Rapid Communication:
Key changes to treatment of multidrug- and rifampicin-resistant tuberculosis

Dennis FALZON
WHO, Global TB Programme

Joint UNICEF, UNFPA and WHO meeting with manufacturers and suppliers

25 September 2018
WHO guidance on treatment & management of drug-resistant TB, 1996 +

- 1996: Guidelines for the programmatic management of drug-resistant tuberculosis
- 2000: Guidelines for the programmatic management of drug-resistant tuberculosis
- 2006: Guidelines for the programmatic management of drug-resistant tuberculosis
- 2008: Companion handbook in the WHO guidelines for the programmatic management of drug-resistant tuberculosis
- 2011: The use of delamanid in the treatment of multidrug-resistant tuberculosis
- 2013: Treatment guidelines for multidrug-resistant tuberculosis
- 2014: The use of delamanid in the treatment of multidrug-resistant tuberculosis
- 2014: Position statements on the use of delamanid & the shorter MDR-TB regimen
- 2016: Hr-TB treatment supplement, 2018
- 2017: WHO best-practice statement on the off-label use of bedaquiline and delamanid for the treatment of multidrug-resistant tuberculosis
- 2018: WHO position statement on the use of delamanid for multidrug-resistant tuberculosis
<table>
<thead>
<tr>
<th>GROUP</th>
<th>MEDICINES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A: Include all three medicines (unless they cannot be used)</td>
<td>Levofloxacin OR Moxifloxacin</td>
</tr>
<tr>
<td></td>
<td>Bedaquiline</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
</tr>
<tr>
<td>Group B: Include both medicines (unless they cannot be used)</td>
<td>Clofazimine</td>
</tr>
<tr>
<td></td>
<td>Cycloserine OR Terizidone</td>
</tr>
<tr>
<td>Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used</td>
<td>Ethambutol</td>
</tr>
<tr>
<td></td>
<td>Delamanid</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
</tr>
<tr>
<td></td>
<td>Imipenem-cilastatin OR Meropenem</td>
</tr>
<tr>
<td></td>
<td>Amikacin (OR Streptomycin)</td>
</tr>
<tr>
<td></td>
<td>Ethionamide OR Prothionamide</td>
</tr>
<tr>
<td></td>
<td><em>p</em>-aminosalicylic acid</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Longer MDR-TB regimens

Notes on use (1)

• The optimal duration of Bdq, Dlm and Lzd is not known. Use of Bdq & Dlm beyond 6 months still considered “off label”

• Z is only counted as an effective agent when DST results confirm susceptibility.

• Am and S are only considered if DST confirms susceptibility and audiometry during treatment can be ensured. S only used if Am cannot (S resistance not detectable with 2\textsuperscript{nd} line HAIN)

• Eto/Pto and PAS only proposed for regimens which do not contain Bdq, Lzd, Cfz or Dlm (or very last resort)
Longer MDR-TB regimens

Notes on use (2)

• Kanamycin (Km) and capreomycin (Cm) linked to poorer outcomes in IPD meta-analysis. A recommendation against their use in longer regimens is made.

• Amoxicillin-clavulanate (Amx-Clv) without carbapenems linked to poorer outcomes. Use only with Imp-Cln or Mpm and do not count as a separate effective agent.

• No patients on thioacetazone (T), and too few on high-dose isoniazid (H^h) and gatifloxacin (Gfx). Therefore not included in the Table.
Longer MDR-TB regimens

Notes on use (3)

• Choice of medicines depends upon the expected balance of effectiveness and harms; preference for oral over injectable agents; the results of drug-susceptibility testing (DST); the reliability of DST methods; population drug resistance levels; history of previous use of the medicine in a patient; drug tolerability; and potential drug-drug interactions.

• Countries should rapidly adjust their national treatment policies, drug procurement plans and monitoring systems to quickly switch MDR-TB patients to the new priority medicines. The strong desirability to have a fully oral treatment implies important changes to country policies, drug procurement plans and training of health care staff.
Shorter MDR-TB regimen

Data

- STREAM Stage 1 trial showed that in patients eligible for the shorter MDR-TB regimen, the likelihood of treatment success was very similar to the one of longer MDR-TB regimens.

- Observational studies of shorter MDR-TB regimens also showed a comparable likelihood of treatment success with longer regimens overall, but with a lower likelihood of treatment interruption. However, shorter regimens were associated with higher failure and relapse compared to longer regimens, especially when resistance was present or when longer regimens included one or more of the medicines listed in Group A.

- Shorter regimens with BDQ – no outcome data available.
Shorter MDR-TB regimen

Notes on use

• Programmes already implementing the shorter MDR-TB regimen with good results and capacity to monitor for ototoxicity
  • switch from Km to Am
  • while Km is used close follow-up for non-response to treatment or early relapse
  • apply a low threshold to switch non responders to a new longer regimen

• Programmes planning to offer the shorter regimen to newly-diagnosed patients are advised to continue only if they have DST capacity to exclude at least FQ and SLI resistance

• Programmes considering modified shorter regimens (e.g. replacing injectable with BDQ) can do so as operational research
Stressing need for …

• Improved DST capacity to triage better the patients to right treatment
• Collection of data for both programmatic care and OR with a view to contribute to both local and global policy making
• Appropriate patient counselling for informed decision-making ahead of start of any MDR-TB treatment
• Update of patient information materials to reflect the new changes so that patients are appropriately informed about their treatment options
• Social support to enable adherence to treatment
• Active TB drug safety monitoring and management (aDSM) is essential for all patients on MDR-TB treatment.
WHO task force to support country transition

Objectives

• To assess and provide solutions to the short-term and longer-term operational implications of the new WHO recommendations on national MDR-TB guidelines, training of key staff, funding, targets, and adjustment of short and longer-term procurement plans;
• To work together to assess country-specific challenges and provide solutions, especially during the transition phase, and to ensure that the transition is followed up by support to countries for full implementation of the new guidelines;
• To maintain active and clear communication between all major stakeholders on the actions undertaken to support transition