State of the State in TB Control

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North Carolina TB Medical Director
Division of Infectious Diseases, Duke University Medical Center
TB is history they say,
Less tomorrow than today.
2011 was a banner year,
From TB we had little to fear.
But money’s tight, that’s for sure,
And it still takes 6 months for cure.
AG Holley’s being sold,
To build a golf course for the old.
Will our office furniture go to pawn,
To keep our programs soldiering on?

TB News in 2012

• Case counts continue to drop
• Change in NC TB regulations
• More data on IGRAs coming
• New regimen for latent TB
• Hope for new therapies
TB in NC

- Incidence estimated 2.5/100 K in 2011
  - 3.6/100K in 2008
- National incidence 3.4/100 K
- By far the lowest case number and incidence rate ever recorded
Rule Change

- Updating of NC rules related to TB
- Designed to streamline public health practice
- Facilitate newer technologies

Rule Change-Respiratory Isolation

- Traditionally 3 negative AFB smears required to get off isolation
- Sets of sputums collected every 1-2 weeks
- CDC guidelines actually only require 2 consecutive specimen, collection at monthly intervals
**Rule Change-Respiratory Isolation**

- Temporary rule change effective 8/1/2011 reduced number of specimens from 3 to 2
- Permanent rule change effective 8/1/2012
- This applies only to OUTPATIENT isolation—hospital infection control policies/CDC guidelines still apply for inpatients

**Rule Change-TB Screening**

- New blood tests for TB infection have been available in the US for several years
- In NC, we have access to both:
  - Quantiferon Gold in-tube®
  - T-SPOT.TB®
- Both are FDA-approved
Rule Change-TB Screening

- Rule change permits use of blood tests wherever TST would have been used
- Specifically:
  - Contacts
  - TB suspects
  - HIV +
  - DOC employees/inmates
  - SNF employees/residents

Rule Change-TB Screening

- A single blood test replaces two-step testing
- Two-step testing otherwise required on employment for
  - DOC employees
  - SNF employees/residents
  - Adult day care for HIV/AIDS
- No need to 2-step if done before
- 1-step only if TST done in past year
IGRAs in 2012

• Two tests clinically available
  – Quantiferon Gold in-tube®
  – T-SPOT.TB®
• Permit screening for LTBI with single blood draw
• Direct cost significantly more expensive than TST

IGRAs in 2012

• Key questions still unanswered:
  – How well do IGRAs work in predicting progression to TB?
  – What is the significance of discordant test results?
  – How do we deal with test-retest variability?
QFT in German Contacts

- Update of 2009 study examining relative ability of QFT and TST to predict future TB in contacts to active TB
- Examined contacts of smear-positive cases in Hamburg, Germany 2005-2008
- Followed up until 2010

Diel R et al., American Journal of Respiratory and Critical Care Medicine 2011; 183: 88

1417 Close Contacts

1335 with valid TST/QFT

954 available for f/u

903 untreated

79 refused TST (QFT only)

3 indet QFT

381 relocated

51 completed LTBI rx
Caveats

- Relatively small number of active TB cases (only 11 culture-confirmed)
- Large discrepancy between % positive with TST and QFT not seen in all studies
- Don’t know if this applies to reactors, other high-risk populations
TBESC TO 1

- 10-year study that will enroll over 40,000 high-risk persons
- Each person will get TST, QFT, T-SPOT
- Persons positive by any test will get f/u for 2 yrs
- Who knows if we’ll be using the same tests by then…

New Therapies

- Need alternative treatments for patients with drug intolerance
- Need alternative treatments for patients with drug resistance
- Ideally want shorter, better-tolerated regimens for all patients
New Regimen for Latent TB

- Shorter!
- Better tolerated!
- Higher completion!
- Stay tuned for David Holland’s talk…

Active TB Treatment Studies

- NC has a long history of participation in TB research
- Several counties have contributed patients to active treatment protocols
- This commitment to advancing TB care is paying off!
Rifapentine-TBTC Study 29
Sputum smear (+) PTB suspect

Randomization
stratified by region, cavitation

RIF 10 mg/kg
INH+PZA+EMB
5/7 for 8 weeks
without food

RPT 10 mg/kg
INH+PZA+EMB
5/7 for 8 weeks
without food

study visits q2wks:
*safety
*sputum culture

End of intensive phase (= wk 8): assess for primary endpoints

ATS/CDC/IDSA-recommended continuation phase regimen

Study Setting
U.S. Centers for Disease Control and Prevention

TB Trials Consortium 2010-2020
TBTC Study 29

• Primary Objective
  – Compare, by treatment regimen, the proportion of individuals having negative sputum cultures at the end of intensive phase TB treatment (surrogate marker of durable cure)

• Secondary Objectives
  – Compare safety and tolerability
  – Compare time to culture conversion
  – Determine PK parameters

Endpoints

• Co-primary efficacy endpoints
  – Culture status in liquid MGIT media at completion of intensive phase treatment
  – Culture status on solid LJ media at completion of intensive phase treatment

• Secondary efficacy endpoints
  – Time to first negative culture, collected at 2, 4, 6, 8 weeks
  – Time to stable culture conversion

• Tolerability and Safety
  – Discontinuation of intensive phase therapy
  – Adverse events, by severity and type
Enrollment and Disposition of Study 29 Participants

- Screened N=1549
  - Not enrolled N=1018
  - Enrolled, Randomized N=531
    - Rifampin N=255
      - Not Protocol Correct N=74
      - Protocol Correct N=181
    - Rifapentine N=276
      - Not Protocol Correct N=70
      - Protocol Correct N=206

Other reasons for non-enrollment:
- Drug resistant (30)
- Missing DST result (6)
- No baseline or MTB pos (25)
- Protocol violation (16)
- Missing/resident in 8+ wk (9)
- Lost to follow-up (1)
- Other (6)

- Drug resistant (21)
- Missing DST result (7)
- No baseline or MTB pos (15)
- Protocol violation (11)
- Missing/resident in 8+ wk (5)
- Lost to follow-up (2)
- Other (6)

Baseline characteristics (liquid culture protocol correct group)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rifampin N=179</th>
<th>Rifapentine N=202</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (IQR)</td>
<td>34 (26, 47)</td>
<td>32 (26, 46)</td>
</tr>
<tr>
<td>Median BMI (IQR)</td>
<td>20 (18, 22)</td>
<td>20 (18, 23)</td>
</tr>
<tr>
<td>% female</td>
<td>37</td>
<td>30</td>
</tr>
<tr>
<td>% @ African sites</td>
<td>52</td>
<td>55</td>
</tr>
<tr>
<td>% HIV-positive</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>% with cavitation on CXR</td>
<td>69</td>
<td>68</td>
</tr>
<tr>
<td>% with smear grade 3 or 4</td>
<td>60</td>
<td>64</td>
</tr>
<tr>
<td>Median # days prior TB tx (IQR)</td>
<td>2 (0, 4)</td>
<td>2 (0, 4)</td>
</tr>
</tbody>
</table>
## Efficacy: Primary Endpoints

% of subjects having negative sputum cultures at end of intensive phase in the Protocol Correct analysis group

<table>
<thead>
<tr>
<th>Culture Medium</th>
<th>Rifampin</th>
<th>Rifapentine</th>
<th>p</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>liquid</td>
<td>128/179 71.5%</td>
<td>152/202 75.3%</td>
<td>0.48</td>
<td>3.7 (-5.7, 13.2)</td>
</tr>
<tr>
<td>solid</td>
<td>152/171 88.9%</td>
<td>182/198 91.9%</td>
<td>0.42</td>
<td>3.0 (-3.6, 9.6)</td>
</tr>
</tbody>
</table>

### Multivariate Logistic Regression Model for Sputum Culture Negativity at End of Intensive Phase for Protocol Correct Analysis Group, Liquid Media

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifapentine vs Rifampin</td>
<td>1.27</td>
<td>0.79, 2.03</td>
<td>0.33</td>
</tr>
<tr>
<td>Assignment stratum</td>
<td></td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>Non-Africa, non-cavitary</td>
<td>1.00</td>
<td>(ref)</td>
<td></td>
</tr>
<tr>
<td>Non-Africa, cavitary</td>
<td>1.45</td>
<td>0.37, 5.66</td>
<td>0.59</td>
</tr>
<tr>
<td>Africa, non-cavitary</td>
<td>0.40</td>
<td>0.15, 1.06</td>
<td>0.07</td>
</tr>
<tr>
<td>Africa, cavitary</td>
<td>0.77</td>
<td>0.19, 3.12</td>
<td>0.72</td>
</tr>
<tr>
<td>Female</td>
<td>2.78</td>
<td>1.59, 4.84</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>High bacillary load – smear Gr 3, 4</td>
<td>0.34</td>
<td>0.19, 0.58</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fever</td>
<td>0.37</td>
<td>0.17, 0.84</td>
<td>0.01</td>
</tr>
<tr>
<td>Productive cough</td>
<td>0.12</td>
<td>0.01, 0.91</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cavitation size (baseline CXR)</td>
<td></td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td>Extent of disease (baseline CXR)</td>
<td></td>
<td></td>
<td>0.52</td>
</tr>
</tbody>
</table>
Safety and Tolerability

<table>
<thead>
<tr>
<th></th>
<th>Rifampin N=254</th>
<th>Rifapentine N=275</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx discontinued</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Due to toxicity</td>
<td>15.7%</td>
<td>14.5%</td>
<td>0.79</td>
</tr>
<tr>
<td>Due to hepatitis</td>
<td>1.2%</td>
<td>1.5%</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>0.8%</td>
<td>1.5%</td>
<td>0.69</td>
</tr>
<tr>
<td>Adverse Events related</td>
<td>18.1%</td>
<td>22.6%</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>5.9%</td>
<td>8.0%</td>
<td>0.40</td>
</tr>
<tr>
<td>Serious Adverse Events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Related</td>
<td>3.9%</td>
<td>6.9%</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>0.4%</td>
<td>1.1%</td>
<td>0.62</td>
</tr>
<tr>
<td>Hepatitis*</td>
<td>2.8%</td>
<td>3.6%</td>
<td>0.63</td>
</tr>
<tr>
<td>Deaths</td>
<td>0%</td>
<td>1.1%</td>
<td>0.28</td>
</tr>
</tbody>
</table>

*Transaminases and/or bilirubin >5x ULN, or >3x ULN with symptoms

Study 29 Summary

- The activity of the RPT regimen was not superior to that of the RIF regimen, based on the endpoint of culture status at completion of intensive phase treatment
  - There was a trend towards superiority of the RPT regimen in “non-cavitary” pulmonary disease

- A regimen containing RPT 10 mg/kg administered 5 days/week without concomitant food, for approximately 8 weeks, was safe and well-tolerated

- Additional trials are needed to define the optimal dose of RPT and its role in TB treatment.
  - S29X (RPT dose-escalation, phase II) ongoing
Where to Go From Here?

• Exciting developments in the drug landscape in the past several years
• Not-so-exciting developments in the world economy ➔ decreased funding for clinical trials

Drug Resistance

• Drug susceptible TB
  – 6 months of treatment
  – Cost of therapy ~$20
  – Cure rate ~95%
• MDR TB (Resistant to INH + RIF)
  – 18-24 months of treatment
  – Best cost (GLC) of therapy ~$5000
  – Cure rate 60-80%
Drug Resistance

• XDR TB (MDR + resistant to FQ, 2nd line injectable)
  – ? Duration of treatment
  – ? Cure rate (maybe 30%, best case)
  – ? Treatment cost (beaucoup moneys)

New Drugs for MDR

• MDR not common in US, but each case has major impact
• MDR increasingly common in the world
• XDR a major concern worldwide—each case is a “public health disaster”
• Need better treatments
• Fortunately, some are “in the pipeline”
## Investigational Drugs

<table>
<thead>
<tr>
<th>ATP synthase inhibitors</th>
<th>Oxazolidinones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedaquiline (TMC207)</td>
<td>Sutezolid (PNU-100480)</td>
</tr>
</tbody>
</table>

### Nitroimidazoles
- Delamanid (OPC-67683)
- PA-824 (Pa)

### Ethylenediamines
- SQ109 (Q)

## Bedaquiline Phase II for MDR

- 8-week randomized, placebo-controlled study
- Bedaquiline added to “optimized background regimen”
- Primary endpoint: time to culture conversion in liquid media

NEJM 2009; 360: 2397
Bedaquiline Phase II MDR

Discontinuation=failure to convert analysis at 24 weeks:
• Time to 50% culture conversion 78 vs. 129 days
• 81% vs. 65% culture conversion at 24 weeks


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Table 1: Demographic and Baseline Clinical Characteristics and Drug Susceptibility of the Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TBSDF (n=22)</th>
<th>Placebo (n=25)</th>
<th>Total (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex: M+F</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>35</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Range</td>
<td>10-57</td>
<td>10-57</td>
<td>10-57</td>
</tr>
<tr>
<td>Body mass index*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>18.2</td>
<td>18.5</td>
<td>18.3</td>
</tr>
<tr>
<td>Range</td>
<td>14.2-26.9</td>
<td>13.8-20.9</td>
<td>13.8-26.9</td>
</tr>
<tr>
<td>Race: black</td>
<td>18 (82%)</td>
<td>17 (68%)</td>
<td>35 (74%)</td>
</tr>
<tr>
<td>White</td>
<td>3 (14%)</td>
<td>3 (12%)</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (5%)</td>
<td>1 (4%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>IV patients</td>
<td>3 (14%)</td>
<td>3 (12%)</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>IV self-care</td>
<td>3 (14%)</td>
<td>3 (12%)</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>Median</td>
<td>675</td>
<td>580</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>140-1187</td>
<td>290-1127</td>
<td></td>
</tr>
<tr>
<td>Sputum culture: M+F (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caroia et al.</td>
<td>6 (28%)</td>
<td>7 (28%)</td>
<td>13 (28%)</td>
</tr>
<tr>
<td>Caroia et al.</td>
<td>14 (65%)</td>
<td>13 (52%)</td>
<td>27 (58%)</td>
</tr>
<tr>
<td>NaF, %</td>
<td>3 (14%)</td>
<td>4 (16%)</td>
<td>7 (15%)</td>
</tr>
<tr>
<td>Susceptibility results: M+F (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sputum culture: M+F (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caroia et al.</td>
<td>10 (45%)</td>
<td>14 (56%)</td>
<td>24 (51%)</td>
</tr>
<tr>
<td>Caroia et al.</td>
<td>25 (115%)</td>
<td>25 (100%)</td>
<td>50 (105%)</td>
</tr>
<tr>
<td>NaF, %</td>
<td>3 (14%)</td>
<td>2 (8%)</td>
<td>5 (11%)</td>
</tr>
<tr>
<td>Susceptibility results: M+F (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caroia et al.</td>
<td>15 (68%)</td>
<td>34 (100%)</td>
<td>49 (100%)</td>
</tr>
<tr>
<td>Caroia et al.</td>
<td>15 (68%)</td>
<td>34 (100%)</td>
<td>49 (100%)</td>
</tr>
<tr>
<td>NaF, %</td>
<td>14 (63%)</td>
<td>15 (60%)</td>
<td>29 (62%)</td>
</tr>
<tr>
<td>Total score in culture %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caroia et al.</td>
<td>14 (63%)</td>
<td>14 (63%)</td>
<td>28 (60%)</td>
</tr>
<tr>
<td>Caroia et al.</td>
<td>31 (140%)</td>
<td>31 (125%)</td>
<td>62 (130%)</td>
</tr>
</tbody>
</table>

* Body mass index is the weight in kilograms divided by the square of the height in meters.
* Test was determined by the virologist.
* Susceptibility results are for 22 patients. 17 are in the TBSDF group and 5 are the placebo group.
* Susceptibility results are for 22 patients. 17 are in the TBSDF group and 5 are the placebo group.
* Caroia et al. (2009) NEJM; Buxton et al (2012) AAC
**Bedaquiline Current Status**

- Company filed for accelerated approval with FDA 7/3/12
- Approval would be for treatment of MDR TB
- Potential for this drug to be used in treatment-shortening regimens…

**Delaminid Phase II for MDR**

- 8-week randomized, double-blind, placebo-controlled study
- Multinational
- Delaminid added to “optimized background regimen” at 2 different doses (100 bid or 200 bid)
- Primary endpoint: proportion with sputum culture conversion in liquid media at 8 wks

*NEJM 2012; 360: 2397*
Table 1. Demographic and Baseline Clinical Characteristics of the Modified Intention-to-Treat Population for the Primary Efficacy Analysis. 7

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Delampanel, 100 mg Twice Daily (N = 141)</th>
<th>Delampanel, 200 mg Twice Daily (N = 138)</th>
<th>Placebo (N = 135)</th>
<th>Total (N = 403)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>Median 36</td>
<td>35</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>Range 26—63</td>
<td>18–63</td>
<td>18–63</td>
<td>18–63</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>91 (64.5)</td>
<td>95 (69.9)</td>
<td>89 (71.2)</td>
<td>275 (68.8)</td>
</tr>
<tr>
<td>Body-mass index</td>
<td>Median 19.5</td>
<td>19.5</td>
<td>19.5</td>
<td>19.5</td>
</tr>
<tr>
<td></td>
<td>Range 12–31</td>
<td>12–40</td>
<td>12–31</td>
<td>12–40</td>
</tr>
<tr>
<td>Region — no. (%)</td>
<td>Americas 39 (27.7)</td>
<td>38 (27.8)</td>
<td>39 (31.2)</td>
<td>116 (28.9)</td>
</tr>
<tr>
<td></td>
<td>Southeast Asia 43 (30.5)</td>
<td>47 (34.6)</td>
<td>45 (36.0)</td>
<td>135 (33.6)</td>
</tr>
<tr>
<td></td>
<td>Northeast Asia 29 (20.6)</td>
<td>28 (20.6)</td>
<td>25 (18.9)</td>
<td>82 (20.4)</td>
</tr>
<tr>
<td></td>
<td>Eastern Europe or Mediterranean 30 (21.3)</td>
<td>23 (16.9)</td>
<td>16 (12.8)</td>
<td>69 (17.2)</td>
</tr>
<tr>
<td>Living cavities — no. (%)</td>
<td>Absent 44 (31.2)</td>
<td>43 (31.6)</td>
<td>38 (30.4)</td>
<td>125 (31.1)</td>
</tr>
<tr>
<td></td>
<td>Unilateral 60 (42.6)</td>
<td>56 (41.2)</td>
<td>60 (48.0)</td>
<td>176 (43.8)</td>
</tr>
<tr>
<td></td>
<td>Bilateral 37 (26.2)</td>
<td>37 (27.2)</td>
<td>27 (20.6)</td>
<td>101 (25.1)</td>
</tr>
<tr>
<td>Previous treatment — no. (%)</td>
<td>&lt;30 days before randomization 14 (10.3)</td>
<td>14 (10.3)</td>
<td>14 (10.3)</td>
<td>43 (10.6)</td>
</tr>
<tr>
<td></td>
<td>≤30 days before randomization 90 (62.0)</td>
<td>88 (63.7)</td>
<td>79 (62.1)</td>
<td>257 (64.0)</td>
</tr>
<tr>
<td></td>
<td>First-line only 11 (7.8)</td>
<td>12 (9.1)</td>
<td>13 (9.7)</td>
<td>36 (9.0)</td>
</tr>
<tr>
<td></td>
<td>Second-line or without first-line 48 (34.1)</td>
<td>49 (35.6)</td>
<td>45 (33.6)</td>
<td>143 (35.5)</td>
</tr>
<tr>
<td></td>
<td>Third-line or without first-line or second-line 18 (12.8)</td>
<td>22 (16.4)</td>
<td>22 (16.4)</td>
<td>62 (15.4)</td>
</tr>
</tbody>
</table>
Delaminid Phase II

- Only adverse effect more common in delaminid group was QT prolongation
  - 3.8% in placebo group
  - 9.9% in 100 bid group
  - 13.1% in 200 bid group
- All asymptomatic, no clinical events
- Pk substudy demonstrated nonlinear AUC increase with dose increase
**Summary**

- Continued decline in TB cases in 2011
- Concern that the program will be eliminated before the disease is eliminated
- Streamlining the rules to make public health practice more efficient
- New drugs may change the game in the next 5-10 years