Transitioning to new MDR-TB policy in endTB project countries

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GLOBAL CONSULTATION ON TRANSITION TOWARDS NEW AND BETTER TREATMENTS OF DRUG RESISTANT TB AND LATENT TB INFECTION
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Transitioning to new MDR-TB policy

- ”Output 1 & 3” activities are designed to help endTB countries transition:
  1. Remove barriers to access (including removing importation barriers, cost of new TB drugs, and lack of expertise to perform good aDSM).
  2. Gain practical experience in using the new TB drugs (Bdq and Dlm) and re-purposed TB drugs (Lzd and Cfz).
  3. Help countries interpret WHO guidelines.
  4. Adapt national guidelines to include new and repurposed TB drugs.
- The foundation for transitioning to new WHO MDR-TB policy has been set in all endTB countries.

The endTB Clinical Guide is our major tool that helps endTB countries transition treatment policies into national guidelines:

- Helps interprets WHO policy on using new TB drugs.
- Provides practical advice on regimen design and how to do good aDSM.

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Version 5.0 will be produced shortly after the WHO MDR-TB Guidelines and WHO Companion Handbook are finalized.

Extensive MDR-TB policy changes are anticipated in every country

- The August 2018 release of the *WHO's Rapid Communication: Key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB)* means many policy changes are instore:
  - All oral regimens should be come the norm (very rarely patients will require treatment with an injectable);
  - All patients should have access and good safety monitoring to include a fluoroquinolone, bedaquiline and linezolid in their regimen – Group A drugs are associated with less death and less failure/relapse.
  - Patient information material needs to reflect the new changes so that patients are appropriately informed about MDR-TB treatment options.
  - Proper aDSM in every program is a must, especially if linezolid is being used or multiple QT prolonging drugs.

Adapting new TB drugs was very slow: Will transitioning to new better all oral regimens also be slow?

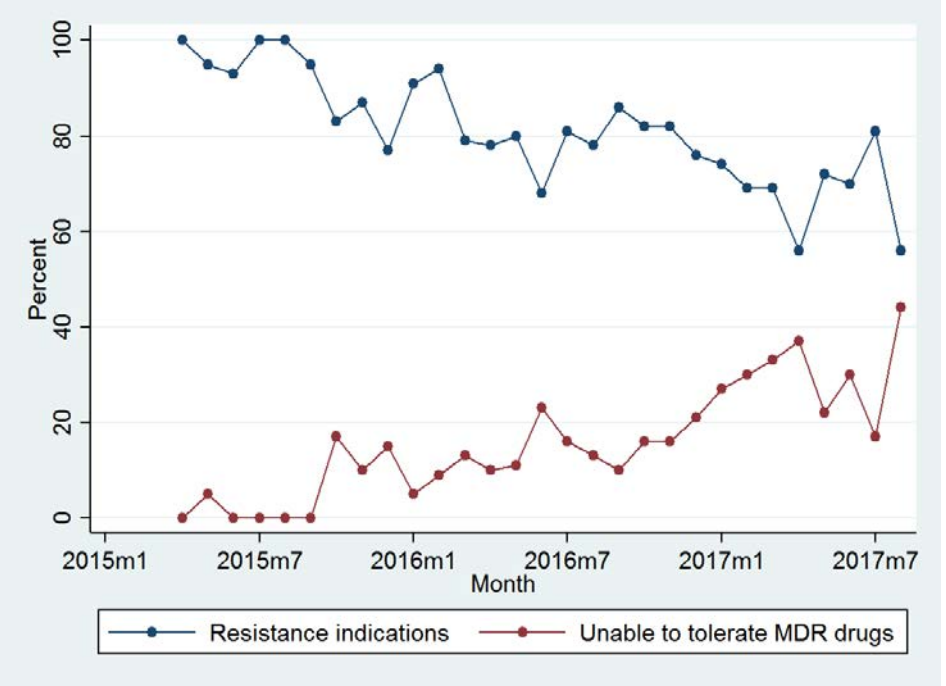
- Our experience is that most countries want to do what the WHO recommends, however, many things get in the way.
- The big three barriers:
  - **Insufficient technical capacity.**
  - **Large financial resources are needed.**
  - **Evidence is not complete.** WHO recommendations are based on evidence, but evidence is sparse on some of the policy decision points so countries decide to wait before implementing a change.

An Example in the endTB Project where policy change happened slowly:

- In 2016, the WHO policy on indications for when to use new TB drugs could be classified under three areas:
  1. Second-line drug resistance;
  2. As a drug replacement for toxicity or intolerability to a second-line drug;
  3. In any MDR-TB patient with a risk for a poor outcome;

An Example in endTB where policy change happened slowly:

- In 2014 WHO policy on indications for when to use new TB drugs could be classified under three areas:
  1. Second-line drug resistance; - **happened quickly**
  2. As a drug replacement for toxicity or intolerability to a second-line drug; **happened fairly quickly for the injectable, slower for other second-line drugs.**
  3. In any MDR-TB patient with a risk for a poor outcome; **Did not happen at scale in any country (except Lesotho).**



Why did the third indication for new TB drugs never get adopted by countries?

Let's examine why this one particular policy change never got implemented.

If we can understand why it did not get adopted, we can do things differently and get the better all oral regimens to patients sooner.

Why did the third indication for new TB drugs never get adopted by countries?

It was clearly written in the WHO Guidelines and in the endTB Clinical Guide.

2. The second eligibility group includes any patient who has a high risk of unfavorable outcome for whom a stronger regimen is recommended:
   a. Patients with extensive or advanced disease (X-ray demonstrating cavitary disease, bilateral lesions, or extensive parenchymal damage or multiple system involvement).
   b. Patients with increased likelihood of acquisition of additional resistance, treatment failure, or death due to co-morbidities or other conditions (drug contraindication, patients with low body mass index (BMI), HIV, diabetes).
   c. Patients coming from catchment areas that have poor MDR-TB treatment outcomes despite good programmatic conditions (e.g. sites with extensive second-line drug resistance background).

Patients should have a sputum sample collected for second-line DST at the time of starting treatment with new TB drugs. Second-line DST is important because the second-line resistance pattern can affect the design of the treatment regimen.

Of note, based on the above criteria, second-line DST is not a requirement for the use of new drugs. Some patients may be treated with new drugs without second-line DST, based on a clinical history that a regimen with five likely effective drugs including a fluoroquinolone and an injectable is not possible; intolerance to a key second-line anti-TB drug; or have a high risk of unfavorable outcome.

MDR-TB programs with success rates below 80% should consider redesigning their standardized and individualized regimens to include the new and repurposed TB drugs. This is especially true for programs with poor treatment outcomes despite strong program management and patient support. See Section 4.1 on constructing an MDR-TB regimen for more information.

endTB Clinical Guide:

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Why did the third indication for new TB drugs never get adopted by countries?

Possible reasons:

- Lack of technical capacity;
- Insufficient resources;

endTB able to remove these first two barriers

- Incomplete evidence;
- There was little uniform messaging that countries should adopt indication number 3.
- Major funders like the GF were not fully briefed on this reason, so even if a country wanted to do it, the funders might not agree.
- Unclear guidance on the indication. The WHO guidelines did not define in detail what was a “risk for poor outcomes” that would indicate a new TB drug is needed.
- Others?

Why did the third indication for new TB drugs never get adopted by countries?

Exploring the importance of unclear guidance:

- The WHO guidelines did not define in detail what was a "risk for poor outcomes" that would indicate a new TB drug is needed. (Risk factors for poor outcomes are well known).

RISK FACTORS FOR A POOR OUTCOME:

- Lung cavitations[1,3,4]
- Older age[1,2,3,6,7]
- Comorbidities[1,5,7] (diabetes)
- Weight < 40 kg[1] or low BMI[7]
- Smear positivity[3] and smear grade (3+)[6]
- HIV infection[3,7]

1. Ahmad et al, IJTLD 2015
2. Chiang et al, ERJ 2006
3. Balabanova et al, BMJ Open 2011
4. Yew et al, Chest 2000
5. Anderson et al, Eurosurv 2011
6. Velazquez, CID 2014
7. Mitnick et al, Plos One 2013
8. Bonnet et al, IJLTUD 2016

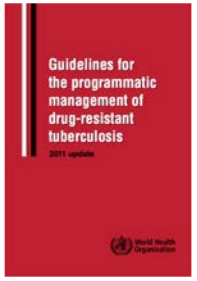
Policy transition to new better all oral regimens; Will it be slow again? How can it happen quickly?

- Need to remove all barriers:
  - **Insufficient technical capacity.** The technical capacity has been built in endTB countries (while more has to be done, the foundation is there).
  - **Large financial resources are needed.** Some countries are identifying the necessary resources, often the GF. Resources for good aDSM must be included.
  - **Evidence is not complete**. While evidence is not complete, there is much we can do to guide countries in this area.
    - Clear messaging on interpretation of the WHO guidelines.
    - Consideration of evidence outside of the IPD meta-analysis.
    - Frequent review of endTB evidence and evidence from other countries using new TB drugs (i.e. South Africa).

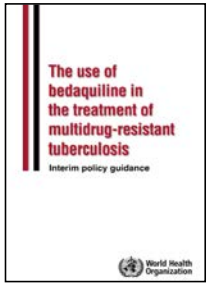
ULTIMATE GOAL:

The endTB project will continue to inform WHO TB guidelines

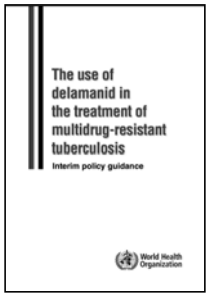
Likely updated guidelines will be needed every year



2011
DR-TB Guidelines

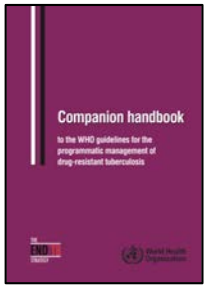


June 2013
WHO Bedaquiline Guidance

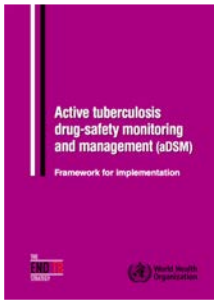


October 2014
WHO Delamanid Guidance

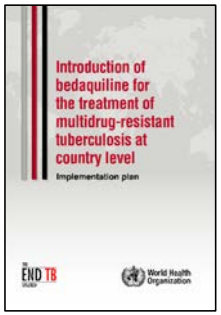
2014
WHO Policy Implementation Package



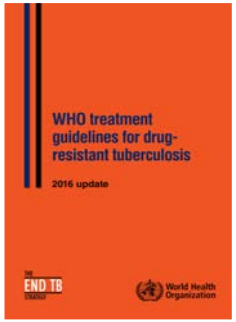
Jan 2015
Companion Handbook, Bdq and Dlm included



Nov 2015
aDSM Guide



Nov 2015
Bdq Country Implementation



April 2016
New DR-TB guidelines

March 2017
Updated Bdq guidance

August 2018
Rapid Communication

2018

New WHO guidelines with mostly all oral regimens

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New WHO guidelines with novel all oral short regimens

Thank you