Tuberculosis and Diabetes

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Disclosures

- None
Objectives

- Recognize the global epidemics of diabetes and TB
- Review the impact of diabetes on the development/treatment of TB
- Discuss Virginia's therapeutic drug monitoring (TDM) program for TB/diabetes patients
Diabetes (DM)

- In 2014 387 million people had diabetes (8.3% prevalence)
- The International Diabetes Federation (IDF) predicts that the number of diabetics will rise by 55% in the next 20 years
- By 2035, 592 million people will have diabetes
- 77% from low/middle income countries
Annual Number of New Cases of Diabetes Among Adults Aged 18-79
- Every 7 seconds someone dies from diabetes (4.9 million deaths in 2014)
- 1 in 9 healthcare dollars is spent on diabetes (US $612 billion in 2014)
Nearly 50% of individuals with diabetes are unaware that they have it until they develop a complication of the disease.
1 in 10 North Carolinians has diabetes

Diabetes is the 7th leading cause of death in North Carolina
"I'm afraid you've got diabetes."
Tuberculosis (TB)

- In 2013, 9 million people became ill with TB
- 1.5 million people died
- About 25% were co-infected with HIV
- 1/3 of world's population is infected with TB
Reported TB Cases
United States, 1982–2013*

*Updated as of June 11, 2014.
Number of TB Cases in U.S.-born vs. Foreign-born Persons, United States, 1993–2013*

*Updated as of June 11, 2014.
Figure 3. North Carolina 2014 Tuberculosis Cases by County

Number

- 1 - 2
- 3 - 7
- 8 - 16
- 17 - 22
- None

N=195
Around 1000 AD Avicenna recorded that TB or "pthisis" caused complications among diabetics and that diabetes was responsible for increasing their risk of developing TB.
"In the latter half of the 19th century the diabetic patient appeared doomed to die of pulmonary TB if he succeeded in escaping coma."
Diabetes and tuberculosis—a wake-up call

As the time of reckoning for the Millennium Development Goals (MDGs) approaches, it seems that there will be cause for celebration in the domain of tuberculosis. The goal of reversing tuberculosis incidence by 2015 has already been reached, a testament to the efforts of organisations—from local providers to multilateral agencies—that have pulled together to combat this scourge.

But another, seemingly more insidious, epidemic is threatening further progress with respect to global tuberculosis control. The prevalence of obesity—and associated type 2 diabetes—is rising faster than anyone would have predicted only 30 years ago, and the interactions between tuberculosis and diabetes are of concern. These interactions are explored in depth in three Series papers in this issue of *The Lancet Diabetes & Endocrinology*.

Diabetes has long been known to be a risk factor for active tuberculosis and reactivation of latent tuberculosis. It is also associated with worse tuberculosis treatment outcomes. Additionally, tuberculosis infection adding the increasing burden of diabetes and other non-communicable diseases (NCDs) into the mix will be an extra strain with which many countries will struggle to cope. The fact that the NCDs will worsen the burden of communicable diseases could be the straw that breaks the camel’s back for some health systems.

On the other hand, this interaction between communicable diseases and NCDs could provide the wake-up call that health providers need to kick NCD prevention programmes into action. Up until very recently, the global health community had largely ignored the rise in prevalence of obesity and associated NCDs. Communicable diseases continue to receive the lion’s share of funding, even after the 2011 UN high-level meeting on NCDs set the target of a 25% reduction in NCDs by 2025. The knowledge that a strong reduction in communicable diseases will be impossible to achieve without a concomitant reduction in obesity and diabetes should provide impetus for the global community and local providers to start to invest...
TUBERCULOSIS & DIABETES
The growing threat of the double burden of diabetes and tuberculosis

Diabetics have 2-3X increased risk of developing TB
Table 1  Top 10 countries with the highest incidence of TB associated with DM (adapted from Lönnroth et al.⁷)

<table>
<thead>
<tr>
<th>Country</th>
<th>TB incidence (all age groups) /100000</th>
<th>Adults with DM Million</th>
<th>Population attributable fraction of DM for adult TB cases %</th>
<th>Adult TB cases associated with DM, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>176</td>
<td>65</td>
<td>15</td>
<td>302 000</td>
</tr>
<tr>
<td>China</td>
<td>73</td>
<td>98</td>
<td>17</td>
<td>156 000</td>
</tr>
<tr>
<td>South Africa</td>
<td>1 000</td>
<td>3</td>
<td>15</td>
<td>70 000</td>
</tr>
<tr>
<td>Indonesia</td>
<td>185</td>
<td>9</td>
<td>10</td>
<td>48 000</td>
</tr>
<tr>
<td>Pakistan</td>
<td>231</td>
<td>7</td>
<td>12</td>
<td>43 000</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>225</td>
<td>5</td>
<td>10</td>
<td>36 000</td>
</tr>
<tr>
<td>Philippines</td>
<td>265</td>
<td>3</td>
<td>11</td>
<td>29 000</td>
</tr>
<tr>
<td>Russia</td>
<td>91</td>
<td>11</td>
<td>17</td>
<td>23 000</td>
</tr>
<tr>
<td>Myanmar</td>
<td>377</td>
<td>2</td>
<td>11</td>
<td>21 000</td>
</tr>
<tr>
<td>Democratic Republic of Congo</td>
<td>327</td>
<td>2</td>
<td>10</td>
<td>19 000</td>
</tr>
</tbody>
</table>

TB = tuberculosis; DM = diabetes mellitus.

Globally, 15% of TB cases are attributed to diabetes.
TB/DM "Co-epidemic"

- Involves interaction between infection and a non-communicable chronic disease
- Potentially has a greater global impact than TB/HIV: DM occurs in all countries and affects individuals regardless of socioeconomic status
- Diabetes diagnostics and care is not widely available or free in many developing countries
<table>
<thead>
<tr>
<th>Region</th>
<th>TB Patients w/ Diabetes</th>
<th>Year Published</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karnataka State, India</td>
<td>32%</td>
<td>2011</td>
</tr>
<tr>
<td>Kerala State, India</td>
<td>44%</td>
<td>2012</td>
</tr>
<tr>
<td>Tamil Nadu State, India</td>
<td>25%</td>
<td>2012</td>
</tr>
<tr>
<td>Texas, USA</td>
<td>39%</td>
<td>2011</td>
</tr>
<tr>
<td>Mexico</td>
<td>36%</td>
<td>2011</td>
</tr>
<tr>
<td>Tanzania</td>
<td>17%</td>
<td>2011</td>
</tr>
<tr>
<td>Pakistan</td>
<td>16%</td>
<td>2012</td>
</tr>
<tr>
<td>South Pacific</td>
<td>40-45%</td>
<td>2013</td>
</tr>
</tbody>
</table>
Figure: Projected prevalent diabetes cases and current worldwide tuberculosis incidence

Estimated number and percent of individuals with diabetes mellitus in 2010 compared with 2030 projections are shown. Tuberculosis incidence per 100 000 population data for 2007 are shown. Data from International Diabetes Foundation and WHO.

Figure 2: Scenarios of diabetes prevalence aggregated for 13 countries with high tuberculosis burden (A) and projected tuberculosis incidence (B), mortality (C), and prevalence (D) in these countries under different scenarios of diabetes, 2015–35. The lines in panels B, C, and D represent the means of posterior simulations from the calibrated models. Table 1 shows definitions of diabetes scenarios. The appendix shows country-specific results.
• TB patients with diabetes are 2x more likely to have failure or death during TB treatment
• TB patients with diabetes are 4x more likely to relapse after TB treatment completion
How does DM increase risk of TB?

Does TB increase risk of DM?

1. Stress of severe chronic infection increases insulin resistance
2. Increasing insulin demand may unmask preexisting insulin resistance and lead to hyperglycemia
3. This may be reversible after infection brought under control
4. Or may precipitate diabetes
Clinical Presentation of TB/DM

- Presentation: more likely to have fever, hemoptysis
- More likely to be smear positive
- Higher bacillary load
- Delayed culture conversion rates
X-ray in TB/DM

- Chiang et al found TB/DM more likely to have:
  - opacities in lower lungs
  - parenchymal lesions
  - any cavity, multiple cavities and large cavities (>3 cm)
Other complications of treating TB/DM

- Infection usually raises blood glucose levels making DM more difficult to control
- Rifampin induces metabolism of anti-diabetes medications (sulfonylureas)
Figure 1. Diabetes is associated with increased progression to active tuberculosis and unfavourable clinical outcomes. Following exposure to *Mycobacterium tuberculosis* (*Mtb*), immunocompetent hosts predominantly develop latent infection (90%), with only 10% developing active tuberculosis (blue arrows). This is reversed in immunocompromised hosts, such as individuals with diabetes, who predominantly develop active infection (red arrows). In immunocompromised hosts, the annual risk of reactivation of latent tuberculosis exceeds 10%, compared with a lifetime risk of only 10–20% in immunocompetent hosts. Along with a predisposition for developing active disease, more unfavourable outcomes of tuberculosis, including lower lung involvement, cavitary lesions, extrapulmonary disease, relapse and death, are associated with co-morbid diabetes.
631,194 Virginians have diabetes, that's about 1 out of every 11 people.

1 out of 4 do not know they have diabetes.

- Diabetes is consistently the most common TB risk factor observed in Virginia.
- In 2014, 33 (17%) TB cases had diabetes.
TDM in Virginia

- Instituted in 2007 for "slow responders"
- "Slow response": $\geq 30$ days patient has $\geq 2$ of the following:
  - AFB smear positive
  - No improvement in TB-specific symptoms
  - No improvement in chest x-ray
Table 3. Risk factors for INH or RIF serum concentration levels below the expected range 2 hours after medication administration among persons with slow responses, therapeutic drug monitoring, Virginia, USA, March 1, 2007–May 1, 2009*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal INH, n = 16, no. (%)</th>
<th>Low INH, n = 23, no. (%)</th>
<th>Bivariate risk ratio (95% CI); p value</th>
<th>Normal RIF, n = 20, no. (%)</th>
<th>Low RIF, n = 22, no. (%)</th>
<th>Bivariate risk ratio (95% CI); p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40–64</td>
<td>7 (44)</td>
<td>8 (35)</td>
<td>0.57 (0.12–2.80); p = 0.49</td>
<td>8 (40)</td>
<td>7 (32)</td>
<td>0.44 (0.10–1.90); p = 0.27</td>
</tr>
<tr>
<td>&gt;65</td>
<td>5 (31)</td>
<td>7 (30)</td>
<td>0.70 (0.13–3.70); p = 0.67</td>
<td>7 (35)</td>
<td>5 (22)</td>
<td>0.36 (0.07–1.70); p = 0.20</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>11 (69)</td>
<td>15 (65)</td>
<td>Referent</td>
<td>13 (65)</td>
<td>15 (68)</td>
<td>Referent</td>
</tr>
<tr>
<td>F</td>
<td>5 (31)</td>
<td>8 (35)</td>
<td>1.2 (0.30–4.60); p = 0.82</td>
<td>7 (35)</td>
<td>7 (32)</td>
<td>0.87 (0.24–3.10); p = 0.81</td>
</tr>
<tr>
<td><strong>Race/Ethnicity</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1 (6)</td>
<td>3 (13)</td>
<td>1.9 (0.16–22.30); p = 0.61</td>
<td>3 (15)</td>
<td>1 (5)</td>
<td>0.37 (0.3–4.2); p = 0.42</td>
</tr>
<tr>
<td>Asian</td>
<td>7 (44)</td>
<td>11 (48)</td>
<td>Referent</td>
<td>10 (50)</td>
<td>9 (41)</td>
<td>Referent</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>6 (38)</td>
<td>4 (17)</td>
<td>0.42 (0.09–2.10); p = 0.43</td>
<td>3 (15)</td>
<td>8 (36)</td>
<td>3.0 (0.60–14.70); p = 0.18</td>
</tr>
<tr>
<td>Black</td>
<td>2 (12)</td>
<td>5 (22)</td>
<td>1.6 (0.24–10.60); p = 0.63</td>
<td>4 (20)</td>
<td>4 (18)</td>
<td>1.1 (0.21–5.80); p = 0.90</td>
</tr>
<tr>
<td><strong>Foreign-born</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>No</td>
<td>3 (19)</td>
<td>6 (26)</td>
<td>Referent</td>
<td>6 (30)</td>
<td>3 (14)</td>
<td>Referent</td>
</tr>
<tr>
<td>Yes</td>
<td>13 (81)</td>
<td>17 (74)</td>
<td>0.65 (0.14–3.10); p = 0.59</td>
<td>14 (70)</td>
<td>19 (86)</td>
<td>2.7 (0.58–12.80); p = 0.21</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>10 (63)</td>
<td>13 (57)</td>
<td>Referent</td>
<td>16 (80)</td>
<td>9 (41)</td>
<td>Referent</td>
</tr>
<tr>
<td>Yes</td>
<td>6 (37)</td>
<td>10 (43)</td>
<td>1.3 (0.35–4.70); p = 0.71</td>
<td>4 (20)</td>
<td>13 (59)</td>
<td>5.8 (1.4–23.1); p = 0.01†</td>
</tr>
<tr>
<td><strong>Alcohol abuse</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>15 (94)</td>
<td>22 (96)</td>
<td>Referent</td>
<td>18 (90)</td>
<td>20 (91)</td>
<td>Referent</td>
</tr>
<tr>
<td>Yes</td>
<td>1 (6)</td>
<td>1 (4)</td>
<td>0.69 (0.40–11.70); p = 0.79</td>
<td>2 (10)</td>
<td>2 (9)</td>
<td>0.90 (0.12–7.10); p = 0.92</td>
</tr>
<tr>
<td><strong>Dose interval</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>8 (50)</td>
<td>19 (83)</td>
<td>Referent</td>
<td>11 (65)</td>
<td>16 (73)</td>
<td>Referent</td>
</tr>
<tr>
<td>Biweekly</td>
<td>8 (50)</td>
<td>4 (17)</td>
<td>0.21 (0.05–0.90); p = 0.04†</td>
<td>6 (35)</td>
<td>6 (27)</td>
<td>0.88 (0.23–3.30); p = 0.85</td>
</tr>
</tbody>
</table>

*INH, isoniazid; RIF, rifampin; CI, confidence interval. Low is defined as below expected range; normal is defined as within or above expected range.
†Adjusted odds ratio 5.7 (1.2–25.7); p = 0.03.
‡Adjusted odds ratio 0.47 (0.09–2.50); p = 0.37.
Clinical Study

Early Therapeutic Drug Monitoring for Isoniazid and Rifampin among Diabetics with Newly Diagnosed Tuberculosis in Virginia, USA

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² Tuberculosis Control and Prevention, Virginia Department of Health, Richmond, VA, USA

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- Diabetics accounted for 10-15% of annual TB cases in Virginia, but 40% of slow responders
- In 2011, a statewide initiative was started to perform TDM in diabetics at 2 weeks after initiating TB therapy
- 76% (16/21) diabetics had a low INH or RIF level
- Majority of patients' levels corrected after single dose increase in INH/RIF with no major toxicity
- 82% converted sputums in < 2 months
<table>
<thead>
<tr>
<th>Group</th>
<th>Reason for TDM</th>
<th>Drugs to check</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>All diabetics</td>
<td>Any client with known diabetes* as soon as feasible after treatment initiation (ideally at 2 weeks after treatment initiation and not more than 4 weeks after treatment start)</td>
<td>Isoniazid and Rifampin ONLY: 2 hours after DOT</td>
<td>Automatic dose adjustment for low level (See Table 2). No follow-up drug levels checked.</td>
</tr>
</tbody>
</table>
| Slow responders | In any client with slow response suggested by either or both of the following:  
  a. For clients with smear positive pulmonary TB, sputum smear (+) not decreasing [adequate decrease is 4+ to 2+; 3+ to 1+; or 2+/1+ to smear negative]  
  b. no improvement in TB symptoms (e.g. no weight gain, no reduction in cough, persistent fever, or worsening of chest x-ray if performed) | Isoniazid and Rifampin ONLY: 2 hours after DOT                                 | Dose increases in consultation with DDP-TB staff.  
  Follow-up drug levels checked.  
  Goal is to achieve levels in the expected range although this is not always possible, especially with INH. |
| Others       | Other scenarios in discussion with TB consultants (e.g., new clinical deterioration and unclear if related to TB, client receiving selected second-line TB medications, client with HIV infection and CD4<100, client with early relapse) | Case-by-case                                                                  | Case-by-case                                                              |
Table 2. Dose adjustment for diabetics with early routine TDM

<table>
<thead>
<tr>
<th></th>
<th>Normal drug levels</th>
<th>Sub-target INH, normal RIF</th>
<th>Normal INH, Sub-target RIF</th>
<th>Sub-target INH and Sub-target RIF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initiation regimen</strong>*</td>
<td>Continue INH 300 mg M-F; RIF 600 mg M-F</td>
<td>Finish initiation with INH 450 mg M-F; RIF 600 mg M-F</td>
<td>Finish initiation with INH 300 mg M-F; RIF 900 mg M-F</td>
<td>Finish initiation with INH 450 mg M-F; RIF 900 mg M-F</td>
</tr>
<tr>
<td><strong>Continuation regimen</strong></td>
<td>Continue INH and RIF (biweekly acceptable)</td>
<td>INH 900 mg and RIF 600 mg, thrice weekly</td>
<td>INH 900 mg and RIF 900 mg, thrice weekly</td>
<td>INH 900 mg and RIF 900 mg, thrice weekly</td>
</tr>
</tbody>
</table>

*All initiation phase regimens assume concomitant pyrazinamide and ethambutol, and common adult target doses of isoniazid (INH) of 5-10 mg/kg and rifampin (RIF) of 10 mg/kg. M-F= Monday through Friday, 5 x weekly schedule. Sub-target concentrations are any below the expected range.

- Screen all TB patients for diabetes with HbA1c
- Repeat drug levels are not performed after the dose adjustment
- Dose counting to determine duration of treatment is not altered based on TDM result
Study period 2013-2014: N=375

*DM by patient report and/or HgbA1c ≥ 6.5%
N=60

excluded

Sputum culture negative
Extrapulmonary TB
Any first-line drug resistance
Other immunosuppression (eg. HIV)
No early TDM

N=19 DM/TB included that received early TDM

matched 1:1

N=19 non-DM/TB (HgbA1c < 6.5% and/or chart eval)
Based on age (+/- 10 years), smear status (positive or negative), and gender

Time to sputum culture conversion?

*All patients with known or newly diagnosed DM (HgbA1c ≥ 6.5%) are recommended for early therapeutic drug monitoring and educational flipchart (aim to facilitate linkage to DM care)

Adapted from the Australian Respiratory Council's flip chart, "Key Messages for TB & Diabetes" and Hawaii Dept. Health TB Control program.

Heysell et al. 2015 National TB Conference
Key Messages for TB & Diabetes

VDH VIRGINIA DEPARTMENT OF HEALTH
Promoting & Protecting the Health of All Virginians
www.vdh.virginia.gov

UNIVERSITY of VIRGINIA
Week 3

Diabetes can be controlled through a healthy lifestyle

How can diabetes be controlled?
Week 3

Diabetes can be controlled through a healthy lifestyle

How can diabetes be controlled?

- Make healthy food choices.
- Get regular exercise.
- Stop smoking – seek help to quit.
- Avoid or cut down your alcohol/beer/wine.
Early therapeutic drug monitoring for DM/TB:
2hr serum concentrations for isoniazid and rifampin (only) at ~2 weeks after initiation, with single dose increase (only) if below expected range

N=19 DM/TB*
- 10 (53%) men
- 16 (84%) smear positive
- Mean age was 61.5 years ± 13.6 (compared to non-DM/TB controls of 58.7 ± 15.7 [p=0.57])

*Of note, 10 (53%) also had cavitary disease by CXR

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mean C2hr</th>
<th>Below expected range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid (n=19)</td>
<td>2.5 μg/ml ±1.8</td>
<td>12 (63%)</td>
</tr>
<tr>
<td>Rifampin (n=17)</td>
<td>8.4 μg/ml ±6.8</td>
<td>8 (47%)</td>
</tr>
<tr>
<td>Rifabutin (n=1)</td>
<td>0.57 μg/ml</td>
<td>0</td>
</tr>
</tbody>
</table>

Time to sputum culture conversion:
- DM/TB: 36 days ± 21.9
- non DM/TB: 58.8 days ± 34.6 (p=0.02)
Future Directions

• More complete HbA1c screening
• Improved documentation of diabetes therapies (metformin)
• Document new diagnoses of diabetes
• Document linkage to diabetes care
Acknowledgements

• VDH: Jane Moore, Debbie Staley, Denise Dodge

• UVA: Eric Houpt, Scott Heysell
Resources

• http://www.thelancet.com/cms/attachment/2025646995/2045013783/mc2.mp4
• www.idf.org/diabetesatlas
Figure: Incidence of tuberculosis and prevalence of diabetes in adults in different WHO regions