Substance Abuse and Tuberculosis
Oklahoma City, Oklahoma
November 17, 2010

Co-morbidities that Impact Managing TB
Lisa Armitige, MD, PhD
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Co-morbidities in Substance Abuse that Impact Managing TB

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Medical Co-Morbidities

- Tobacco smoke
- HIV
- Malnutrition
- Hepatic disease
Global lung health: the colliding epidemics of tuberculosis, tobacco smoking, HIV and COPD
van Zyl Smit et al, Eur Respir J 2010, 35; 27

- In 2006 approximately 5.8 trillion cigarettes were manufactured; an average of 2.4/day for all 6.5 billion inhabitants of earth

- Current estimates of tobacco smoking rates are 49% males, 8% females in low and middle income countries (37% and 21% respectively in high-income countries)

- In 2004, COPD was the 4th leading cause of death worldwide (5.1% of total deaths)

- By 2030, COPD will be the 3rd leading cause of death globally, eclipsing deaths by TB and HIV

Association between Tobacco Smoking and Active Tuberculosis in Taiwan
Hsien-Ho et al AJRCCM 2009, 180; 475

- Prospective cohort study in Taiwan: 17,699 participants, 2001-2004

- Current smoking associated with twofold increased risk of active TB
  - Association stronger for patients < 65 years
  - Significant dose-response relations
    - Cigarettes per day
    - Years of smoking
    - Pack years
Smoking, drinking and incident tuberculosis in rural India: population-based case-control study
Gajalakshmi et al Int J Epidemiol 2009, 38; 1018

- Case-control study from India: 1839 males, 870 females

- NO WOMEN SMOKED or DRANK ALCOHOL!

- 82% TB cases vs 55% of controls smoked
  - RR 2.2 (for alcohol consumption RR 1.5)

- Conclusion: increased incidence of pulmonary TB among those who smoke and among those who drink

Association between Tobacco Smoking and Active Tuberculosis in Taiwan
Hsien-Ho et al AJRCCM 2009, 180; 475

- “The finding that smoking increased the risk of tuberculosis suggests that tobacco control be considered as an important component in the global effort to eliminate tuberculosis”.

- “…policy makers and public health personnel should consider addressing tobacco cessation as part of TB control.”
Systematic Reviews and Meta-analyses evaluating tuberculosis and cigarette smoking

• Slama et al, Int J Tuberc Lung Dis 2007, 11; 1049
  • “Tobacco and tuberculosis: a qualitative systematic review and meta-analysis”

• Lin et al, PLoS Med 2007, 4; e20
  • “Tobacco smoke, indoor air pollution and tuberculosis: a systematic review and meta-analysis”

• Bates et al Arch Intern Med 2007
  • Smokers almost twice as likely to be infected with TB and to progress to active disease. 2/3 studies suggest smokers almost twice as likely to die from TB

Systematic Reviews and Meta-analyses evaluating tuberculosis and cigarette smoking

• Approximately 13% of the TB cases in the world each year may be attributable to tobacco exposure.

• “Tobacco cessation must become an integral part of all TB control programmes.”
Pulmonary Impairment After TB
Pasipanodya et al Chest 2007, 131; 1817

- 107 TB patients compared with 210 LTBI patients
- Pulmonary function impairment present in 59% of TB patients vs 20% LTBI patients
- TB survivors more than 5.4 times more likely to have abnormal pulmonary function tests than LTBI patients
- “For many persons with TB, a microbiological cure is the beginning not the end of their illness.”

HIV
Outcomes of Exposure to *M. tuberculosis*

Inhalation of Droplet Nuclei

Regional replication in lungs, dissemination

~90% Killing, clearance of organisms  ~5% Latent disease  ~5% Active disease

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

Inhalation of Droplet Nuclei

Regional replication in lungs, dissemination

~90% Killing, clearance of organisms  ~5% reactivation lifetime  10% reactivation per year  ~5% Active disease  Up to 36% active disease
**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)

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**Quantiferon Gold In-Tube**

![Distribution of Quantiferon Gold In-Tube results by CD4 lymphocyte count. Proportion of both negative and indeterminate results increased with falling CD4 lymphocyte count.](image)

**Table 2. Distribution of Quantiferon Gold In-Tube results by HIV status, CD4 lymphocyte count, treatment period and TST result.**

<table>
<thead>
<tr>
<th>CD4 count cells/µl</th>
<th>&lt; 200</th>
<th>200 to 399</th>
<th>400 to 599</th>
<th>600 or more</th>
<th>Positive</th>
<th>Negative</th>
<th>Indeterminate</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV negative</td>
<td>0.00%</td>
<td>0.00%</td>
<td>0.00%</td>
<td>0.00%</td>
<td>0.00%</td>
<td>0.00%</td>
<td>0.00%</td>
</tr>
<tr>
<td>HIV positive</td>
<td>0.00%</td>
<td>0.00%</td>
<td>0.00%</td>
<td>0.00%</td>
<td>0.00%</td>
<td>0.00%</td>
<td>0.00%</td>
</tr>
</tbody>
</table>

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**Clinical Microbiology and Infection, Volume 10 Number 5, May 2004**

**Quantiferon Gold In-Tube**

![Quantiferon Gold In-Tube](image)
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 assays in the diagnosis of pulmonary tuberculosis in patients with advanced HIV infection

Cattamanchi et al. *BMC Infectious Diseases* 2010, 10:75

**Figure 1 Study population: 244 patients eligible for the study.**

<table>
<thead>
<tr>
<th>IGRA Results</th>
<th>Positive TB Cultures</th>
<th>Negative TB Cultures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Done</td>
<td>14 (1%)</td>
<td>19 (9%)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>38 (16%)</td>
<td>36 (17%)</td>
</tr>
<tr>
<td>Negative</td>
<td>23 (10%)</td>
<td>49 (23%)</td>
</tr>
</tbody>
</table>

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

*Note: A positive IGRA result was considered positive.*
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 (&gt; 5 mm without BCG)</td>
<td>30%*</td>
<td>50%*</td>
<td>[23]</td>
</tr>
<tr>
<td>Acid-fast bacilli on smear</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>Mycobacteremia</td>
<td>20-49%</td>
<td>0-7%</td>
<td>[22,30]</td>
</tr>
</tbody>
</table>

Current Antiretroviral Medications

**NRTI**
- Abacavir
- Didanosine
- Emtricitabine
- Lamivudine
- Stavudine
- Tenofovir
- Zidovudine

**NNRTI**
- Delavirdine
- Efavirenz
- Etravirine
- Nevirapine

**PI**
- Atazanavir
- Darunavir
- Fosamprenavir
- Indinavir
- Lopinavir
- Nelfinavir
- Ritonavir

**Fusion Inhibitor**
- Enfuvirtide

**CCR5 Antagonist**
- Maraviroc

**Integrase Inhibitor**
- Raltegravir
Effect of rifampin on serum efavirenz levels

Effect on plasma level of efavirenz by rifampin co-administration

Effect of increasing efavirenz dose with rifampin co-administration

Fig. 2. Median plasma efavirenz (EV) concentration-time profiles during week 7 and in combination with rifampin (R) (day 14). One patient from group A-2 was excluded because of very abnormal efavirenz plasma concentrations on day 14.

Fig. 3. Proportion of virological success over the 24-week analysis period for efavirenz dosage of 600 mg (—) or 800 mg (—–).

Effect of efavirenz dosing with rifampin on treatment outcomes

Fig. 1. Immunological outcomes at 48 weeks of antiretroviral therapy between the two treatment groups. —— efavirenz 600 mg/day; —— efavirenz 800 mg/day.
## Rifampin and PIs

**Table 3. Pharmacokinetic interactions between rifampicin or rifabutin**

<table>
<thead>
<tr>
<th>PI</th>
<th>Rifampicin effect on PI</th>
<th>PI's effect on R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saquinavir</td>
<td>99% decrease saquinavir level</td>
<td>Data not reported</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>35% decrease ritonavir level</td>
<td>Unchanged R level</td>
</tr>
<tr>
<td>Indinavir</td>
<td>92% decrease indinavir level</td>
<td>Data not reported</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>82% decrease nelfinavir level</td>
<td>Data not reported</td>
</tr>
<tr>
<td>Lopinavir + ritonavir</td>
<td>75% decrease lopinavir level</td>
<td>Data not reported</td>
</tr>
<tr>
<td>Amprenavir</td>
<td>84% decrease amprenavir level</td>
<td>Unchanged R level</td>
</tr>
</tbody>
</table>

R, rifampicin; RPI, rifabutin; PI, protease inhibitor.

Note: Decrease in serum protease inhibitor level is **NOT** overcome by low dose ritonavir

<table>
<thead>
<tr>
<th>RPI's effect on PI</th>
<th>PI's effect on RPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>45% decrease saquinavir level</td>
<td>Data not reported</td>
</tr>
<tr>
<td>34% decrease indinavir level</td>
<td>20% increase RPI level</td>
</tr>
<tr>
<td>32% decrease nelfinavir level</td>
<td>17% increase RPI level</td>
</tr>
<tr>
<td>Data not reported</td>
<td>20% increase RPI level</td>
</tr>
<tr>
<td>14% decrease amprenavir level</td>
<td>30% increase RPI level</td>
</tr>
<tr>
<td></td>
<td>20% increase RPI level</td>
</tr>
</tbody>
</table>
Overall Treatment Outcomes

Considerations
- Treatment of HIV improves outcomes in patients with TB
  - Decreased death or relapse
  - Multiple medications with multiple potential toxicities that are overlapping
- If the CD4 count is < 200, generally most ID physicians would treat for HIV with treatment for TB
- If the CD4 count is > 200…
  - Arguments to start both treatments concurrently
  - Arguments to delay the start of HAART

When should treatment be started when patient is being treated for TB?

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HIV-infected (n = 156)</th>
<th>HIV-uninfected (n = 156)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), years</td>
<td>35 (20-73)</td>
<td>33 (16-82)</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>52</td>
<td>58</td>
</tr>
<tr>
<td>Black-African ethnicity, %</td>
<td>78</td>
<td>41*</td>
</tr>
<tr>
<td>Pulmonary tuberculosis, %</td>
<td>57</td>
<td>51</td>
</tr>
<tr>
<td>Duration of antituberculosis treatment, median (range), months</td>
<td>6 (1-24)</td>
<td>6 (1-30) *</td>
</tr>
<tr>
<td>No. (%) with available follow-up data</td>
<td>151 (97)</td>
<td>150 (96)</td>
</tr>
<tr>
<td>Duration of follow-up, median (range), months</td>
<td>38 (9-96)</td>
<td>20 (2-60)</td>
</tr>
<tr>
<td>No. (%) followed for &gt;24 months</td>
<td>115 (76)</td>
<td>66 (45)</td>
</tr>
<tr>
<td>No. (%) who discontinued antituberculosis treatment prematurely</td>
<td>9 (6)</td>
<td>6 (4) *</td>
</tr>
<tr>
<td>No. (%) with recurrence of tuberculosis</td>
<td>4 (3)</td>
<td>2 (1) *</td>
</tr>
</tbody>
</table>

* P<.0001.
NIH-Funded Study Finds Early HAART during TB Treatment Boosts Survival Rate in People Co-Infected with HIV and TB

Tuberculosis and diabetes mellitus: Convergence of two epidemics
Dooley and Chaisson Lancet Infect Dis 2009, 9; 737

- “Increasing industrialization and urbanization leads to higher rates of obesity and diabetes”
- In 2000 the number of people with diabetes was 171 million
- In 2030 the anticipated number of people with diabetes is expected to grow to 366 million to 440 million with ¾ of patients with diabetes living in low-income countries
- Diabetes poses a large financial burden in countries with limited resources
Is severity of Diabetes related to the magnitude of risk for developing tuberculosis?

- Olmos et al Rev Med Chile 1989; 117; 979
  - 1592 diabetic patients in Chile
  - 10 yr probability of developing tuberculosis was 25% in IDDM and 4.8% in NIDDM

- Swai et al Trop Doct 1990, 20; 147
  - Diabetic patients followed 1-7 yrs in Tanzania
  - 9% of IDDM patients and 2.7% NIDDM patients developed tuberculosis

- These two studies provide evidence that insulin dependence, as a marker for severity of disease, predicts increased tuberculosis risk.

Is severity of Diabetes related to the magnitude of risk for developing tuberculosis?

  - 4690 elderly diabetic patients in Hong Kong
  - Those with Hgb A1C > 7% had a three times increased risk of active tuberculosis compared with those with Hgb A1c < 7%.

- No clear consensus that diabetic patients are at increased risk for developing or acquiring drug resistant tuberculosis.

- These data suggest that poor glycemic control is a risk factor for tuberculosis.
Response to tuberculosis therapy in Diabetic patients

• Baseline mycobacterial burdens might be higher in diabetic patients than in controls

• Diabetics tend to have modestly longer times to sputum-culture conversion
  - Dooley et al Am J Trop Med Hyg 2009, 80; 634
  - Alisjahbana et al Clin Infect Dis 2007, 45; 428

• Rates of sputum-culture conversion are similar to those of non-diabetic patients by 2-3 months of treatment (see references above)

Response to tuberculosis therapy in Diabetic patients

• Unknown if increased time to culture conversion in diabetic patients leads to higher risk of relapse

• Possible increased risk of treatment failure in diabetics
  • Alisjahbana et al Clin Infect Dis 2007, 45; 428

• 6.5-6.7 times increased risk of death in diabetic patients c/w non-diabetic controls
  • Dooley et al Am J Trop Med Hyg 2009, 80; 634
  • Oursler et al Clin Infect Dis 2002, 34; 752

• Whether aggressive management of diabetes mellitus would improve treatment response remains unclear.
Pharmacologic Interactions in patients with tuberculosis and diabetes

• Diabetes does not alter the pharmacokinetics of anti-tuberculosis drugs during the intensive phase of tuberculosis treatment but...

• Diabetic patients had lower rifampin levels c/w controls in the continuation phase of therapy
  – Nijland et al Clin Infect Dis 2006, 43; 848
  – Ruslami et al Antimicro Ag Chemother 2010, 54; 1068

• Rifampin, a potent inducer of drug metabolizing enzymes, can lead to accelerated metabolism of oral hypoglycemic drugs

Malnutrition
Importance of Nutrition in TB Treatment Response

Patients 10% below ideal body weight at diagnosis

- have a 20% chance of relapse if they don’t regain at least 5% by end of two months of treatment

- If CXR cavitary & 2 mo sputum culture +, 50% chance of relapse


“Weight gain of 5% or less during the first 2 months of therapy is associated with an increased risk of relapse, even after controlling for other factors.”

Lack of Weight Gain and Relapse Risk, TBTC Study 22

- Relapse risk high in those underweight at diagnosis 19.1% versus 4.8%

- Among pts underweight at Dx, weight gain ≤ 5% after 2 mo treatment:
  - Relapse risk 18.4% vs. 10.3%
  - If also cavitary disease: 18.9%
  - If cavitary and + 2 month culture: 50.5%

Hepatic Disease

- Difficulties in treating tuberculosis due to potentially hepatotoxic drugs
- Hepatitis B and C virus infections
- Exacerbated by the need for treatment with multiple classes of medications in treating HIV/TB co-infected patients

Thanks!!

Questions?

1-800-TEX-LUNG