Effectiveness of the WHO regimen for treatment of multidrug resistant tuberculosis (MDR-TB)

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BACKGROUND

• In 2011, 310,000 estimated MDRTB cases
• 60,000 MDRTB cases notified (19%)
  – +++ European countries and South Africa
  – 9% extensively drug resistant tuberculosis (XDRTB)
• < 4% of new and < 6% of previously treated smear-positive cases were tested for MDR-TB in 2011
MDRTB treatment

• Long, toxic, poor outcomes
• 44-58% treatment success
• Based on expert advice and program experience

• 6800 MDRTB patients started on treatment between 2001 and 2012 in MSF supported projects worldwide
• Decision made to optimise the use of the information gathered in MSF projects to guide MDRTB protocols

Global tuberculosis report 2012

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OBJECTIVES

• To describe the MDRTB patients’ characteristics at treatment initiation

• To describe the MDRTB treatment outcomes by drug resistance patterns, treatment history and drugs prescription

• To identify the predictors of unfavourable MDRTB treatment outcome
METHODS (1)

• MDRTB treatment
  – Individualised drug regimens (WHO guidelines)
  – Minimum of 4 drugs to which strain is susceptible
  – Second line drugs (SLD):
    • Fluoroquinolone (FQ): ofloxacin/levofloxacin/moxifloxacin
    • Injectable: kanamycin or capreomycin
      + other drugs (PAS, cycloserine, prothionamide, clofazamine)
  – Minimum of 6 months with injectable
  – Minimum length of treatment 21 months
METHODS (2)

- Outcomes (WHO guidelines)
  - Favourable/success: bacteriologically cured + completed treatment
  - Unfavourable: failure + deaths + defaulters

- Multicentric retrospective cohort of programmatic data
  - Erevan (Armenia), Abkhazia (Georgia), Mathare (Kenya), Shiselweni (Swaziland) and Karakalpakstan (Uzbekistan)

- Study population
  - MDRTB bacteriologically confirmed patients
  - Enrolled until 31.12.2010 for patients’ characteristics at treatment initiation
  - Enrolled until 31.12.2009 for outcomes and predictors
    - Exclusion of patient transferred-out or still on treatment
METHODS (3)

• Data analysis
  – “Intention to treat” analysis including defaulters
  – “On-treatment” analysis excluding defaulters
  – Analysis of predictors
    • Univariate / multivariate analysis: random intercept logistic mixed model
    • Baseline covariates: gender, age, prisoner history, alcohol, MDRTB contact, TB treatment history, diabetes, HIV, cavity, sputum smear, resistance profile and drugs prescribed
    • Follow-up covariates: extension of resistance to FQ and/or injectable, incidence of treatment interruption due to side effects or due to patients’ factors

• Standards of the MSF Ethics Review Board for analysis of routinely collected data
RESULTS

• 1977 MDRTB out of 2492 DRTB patients (79.3%)

• Baseline characteristics
  - From projects in FSU countries 92.6%
  - Male 57.3%
  - Median age, years [IQR] 32 [24 - 43]
  - Ex prisoner 12.7%
  - HIV tested 18.2%
    • Positive 32.0%
  - History of TB treatment (N=1919) 19.4%
    • New cases
    • Prev. Treated 1\textsuperscript{st} line 69.6%
    • Prev. Treated 2\textsuperscript{nd} line 11.0%
  - MDRTB contact (N=936) 21.0%
# Baseline characteristics

- **Median body mass index, Kg/m² [IQR]**  
  18.7 [16.6 - 20.1]

- **Presence of cavities**  
  74.5%

- **Smear-microscopy (N=1744)**
  - Negative  
    12.6%
  - Scanty/1+  
    21.6%
  - 2/3+  
    65.8%

- **Drug resistance profile**
  - MDR simple  
    55.2%
  - Pre-XDR injectables  
    22.4%
  - Pre-XDR FQ  
    2.4%
  - XDR  
    2.2%
  - DST 2nd line missing  
    17.8%
# Treatment outcomes by resistance profile

<table>
<thead>
<tr>
<th></th>
<th>“Intention to treat”</th>
<th>“On treatment”</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Success</td>
</tr>
<tr>
<td>Overall*</td>
<td>1433</td>
<td>56.4</td>
</tr>
<tr>
<td>MDR simple</td>
<td>817</td>
<td>59.7</td>
</tr>
<tr>
<td>Pre-XDR</td>
<td>389</td>
<td>53.2</td>
</tr>
<tr>
<td>1 injectable</td>
<td>146</td>
<td>54.8</td>
</tr>
<tr>
<td>2 injectables</td>
<td>207</td>
<td>55.5</td>
</tr>
<tr>
<td>FQ</td>
<td>36</td>
<td>33.3</td>
</tr>
<tr>
<td>XDR</td>
<td>37</td>
<td>27</td>
</tr>
</tbody>
</table>

*Including 190 patients without susceptibility results to 2nd line drugs
Treatment success by history of drug intake and drug prescription “on treatment analysis”

- **Ethambutol (E)**
  - No difference of success rates according to history of E intake and E prescription

- **Ethionamide (Eto)**
  - Eto susceptible
    - **44% success if past history of Eto intake vs 77% if not, p=0.002**
    - No difference according to Eto prescription (75 vs 77%)

- **Kanamycin (Km) vs capreomycin (Cm) prescription**
  - Km susceptible: **82% success with Km vs 72.5% with Cm, p=0.014**
## Predictors of unfavourable outcomes

### « on-treatment analysis »

- **At treatment initiation**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>aOR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Former prisoner</td>
<td>1.88</td>
<td>1.11 - 3.20</td>
</tr>
<tr>
<td>Treatment history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 1\textsuperscript{st} line drugs</td>
<td>1.97</td>
<td>1.14 - 3.42</td>
</tr>
<tr>
<td>- 2\textsuperscript{nd} line drugs</td>
<td>3.24</td>
<td>1.54 - 6.85</td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- &gt; 18.5Kg/m\textsuperscript{2}</td>
<td>0.45</td>
<td>0.32 - 0.64</td>
</tr>
<tr>
<td>Sputum microscopy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 2+/3+</td>
<td>2.32</td>
<td>1.15 - 4.67</td>
</tr>
<tr>
<td>Resistance profile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Pre-XDR 2 inj.</td>
<td>1.90</td>
<td>1.0 - 3.62</td>
</tr>
<tr>
<td>- Pre-XDR FQ</td>
<td>5.56</td>
<td>2.15 - 14.37</td>
</tr>
<tr>
<td>- XDR</td>
<td>8.16</td>
<td>3.22 - 20.62</td>
</tr>
</tbody>
</table>
### Predictors of unfavourable outcomes

« on-treatment analysis »

#### During treatment

<table>
<thead>
<tr>
<th>Predictor</th>
<th>aOR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extension of resistance to injectable</td>
<td>2.13</td>
<td>1.22 - 3.71</td>
</tr>
<tr>
<td>Extension of resistance to FQ</td>
<td>15.75</td>
<td>9.39 - 26.44</td>
</tr>
<tr>
<td>Treatment interruption due to SE</td>
<td>1.79</td>
<td>1.30 - 2.45</td>
</tr>
<tr>
<td>Prescription of capreomycin</td>
<td>1.54</td>
<td>1.04 - 2.28</td>
</tr>
</tbody>
</table>
DISCUSSION

• Overall poor MDRTB treatment outcomes
• Poor treatment completion
• Predictors of unfavourable outcomes
  – Expected: past TB treatment history, disease progression, resistance to FQ
  – Poor treatment tolerability
  – Capreomycin-based treatment may be less effective than kanamycin
• No role of ethambutol in MDRTB treatment
LIMITATIONS

• Missing data
• Comorbidities poorly documented
• Difference between programs
  – Majority from former soviet countries
    • 65% of patients from the program in Uzbekistan
  – Different program management and changes over time
OPERATIONAL IMPLICATIONS

- MDRTB patients: no resistance to FQ, still susceptible to at least 1 injectable and less advanced disease
  - MDRTB treatment is effective
  - Treatment simplification to improve treatment completion and tolerability
- FQ resistance or resistance to all injectables or advanced disease
  - Treatment is not effective
  - Need for a new regimen with new drugs
- Relevance of ethambutol in the MDRTB regimen?
- Reconsider the role of kanamycin
  - In empirical MDRTB regimen even in settings with Km resistance?
  - Replace capreomycin by kanamycin if Km susceptible?
Acknowledgments

• Patients
• Personnel in charge of the MDRTB patients
• Ministries of Health
• Médecins Sans Frontières
• Elisabeth Sanchez-Padilla from Epicentre
Definitions

• Treatment outcomes
  – Cured: completed treatment and at least 5 consecutive negative cultures in the final 12 months of treatment
  – Treatment completed: completed treatment but does not meet the definition of cure
  – Failure: 2 or more of the 5 cultures recorded in the final 12 months of therapy are positive, or if any one of the final 3 cultures is positive