Tuberculosis in 2017: Searching for new solutions in the face of new challenges

6th TB Symposium – Ministry of Health of the Republic of Belarus, Republican Scientific and Practical Center for Pulmonology and Tuberculosis, and Médecins Sans Frontières

1-2 March, 2017, MINSK, BELARUS

The new WHO treatment guidelines for drug-resistant tuberculosis

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WHO/HQ Global TB Programme, Geneva
Objective of the presentation

An update about the revisions undertaken in 2016 to the WHO policies on the treatment of rifampicin and multidrug-resistant TB
Tuberculosis in 2017: Searching for new solutions in the face of new challenges

WHO guidance on treatment & management of drug-resistant TB, 1996-2016

WHO treatment guidelines for drug-resistant tuberculosis
2016 update

The use of delamanid in the treatment of multidrug-resistant tuberculosis
in children and adolescents
Interim policy guidance

The use of delamanid in the treatment of multidrug-resistant tuberculosis
WHO policy guidance

Guidelines for the programmatic management of drug-resistant tuberculosis
Declaration framework

Guidelines for the programmatic management of drug-resistant tuberculosis
Technical framework

The use of bedaquiline in the treatment of multidrug-resistant tuberculosis
Interim policy guidance

Guidelines for the management of drug-resistant tuberculosis
WHO policy guidance

Guidelines for the management of multidrug-resistant tuberculosis
WHO policy guidance

The use of bedaquiline in the treatment of multidrug-resistant tuberculosis
WHO policy guidance

Tuberculosis Symposium – Ministry of Health of the Republic of Belarus, Republican Scientific and Practical Center for Pulmonology and Tuberculosis, and Médecins Sans Frontières
Tuberculosis in 2017: Searching for new solutions in the face of new challenges

November 2014

GRACE

May 2016

## Certainty of evidence

<table>
<thead>
<tr>
<th>Certainty</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Further research is very unlikely to change our confidence in the estimate of effect.</td>
</tr>
<tr>
<td>Moderate</td>
<td>Further research is likely to have an important impact on our confidence in the effect and may change the estimate.</td>
</tr>
<tr>
<td>Low</td>
<td>Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.</td>
</tr>
<tr>
<td>Very low</td>
<td>Any estimate of effect is very uncertain.</td>
</tr>
</tbody>
</table>

Adapted from Guyatt GH et al. BMJ. 2008 Apr 26,336(7650):924-6
## Implications of the strength of a recommendation for different users

<table>
<thead>
<tr>
<th>Perspective</th>
<th>Strong recommendation</th>
<th>Conditional recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>For patients</td>
<td>Most individuals in this situation would want the recommended course of action and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.</td>
<td>The majority of individuals in this situation would want the suggested course of action, but many would not.</td>
</tr>
<tr>
<td>For clinicians</td>
<td>Most individuals should receive the intervention. Adherence to this recommendation according to the guidelines could be used as a quality criterion or performance indicator.</td>
<td>Recognize that different choices will be appropriate for individual patients, and that patients must be helped to arrive at a management decision consistent with their values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.</td>
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<tr>
<td>For policy-makers</td>
<td>The recommendation can be adapted as policy in most situations.</td>
<td>Policy-making will require substantial debate and involvement of various stakeholders.</td>
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*Adapted from Guyatt GH et al. BMJ. 2008, 336(7652):1049–1051*
WHO guidelines for the treatment of drug-resistant tuberculosis, 2016 update

**Key changes**

- A shorter MDR-TB treatment regimen is recommended for RR-/MDR-TB patients, under eligibility criteria.
- All RR-TB cases to be treated with a MDR-TB regimen, regardless of isoniazid susceptibility.
- The design of longer MDR-TB regimens uses a different regrouping of component medicines.
- Recommendation on partial resection surgery.
In patients with rifampicin-resistant TB or MDR-TB, who have not been previously treated with second-line drugs and in whom resistance to fluoroquinolones and second-line injectable agents has been excluded or is considered highly unlikely, a shorter MDR-TB regimen of 9–12 months may be used instead of a conventional regimen.
Shorter MDR-TB regimen (2)

Main remarks

• Standardized regimen; limited modifications permissible

• 4-6 Km-Mfx-Pto-Cfz-Z-H_{high-dose} -E / 5 Mfx-Cfz-Z-E

• Recommendation applies to adults, children, PLHIV

• Ideally, patients are tested for resistance to fluoroquinolones and second-line injectable drugs; not recommended in case of 2^{nd} line drug resistance, extrapulmonary disease and pregnancy
Shorter MDR-TB regimen (3)

Main remarks

• Monitoring for effectiveness, relapse, and harms (active TB drug safety monitoring and management (aDSM))

• Trials (e.g. STREAM) expected to provide high-certainty evidence

• Lowered costs (<US$1,000 in drug costs/patient)
<table>
<thead>
<tr>
<th>GROUP A</th>
<th>Fluoroquinolones</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Levofloxacin</td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin</td>
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<tr>
<td></td>
<td>Gatifloxacin</td>
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</tbody>
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<table>
<thead>
<tr>
<th>GROUP B</th>
<th>Second-line injectable agents</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Amikacin</td>
</tr>
<tr>
<td></td>
<td>Capreomycin</td>
</tr>
<tr>
<td></td>
<td>Kanamycin</td>
</tr>
<tr>
<td></td>
<td>(Streptomycin)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>GROUP C</th>
<th>Other Core Second-line Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ethionamide / Prothionamide</td>
</tr>
<tr>
<td></td>
<td>Cycloserine / Terizidone</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
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<tr>
<td></td>
<td>Clofazimine</td>
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<table>
<thead>
<tr>
<th>GROUP D</th>
<th>Add-on agents</th>
</tr>
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<tbody>
<tr>
<td>D1</td>
<td>Pyrazinamide</td>
</tr>
<tr>
<td></td>
<td>Ethambutol</td>
</tr>
<tr>
<td></td>
<td>High-dose isoniazid</td>
</tr>
<tr>
<td>D2</td>
<td>Bedaquiline</td>
</tr>
<tr>
<td></td>
<td>Delamanid</td>
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<tr>
<td>D3</td>
<td>( p )-aminosalicylic acid</td>
</tr>
<tr>
<td></td>
<td>Imipenem-Cilastatin</td>
</tr>
<tr>
<td></td>
<td>Meropenem</td>
</tr>
<tr>
<td></td>
<td>Amoxicillin-Clavulanate</td>
</tr>
<tr>
<td></td>
<td>(Thioacetazone)</td>
</tr>
</tbody>
</table>
In patients with rifampicin-resistant TB or MDR-TB, a regimen with at least five effective TB medicines during the intensive phase is recommended, including pyrazinamide and four core second-line TB medicines – one chosen from Group A, one from Group B, and at least two from Group C.

Group A = levofloxacin; moxifloxacin; gatifloxacin
Group B = amikacin, capreomycin, kanamycin, (streptomycin)
Group C = ethionamide / prothionamide, cycloserine / terizidone, linezolid, clofazimine
Longer MDR-TB regimen (2)

Recommendations (2)

If the minimum number of effective TB medicines cannot be composed as given above, an agent from Group D2 and other agents from Group D3 may be added to bring the total to five.

In patients with rifampicin-resistant TB or MDR-TB, it is recommended that the regimen be further strengthened with high-dose isoniazid and/or ethambutol.

Group D2=bedaquiline, delamanid
Group D3=p-aminosalicylic acid, imipenem–cilastatin, meropenem, amoxicillin–clavulanate, (thioacetazone)
Longer MDR-TB regimen (3)

Main remarks

• Evidence relies heavily on observational studies; RCTs rare
• Regimen design is guided by the balance of the benefit that a medicine could add to the risk of harm it could cause (toxicity, drug–drug interaction, or pill burden)
• The detection of resistance to fluoroquinolones and to 2\textsuperscript{nd} line injectable agents is important for regimen design. Line probe assays for these two drug classes - for which WHO guidance has been released in May 2016 - will enhance programme capacity to test for this resistance. Access to reliable DST for pyrazinamide would be helpful as well.
• Linezolid and clofazimine are now core-regimen options
Longer MDR-TB regimen (4)

Main remarks

- Group D consists of Add-on agents, reserved for when an adequate regimen cannot be otherwise composed (replacing the old Group 5). It is split into three subgroups (D1,D2,D3): PAS belongs to D3 and bedaquiline and delamanid to D2

- Macrolides no longer have a role in MDR-TB treatment regimens

- Active TB drug safety monitoring and management (aDSM) to safeguard patient health and to contribute to global knowledge about the safety of individual medicines and drug combinations, especially in novel regimens
aDSM
“active and systematic clinical and laboratory assessment of patients on treatment with new TB drugs, novel MDR-TB regimens or XDR-TB regimens to detect, manage and report suspected or confirmed drug toxicities”

apps.who.int/iris/bibstream/10665/204465/1/WHO_HTM_TB_2015.28_eng.pdf
Longer MDR-TB regimen (5)

Main remarks

• All RR-TB cases to be treated with a recommended MDR-TB regimen, regardless if isoniazid resistance is confirmed or not

• Recommendations apply to adults and children; in children
  • injectable agents may be avoided in mild disease
  • delamanid now included for patients 6-17 years
  • bedaquiline not yet included in policy
Choosing the treatment regimen in patients with confirmed MDR/RR-TB

- Confirmed susceptibility or presumed effectiveness to all medicines in the shorter MDR-TB regimen (isoniazid resistance excepted)
- No exposure to >1 second-line medicines in the shorter MDR-TB regimen for >1 month
- No intolerance to any medicine in the shorter MDR-TB regimen and no risk of toxicity (e.g. drug-drug interactions)
- Pregnancy excluded
- Only pulmonary disease
- All medicines of the shorter MDR-TB regimen available to the programme

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The role of surgery

Recommendation & remarks

In patients with rifampicin-resistant or MDR-TB, elective partial lung resection (lobectomy or wedge resection) may be used alongside a recommended MDR-TB regimen

• Based on IPD and study-level meta-analyses
• Bias to be expected (e.g. confounding by indication, publication)
• Which patients & when would benefit most? The effects in PLWH could not be evaluated
• More radical pneumonectomy does not show the same benefits
• Only to be recommended where specialist services are available
“Bedaquiline may be added to a WHO-recommended regimen in adult patients with pulmonary MDR-TB”

conditional recommendation, very low confidence in estimates of effect

Subject to the following 5 conditions:
1. Treatment under close monitoring
2. Proper patient selection
3. Patient informed consent
4. Treatment as per WHO recommendations
5. Active pharmacovigilance in place
“Delamanid may be added to a WHO-recommended regimen in adult patients with pulmonary MDR-TB”

conditional recommendation, very low confidence in estimates of effect

Subject to the following 5 conditions:

1. Proper patient inclusion
2. Treatment as per WHO recommendations
3. Treatment is closely monitored
4. Active pharmacovigilance in place
5. Patient informed consent obtained

-> October 2016: may be used in patients 6-17 years
For patients with confirmed rifampicin-resistant TB or MDR-TB, SL-LPA may be used as the initial test, instead of phenotypic culture-based DST, to detect resistance to fluoroquinolones and second-line injectable drugs.

Conditional recommendations

May 2016

www.who.int/tb/areas-of-work/laboratory/policy_statements/en/
WHO guidelines for the treatment of drug-resistant tuberculosis, 2016 update

**Treatment of drug-resistant TB: Resources**

The **WHO treatment guidelines for drug-resistant tuberculosis (2016 update)** contains policy recommendations on priority areas in the treatment of drug-resistant tuberculosis. The revision is in accordance with the WHO requirements for the formulation of evidence-informed policy.

The main novelties of the 2016 WHO guidelines are:

- a shorter MDR-TB treatment regimen is recommended under specific conditions;
- medicines used in the design of conventional MDR-TB treatment regimens are now reclassified to reflect updates in the evidence on their effectiveness and safety;
- specific recommendations are made on the treatment of children with rifampicin-resistant or MDR-TB based on a first-ever individual patient data meta-analysis;
- recommendations on the role of surgery in MDR-TB case management are

[www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/resources/](http://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/resources/)
Frequently asked questions about the implementation of the new WHO recommendation on the use of the shorter MDR-TB regimen under programmatic conditions

Version: 20 December 2016

These FAQs are to be read alongside the WHO treatment guidelines for drug-resistant tuberculosis, 2016 update (WHO/HTM/TB/2016.04) and their online annexes released by the Global TB Programme of the World Health Organization (WHO) in May 2016(1),(2). The 2016 guidelines provide more background about the updated WHO recommendation on the shorter MDR-TB regimen since the previous guidelines of 2011(3).

Why are shorter MDR-TB regimens needed?
About 580,000 new cases of rifampicin-resistant (RR-TB) or multidrug-resistant (MDR-TB; RR-TB with additional resistance to isoniazid) emerge each year globally(4). RR-/MDR-TB cannot be treated with the recommended 6-month standard course of medication which is effective in most TB patients(5). Patients with MDR-TB are typically treated with more medicines and for much longer (conventionally over 2 years). This is not only logistically challenging for patients, but also problematic for access to drugs at scale, for patients’ adherence and for the delivery of care.
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Treatment of drug-resistant TB

Resistance to TB drugs is a formidable obstacle to effective TB care and prevention globally. Multidrug-resistant TB (MDR-TB) is multifactorial and fuelled by improper treatment of patients, poor management of supply and quality of drugs, and airborne transmission of bacteria in public places. Case management becomes difficult and the challenge is compounded by catastrophic economic and social costs that patients incur while seeking help and on treatment.

Key topics

Active drug-safety monitoring and management

Active TB drug-safety monitoring and management (aDSM)

The term active TB drug-safety monitoring and management (abbreviated as aDSM) describes a new TB programme component to provide for the active and systematic clinical and laboratory assessment of patients on treatment for XDR-TB, or with new TB drugs or novel MDR-TB regimens to detect, manage and report suspected or confirmed drug toxicities.
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