosis recurrence:
  • HIV-positive 19.7 cases per 100 person-years at risk (95% confidence interval [CI], 16.4–23.7)
  • HIV-negative 7.7 cases per 100 PYAR (95% CI, 6.1–9.8)
Factors associated with TB treatment success among new smear-positive TB patients at Martin Preuss Centre between January 2008 and December 2010 (N = 2,264).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total</th>
<th>Unadjusted Odds Ratio (95% CI)</th>
<th>P-value*</th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV positive</td>
<td>1,275</td>
<td>56%</td>
<td>1.00</td>
<td>0.019</td>
<td>1.00</td>
</tr>
<tr>
<td>HIV negative</td>
<td>989</td>
<td>44%</td>
<td>1.34 (1.05–1.72)</td>
<td></td>
<td>1.49 (1.14–1.94)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td>0.005</td>
<td>1.00</td>
</tr>
<tr>
<td>Male</td>
<td>1,400</td>
<td>62%</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Female</td>
<td>864</td>
<td>38%</td>
<td>1.45 (1.12–1.87)</td>
<td></td>
<td>1.52 (1.17–1.99)</td>
</tr>
<tr>
<td>Age category</td>
<td></td>
<td></td>
<td></td>
<td>0.323</td>
<td>1.00</td>
</tr>
<tr>
<td>15–24</td>
<td>460</td>
<td>20%</td>
<td>0.90 (0.65–1.25)</td>
<td></td>
<td>0.76 (0.54–1.06)</td>
</tr>
<tr>
<td>25–34</td>
<td>985</td>
<td>44%</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>35–44</td>
<td>505</td>
<td>22%</td>
<td>0.98 (0.71–1.36)</td>
<td></td>
<td>1.07 (0.77–1.48)</td>
</tr>
<tr>
<td>45–54</td>
<td>173</td>
<td>8%</td>
<td>0.71 (0.46–1.10)</td>
<td></td>
<td>0.70 (0.45–1.10)</td>
</tr>
<tr>
<td>≥55</td>
<td>141</td>
<td>6%</td>
<td>0.66 (0.41–1.06)</td>
<td></td>
<td>0.57 (0.35–0.93)</td>
</tr>
<tr>
<td>TB Registration year</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2008</td>
<td>791</td>
<td>35%</td>
<td>1.80 (1.34–2.43)</td>
<td></td>
<td>1.79 (1.33–2.41)</td>
</tr>
<tr>
<td>2009</td>
<td>843</td>
<td>37%</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>2010</td>
<td>630</td>
<td>28%</td>
<td>1.23 (0.92–1.65)</td>
<td></td>
<td>1.22 (0.91–1.63)</td>
</tr>
<tr>
<td>TB Treatment site</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPC</td>
<td>912</td>
<td>40%</td>
<td>1.20 (0.94–1.53)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1,352</td>
<td>60%</td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

http://www.plosone.org/article/info:doi/10.1371/journal.pone.0056248
FIGURE 1.26
Treatment outcomes for HIV-positive and HIV-negative TB patients, 2006 cohort. The numbers under the bars are the numbers of patients included in the cohort.

- **HIV+ (12,931)**
  - New smear-positive (data from 55 countries)
  - 95% cured, 4% completed, 1% died, 0% failed, 0% defaulted, 0% transferred, 0% not evaluated

- **HIV- (722,667)**
  - New smear-positive and extrapulmonary (data from 48 countries)
  - 95% cured, 4% completed, 1% died, 0% failed, 0% defaulted, 0% transferred, 0% not evaluated

- **HIV+ (18,298)**
  - Retreatment (data from 31 countries)
  - 95% cured, 4% completed, 1% died, 0% failed, 0% defaulted, 0% transferred, 0% not evaluated

- **HIV- (601,518)**
  - Retreatment (data from 31 countries)
  - 95% cured, 4% completed, 1% died, 0% failed, 0% defaulted, 0% transferred, 0% not evaluated

- **HIV+ (4,765)**
  - Retreatment (data from 31 countries)
  - 95% cured, 4% completed, 1% died, 0% failed, 0% defaulted, 0% transferred, 0% not evaluated

- **HIV- (80,293)**
  - Retreatment (data from 31 countries)
  - 95% cured, 4% completed, 1% died, 0% failed, 0% defaulted, 0% transferred, 0% not evaluated

• HIV testing and counseling for all TB patients or suspects
• All patients with tuberculosis should be tested for HIV
• Co-trimoxazole should be initiated as soon as possible in all HIV-positive TB patients and given throughout TB treatment
• Isoniazid preventive therapy for all persons living with HIV, for at least 6 months
• Intensified case finding
• Infection control for tuberculosis
• Testing for LTBI
  • People living with HIV
  • children below 5 years of age who are household or close contacts of people with TB
Diagnosis of LTBI in HIV-Infected Individuals
**Principle of Testing for LTBI**

Presentation of mycobacterial antigens

- Antigen presenting cell
- Memory T-cell

- IFN-\(\gamma\)
- IL-8, etc.
- TNF-\(\alpha\)

IL-8, etc.
Tuberculin Skin Test (TST)

Inject 0.1 ml of PPD (5 tuberculin units) into forearm between skin layers
Produce wheal (raised area) 6–10 mm in diameter

- Assesses 48–72 hours after injection
- Palpate injection site
- Measure diameter of induration across forearm; only measure induration, not redness
- Record size of induration in millimeters; record “0” if no induration
TST interpretation (Review)

≥ 5 mm induration = “Positive” result

*Highest risk patients for progression to active TB*

- Human immunodeficiency virus (HIV)-positive persons
- Recent contacts of TB case patients
- Persons with fibrotic changes on chest radiograph consistent with prior TB
- Patients with organ transplants and other immunosuppressive conditions
  - e.g. Patients receiving ≥ 15 mg/d of prednisone for ≥ 1 month)
  - Risk of TB in patients with corticosteroids increases with higher dose and longer duration.)
TST interpretation (Review)

> 10 mm induration = “Positive” result

- Recent immigrants (i.e., within past 5 years) from TB endemic countries
- Injection drug users
- Residents and employees of select congregate settings – Examples:
  - Prisons and jails, nursing homes and other long-term care facilities
  - Health care employees - hospitals and other health care facilities
  - Homeless shelters
- Mycobacteriology laboratory personnel
- Persons with immunomodulatory medical conditions – Examples:
  - Silicosis, diabetes mellitus, chronic renal failure, hematologic malignancies (e.g., leukemias and lymphomas), other specific malignancies (e.g., carcinoma of the head, neck, or lung), weight loss >10% of ideal body weight, gastrectomy, and jejunoileal bypass
- Children < 4 years of age, or infants, children and adolescents exposed to adults at high-risk
TST interpretation (Review)
≥ 15 mm induration = “Positive” result

- Persons with no known risk factors for TB
  - Raises question ‘why was a TST performed?’
  - Further exploration of patient’s risk factors and exposure history warranted
  - Ensure results of TST are indeed accurate
Currently Available IGRAs

- **QuantiFERON®** (Cellestis)
  - 2nd generation QFT®-Gold (QFT-G) FDA approved May 2005
  - 3rd generation QFT®-Gold In-Tube (QFT-IT) FDA approved October 2007

- **T-SPOT.® TB** (Oxford Immunotec)
  - Evolved from Elispot
  - FDA approved July 2008
## Comparing TST and IGRA platforms

<table>
<thead>
<tr>
<th>TST</th>
<th>IGRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculin is injected under the skin and produces a delayed-type</td>
<td>Blood is drawn for testing; test measures the immune response to the</td>
</tr>
<tr>
<td>hypersensitivity reaction if the person has been infected with M.</td>
<td>TB bacteria in whole blood</td>
</tr>
<tr>
<td>tuberculosis</td>
<td></td>
</tr>
<tr>
<td>Requires two or more patient visits to conduct the test</td>
<td>Requires one patient visit to conduct the test</td>
</tr>
<tr>
<td>Results are available 48 to 72 hours later</td>
<td>Results can be available in 24 hours (depending on the batching of</td>
</tr>
<tr>
<td></td>
<td>specimens by the laboratory and transport)</td>
</tr>
<tr>
<td>Can cause booster phenomenon</td>
<td>Does not cause booster phenomenon</td>
</tr>
<tr>
<td>Reading by HCW may be subjective</td>
<td>Laboratory test not affected by HCW perception or bias</td>
</tr>
<tr>
<td>BCG vaccination can cause false-positive result</td>
<td>BCG vaccination does not cause false-positive result and infection</td>
</tr>
<tr>
<td></td>
<td>with most nontuberculous mycobacteria does not cause false-positive</td>
</tr>
<tr>
<td></td>
<td>result</td>
</tr>
<tr>
<td>A negative reaction to the test does not exclude the diagnosis of</td>
<td>A negative reaction to the test does not exclude the diagnosis of</td>
</tr>
<tr>
<td>LTBI or TB disease</td>
<td>LTBI or TB disease</td>
</tr>
</tbody>
</table>
Comparison of sensitivity of IGRAs between HIV-infected and HIV-uninfected patients with culture-confirmed tuberculosis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Sensitivity in HIV-pos n/N (%)</th>
<th>Sensitivity in HIV-neg n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>QFT-GIT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tsiouris et al. [19]</td>
<td>South Africa</td>
<td>17/26 (65)</td>
<td>11/15 (73)</td>
</tr>
<tr>
<td>Chee et al. [20]</td>
<td>Singapore</td>
<td>4/7 (57)</td>
<td>220/273 (81)</td>
</tr>
<tr>
<td>Garcia-Gasalla et al. [25]</td>
<td>Spain</td>
<td>12/13 (92)</td>
<td>85/105 (81)</td>
</tr>
<tr>
<td>Legesse et al. [29]</td>
<td>Ethiopia</td>
<td>13/19 (68)</td>
<td>20/31 (65)</td>
</tr>
<tr>
<td>Ling et al. [31]</td>
<td>South Africa</td>
<td>29/43 (67)</td>
<td>67/82 (82)</td>
</tr>
<tr>
<td>Dheda et al. [33]</td>
<td>South Africa</td>
<td>1/5 (20)</td>
<td>11/15 (73)</td>
</tr>
<tr>
<td><strong>T-SPOT.TB</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chee et al. [20]</td>
<td>Singapore</td>
<td>7/7 (100)</td>
<td>247/267 (93)</td>
</tr>
<tr>
<td>Ling et al. [31]</td>
<td>South Africa</td>
<td>35/43 (81)</td>
<td>70/82 (85)</td>
</tr>
<tr>
<td>Dheda et al. [33]</td>
<td>South Africa</td>
<td>5/5 (100)</td>
<td>14/15 (93)</td>
</tr>
</tbody>
</table>
Head-to-Head Comparison of Sensitivity Between IGRAs and TST in HIV-infected Patients with Culture-Confirmed Tuberculosis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>IGRA</th>
<th>Sensitivity IGRA</th>
<th>Sensitivity TST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tsiouris et al. [19]</td>
<td>South Africa</td>
<td>QFT-GIT</td>
<td>17/26 (65)</td>
<td>22 (85)</td>
</tr>
<tr>
<td>Aichelburg et al. [22]</td>
<td>Austria</td>
<td>QFT-GIT</td>
<td>10/11 (91)</td>
<td>8 (80)*</td>
</tr>
<tr>
<td>Kabeer et al. [23]</td>
<td>India</td>
<td>QFT-GIT</td>
<td>29/44 (66)</td>
<td>11 (25)</td>
</tr>
<tr>
<td>Garcia-Gasalla et al. [25]</td>
<td>Spain</td>
<td>QFT-GIT</td>
<td>9/13 (69)</td>
<td>5 (42)**</td>
</tr>
<tr>
<td>Rangaka et al. [32]</td>
<td>South Africa</td>
<td>QFT-GIT</td>
<td>32/50 (64)</td>
<td>34 (68)</td>
</tr>
<tr>
<td>Vincenti et al. [38]</td>
<td>Italy</td>
<td>T-SPOT.TB</td>
<td>11/13 (85)</td>
<td>6 (46)†</td>
</tr>
</tbody>
</table>
Head-to-Head Comparison of Sensitivity Between QFT-GIT and T-SPOT.TB in HIV-Infected Patients with Culture-Confirmed Tuberculosis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Sensitivity QFT-GIT n/N (%)</th>
<th>Sensitivity T-SPOT.TB n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chee et al. [20]</td>
<td>Singapore</td>
<td>4/7 (57)</td>
<td>7/7 (100)</td>
</tr>
<tr>
<td>Markova et al. [21]</td>
<td>Bulgaria</td>
<td>12/13 (92)</td>
<td>8/13 (62)</td>
</tr>
<tr>
<td>Leidl et al. [24]</td>
<td>Uganda</td>
<td>13/19 (68)</td>
<td>17/19 (89)</td>
</tr>
<tr>
<td>Ling et al. [31]</td>
<td>South Africa</td>
<td>29/43 (67)</td>
<td>35/43 (81)</td>
</tr>
<tr>
<td>Dheda et al. [33]</td>
<td>South Africa</td>
<td>1/5 (20)</td>
<td>5/5 (100)</td>
</tr>
</tbody>
</table>
Sensitivity of IGRAs in HIV-infected Patients in Four Systematic Reviews

<table>
<thead>
<tr>
<th></th>
<th>Cattamanchi (Ref. [10])</th>
<th>Metcalfe (Ref. [11])</th>
<th>Chen (Ref. [12])</th>
<th>Santin Current SR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-burden TB settings</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- QFT-GIT</td>
<td>61% (47–75)</td>
<td>65% (52–77)</td>
<td>N.D.</td>
<td>61% (53–69)</td>
</tr>
<tr>
<td>- T-SPOT.TB</td>
<td>72% (62–81)</td>
<td>68% (56–80)</td>
<td>N.D.</td>
<td>65% (54–74)</td>
</tr>
<tr>
<td>Low-burden TB settings</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- QFT-GIT</td>
<td>67% (47–83)†</td>
<td>N.D.</td>
<td>N.D.</td>
<td>59% (46–71)</td>
</tr>
<tr>
<td>- T-SPOT.TB</td>
<td>94% (73–100)†</td>
<td>N.D.</td>
<td>N.D.</td>
<td>69% (47–99)†</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- QFT-GIT</td>
<td>N.D.</td>
<td>N.D.</td>
<td>69% (62–71)</td>
<td>61% (54–67)</td>
</tr>
<tr>
<td>- T-SPOT</td>
<td>N.D.</td>
<td>N.D.</td>
<td>66% (60–71)</td>
<td>65% (56–74)</td>
</tr>
</tbody>
</table>
Which IGRA is better for CD4 < 200

• Three studies evaluated the effect of CD4 + cell counts on sensitivity of QFT-GIT
  – One study reported a decrease in its sensitivity with fewer than 200 circulating CD4 + T-cell counts
  – Another found no differences in CD4 + T-cell counts between patients with positive and negative QFT-GIT results
  – Another study found higher sensitivity in patients with <200 CD4 + cells than in those with > 200 CD4 + cells
• None of the three studies assessing TSPOT. TB reported a relationship between lower sensitivity and lower CD4 + T-cell counts
  – The sensitivity of T-SPOT.TB in one study was higher in patients with CD4 + cells < 200 than in those with CD4+ cells > 200 cells
• Progressive immunodeficiency is associated with decreased sensitivity of IGRAs
  • It may have less impact on the sensitivity of IGRAs than on the sensitivity of TST
• Both TST and FDA-approved IGRAs are appropriate for TB screening in HIV-infected individuals
• No definitive comparison favoring one over the other
• Routine use of both TST and IGRAs to screen for LTBI is not recommended
Diagnosis of Active Tuberculosis in the Setting of HIV
TB in the Setting of HIV: Clinical Presentation

• In general, similar to that seen in HIV-uninfected patients

• However, differential diagnosis broader
  – HIV itself
  – Other opportunistic infections

• Extrapulmonary
  – HIV main risk factor
  – 35-80% vs. 15-50%
  – Bones and joints, lymph nodes, the pleura, peritoneum, CNS
Laboratory Diagnosis of Active TB

• Sputum smear
  – HIV-infected patients are more likely to have smear-negative pulmonary TB
  – Range 31 – 81%

• CXR
  – Individuals with advanced HIV are likely to have atypical presentations
    • Lower lobe locations
    • Less cavities
    • Consolidation
    • Intrathoracic LAD
    • May appear normal
Treatment of Tuberculosis
# Treatment of LTBI

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Duration</th>
<th>Interval</th>
<th>Minimum doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>9 months</td>
<td>Daily</td>
<td>270</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice weekly*</td>
<td>76</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>6 months</td>
<td>Daily</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice-weekly</td>
<td>52</td>
</tr>
<tr>
<td>Isoniazid and Rifapentine</td>
<td>3 months</td>
<td>Once weekly</td>
<td>12</td>
</tr>
<tr>
<td>Rifampin</td>
<td>4 months</td>
<td>Daily</td>
<td>120</td>
</tr>
</tbody>
</table>
Factors associated with TB treatment success among new smear-positive TB/HIV co-infected patients at Martin Preuss Centre between January 2008 and December 2010 (N = 1,275).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total</th>
<th>Unadjusted Odds Ratio (95% CI)</th>
<th>P-value*</th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>P-value</td>
<td>P-value</td>
<td></td>
</tr>
<tr>
<td>ART Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On ART</td>
<td>492</td>
<td>39%</td>
<td>0.005</td>
<td>1.83 (1.29–2.60)</td>
<td>0.001</td>
</tr>
<tr>
<td>Not on ART</td>
<td>783</td>
<td>61%</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>520</td>
<td>41%</td>
<td>0.031</td>
<td>1.44 (1.03–2.01)</td>
<td>0.032</td>
</tr>
<tr>
<td>Male</td>
<td>755</td>
<td>59%</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Age at TB registration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15–24</td>
<td>169</td>
<td>13%</td>
<td>0.515</td>
<td>0.70 (0.44–1.12)</td>
<td>0.373</td>
</tr>
<tr>
<td>25–34</td>
<td>619</td>
<td>49%</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>35–44</td>
<td>350</td>
<td>27%</td>
<td>0.98 (0.67–1.43)</td>
<td>1.06 (0.72–1.55)</td>
<td></td>
</tr>
<tr>
<td>45–54</td>
<td>200</td>
<td>8%</td>
<td>0.70 (0.40–1.21)</td>
<td>0.73 (0.42–1.28)</td>
<td></td>
</tr>
<tr>
<td>≥55</td>
<td>37</td>
<td>3%</td>
<td>1.35 (0.47–3.90)</td>
<td>1.43 (0.49–4.17)</td>
<td></td>
</tr>
<tr>
<td>TB Registration year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>421</td>
<td>33%</td>
<td>0.004</td>
<td>2.17 (1.46–3.22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2009</td>
<td>496</td>
<td>39%</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>358</td>
<td>28%</td>
<td>1.31 (0.91–1.90)</td>
<td>1.22 (0.84–1.78)</td>
<td></td>
</tr>
</tbody>
</table>

A comparison of TB treatment outcomes in HIV-TB co-infected patients diagnosed with TB taking and not taking ART

<table>
<thead>
<tr>
<th>Treatment outcome</th>
<th>Not on ART (n = 1024) N (%)</th>
<th>On ART (n = 4016) N (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment success</td>
<td>552 (54)</td>
<td>3191 (79.5)</td>
<td>1.47 (1.39-1.56)</td>
</tr>
<tr>
<td>Death</td>
<td>256 (25)</td>
<td>541 (13.5)</td>
<td>0.53 (0.47-0.61)</td>
</tr>
<tr>
<td>Default</td>
<td>105 (10.3)</td>
<td>118 (3)</td>
<td>0.28 (0.22-0.36)</td>
</tr>
<tr>
<td>Failure</td>
<td>10 (1)</td>
<td>13 (0.3)</td>
<td>0.33 (0.14-0.75)</td>
</tr>
</tbody>
</table>
TB and HIV coinfection: Treatment Issues

- Drug-drug interactions
- Overlapping drug toxicities
- Pill Burden
- Immune-reconstitution inflammatory syndrome (IRIS)
- Sequencing with antiretroviral therapy
- Highly intermittent Dosing
- TB treatment outcome in HIV
- ART treatment effect on TB incidence
**Treatment of Active Tuberculosis in HIV-Coinfected Patients: A Systematic Review and Meta-Analysis**

Faiz A. Khan, Jessica Minion, Madhukar Pai, Sarah Royce, William Burman, Anthony D. Harries, and Dick Menzies

1Montreal Chest Institute, McGill University Health Centre; 2Department of Epidemiology, Biostatistics & Occupational Health, McGill University, Montreal, Canada; 3University of California, San Francisco; 4Denver Public Health, Denver, Colorado; 5International Union against Tuberculosis and Lung Disease, Paris, France; and London School of Hygiene and Tropical Medicine, London, United Kingdom

Clinical Infectious Diseases 2010; 50(9):1288–1299

Meta-analysis of 27 studies

Duration of rifamycin therapy of $\geq 6$ months and daily therapy in the initial intensive phase were associated with lower risk of failure and/or relapse in HIV-positive patients with active TB.
Acquired Rifamycin Resistance with Twice-Weekly Treatment of HIV-related Tuberculosis

William Burman, Debra Benator, Andrew Vernon, Awal Khan, Brenda Jones, Claudia Silva, Chris Lahart, Stephen Weis, Barbara King, Bonita Mangura, Marc Weiner, Wafaa El-Sadr, and the Tuberculosis Trials Consortium

Denver Public Health; University of Colorado Health Sciences Center, Denver, Colorado; Veterans Affairs Medical Center of Washington, DC; George Washington University Medical Center, Washington, DC; Centers for Disease Control and Prevention, Atlanta, Georgia; Los Angeles County–University of Southern California Medical Center, Los Angeles, California; Baylor College of Medicine, Houston; Tarrant County Public Health Department; University of North Texas Health Sciences Center, Fort Worth; University of Texas Health Science Center; South Texas Veterans Health Care System, San Antonio, Texas; University of Medicine and Dentistry of New Jersey–New Jersey Medical School National Tuberculosis Center, Newark, New Jersey; Harlem Hospital Center; and Columbia University College of Physicians and Surgeons, New York, New York

Am J Respir Crit Care. 2006;173:350–356

• 169 HIV-infected patients with culture-confirmed TB
• Median CD4 cell count 90 cells/mm³
• Median HIVRNA 5.3 log10 copies/ml

• DOT rifabutin, isoniazid, pyrazinamide, and ethambutol for 2 months (given daily, thrice-weekly, or twice-weekly per the local tuberculosis control program)
• Followed by rifabutin plus isoniazid for 4 months twice weekly.

Nine (5.3%) patients had culture-positive treatment failure (n=3) or relapse (n=6). Eight of these nine (89%) cases had isolates with acquired rifamycin resistance.
Acquired rifamycin monoresistance in patients with HIV-related tuberculosis treated with once-weekly rifapentine and isoniazid

Lancet.1999;353(9167):1843-1847

Andrew Vernon, William Burman, Debra Benator, Awal Khan, Lorna Bozeman, for the Tuberculosis Trials Consortium

- 61 adults with culture-positive, drug-susceptible pulmonary tuberculosis
- Completed 2 months of isoniazid, rifampin, pyrazinamide, ethambutol
- Median CD4 cell count 118 cells/mm³ for the once weekly arm and 137 cells/mm³ for the twice weekly arm

- Randomly assigned to (for an additional 16 weeks, DOT)
  - 900 mg isoniazid and 600 mg rifapentine once weekly or
  - 900 mg isoniazid and 600 mg rifampin twice weekly.

- Five of 30 patients in the once-weekly isoniazid/rifapentine group relapsed, compared with three of 31 patients in the twice weekly isoniazid/rifampin group (p=0.41).

- Four of five relapses in the once-weekly isoniazid/rifapentine group had monoresistance to rifamycin, compared with none of three in the rifampin group (p=0.05).
Treatment of TB in HIV-infected individuals is the same as for those who are HIV uninfected.

Treatment of TB in HIV-infected individuals should include an initial 4-drug combination of isoniazid, rifampin, pyrazinamide, and ethambutol.

DOT is recommended for all patients with suspected HIV-related TB.

Daily therapy (5–7 days per week) given as DOT is recommended during the intensive phase.

Daily (5–7 days per week) or thrice-weekly dosing is recommended during the continuation phase.

Once- or twice-weekly dosing during the continuation phase assoc. with treatment failure/relapse with acquired rifamycin resistance.
TB/HIV Treatment Issues: Drug Interactions

• Rifamycins induce hepatic cytochrome P450 (CYP3A4) enzymes, accelerating metabolism of:
  – Protease inhibitors (PIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), etc.
  – Rifampicin >> Rifabutin

• For patients receiving PIs or NNRTIs, substitute rifabutin for rifampin, if available

• Alternative non-rifamycin regimens less optimal, longer duration of therapy
When to start ART after recent diagnosis of OI?
Immune Reconstitution Inflammatory Syndrome (IRIS)

- Clinical worsening in the setting of an adequate response to ART
  - “Paradoxical” worsening of previously known treated (completed or ongoing) opportunistic pathogen
  - “Unmasking” of subclinical opportunistic pathogen
Incidence of Tuberculosis Immune Reconstitution Inflammatory Syndrome (IRIS) in Human Immunodeficiency Virus (HIV)–Tuberculosis Coinfection.

<table>
<thead>
<tr>
<th>Study no.</th>
<th>Study, year</th>
<th>Years studied</th>
<th>Incidence of tuberculosis IRIS among HIV-positive patients with tuberculosis, proportion (%)</th>
<th>Median baseline parameters</th>
<th>Median time, days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Age of patients, years</td>
<td>CD4 cell count, cells/μL</td>
<td>Viral load, log_{10} copies/mL</td>
</tr>
<tr>
<td>1</td>
<td>Narita et al [82], 1998</td>
<td>1996–1997</td>
<td>12/33 (36)</td>
<td>40°</td>
<td>51°</td>
</tr>
<tr>
<td>2</td>
<td>Breton et al [83], 2004</td>
<td>1996–2001</td>
<td>16/37 (43)</td>
<td>35</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>Breen et al [84], 2004</td>
<td>1997–2002</td>
<td>14/50 (28)</td>
<td>36</td>
<td>NA</td>
</tr>
<tr>
<td>4</td>
<td>Kumarasamy et al [85], 2004</td>
<td>2000–2003</td>
<td>11/144 (8)</td>
<td>29</td>
<td>123</td>
</tr>
<tr>
<td>5</td>
<td>Lawn et al [80], 2007</td>
<td>2002–2005</td>
<td>19/160 (12)</td>
<td>35</td>
<td>68</td>
</tr>
</tbody>
</table>

**NOTE.** ART, antiretroviral therapy; NA, not available.

° Mean.
IRIS

• **Risk factors**
  – Disseminated TB
  – Shorter delay between onset of TB and ART drugs
  – Low baseline CD4, higher baseline viral load
  – Greater CD4 or viral load response to ART

• **Timing of onset**
  – Usually within first 6 weeks of ART (often 2–3 weeks, but can be months after ART started)
Clinical presentation:

- Fever
- Nodal enlargement
- Worsening pulmonary infiltrates with or without respiratory symptoms
- Local worsening in extrapulmonary sites
IRIS Differential Diagnosis

- TB treatment failure
- Drug-resistant TB
- ART failure
- Other opportunistic (or non-opportunistic) infections
- Lymphoma, Kaposi’s sarcoma
- Hypersensitivity drug reactions
IRIS Management

• Continue TB treatment
• Continue ART
• Exclude TB treatment failure
  – Adherence
  – Drug resistance
• Exclude additional/new diagnosis
• Consider NSAIDS, steroids
• Drainage of lesions
# Randomized Trials of Early Versus Late ART in Patients co-infected with HIV and Tuberculosis

## Study Details

<table>
<thead>
<tr>
<th>Study</th>
<th>SAPIT</th>
<th>SAPIT</th>
<th>CAMELIA</th>
<th>STRIDE</th>
<th>TIME</th>
<th>TB-HAART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>642 (429 vs 213)</td>
<td>429 (214 vs 215)</td>
<td>661 (332 vs 329)</td>
<td>806 (405 vs 401)</td>
<td>156 (79 vs 77)</td>
<td>1538 (767 vs 771)</td>
</tr>
<tr>
<td>Trial design</td>
<td>Open label</td>
<td>Open label</td>
<td>Open label</td>
<td>Open label</td>
<td>Open label</td>
<td>DB, PC</td>
</tr>
<tr>
<td>Baseline CD4 (median; cells per μL)</td>
<td>&lt;500 (150)</td>
<td>&lt;500 (150)</td>
<td>≤200 (25)</td>
<td>&lt;250 (77)</td>
<td>&lt;350 (43)</td>
<td>&gt;220 (367)</td>
</tr>
<tr>
<td>Early ART group</td>
<td>≤4 weeks</td>
<td>≤4 weeks</td>
<td>≤2 weeks</td>
<td>≤2 weeks</td>
<td>≤4 weeks</td>
<td>≤2 weeks</td>
</tr>
<tr>
<td>Late ART group</td>
<td>At 6 months</td>
<td>≤8 weeks</td>
<td>≤8 weeks</td>
<td>8-12 weeks</td>
<td>≤12 weeks</td>
<td>At 6 months</td>
</tr>
<tr>
<td>Median follow-up (months)</td>
<td>12.1</td>
<td>17.7</td>
<td>25</td>
<td>25</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>IRR (95% CI; p value), early vs late ART Deaths or AIDS (per 100 person years)</td>
<td>0·44 (0·25 to 0·79; p=0·003)</td>
<td>0·96 (0·44 to 2·10; p=0·91)</td>
<td>IRR 0·32, 95% CI 0·07–1·13; p=0·06 for CD4 ≤ 50</td>
<td>0·62 (0·44 to 0·86; p=0·006)</td>
<td>0·32 (−1·8 to 8·1; p=0·45) \ Fewer new AIDS and death \ For CD4 ≤ 50</td>
<td>0·84 (0·25 to 2·90; p=0·99)</td>
</tr>
</tbody>
</table>
Deferred ART 2 months post TB Rx
\( (n = 126) \)

Immediate ART within 1 wk post TB Rx
\( (n = 127) \)

**Immediate ART** within 1 wk post TB Rx

**Deferred ART** 2 months post TB Rx

ART-naïve, TBM suspects
\( (N = 253) \)

Median CD4+ 40
Median viral load 5.4 log10 copies

High mortality in both groups at 9 months but no significant difference:
76 in the immediate ART vs. 70 in the deferred ART (HR 12; 95% confidence interval, .81–1.55; \( P \leq .50 \)).

Immediate ART associated with more grade 4 adverse events
<table>
<thead>
<tr>
<th>CD4</th>
<th>Start ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤50 cells/µL</td>
<td>Within 2 weeks of TB Rx</td>
</tr>
<tr>
<td>≥50 cells/µL</td>
<td>Can defer ART beyond 2 weeks but should start within 8 weeks</td>
</tr>
</tbody>
</table>

In patients with TB meningitis and low CD4 cell counts, early ART may pose a risk that calls for careful monitoring and consultation with experts.
Tuberculosis in the Setting of HIV

Summary

• Substantial global disease burden, individually and as coinfection
• HIV adversely affects the entire spectrum of the natural history of tuberculosis
• Difficulties in diagnosis and treatment
• Simultaneous ART and TB treatment is challenging, but manageable
• ART is critical for a positive outcome of tuberculosis and HIV