Transitioning to new MDR-TB policy in endTB project countries

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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 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.

endTB Clinical Guide:

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....
Possible reasons:
• Lack of technical capacity;
• Insufficient resources;
• 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?

endTB able to remove these first two barriers
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\(^3,7\)

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1. Ahmad et al, IJTLD 2015  
2. Chiang et al, ERJ 2006  
5. Anderson et al, Eurosurv 2011  
6. Velazquez, CID 2014  
7. Mitnick et al, Plos One 2013  
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

2011
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Nov 2015
aDSM Guide

2018
New WHO
guidelines with
mostly all oral
regimens

2018
New WHO
guidelines with
novel all oral
short regimens
Thank you