New Frontiers: Innovation and Access

New Guidelines: An Opportunity for National Programmes and Patients:
Evidence for new WHO recommendations on MDR-TB treatment

Cathy Hewison, Médecins Sans Frontières

February 28th - March 1st 2019
Overview

• New drug hierarchy for MDR-TB

• Number drugs in a long MDR-TB regimen

• Choice of regimen for MDR-TB
One important factor that lowered the strength of all recommendations made in these guidelines was the variability in values and preferences of those affected by these policies as perceived by the GDG members.
New drug hierarchy for MDR-TB

<table>
<thead>
<tr>
<th>Out with the old...</th>
<th>In with the new...</th>
</tr>
</thead>
<tbody>
<tr>
<td>Out Km and Cm</td>
<td>✓ In Bdq</td>
</tr>
<tr>
<td>Out Pto</td>
<td>✓ In Lzd</td>
</tr>
<tr>
<td>Out Z</td>
<td>✓ In Cfz</td>
</tr>
</tbody>
</table>

The feasibility of effective and **fully oral treatment regimens** for most patients

---

1: WHO Rapid Communication, August 2018
WHO Individual Patient Data (IPD) analysis

Group A: Medicines to be prioritised: levofloxacin/moxifloxacin, bedaquiline and linezolid (strong recommendation)

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Treatment failure or relapse versus treatment success</th>
<th>Death versus treatment success</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number treated</td>
<td>Adjusted Odds Ratio (95% CI)</td>
</tr>
<tr>
<td>Levofloxacin OR moxifloxacin</td>
<td>3,143</td>
<td>0.3 (0.1-0.5)</td>
</tr>
<tr>
<td>Bedaquiline</td>
<td>1,391</td>
<td>0.3 (0.2-0.4)</td>
</tr>
<tr>
<td>Linezolid</td>
<td>1,216</td>
<td>0.3 (0.2-0.5)</td>
</tr>
</tbody>
</table>

1: WHO pre-final guidelines 2019
Supporting evidence for new drug hierarchy

South Africa:
- better favourable outcomes and less mortality in XDR patients than MDR patients treated with standard regimen

Armenia:
- 30% increase in treatment success in similar patients

Belarus:
- 92.7% success rate

What other evidence supports the use of bedaquiline and linezolid as group A drugs for all patients on long regimens?

What is missing from WHO evidence

Safety and effectiveness of bedaquiline beyond 6 months

What the WHO IPD cannot tell us, can other evidence can?

- Evidence of reversion when stopping Bdq at 6 months
- Belarus: mean 9 months (268 days), significantly less adverse events in second 6 months
- France: no safety issues
- endTB: 923/2241 patients (41%) > 6 months, median duration 10 months (317 days)

<table>
<thead>
<tr>
<th>N=146</th>
<th>First 6 months Bdq</th>
<th>Second 6 months Bdq</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of QtcF prolongation events of clinical relevance (grade 3 and 4)</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Number of patients with QtcF prolongation events of clinical relevance (grade 3 and 4)</td>
<td>6 (4.1%)</td>
<td>0</td>
</tr>
</tbody>
</table>
What is missing from WHO evidence?

« Optimal duration of Lzd is not established »

Use for at least 6 months was shown to be highly effective, although toxicity may limit its use »

What the WHO IPD cannot tell us, but other evidence can?

- Known time associated adverse events associated with Linezolid
- IPD only 300 of 13,000 had Lzd, 70% <18 months
- Nix: pretomanid-bedaquiline-linezolid (1200 mg), 29% permanently discontinuation of linezolid
- endTB: AE often associated with linezolid and injectables

1: WHO Rapid communication, 2018; 9: Conradie et al, UNION conference 2019; 10: endTB interim analysis 2018; 17: various linezolid related articles
## endTB safety analysis

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Patients with ≥ 1 N, % (95% CI)</th>
<th>Person time exposure (months)</th>
<th>Incidence per 100 person-months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QT prolongation ≥ grade 3 (bedaquiline and/or delamanid)</td>
<td>34/1244</td>
<td>2.7 (1.5-4.8)</td>
<td>0.18 (0.13-0.26)</td>
</tr>
<tr>
<td>Hearing loss all grade (injectable)</td>
<td>128/643</td>
<td></td>
<td>3.36 (2.83-4.00)</td>
</tr>
<tr>
<td>Hearing loss all grade; Acute renal failure ≥ grade 2; or Hypokalemia, hypomagnesemia (injectable)</td>
<td>229/643</td>
<td>35.6</td>
<td>6.16 (5.46-6.93)</td>
</tr>
<tr>
<td>Peripheral neuropathy ≥ grade 2; Myelosuppression; or Optic neuritis all grades (linezolid)</td>
<td>112/1020</td>
<td>11.0</td>
<td>0.94 (0.78-1.13)</td>
</tr>
</tbody>
</table>
What is missing from WHO analysis

Concurrent use of Bdq and Dlm was insufficient for review:

What the WHO IPD cannot tell us, but other evidence can?

- Small published cohorts showing no increase in safety issues \(^{14, 15}\)

- endTB analysis\(^7\): 2241 patients enrolled before May 2018
  - 334 (15%) patients had Dlm and Bdq concomittantly
    - 90% also had Cfz, 10% also FQ
    - 219 started Dlm and Bdq together
    - 115 had one added to the other (Dlm added to a Bdq containing regimen, or Bdq added to Dlm containing regimen)
  - 238 had more than 24 weeks of Dlm and Bdq together in a MDRTB regimen
  - Amongst 42 patients with 6 months minimum of followup only 1 QTcF > 500 msec

New drug hierarchy for MDR-TB

- Cost effectiveness of bedaquiline containing regimens has been published\textsuperscript{11, 12}
- All oral regimens likely to be
  - more effective regimens, less transmission
  - Less morbidity and disability, less mortality
  - Easier to administer: less HR, injectable needs
  - More acceptable to patients
  - More flexible treatment delivery options
  - More feasible: monitoring more accessible
  - more tolerable, less adverse event management

What the WHO IPD cannot tell us, but other evidence can?

\textsuperscript{1} WHO Rapid communication, 2018; 11. Wolfson et al, PLoS 12: Codecasaa et al, 2017
Number drugs long MDR-TB regimens

What is the optimum number of effective drugs in a long regimen?

- IPD: Risk for treatment failure, relapse and death was comparable when the treatment started with 4, 5 or 6 medicines likely to be effective
  - Longer regimens with old drugs
- PETTS study: 5 or more effective drugs at the start of treatment
  - Higher successful outcome (p-value < 0.001)
  - Less acquired resistance (p-value < 0.001)
- How many drugs are needed in regimens with new drugs?

1: WHO Rapid communication, 2018; 13: PETTs
Number drugs long MDR-TB regimens

What is the optimum number of effective drugs in a long regimen?

To consider

- Likely effectiveness
  - Cs resistance: widely used and no reliable DST
  - Z: high resistance in MDRTB patients

- If stopping a drug consider
  - effectiveness
  - Tolerability
  - Linezolid known adverse events

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Absolute risk of AE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median %</td>
</tr>
<tr>
<td>Bedaquiline</td>
<td>2.4%</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>2.9%</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>3.6%</td>
</tr>
<tr>
<td>Levofoxacin</td>
<td>4.1%</td>
</tr>
<tr>
<td>Cycloserine / terizidone</td>
<td>7.8%</td>
</tr>
<tr>
<td>Linezolid</td>
<td>17.2%</td>
</tr>
</tbody>
</table>

1: WHO pre-final guidelines, 2019;
Choice of MDRTB regimen

Should all oral regimens be used instead of shorter regimens that use an injectable?

- The shorter regimen (WHO 2016) performs similar to the older longer regimen.
- The shorter regimen was not compared to the new longer all oral regimen that uses bedaquiline.
- Toxicity of injectables well documented:
  - The shorter (WHO 2016) or longer regimen with an injectable even with monitoring, can result in hearing loss (6-7% of patients)\textsuperscript{16}, permanent tinnitus, renal failure, electrolyte disturbances and death.

1: WHO Rapid communication, 2018; 16: STREAM preliminary results, Union conference 2018
Choice of MDRTB regimen

Should all oral regimens be used instead of shorter regimens that use an injectable?

• WHO recommends if a patient prefers an all oral regimen they should NOT be forced to take a shorter regimen with an injectable
  
  – An all-oral regimen 18-20 months base on the new WHO hierarchy of TB drugs
  
  – An all-oral regimen of 9-12 months done under operational research conditions

1: WHO Rapid communication, 2018;
Evidence currently lacking on the effect of replacing any of the agents with alternatives in the shorter regimen (WHO 2016)

- What are novel or modified shorter regimens?
  - that are based around two or more Group A drugs
    - e.g. replacing the injectable with bedaquiline or other oral agents
    - replacing moxifloxacin with levofloxacin
  - based on shorter regimens presently being tested in clinical trials
    - STREAM II
    - endTB

1: WHO Rapid communication, 2018;
What are operational research conditions

Choice of MDRTB regimen

<table>
<thead>
<tr>
<th></th>
<th>Programmatic conditions</th>
<th>Operational research conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethics approval</td>
<td>x  No</td>
<td>✓  Yes</td>
</tr>
<tr>
<td>Protocol</td>
<td>✓  Yes</td>
<td>✓  Yes</td>
</tr>
<tr>
<td>Patient informed consent</td>
<td>✓  Yes</td>
<td>✓  Yes</td>
</tr>
<tr>
<td>aDSM</td>
<td>✓  Yes</td>
<td>✓  Yes</td>
</tr>
<tr>
<td>Monitoring</td>
<td>✓  Yes</td>
<td>✓  Yes</td>
</tr>
<tr>
<td>Reporting results</td>
<td>✓  Yes</td>
<td>✓  Yes</td>
</tr>
</tbody>
</table>

Most patients can benefit from more effective, less toxic, all oral regimens

WHO IPD analysis cannot tell us everything

- eg optimal duration of drugs such as bedaquiline and linezolid
- Other evidence exists to guide us
- Use clinical judgement and basic principles of MDR-TB treatment

Modified shorter regimens could be more adapted to patient needs and epidemiological profile in the region

- Operational research conditions are possible in programs
- Evidence needed: please collect some 😊
Thanks

- To all those contributing to better knowledge on best treatment practices for MDR-TB
  - Patients contributing their data
  - Programs collecting data
  - Clinicians and researchers
3. Long-term bedaquiline-related treatment outcomes in patients with extensively drug-resistant tuberculosis from South Africa, Eur Respir J 2018;Olayanju et al
7: WHO, Global consultation on transition towards new and better treatments of drug-resistant TB and latent TB infection, November 2018
8: Long-term outcome and safety of prolonged bedaquiline treatment for multidrug-resistant tuberculosis; Eur Resp J 2017, Guglielmetti et al

9: Nix-TB, Sustained high rate of successful treatment outcomes: Interim results of 75 patients in the Nix-TB clinical study of pretomanid, bedaquiline and linezolid, UNION conference 2019; Conradie et al

10: Bedaquiline- and delamanid-containing regimens achieve excellent interim treatment response without safety concerns: endTB interim analysis http://www.endtb.org/resources/endtb-interim-analysis-july2018


Lorenzo Guglielmetti et al, European Respiratory Journal 2018; DOI: 10.1183/13993003.02550-2017

15. Early safety and efficacy of the combination of bedaquiline and delamanid for the treatment of patients with drug-resistant tuberculosis in Armenia, India, and South Africa: a retrospective cohort study
Gabriella Ferlazzo et al, 2018, DOI:https://doi.org/10.1016/S1473-3099(18)30100-2

16. STREAM 1: UNPUBLISHED, Union conference The Hague, 2018

18: Evidence exists that stopping Bdq routinely at 6 months is associated with high rates of reversion, with 19% (10/51) patients reverting to positive cultures after conversion in cohorts from Georgia and Armenia, Hewison C. et al. Int J Tuberc Lung Dis. 2018 Jul 1;22(7):766-772.
17: Linezolid references:


f) Hughes et al. Linezolid in HIV patients
Extra slide if needed
## endTB safety analysis

<table>
<thead>
<tr>
<th>AE term and grade</th>
<th>Patients N (%)</th>
<th>Time to first AE Median [IQR]</th>
<th>Incidence /100 person-months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypokalemia/ hypomagnesia</td>
<td>327 (26.3)</td>
<td>3.0 [1.0-8.0]</td>
<td>2.15 (1.93-2.40)</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>211 (17.0)</td>
<td>3.7 [2.0-6.9]</td>
<td>1.29 (1.13-1.47)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>107 (8.6)</td>
<td>4.1 [2.0-7.5]</td>
<td>0.60 (0.50-0.73)</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>71 (5.7)</td>
<td>2.1 [1.0-7.0]</td>
<td>0.38 (0.30-0.49)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>59 (4.7)</td>
<td>4.0 [2.9-7.3]</td>
<td>0.32 (0.25-0.42)</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>52 (4.2)</td>
<td>1.9 [0.9-5.2]</td>
<td>0.28 (0.22-0.37)</td>
</tr>
<tr>
<td>Myelosupression</td>
<td>49 (3.9)</td>
<td>1.9 [0.6-4.9]</td>
<td>0.27 (0.20-0.35)</td>
</tr>
<tr>
<td>QT prolongation</td>
<td>34 (2.7)</td>
<td>2.0 [0.7-6.4]</td>
<td>0.18 (0.13-0.26)</td>
</tr>
<tr>
<td>Optic neuritis</td>
<td>30 (2.4)</td>
<td>7.2 [3.6-13-1]</td>
<td>0.16 (0.11-0.23)</td>
</tr>
</tbody>
</table>

10: endTB interim analysis 2018