Data on TB regimens – what next?

Dr Jennifer Hughes
Médecins Sans Frontières (MSF)
• 21-yr old HR Mx student
• HIV neg, primary XDR-TB
• 3 mths MDR Tx (went deaf), 6 mths XDR Tx in hospital, culture reconverted at month 10

• 19-yr old engineering student
• HIV neg, primary XDR-TB
• 4 months MDR Tx before Dx

• 32-yr old mother of one
• HIV pos, primary pre-XDR-TB (Ami)
• 4 mths Reg I Tx, one month MDR Tx before Dx
SA: XDR-TB treatment outcomes

Treatment outcomes for 623 TB patients with XDR-TB in South Africa, 2010

- Died 49%
- Cured 12%
- Not evaluated 17%
- Treatment failed 8%
- Lost to follow-up 9%
- Completed 6%

Source: WHO TB report 2013
Existing:
• Fluoroquinolones
• Injectables
• Ethionamide
• Terizidone
• PAS

Re-purposed:
• Linezolid
• Clofazimine
• High dose INH

New:
• Bedaquiline
• Delaminid
• PA-824
• PNU-100480
• SQ-109
**LINEZOLID**

**Systematic Review**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Reference</th>
<th>Proportion (95% CI)</th>
<th>Number</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fortum</td>
<td>2005</td>
<td>22</td>
<td>50.00 (4.75, 95.25)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>von der Lippe</td>
<td>2006</td>
<td>23</td>
<td>86.69 (61.55, 99.39)</td>
<td>10</td>
<td>9</td>
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<tr>
<td>Park</td>
<td>2006</td>
<td>12</td>
<td>37.06 (2.68, 82.90)</td>
<td>3</td>
<td>1</td>
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<tr>
<td>Yew</td>
<td>2008</td>
<td>24</td>
<td>29.50 (1.84, 71.93)</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Jeon</td>
<td>2009</td>
<td>25</td>
<td>68.92 (34.99, 94.12)</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Koh</td>
<td>2009</td>
<td>21</td>
<td>64.45 (28.36, 92.97)</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Migliori</td>
<td>2009</td>
<td>11</td>
<td>77.67 (64.80, 88.29)</td>
<td>46</td>
<td>36</td>
</tr>
<tr>
<td>Nam</td>
<td>2009</td>
<td>20</td>
<td>54.18 (26.82, 80.24)</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Udwadia</td>
<td>2009</td>
<td>26</td>
<td>60.54 (33.25, 80.74)</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>Anger</td>
<td>2010</td>
<td>10</td>
<td>67.68 (44.32, 87.13)</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Schecter</td>
<td>2010</td>
<td>27</td>
<td>86.60 (71.15, 96.70)</td>
<td>25</td>
<td>22</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td><strong>67.99 (58.00, 77.99)</strong></td>
<td></td>
<td></td>
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</tbody>
</table>

NOTE: Weights are from random effects analysis

68% Tx success

148 patients

Linezolid for chronic XDR-TB: clinical trial

- 41 XDR-TB patients
- Previously unresponsive to treatment
- 87% culture conversion within 6 months
- 82% sig AEs
- 300 mg daily may be acceptable

Lee et al, NEJM 2012
Pfizer holds a monopoly on linezolid sales in SA
No alternative generic registered yet

<table>
<thead>
<tr>
<th>Purchaser</th>
<th>Supplier</th>
<th>Price (600 mg tablet)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SA Government</td>
<td>Pfizer</td>
<td>R 287.9*</td>
</tr>
<tr>
<td>SA Private Sector</td>
<td>Pfizer</td>
<td>R 715.24**</td>
</tr>
<tr>
<td>Global Fund</td>
<td>Hetero</td>
<td>R74 ***</td>
</tr>
</tbody>
</table>

*Expired antibiotics tender price
**Single Exit Price
***not available in South Africa

With mark-ups, MSF in South Africa pays approximately **R123,000 per patient** for a 6-month supply of linezolid
BEDAQUILINE

• First new drug for TB in 50 years
• Diarylquinolone compound
• New mechanism of action:
  – specifically inhibits ATP-synthase in mycobacteria
• Long terminal half life of ~5 months
• Toxicities:
  – QT prolongation and raised hepatic enzymes
Bedaquiline (TMC207)

Phase 2 results

- No cross-resistance
- No additional side effects
- Less acquired drug resistance during treatment

Diacon et al, NEJM 2009, and Diacon et al AAC 2012
Access to Bedaquiline

- US FDA granted accelerated approval of BDQ in 2012 for DR-TB
- MCC registration in SA still pending
- Cost in SA? ~R10,000 for 6-month course
- BDQ accessible in SA only through BCAP for selected pre-XDR and XDR patients with PTB
1. At least one new class of drug
2. Contains 3 to 5 effective drugs (minimum 3), each of them from a different class of drugs
3. No injectables
4. Broad backbone that can be used for MDR and XDR
5. Simple dosing schedule
6. Limited side effects profile requiring limited monitoring
7. Shorter duration (aiming at 6 months but max 9 months)
8. Minimal interaction with ART

http://www.who.int/bulletin/volumes/92/1/13-122028.pdf
Challenges for regimen trials

• Pharmaceutical companies design trials to get the new drug registered
• They are not designing the best possible regimen
• Patents on individual drugs may hinder research into better regimens

• Hard to find funding for pragmatic trials that will work in real program settings
• Limited trial capacity in high DR-TB burden settings
<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimen</th>
<th>Injectable</th>
<th>Treatment duration</th>
<th>Current status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delaminid (Otsuka)</td>
<td>Delaminid (OPC67683) and OBT</td>
<td>Yes</td>
<td>Standard (18-24 mths)</td>
<td>Phase III, ongoing</td>
</tr>
<tr>
<td>STREAM (MRC)</td>
<td>Modified Bangladesh regimen (Gfx/Cfz/E/Z/ Pto/Ka/hdINH) vs WHO std regimen</td>
<td>Yes</td>
<td>9 mths</td>
<td>Recruitment ongoing</td>
</tr>
<tr>
<td>Bedaquiline (Janssen)</td>
<td>Bedaquiline into 2 additional arms of STREAM trial</td>
<td>Yes (4 mth)</td>
<td>6 mths 9 mths</td>
<td>Recruitment ongoing</td>
</tr>
<tr>
<td>PaMZ</td>
<td>PA-824/Moxi/PZA (4-6mths) vs RHZE for DS-TB; one arm MDR</td>
<td>No</td>
<td>Not yet enrolling</td>
<td></td>
</tr>
<tr>
<td>MARVEL (ACTG)</td>
<td>BDQ/PA-824/PZA/LZD +/- Lfx</td>
<td>No</td>
<td>6 mths</td>
<td>Protocol being finalised</td>
</tr>
<tr>
<td>PaBZ (TB Alliance)</td>
<td>BDQ/PA-824/PZA for DS-TB; Mfx added for one MDR arm</td>
<td>No</td>
<td>Not yet enrolling</td>
<td></td>
</tr>
<tr>
<td>NIX-TB</td>
<td>BDQ/PA-824/LZD for XDR-TB</td>
<td>No</td>
<td>6-9 mths</td>
<td>Not yet enrolling</td>
</tr>
<tr>
<td>OPTI-Q</td>
<td>High dose Lfx and OBT for MDR</td>
<td>Yes</td>
<td>Standard (18-24 mths)</td>
<td>Not yet enrolling</td>
</tr>
<tr>
<td>DDI study (ACTG)</td>
<td>BDQ / DEL interaction (to assess for future regimen options)</td>
<td>-</td>
<td>-</td>
<td>Approved</td>
</tr>
</tbody>
</table>
Overview of trials

- [http://www.resisttb.org/?page_id=1602](http://www.resisttb.org/?page_id=1602)

Results of trials unlikely to be available very soon:

- **2014**
  - Delamanid phase III
- **2016**
  - STREAM /BdQ phase III trial
- **2018**
  - MARVEL Phase II (2 months)
- **2020**
  - MARVEL Phase III Trial
- **2022**
  - New regimen (new drugs) available 2022?

Bedaquiline, Delamanid, linezolid restricted use as group 5 drugs only?
1. What do we do in the meantime?

**MDR regimens**

- Robust standard regimen for all new RR-TB cases, ensure at least 4 effective drugs
- Low threshold for modification of MDR regimen if inadequate (need alternative drugs available)
- Identify MDR failure early and amend regimen
The standard MDR regimen (SA)

PZA / Kana / Mfx / Tzd / Eto

• Is PZA reliable? – no DST
• INH mutations: inhA – is Eto effective?
• Evidence for Tzd?
• 10% XDR prevalence – Ka +/or Mfx ineffective?
  – Only detected later if 2nd line DST followed up

• Are we driving development of XDR TB...??
A slightly more empiric approach

- Suggested initial MDR regimen on GXP RR-TB:
  
PZA / EMB / Kana / Mfx / Tzd / Eto / hdINH

- EMB – well tolerated and potentially effective in 50%
- Modify when INH mutation info available:
  - inhA > remove Eto
  - katG > remove hdINH
  - both > use alternative (PAS/Cfz), and request 2nd line LPA to r/o XDR early

- If any drug not tolerated, consider substitution early:
  - LZD / PAS / Cfz
2. What do we do in the meantime?

**XDR regimens**

- One chance at providing an effective regimen
  - no use ‘saving’ drugs for salvage regimens

- Access effective drugs and start treatment asap

- Use rapid diagnostics to detect XDR early
  - MDR treatment is inadequate for XDR, may lead to development of further resistance
Cases with pre-XDR or XDR-TB
Khayelitsha 2010-2013

>85% started DR-TB treatment; 12% died before start
"Strengthened Regimen" pilot

- Since July 2011:
  - pre-XDR or XDR-TB results identified (clinics, NHLS, MSF)
  - MDR failure (delayed conversion or reconversion) referred

- Clinically stable patients with good compliance on MDR treatment are offered modified regimens in PHC
- **Drug regimens individually tailored**
  - DST pattern; genotyping results
  - Prior Tx history
  - Co-morbidities and concomitant meds
- Agreed by TB hospital clinicians and local experts

- **Drugs** sourced:
  - Z/E/Ka/Mfx/Tzd/Eto (PHC)
  - hdLfx and hdINH (PHC)
  - Cm, Cfz, PAS (TB hospital)
  - LZD from MSF
  - (BDQ from BCAP...)
BDQ Clinical Access Programme

• BCAP – mix between a clinical trial and CU
  – no comparison arm
  – allows access to BDQ (in an OBR) for pre-XDR and XDR patients with limited treatment options
  – eligible patients presented to Clinical Committee
  – progress and adverse events closely monitored

• Specific eligibility criteria
  – MDR excluded, but HIV pts on ART included
Patients NOT eligible for BCAP

• MDR
• EPTB – hip / sternum etc
• Uncontrolled HIV
• Poly-resistance – e.g. INH and Ofx
• Age under 18yrs
• XDR failure

• In Khayelitsha, these patients may still be offered LZD as part of Strengthened Regimen pilot
### Description of Khay SR cohort

- 46 pts enrolled on SR in Khayelitsha to date

<table>
<thead>
<tr>
<th></th>
<th>SR with LZD</th>
<th>SR with LZD and BDQ</th>
<th>HIV STATUS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pos</td>
</tr>
<tr>
<td>XDR</td>
<td>5 PTB</td>
<td>1 EPTB</td>
<td>6</td>
</tr>
<tr>
<td>PRE-XDR</td>
<td>10 PTB</td>
<td>3 EPTB</td>
<td>15</td>
</tr>
<tr>
<td>MDR failure</td>
<td>4</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Poly-resistant</td>
<td>1 (Rif + Ofx)</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td><strong>TOTALS</strong></td>
<td><strong>24</strong></td>
<td><strong>22</strong></td>
<td><strong>24</strong></td>
</tr>
</tbody>
</table>
Strengthened regimen patients since July 2011: Interim outcomes August 2014

- **Started SR**: 24
  - **SR BDQ and LZD**: 22
  - **SR on LZD**: 24
  - **Still on SR Tx**: 17
    - **BDQ**: 9
    - **LZD**: 8
  - **Tx success**: 7
  - **LFT**: 2
    - **BDQ**: 1
    - **LZD**: 1
  - **RIP**: 2
  - **Tx Failure**: 4
  - **T/F out**: 3
  - All died

Interim outcomes August 2014

- Sputum
  - **Neg**: 12
    - **BDQ**: 12
    - **LZD**: 2
  - **Pos**: 5
    - **BDQ**: 3
    - **LZD**: 4
  - **EPTB**: 3
    - **BDQ**: -
    - **LZD**: 3

Strengthened regimen patients since July 2011:
FUTURE...

- Empiric regimen for all RR-TB
- **Tailor down** according to DST

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Downsides</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Strong initial regimen for all</td>
<td>• Cost for all RR-TB pts</td>
</tr>
<tr>
<td>• Covers all R patterns</td>
<td>• Pill burden</td>
</tr>
<tr>
<td>• Can remove drugs if not tolerated without</td>
<td>• Interactions with ARVs</td>
</tr>
<tr>
<td>compromised regimen</td>
<td>• Toxicity for some</td>
</tr>
<tr>
<td>• Improved culture conversion?</td>
<td></td>
</tr>
</tbody>
</table>
Summary

• Current DR-TB regimens not good enough

• Need to improve access to newly available and repurposed drugs for better regimens

• Need to urgently implement use of better available drugs to improve regimens while waiting for regimen trials results
QUESTIONS?

Acknowledgements:
SR patients in Khayelitsha
MSF Khayelitsha staff
CoCT and PGWC
NDOH and BCAP