HIV co-infection excludes many drug-resistant tuberculosis patients from clinical trials with novel antituberculosis drugs

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Ernst Ludwig Kirchner. Blick auf Davos. 1924. Bündner Kunstmuseum Chur, Switzerland
The Magic Mountain

- Sunlight
- Nutrition
- Supine
1800s: Improved socioeconomic conditions
1882: M tbc discovered
1895: X-rays discovered
1920: BCG
1944 - 1961: TB DRUGS

Vaccines, Diagnostics, Treatments
Globally:
• 8.7 million cases
• 1.1 million HIV associated
• 0.63 million MDR
• 1.42 million deaths

~26,000 cases of TB annually (~24 000 PTB); 10% children (<8 years)
• TB incidence: 993/100 000
• HIV prevalence in TB cases: 51% (28-67%)
• Decentralized service with approx. 100 primary health (TB clinics) facilities offering TB services

WHO Global Tuberculosis Report 2012
Drug development

Cost for developing one new drug: USD 800 to 1,000 million

IND: Investigational new drug (registration for trials)
NDA: New drug application (registration for market)
Figure 2: History of drug discovery and development of treatment regimens for tuberculosis

Compounds that are in the early-stage of development, but for which there are no human proof-of-concept data, are not shown. Arrow with dashed line represents future regimen. Red dots represent when the drugs were first reported.
Study design:

- Retrospective study
- File review
- Brooklyn Chest Hospital
- 421 patient records reviewed in 2010
- Reference protocol TMC207-C209
- Simulated screening process
# Trial screening simulation

<table>
<thead>
<tr>
<th>Reason for exclusion</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV – low CD4 count</td>
<td>79</td>
<td>18.5</td>
</tr>
<tr>
<td>Rifampicin-mono-resistant</td>
<td>72</td>
<td>17.1</td>
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<tr>
<td>Death</td>
<td>29</td>
<td>6.9</td>
</tr>
<tr>
<td>HIV – ARV therapy</td>
<td>28</td>
<td>6.7</td>
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<tr>
<td>Location</td>
<td>24</td>
<td>5.7</td>
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<tr>
<td>XDR-TB</td>
<td>8</td>
<td>1.9</td>
</tr>
<tr>
<td>Previous drug trial</td>
<td>7</td>
<td>1.7</td>
</tr>
<tr>
<td>Substance abuse</td>
<td>6</td>
<td>1.4</td>
</tr>
<tr>
<td>Too ill</td>
<td>4</td>
<td>1</td>
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<tr>
<td>Disallowed medication</td>
<td>3</td>
<td>0.7</td>
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</tbody>
</table>
Main reasons for exclusion

FIG. 1 MAJOR FACTORS CONTRIBUTING TO EXCLUSION AND NUMBER QUALIFIED FOR SCREENING

- Dead
- Rifampicin monoresistance
- HIV-related (low CD4 count, ARVs)
- Qualified for screening
- Excluded, other reasons
# Combinations of criteria

<table>
<thead>
<tr>
<th>Number of criteria</th>
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<tbody>
<tr>
<td><strong>One criterion</strong></td>
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<tr>
<td>Death</td>
<td>29</td>
<td>6.9</td>
</tr>
<tr>
<td>HIV – low CD4</td>
<td>25</td>
<td>5.9</td>
</tr>
<tr>
<td>RIF-mono</td>
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<td>5.9</td>
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<tr>
<td><strong>Two criteria</strong></td>
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<td></td>
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<tr>
<td>HIV – low CD4/HIV - ARV</td>
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<td>5.3</td>
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<tr>
<td>HIV – low CD4/RIF mono</td>
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<td>1.9</td>
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<tr>
<td>Defaulter</td>
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<td>1.2</td>
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<tr>
<td><strong>Three criteria</strong></td>
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<tr>
<td>HIV – low CD4/HIV – ARV/RIF mono</td>
<td>8</td>
<td>1.9</td>
</tr>
<tr>
<td>HIV – low CD4/HIV – ARV/too ill</td>
<td>8</td>
<td>1.9</td>
</tr>
<tr>
<td>HIV – low CD4/HIV – ARV/Moxifloxacin</td>
<td>4</td>
<td>1.0</td>
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</tbody>
</table>
Conclusion

• Death, mono-resistance and HIV excluded 50% of potential participants
• 13% qualified for formal screening
• 3% were eventually screened
28 June 2005
First TMC207 dose to a TB patient
Bedaquiline for 8 weeks

8.7% culture negative

47.5% culture negative

Bedaquiline for 24 weeks

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Bedaquiline</th>
<th>Placebo</th>
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<tr>
<td>58</td>
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<tr>
<td>3</td>
<td>5</td>
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</table>

Time to Culture Conversion

- Placebo plus background regimen
- Bedaquiline plus background regimen

Rifampin revolutionized the treatment of DS-TB by shortening it from 18 to 9m.

1970: rifampin
- First line regimen in DS-TB
- 2 month culture conversion
  - Streptomycin + INH: 49%
  - Streptomycin + INH + rifampin: 69%
- $\Delta = 20\%$

2012: bedaquiline
- Second line regimen in MDR-TB
- 6 month culture conversion
  - 5-drug background + placebo: 58%
  - 5-drug background + BDQ: 79%
- $\Delta = 21\%$

Bedaquiline could play a significant role in MDR-TB treatment.

Has a 20% Improvement in Culture Conversion Rate Ever Been Seen Before?
3 Dec 2012 (7y, 5m, 5d later)
Experts at FDA hearing vote for registration
Nov 2014
Experts at Bedaquiline (Sirturo®) launch in South Korea