Newer anti-TB drugs and regimens

DM Seminar
31-10-14
Why are newer drugs/regimens needed?

Problems with current drugs/regimens

- Drug resistance
- Drug interaction of anti-tubercular drugs with ART
- Long duration of ATT
- Long duration of Rx of latent TB

Solutions (Newer drugs/regimens)

- Novel MoA
- Less drug interaction
- More potent
- Better regimens
Discovery of drugs for tuberculosis

1943 Streptomycin

1948 PAS

1951 Thiacetazone

1952 Isoniazid

1954 Pyrazinamide

1955 Cycloserine

1957 Kanamycin

1960 Ethionamide

1961 Ethambutol

1963 Capreomycin

1963 Rifampicin

1982 Ofloxacin

1992 Gatifloxacin

1996 Moxifloxacin

2000 PA-824

2005 TMC-207

2006 OPC-67683

1940

1950

1960

1970

1980

1990

2000

2010

1952 First regimen: streptomycin, aminosalicylic acid, and isoniazid

18 months of treatment

1960s Aminosalicylic acid replaced with ethambutol: streptomycin, isoniazid, and ethambutol

1963 First randomised trial: streptomycin monotherapy led to streptomycin resistance

1970s Addition of rifampicin: streptomycin, isoniazid, rifampicin and ethambutol

9–12 months of treatment

1980s Streptomycin replaced with pyrazinamide: isoniazid, rifampicin, pyrazinamide, ethambutol

6–8 months, oral treatment

2010s Potential new regimen

2–4 months, oral treatment?

TMC 207 = Bedaquiline; OPC-67683 = Delamanid

Lancet 2010; 375: 2100–09
Global TB Drug Pipeline

Preclinical Development

- Early Stage Development
  - CPZEN-45
  - BTZ043
  - DC-159a
  - SQ609
  - SQ641
  - TBI-166
- GLP Tox.
  - PBTZ169
  - TBA-354
  - Q203

Clinical Development

- Phase I
- Phase II
- Phase III
  - AZD5847
  - Bedaquiline
    (TMC-207) for DS-TB
  - Linezolid
  - Novel Regimens
    - PA-824
    - Rifapentine for DS-TB
    - SQ-109
    - Sutezolid
      (PNU-100480)
  - Delamanid
    (OPC-67683)
  - Gatifloxacin
  - Moxifloxacin
  - Rifapentine for LTBI
  - Bedaquiline
    (TMC-207) for MDR-TB

Chemical classes: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone

1 Details for projects listed can be found at [http://www.newtbdrugs.org/pipeline.php](http://www.newtbdrugs.org/pipeline.php) and ongoing projects without a lead compound series identified can be viewed at [http://www.newtbdrugs.org/pipeline-discovery.php](http://www.newtbdrugs.org/pipeline-discovery.php).

2 Combination regimens: NC-001-(J-M-Pa-Z), phase 2a, NCT01215851; NC-002-(M-Pa-Z), phase 2b, NCT01498419; NC-003-(C-J-Pa-Z), phase 2a, NCT01691534; PanACEA-MAMS-TB-01-(H-R-Z-E-Q-M), phase 2b, NCT01785186.

3 Drug candidate currently in combination regimen in clinical testing

4 Submitted for approval or approved by stringent regulatory authority (i.e., FDA, EMA, WHO Prequalification)

5 New chemical entity

* Projects that have been completed

www.newtbdrugs.org

Updated: August 2014
MoA of newer drugs

TMC 207 = Bedaquiline; OPC-67683 = Delamanid

Lancet 2010; 375: 2100–09
Delamanid
Delamanid

- OPC-67683
- Nitro-dihydro-imidazooxazole derivative
- Inhibits mycolic acid synthesis and cell respiration
- Developed by Otsuka Pharmaceutical, Japan
- Marketed as DELTYBA 50mg tabs
Delamanid for Multidrug-Resistant Pulmonary Tuberculosis

Maria Tarcela Gler, M.D., Vija Skripconoka, M.D., Epifanio Sanchez-Garavito, M.D., Heping Xiao, M.D., Jose L. Cabrera-Rivero, M.D., Dante E. Vargas-Vasquez, M.D., Mengqiu Gao, M.D., Ph.D., Mohamed Awad, M.B., B.Ch., M.D., Seung-Kyu Park, M.D., Ph.D., Tae Sun Shim, M.D., Ph.D., Gee Young Suh, M.D., Manfred Danilovits, M.D., Hideo Ogata, M.D., Anu Kurve, M.D., Joon Chang, M.D., Ph.D., Katsuhiro Suzuki, M.D., Thelma Tupasi, M.D., Won-Jung Koh, M.D., Barbara Seaworth, M.D., Lawrence J. Geiter, Ph.D., and Charles D. Wells, M.D.
Methods

• Multinational Phase 2 trial
• 481 patients (only 4 were HIV-positive) with pulmonary MDR TB
• Patients with Karnofsky scores <50% and HIV-positive patients with CD4 count <350 or on ART were excluded
• Randomized to receive for 2 months
  • Delamanid 100 mg BD (161 patients) or
  • Delamanid 200 mg BD (160 patients) or
  • Placebo (160 patients) for 2 months
• All were given along with a background drug regimen developed according to WHO guidelines (4-5 drugs)
Sputum culture conversion (2 months)

Kaplan–Meier curves representing the time to conversion according to culture medium type showed 10% separation between the delamanid groups and the placebo group by day 36 with MGIT

Adverse events

• Prolonged QT interval
  • Delamanid 200 mg BD (13.1%)
  • Delamanid 100 mg BD (9.9%)
  • Placebo group (3.8%)

• No episodes of prolonged QT interval were associated syncope or arrhythmias
EMA Approval

• On November 22, 2013, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMA) recommended granting of a conditional marketing authorisation for delamanid

• Deltyba is indicated for use as part of an appropriate combination regimen for pulmonary MDR-TB in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability
Bedaquiline
Bedaquiline

- Diarylquinoline
- Inhibits mycobacterial ATP synthase
- Developed by Janssen (pharmaceuticals unit of Johnson and Johnson)
- Marketed as SIRTURO (TMC207) 100mg tabs
Multidrug-Resistant Tuberculosis and Culture Conversion with Bedaquiline

Andreas H. Diacon, M.D., Ph.D., Alexander Pym, M.D., Ph.D., Martin P. Grobusch, M.D., Ph.D., Jorge M. de los Rios, M.D., Eduardo Gotuzzo, M.D., Irina Vasilyeva, M.D., Ph.D., Vaira Leimane, M.D., Koen Andries, D.V.M., Ph.D., Nyasha Bakare, M.D., M.P.H., Tine De Marez, Ph.D., Myriam Haxaire-Theeuwes, D.D.S., Nacer Lounis, Ph.D., Paul Meyvisch, M.Sc., Els De Paepe, M.Sc., Rolf P.G. van Heeswijk, Pharm.D., Ph.D., and Brian Dannemann, M.D., for the TMC207-C208 Study Group*
Methods

• Phase 2b, multi-national trial
• 2 sites from India: Tuberculosis research centre & National Institute for Research in Tuberculosis (Both in Chennai) & AIIMS, New Delhi
• 160 newly diagnosed, smear-positive MDR PTB patients
• HIV-positive patients with CD4 count <300 excluded
• 400 mg of bedaquiline OD for 2 weeks, followed by 200 mg thrice a week for 22 weeks, or placebo
• Both were used in combination with a 5-drug, second-line background regimen (ethionamide, pyrazinamide, ofloxacin, kanamycin, and cycloserine) consistent with WHO recommendations for Rx of MDR TB at that time
Bedaquiline vs Placebo

- Median time to culture conversion 83 vs 125 days (P<0.001)
- Rate of culture conversion
  - at 24 weeks (79% vs. 58%, P=0.008) and
  - at 120 weeks (62% vs. 44%, P=0.04)
**Bedaquiline vs Placebo**

Cure rates* at 120 weeks
58% vs 32% (P=0.003)

(*Based on WHO outcome definitions for MDR TB)
Bedaquiline vs Placebo: Adverse events

• Most frequent adverse events
  • Nausea (41% vs 37%)
  • Arthralgia (37% vs 27%)
  • Vomiting (29% vs 27%)
  • Most were severity grade 1 or 2

• QTc prolongation
  • Mean increase in QTc from baseline (at 24 weeks): 15.4 vs 3.3 msec (P<0.001)
  • Only 1 patient on bedaquiline had QTc >500ms (once)
  • No dysrhythmias
Bedaquiline vs Placebo: Deaths

**Bedaquiline: 10 deaths**
- 5/10 Progression of disease
- 4/10 Unrelated causes
- 1 due to motor-vehicle accident

**Placebo: 2 deaths**
- 2/2 Progression of disease
<table>
<thead>
<tr>
<th>Subject</th>
<th>Treatment arm</th>
<th>Category</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>208–4041</td>
<td>BDQ</td>
<td>Non-responder; converted; discontinued</td>
<td>Alcohol poisoning</td>
</tr>
<tr>
<td>208–4153</td>
<td>BDQ</td>
<td>Non-responder; relapse</td>
<td>TB-related illness</td>
</tr>
<tr>
<td>208–4224</td>
<td>BDQ</td>
<td>Non-responder; relapse</td>
<td>TB-related illness</td>
</tr>
<tr>
<td>208–5069</td>
<td>BDQ</td>
<td>Non-responder; converted; discontinued</td>
<td>Cirrhosis, hepatitis, anaemia</td>
</tr>
<tr>
<td>208–4399</td>
<td>BDQ</td>
<td>Responder; converted</td>
<td>Cerebrovascular accident</td>
</tr>
<tr>
<td>208–5067</td>
<td>BDQ</td>
<td>Responder; converted</td>
<td>Peritonitis and septic shock</td>
</tr>
<tr>
<td>208–4120</td>
<td>Placebo</td>
<td>Non-responder; failure to convert</td>
<td>Haemoptysis (TB)</td>
</tr>
</tbody>
</table>

Deaths during long-term survival follow-up of prematurely withdrawn subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>Treatment arm</th>
<th>Category</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>208–4127</td>
<td>BDQ</td>
<td>Non-responder; failure to convert</td>
<td>TB-related illness</td>
</tr>
<tr>
<td>208–4145</td>
<td>BDQ</td>
<td>Non-responder; relapse</td>
<td>TB-related illness</td>
</tr>
<tr>
<td>208–4378</td>
<td>BDQ</td>
<td>Non-responder; relapse</td>
<td>Motor vehicle accident</td>
</tr>
<tr>
<td>208–4464</td>
<td>BDQ</td>
<td>Non-responder; failure to convert</td>
<td>TB-related illness</td>
</tr>
<tr>
<td>208–4155</td>
<td>Placebo</td>
<td>Non-responder; failure to convert</td>
<td>TB-related illness</td>
</tr>
</tbody>
</table>
Bedaquiline: FDA approval

- On Dec. 28, 2012 the U.S. FDA approved SIRTURO (bedaquiline) as part of combination therapy to treat adults with MDR PTB when other alternatives are not available
- SIRTURO was approved under the FDA’s accelerated approval program (based on surrogate endpoints predicting clinical benefit e.g., conversion of sputum culture)
- SIRTURO carries a Boxed Warning regarding
  - Potential for QT prolongation
  - Deaths in patients treated with Sirturo
Bedaquiline: First’s

• It was the first new anti-TB drug to be FDA approved after 1998 (Rifapentine was approved in 1998)

• It was the first anti-TB drug with a novel MoA to be FDA approved after 40 years (Rifampicin was approved in 1974)

• It was the first anti-TB drug to be introduced specifically for the Rx of MDR-TB in combination with other drugs
Linezolid
LRS (Delhi) experience

- 29 MDR-TB Rx failure patients (16 with XDR-TB and the remaining 13 with Pre-XDR TB [MDR-TB with resistance to any quinolone but sensitive to injectables])
- Daily unsupervised therapy with linezolid (600mg od/bd), one injectable agent, one fluoroquinolone and two or more other drugs (median of six anti-mycobacterial agents)
- Besides linezolid, capreomycin, moxifloxacin, levofloxacin and amoxycillin-clavulanic acid were used in 41.4%, 58.6%, 41.4%, and 79.3% of patients

Eur Respir J 2012; 39: 956–962
Results

- Interim favourable outcome (Cured + Completed >12 Mo Rx and are culture negative) = 21 (72.4%)
- 72.2% in the od group and 72.7% in the bd group achieved interim favourable outcome (P = 1)

<table>
<thead>
<tr>
<th>TABLE 6: Treatment outcomes in 29 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>---------------</td>
</tr>
<tr>
<td>Cured</td>
</tr>
<tr>
<td>Still on treatment†</td>
</tr>
<tr>
<td>Failed</td>
</tr>
<tr>
<td>Default</td>
</tr>
<tr>
<td>Died</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

Data are presented as n (%), unless otherwise stated. XDR: extremely drug resistant; TB: tuberculosis; pre-XDR-TB: multidrug resistant-TB plus quinolone resistance without resistance against injectables. #: Yates' correction applied; †: all patients completed >12 months of treatment and, to date, are persistently culture negative; †+: Fisher's exact test applied.
Results

- Linezolid had to be stopped in 3 (10.3%) patients due to adverse reactions
- Severe anaemia, peripheral neuritis and optic neuritis; each in one patient
- All 3 were taking linezolid 600mg bd
Linezolid for Treatment of Chronic Extensively Drug-Resistant Tuberculosis

Seoul, South Korea

- 41 patients with sputum-culture–positive XDR TB (who had not had a response to any available chemotherapeutic option during the previous 6 months)
- Randomly assigned to linezolid (600mg/d) that started immediately or after 2 months, without a change in their background regimen
- After confirmed sputum-smear conversion or 4 months (whichever came first), patients underwent a second randomization to continued linezolid at a dose of 600mg/d or 300mg/d for at least an additional 18 months

Results

• 3 patients were withdrawn before initiating linezolid
• By 4 months, 15/19 patients (79%) in the immediate-start group and 7/20 (35%) in the delayed-start group had culture conversion (P=0.001)
• 34/38 (87%) had a negative sputum culture within 6 months of addition of linezolid
• 13/38 (34%) patients completed therapy without relapse
• 4 cases of acquired resistance to linezolid were observed

Clinically significant adverse events possibly or probably related to linezolid

<table>
<thead>
<tr>
<th>Condition</th>
<th>Total</th>
<th>0-4 Mo</th>
<th>4-8 Mo</th>
<th>8-12 Mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelosuppression</td>
<td>6</td>
<td>5</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>20</td>
<td>5</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Optic neuropathy</td>
<td>6</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Hepatic enzyme elevation</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

- Of the 38 patients with exposure to linezolid, 31 (82%) had clinically significant adverse events that were possibly or probably related to linezolid
- 3 patients who discontinued therapy owing to adverse events (2 optic neuropathy, 1 anaemia)
- Patients who received 300 mg/d after the second randomization had fewer adverse events than those who continued taking 600 mg/d
Shorter ATT regimes
Shorter regimes: Potential candidates

• Rifapentine
  • Once weekly dosing: Half-life of rifapentine (active metabolite) vs rifampicin is 13-24 h vs 2-3 h

• Moxi/Gatifloxacin
  • Faster culture conversion rates compared to conventional regimes in animal studies and human pilot studies
  • Early bactericidal activity of moxifloxacin was comparable to that of isoniazid (Am J Respir Crit Care Med. 2003 Dec 1;168(11):1342-5; Antimicrob Agents Chemother. 2004 Mar;48(3):780-2)
NIRT, Chennai trial

Randomized Clinical Trial of Thrice-Weekly 4-Month Moxifloxacin or Gatifloxacin Containing Regimens in the Treatment of New Sputum Positive Pulmonary Tuberculosis Patients

Mohideen S. Jawahar¹*, Vaithilingam V. Banurekha¹, Chinnampedu N. Paramasivan¹, Fathima Rahman¹, Rajeswari Ramachandran¹, Perumal Venkatesan¹, Rani Balasubramanian¹, Nagamiah Selvakumar¹, Chinnaiyan Ponnuraja¹, Allaudeen S. Iliayas², Navaneethapandian P. Gangadevi², Balambal Raman¹, Dhanaraj Baskaran¹, Santhanakrishnan R. Kumar², Marimuthu M. Kumar², Victor Mohan², Sudha Ganapathy¹, Vanaja Kumar¹, Geetha Shanmugam¹, Niruparani Charles¹, Murugesan R. Sakthivel², Kannivelu Jagannath³, Chockalingam Chandrasekar⁴, Ramavaram T. Parthasarathy⁵, Paranji R. Narayanan¹

¹National Institute for Research in Tuberculosis (formerly Tuberculosis Research Centre), Chennai, India, ²National Institute for Research in Tuberculosis (formerly Tuberculosis Research Centre), Madurai, India, ³Institute of Thoracic Medicine, Chennai, India, ⁴Government Rajaji Hospital, Madurai, India, ⁵Government Tiruvalam Hospital, Chennai, India

Patients

• 416 patients
• 2 centres: Chennai, Madurai
• Newly diagnosed, previously untreated, sputum smear +ve PTB
• HIV+ve, diabetics excluded
Regimens

• 3 groups
  • 2HRZE + 4HR (Control gp)
  • 2HRZG + 2HRG (Gatiflox gp)
  • 2HRZM + 2HRM (Moxiflox gp)

• All were thrice-weekly
• DOT
## Efficacy & safety outcomes

<table>
<thead>
<tr>
<th></th>
<th>Control gp</th>
<th>Gatiflox gp</th>
<th>Moxiflox gp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture negativity at 2 months</td>
<td>78%</td>
<td>83%</td>
<td>88%</td>
</tr>
<tr>
<td>Culture negativity at end of Rx</td>
<td>95%</td>
<td>95%</td>
<td>99%</td>
</tr>
<tr>
<td>Unfavorable response at the end of Rx*</td>
<td>2%</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Recurrence in the next 24 months†</strong></td>
<td>6%</td>
<td>15%</td>
<td>11%</td>
</tr>
<tr>
<td>Acquired resistance‡</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>GI symptoms#</td>
<td>9%</td>
<td>23%</td>
<td>22%</td>
</tr>
<tr>
<td>Seizures (No.)</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>QTc prolongation (No.)</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Dysglycemia</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Unfavourable response included Rx failure, Rx change & death
†Majority of recurrences occurred within 6 months of stopping Rx
‡Both were INH resistance
# GI symptoms included nausea, vomiting, abdominal discomfort

**Study was prematurely terminated by DSMB due to high TB recurrence rates in both the study arms compared to the control arm**
Four-Month Moxifloxacin-Based Regimens for Drug-Sensitive Tuberculosis

Patients

• Newly diagnosed, previously untreated, smear positive PTB patients with culture confirmed susceptibility to rifampin and fluoroquinolones
• HIV+ve with CD4 <250 or on ART excluded
• 1931 underwent randomization: 909 in South Africa, 376 in India, 212 in Tanzania, 136 in Kenya, 119 in Thailand, 69 in Malaysia, 66 in Zambia, 22 in China, and 22 in Mexico
Regimes

- Control group: HRZE (8 weeks) + HR (18 weeks)
- INH group: HRZM (8 weeks) + HRM (9 weeks)
- EMB group: MRZE (8 weeks) + MR (9 weeks)

- All drugs were given daily (DOT)
- Moxifloxacin 400mg was used
- Double-blind trial
Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Control gp</th>
<th>INH gp</th>
<th>EMB gp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite unfavourable outcome*: Per-protocol analysis</td>
<td>8%</td>
<td>15%</td>
<td>20%</td>
</tr>
<tr>
<td>Composite unfavourable outcome*: Modified ITT analysis</td>
<td>16%</td>
<td>23%</td>
<td>24%</td>
</tr>
<tr>
<td>Relapse**: Per-protocol analysis</td>
<td>2%</td>
<td>9%</td>
<td>12%</td>
</tr>
<tr>
<td>Relapse**: Modified ITT analysis</td>
<td>2%</td>
<td>8%</td>
<td>12%</td>
</tr>
<tr>
<td>Median time to culture negative status in weeks (95% CI): LJ solid media†</td>
<td>6.0 (6.0, 6.1)</td>
<td>6.0 (5.1, 6.0)</td>
<td>6.0 (5.7, 6.0)</td>
</tr>
<tr>
<td>Median time to culture negative status in weeks (95% CI): MGIT liquid media†</td>
<td>11.9 (8.1, 12.0)</td>
<td>8.0 (8.0, 9.9)</td>
<td>8.0 (8.0, 8.1)</td>
</tr>
</tbody>
</table>

* Composite unfavourable outcome (bacteriologically or clinically defined failure or relapse within 18 months after randomization)

**The most common reason for an unfavorable outcome was relapse after conversion to culture-negative status after the end of active treatment
In the per-protocol analyses, the time to an unfavorable outcome was shorter in the isoniazid group than in the control group (hazard ratio, 1.87; 97.5% CI, 1.07 to 2.67) and was further reduced in the ethambutol group (hazard ratio, 2.56; 97.5% CI, 1.51 to 3.60).
Time to culture-negativity

In Kaplan–Meier analyses, patients in the isoniazid group and the ethambutol group had conversion to culture-negative status sooner than those in the control group in sputum analyses with the use of Lowenstein–Jensen solid medium and MGIT medium.

Median time to culture negative status in weeks (95% CI)

- **LJ solid media**
  - Control group: 6.0 (6.0, 6.1)
  - INH group: 6.0 (5.1, 6.0)
  - Ethambutol group: 6.0 (5.7, 6.0)

- **MGIT liquid media**
  - Control group: 11.9 (8.1, 12.0)
  - INH group: 8.0 (8.0, 9.9)
  - Ethambutol group: 8.0 (8.0, 8.1)
Adverse events

• No significant difference in the incidence of grade 3 or 4 adverse events.

• No significant between-group differences in tendinopathy, seizure, clinically significant cardiac toxicity, hepatic dysfunction, hypoglycemia or hyperglycemia, and peripheral neuropathy.
Resistance

• 4 cases of resistance:
  • Control group: 3 (two for rifampin and one for isoniazid)
  • INH group: None
  • Ethambutol group: 1 (for moxifloxacin)
High-Dose Rifapentine with Moxifloxacin for Pulmonary Tuberculosis


for the RIFAFQUIN Trial Team*

Patients

• Newly diagnosed, previously untreated, smear positive PTB patients
• HIV+ patients with CD4 <200 or on ART were initially excluded. However, later, those with CD4 >150 or starting ART at screening were included
• 827 patients from South Africa, Zimbabwe, Botswana, and Zambia were enrolled
• 28% of patients were coinfected with HIV
RIFAQUIN: Regimens

- Moxifloxacin 400mg was used
- 2HRZE (daily) + 4HR (daily) (Control regimen)
- 2MRZE (daily) + 2MRp (twice weekly) (Rp 900mg)
- 2MRZE (daily) + 4MRp (once weekly) (Rp 1200mg)
- Intensive phase was directly observed at the health facility (DOT)
- Continuation phase
  - Control regimen was supervised by a relative or another person
  - Study regimens were directly observed at the health facility
- Open label
Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Control gp</th>
<th>4M gp</th>
<th>6M gp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite unfavourable outcome*: Per-protocol analysis</td>
<td>4.9%</td>
<td>18.2%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Composite unfavourable outcome*: Modified ITT analysis</td>
<td>14.4%</td>
<td>26.9%</td>
<td>13.7%</td>
</tr>
<tr>
<td>Relapse (Culture-confirmed)</td>
<td>2.4%</td>
<td>11.5%</td>
<td>2.2%</td>
</tr>
</tbody>
</table>

*Composite unfavourable outcome included **failure, relapse or death**

Moxifloxacin substitution for INH in the intensive phase reduced the proportion of patients with positive cultures at 2 months from 14.6% to 9.6%
With the 4-month regimen, 24/30 unfavorable outcomes (80%) occurred <6 months after the end of Rx
Non-inferiority analysis

The dashed line represents the 6 percentage-point margin of noninferiority (as compared to control)

Compared to the control regimen:
- 4-month MOX-RPT regimen was inferior
- 6-month MOX-RPT regimen was non-inferior
Adverse events & deaths

<table>
<thead>
<tr>
<th>Event</th>
<th>Control gp</th>
<th>4M gp</th>
<th>6M gp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 or 4 adverse events possibly or probably related to study drug (No.)</td>
<td>6</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Death due to any cause (No.)</td>
<td>6</td>
<td><strong>12</strong></td>
<td>7</td>
</tr>
<tr>
<td>Death possibly related to TB (No.)</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
## Adherence

<table>
<thead>
<tr>
<th></th>
<th>Control gp</th>
<th>4M gp</th>
<th>6M gp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportions of patients with adherence rates ≥89%</td>
<td>75.3%</td>
<td><strong>81.4%</strong></td>
<td><strong>80.9%</strong></td>
</tr>
<tr>
<td>Proportions of patients with adherence rates ≥95%</td>
<td>48.7%</td>
<td><strong>76.7%</strong></td>
<td><strong>76.9%</strong></td>
</tr>
</tbody>
</table>

*Adherence during first 2 months was similar between all groups*
Acquired resistance

- Only 1 case in control group to rifampicin (HIV+ve, Poor adherence)
A Four-Month Gatifloxacin-Containing Regimen for Treating Tuberculosis

Corinne S. Merle, M.D., Katherine Fielding, Ph.D., Omou Bah Sow, M.D., Martin Gninafon, M.D., Mame B. Lo, M.D., Thuli Mthiyane, M.Sc., Joseph Odhiambo, M.D., Evans Amukoye, M.D., Boubacar Bah, M.D., Ferdinand Kassa, M.D., Alimatou N’Diaye, M.D., Roxana Rustomjee, M.D., Bouke C. de Jong, M.D., Ph.D., John Horton, M.D., Christian Perronne, M.D., Charalambos Sismanidis, Ph.D., Olivier Lapujade, B.Sc., Piero L. Olliaro, M.D., Ph.D., and Christian Lienhardt, M.D., Ph.D., for the OFLOTUB/Gatifloxacin for Tuberculosis Project*

Patients

• Newly diagnosed sputum-positive PTB
• 1836 patients from five sub-Saharan African countries: Benin, Guinea, Kenya, Senegal, and South Africa were enrolled
• Patients with prior history of ATT within last 3 years, diabetics, HIV stage 3 & 4 patients were excluded
Regimes

- 2HRZE + 4HR
- 2HRZG + 2HRG
- Gatifloxacin 400mg/d was used irrespective of body weight
- All drugs were administered 6 days a week (DOT)
  - Intensive phase: daily DOT by health centre staff
  - Continuation phase: Boxes provided to supervisor every 2 weeks who would ensure their daily intake
- Open label trial
Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Control gp (%)</th>
<th>Gatiflox gp (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite unfavourable outcome*: Per-protocol analysis†</td>
<td>11.3%</td>
<td>17.7%</td>
</tr>
<tr>
<td>Composite unfavourable outcome*: Modified ITT analysis††</td>
<td>17.2%</td>
<td>21%</td>
</tr>
<tr>
<td>Rx failure</td>
<td>2.4%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Recurrence (relapse or reinfection)</td>
<td>7.1%</td>
<td>14.6%</td>
</tr>
<tr>
<td>Dropouts</td>
<td>5%</td>
<td>2.7%</td>
</tr>
</tbody>
</table>

*Composite unfavourable outcome (at 24 months) included failure, recurrence (relapse or reinfection), death or study dropout during Rx

† Adjusted Difference, Experimental Group–Control Group: 5.5 (1.6 to 9.4)

†† Adjusted Difference, Experimental Group–Control Group: 3.5 (−0.7 to 7.7)

No significant difference in smear positivity or culture positivity at 2 months
Subgroup analysis: Unfavourable outcomes in modified ITT population

Rate of cavitary disease was 20% in Benin, Guinea, and Kenya and 90% in Senegal and South Africa.
Adverse events

• No difference in serious adverse events, QTc interval, hyperglycemia
<table>
<thead>
<tr>
<th>Regimen</th>
<th>REMoxTB, Gillespie NEJM 2014</th>
<th>RIFAQUIN, Jindani NEJM 2014</th>
<th>OFLOTUB, Merle NEJM 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group:</td>
<td>HRZE (8 weeks) + HR (18 weeks)</td>
<td>2HRZE (daily) + 4HR (daily)</td>
<td>2HRZE + 4HR</td>
</tr>
<tr>
<td>INH group:</td>
<td>HRZM (8 weeks) + HRM (9 weeks)</td>
<td>2MRZE (daily) + 2MRp (twice weekly)</td>
<td>2HRZG + 2HRG</td>
</tr>
<tr>
<td>EMB group:</td>
<td>MRZE (8 weeks) + MR (9 weeks)</td>
<td>2MRZE (daily) + 4MRp (once weekly)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Efficacy outcomes</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite unfavourable outcome</td>
<td>8% vs 15% vs 20%</td>
<td>4.9% vs 18.2% vs 3.2%</td>
<td>11.3% vs 17.7%</td>
</tr>
<tr>
<td>Relapse</td>
<td>2% vs 9% vs 12%</td>
<td>2.4% vs 11.5% vs 2.2%</td>
<td>7.1% vs 14.6%</td>
</tr>
<tr>
<td>Time to culture negativity (weeks)</td>
<td>11.9 vs 8 vs 8‡</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Culture positivity at 2 months</td>
<td>N/A</td>
<td>14.6% (Control) vs 9.6% (Moxiflox)</td>
<td>No difference</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Safety outcomes</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events</td>
<td>No difference</td>
<td>No difference</td>
<td>No difference</td>
</tr>
<tr>
<td>Death (Any cause)</td>
<td>2% vs 2% vs 1%</td>
<td>2.2% vs 4.4% vs 2.5%</td>
<td>1.4% vs 1.2%</td>
</tr>
<tr>
<td>Adherence</td>
<td>N/A</td>
<td>Similar in initial 2 months. Thereafter, better in both MOX-RPT groups.</td>
<td>N/A</td>
</tr>
<tr>
<td>Resistance</td>
<td>3 vs 0 vs 1</td>
<td>1 vs 0</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Concerns raised

• Extrapolation of data from mouse models:
  • Mice studies predicted that the inclusion of moxifloxacin would result in shortening of Rx duration by 1-2 months
  • Dormant bacilli less common in mice compared to humans
• Poor predictability of culture conversion when used as a surrogate for long-term outcomes
Rifapentine
Substitution of Rifapentine for Rifampin During Intensive Phase Treatment of Pulmonary Tuberculosis: Study 29 of the Tuberculosis Trials Consortium

Susan E. Dorman,1 Stefan Goldberg,2 Jason E. Stout,3 Grace Muzanyi,4 John L. Johnson,4,5 Marc Weiner,6 Lorna Bozeman,2 Charles M. Heilig,2 Pei-Jean Feng,2 Ruth Moro,2 Masahiro Narita,7 Payam Nahid,8 Susan Ray,9 Edward Bates,10 Betial Haile,11 Eric L. Nuemberger,1 Andrew Vernon,2 Neil W. Schluger,12 and the Tuberculosis Trials Consortium

1Johns Hopkins University School of Medicine, Baltimore, Maryland; 2Centers for Disease Control and Prevention, Atlanta, Georgia; 3Duke University School of Medicine, Durham, North Carolina; 4Uganda-Case Western Reserve University Research Collaboration, Kampala, Uganda; 5Case Western Reserve University School of Medicine, Cleveland, Ohio; 6University of Texas Health Science Center at San Antonio and the South Texas VAMC, San Antonio; 7University of Washington, Seattle; 8University of California, San Francisco; 9Emory University School of Medicine, Atlanta, Georgia; 10University of North Texas, Denton; 11Westat, Inc., Rockville, Maryland; and 12Columbia University Medical Center, New York.
Method

• Multicentre phase 2 trial
• 531 adults with sputum smear-positive PTB
• Rifapentine 10 mg/kg/dose vs Rifampin 10 mg/kg/dose
• Both administered 5 days per week for 8 weeks (intensive phase) along with HZE
• Open label
• DOT
• Continuation phase INH + RMP in both groups
Results

No difference in adverse events or drug discontinuation
# Rifapentine for LTBI: RCTs

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schechter AJRCCM 2006</td>
<td>399 household contacts of patients with pulmonary TB</td>
<td>RPT 900 mg + INH 900 mg once wkly for 12 wk Vs</td>
<td><strong>TB incidence:</strong> 4 cases of TB occurred. 3 in RMP+PZA arm and 1 in RPT+INH arm (1.46 vs. 0.52%; difference, 0.94%; 95% CI, −1.6 to 3.7%) <strong>Hepatotoxicity:</strong> 20/193 (10%) receiving RMP+PZA experienced grade 3 or 4 hepatotoxicity, compared with 2/206 (1%) on RPT+INH (p &lt; 0.001) hence study prematurely halted</td>
</tr>
<tr>
<td>Martinson NEJM 2011</td>
<td>1148 adults with HIV infection (Not on ART) and a positive TST [Median CD4 484]</td>
<td>RPT (900 mg) + INH (900 mg) wkly for 12 wks, RMP (600 mg) + INH (900 mg) twice weekly for 12 wks, INH (300 mg) daily for up to 6 yrs (continuous INH), or INH (300 mg) daily for 6 months (control group)</td>
<td><strong>Incidence rates of active TB or death</strong> were (per 100 person-years): 3.1 in RPT+INH gp, 2.9 in RMP+INH gp, and 2.7 in the continuous-INH gp, as compared with 3.6 in control group (P&gt;0.05 for all comparisons) <strong>SAEs more common in continuous-INH gp</strong> than in other gps (18.4 vs 8.7 to 15.4 per 100 person-years)</td>
</tr>
<tr>
<td>Sterling NEJM 2011 (PREVENT TB)</td>
<td>7731 persons (≥2 years, close contact with TB, TST positive)</td>
<td>3 months of directly observed once-weekly RPT (900 mg) + INH (900 mg) (combination-therapy gp) Vs 9 months of self-administered daily INH (300 mg) (isoniazid-only group)</td>
<td><strong>TB development &amp; cumulative TB rate:</strong> Combination 7/3986 (0.19%) vs INH 15/3745 (0.43%). <strong>Rx completion rates:</strong> Combination 82.1% vs INH 69.0% (P&lt;0.001) <strong>Permanent drug discontinuation owing to an adverse event:</strong> Combination 4.9% vs INH 3.7% (P=0.009) <strong>Possible hypersensitivity:</strong> Combination 3.8% vs INH 0.5% (P&lt;0.001) <strong>Hepatotoxicity:</strong> Combination 0.4% and INH 2.7% (P&lt;0.001) <strong>Resistance:</strong> 2 INH resistance in INH gp vs 1 RMP resistance in combination gp</td>
</tr>
</tbody>
</table>
## LTBI Rx: CDC 2011

<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><strong>Isoniazid and Rifapentine</strong></td>
<td>3 months</td>
<td><strong>Once weekly</strong>*</td>
<td><strong>12</strong></td>
</tr>
<tr>
<td>Rifampin</td>
<td>4 months</td>
<td>Daily</td>
<td>120</td>
</tr>
</tbody>
</table>

*DOT
Conclusions
Drug-resistant TB

• MDR TB
  • Delamanid and bedaquiline are useful when added to the standard MDR ATT regimen
    • Both decrease the time required for culture conversion and improve culture conversion rates
    • Bedaquiline improves cure rates

• XDR TB
  • Linezolid may improve cure rates
Shorter ATT regimes

• Drug-sensitive TB
  • Quinolone based 4-month ATT regimens are inferior to conventional 6-month ATT regimens (higher relapse rates, despite equal or more rapid culture conversion)
  • Substitution of rifampicin with rifapentine during IP unlikely to help

• LTBI
  • Once weekly INH + Rifapentine (3 months) is the shortest regimen available for LTBI