MDR-TB in South Africa: New Strategies and Policies

Karin Weyer

MRC Unit for TB Operational & Policy Research, Pretoria

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MDR-TB Challenges

- 2nd line drugs much less effective, expensive, toxic
  - Drug costs
    - R 400 (Drug-susceptible TB, new)
    - R 700 (Drug-susceptible TB, reRx)
    - R 20 000 – R30 000 (MDR-TB, standardised)

- Limited number of 2nd line drugs available
- Prolonged treatment required (up to two years)
- Hospitalisation (4-6 months) required
- Patients typically difficult, often with social problems
- Case-holding a major problem
- Clinical management confronted by ethical and legal dilemmas

MDR-TB: Multidrug-resistant TB, ie. resistance to isoniazid and rifampicin, with or without resistance to other 1st line TB drugs
MDR-TB Management

- Standardised regimen based on resistance to ethambutol
- Patients identified through culture and DST (H, R, E)
  - Retreatment, failure and non-converting patients
  - Risk groups (e.g., Health care workers)
- Restricted availability of 2nd line drugs
- Dedicated provincial MDR-TB wards/centres
- Hospitalisation until culture conversion / at least during intensive phase
- MDR-TB management teams
- Electronic DOTSPlus Register
- Dedicated discharge network (PHC clinics)
- Monitoring & evaluation by DOTSPlus Study Group of South Africa, coordinated by MRC
Standardised Treatment Regimen

According to ethambutol resistance

- Intensive phase (4 months)
  - kanamycin, ofloxacin, ethionamide, pyrazinamide, ethambutol or cycloserine
- Continuation phase (12 – 18 months)*
  - ofloxacin, ethionamide, ethambutol or cycloserine

* (Shortened to 12 months following culture conversion)

Doses standardised according to three weight bands (<50kg, 50-65kg, >65kg)

Cycloserine recently replaced by terizidone
MDR-TB Research aimed at Policy and Practice

- National survey of MDR-TB
  - Case finding and total TB burden
  - Drug resistance prevalence
  - Programmatically relevant data

- DOTSPlus for MDR-TB
  - Treatment outcomes
  - Revised management guidelines

- Legal dilemmas in MDR-TB management
1. MDR-TB Survey

- **Study design:** Population based, cross-sectional (WHO protocol)

- **Sampling strategy:** Multistage stratified sampling by Province; Clinics/hospitals sampled with PPS (min 30 sites per Province)

- **Sample size:** 762 culture confirmed TB patients per province, based on pre-set assumptions for MDR prevalence (1%), precision (+/-1%), and design effect = 2

- Consecutive adult TB suspects screened by microscopy and culture

- Unlinked HIV testing on C+ specimens
Results (1)

- Provincial differences confirmed

- Case yield: 32% (range 24% - 45%)
- Smear positivity: 79% (range 72% - 84%)
- S-/C+ proportion: 21% (range 16% - 28%)

- Retreatment rate: 26% (range 17% - 35%), consistently higher than rate reported in NTP registration system (14%)

- HIV prevalence: 55% (range 28% - 72%)
Results (2)

- National MDR-TB levels relatively low, but three Provinces approaching ‘hot spot’ levels
  - New: 1.6% (range 1.0% - 2.7%)
  - Retreatment: 6.7% (range 4.0% - 13.9%)

- Under-detection of MDR-TB in several provinces, largely due to lack of culture investigations

- Prior treatment with unfavourable outcome strongest predictor of MDR-TB, particularly if treated in hospital
Policy Implications

- High case yield among TB suspects
  - Late presentation of patients
  - Selective screening of suspects
  - Screening algorithm too strict

- Health service practices
  - Screening of suspects
  - Obtaining treatment history

- TB practices and procedures in hospitals

- MDR-TB case-finding practices

- MDR-TB resource analysis
  - Need for additional hospital beds
  - Human resource capacity
  - Financial sustainability
2. DOTSPlus for MDR-TB

- Cohort of 315 MDR-TB patients who completed treatment
  - Ethambutol-based: 196 (62.2%)
  - Cycloserine-based: 119 (37.8%)

- Category: 80.3% previous Rx 1st line drugs
- Mean age: 35.6 yrs (range 12 – 69)
- Gender: 65% male, 35% female
- HIV status: 65% known; of these 36% HIV+
Bacteriological Conversion

Month of treatment

Cumulative %

Smear Culture

78.8%
72.8%
Culture conversion by Regimen

Culture conversion by Regimen

Cumulative \%

Month of treatment

E-based

C-based

85.9%

74.5%

p=0.0352
Culture Conversion by HIV Status

![Graph showing culture conversion by HIV status over months of treatment.](image)

- **Cumulative %**
  - HIV+ over M1-M14 range: 85.7% - 80.8%
  - HIV unknown over M1-M14 range: 71.8%

- **Month of treatment**
  - M0 to M14

**HIV pos vs HIV neg:** $p = 0.4323$

**HIV known vs HIV unknown:** $p = 0.0503$
# Treatment Efficacy

(n = 173)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cured (1)</td>
<td>79</td>
<td>45.7</td>
</tr>
<tr>
<td>Rx completed (2)</td>
<td>76</td>
<td>43.9</td>
</tr>
<tr>
<td>Failed</td>
<td>18</td>
<td>10.4</td>
</tr>
</tbody>
</table>

Rx success (1+2) = 89.6%

*Outcomes among patients remaining on treatment
### Treatment Effectiveness*
\[(n = 315)\]

<table>
<thead>
<tr>
<th>Outcome</th>
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<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cured (1)</td>
<td>79</td>
<td>25.1</td>
</tr>
<tr>
<td>Rx completed (2)</td>
<td>76</td>
<td>24.1</td>
</tr>
<tr>
<td>Failed</td>
<td>18</td>
<td>5.7</td>
</tr>
<tr>
<td>Died</td>
<td>47</td>
<td>14.9</td>
</tr>
<tr>
<td>Transferred</td>
<td>2</td>
<td>0.6</td>
</tr>
<tr>
<td>Defaulted</td>
<td>93</td>
<td>29.5</td>
</tr>
</tbody>
</table>

Rx success \((1+2)\) = 49.2%  

*Outcomes among all patients started on treatment
Factors associated with treatment outcome (1)

Explanatory variables
- Demographics (age, gender, race, Province)
- Regimen (E-based / C-based)
- HIV status

Outcome variables grouped for purpose of statistical analysis
- Favourable outcome: Cured, Rx completed
- Unfavourable outcome: Failed, Died, Defaulted
- Omit: Transferred
Factors associated with treatment outcome* (2)

- **Regimen**
  - C-based more likely to succeed

- **Age**
  - Older patients more likely to succeed

- **HIV status known**
  - HIV+ and HIV- more likely to succeed than category ‘HIV unknown’

- **Province**
  - Better outcomes in North West and Mpumalanga than Eastern Cape, Free State and KwaZulu-Natal

*Stepwise logistic regression analysis
Impact of HIV on Death and Default (n = 315)

- **Death (n = 47)**
  - 10 (21.3%) HIV+
  - 10 (21.3%) HIV-
  - 27 (57.5%) HIV status unknown

- **Default (n = 93)**
  - 18 (19.4%) HIV+
  - 45 (48.4%) HIV-
  - 30 (32.2%) HIV status unknown
Conclusions

- MDR-TB treatment in South Africa shows
  - High efficacy: culture conversion and cure/completion high on standardised regimen (especially C-based)
  - but
  - Low effectiveness: high default rates reduce overall treatment success to approx. 50%

- Risk factors for high default rates need to be identified to allow for targeted intervention

- NTP focus needs to be on case-holding to ensure treatment completion
3. Legal issues

- Public health legislation dates back to 1979, with focus on protecting community rights.
- Constitution and Bill of Human Rights focus on balancing individual and community rights.
- Potential conflicts evident.
- MDR-TB management issues:
  - Patient-related
  - Community-related
  - Labour-related
  - All with ethical implications.
Limitations in existing public health legislation and conflict with Constitution confirmed

Legal reform of public health legislation required

Policy recommendations may be subject to challenge in Court

Policy decisions dependent on Health Authority budget and capacity constraints

Health Authorities will ultimately be held responsible, therefore collective decision-making recommended

Ethical issues even more difficult to address
Hospitalisation

- Enforced hospitalisation is an invasion of the fundamental right to freedom and security of the person and may only be considered for:
  - smear-positive patients with a productive cough
  - patients contravening conditions of release

- After lawful procedure has been applied

- Patients should be discharged on request, provided that they do not have a productive cough. They should be adequately counselled on preventive measures and safety procedures and the risks to close contacts. They should be warned to return for regular check-ups, failing which collection and examination may be considered.
Treatment may not be enforced against a patient’s will

Treatment should be continued at the patient’s request, with appropriate counseling and written informed consent, even when
  • the patient is pregnant
  • treatment may severely impair the patient’s health (including children, with parental consent)
  • severe side effects are experienced

Discontinuation of treatment may be considered where
  • default has occurred more than once, subject to discretionary measures and appropriate counselling at the start of treatment
  • additional drug resistance is likely to develop
  • treatment has failed
Disclosure

- Disclosure of patient information to communities constitutes a breach of privacy and there is no law currently allowing public health officials to disclose a patient’s MDR-TB status.
- Disclosure to high-risk contacts of infectious patients should however be considered, as omission may attract legal liability.
- Notification (to health authorities) does not mean that disclosure (to communities) is legal.
- One exception relates to regulations requiring parents to disclose a learner’s TB status to the principal of a teaching institution. This also applies to MDR-TB. Disclosure by health officials should therefore be considered if parents refuse.