# A Case-Based Discussion on the Use of Delamanid and Bedaquiline in Children with MDR-TB

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# Objectives

- To review the data on delamanid and bedaquiline in the pediatric population
- To discuss clinical recommendations on the use of these drugs in children
- To present recommended screening and monitoring for children receiving bedaquiline and delamanid for MDR-TB
- To review key areas for future research

# Child 1

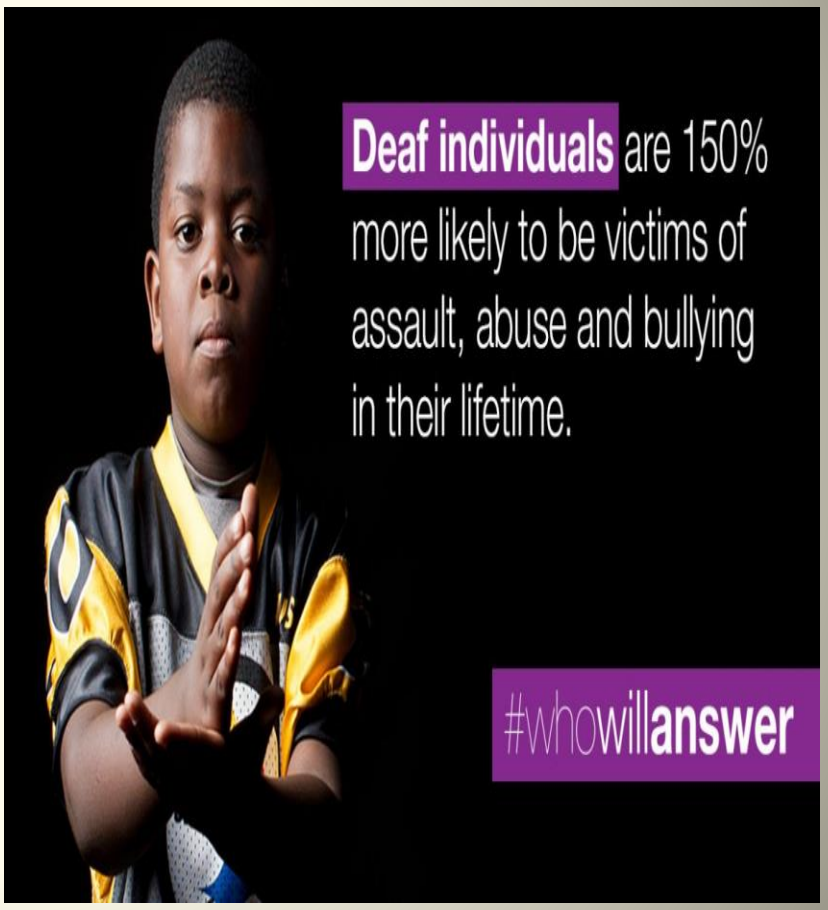
- TF is a 7 year-old boy with HIV whose mother recently died of MDR-TB that was also resistant to ofloxacin and kanamycin.
- He presents with fever, cough, and weight loss and has a chest radiograph and clincal examination consistent with TB.
- A sputum is sent for GeneXpert and culture; the Xpert is positive for M. tuberculosis and Rifampin resistance, but the culture specimen is lost.
- Of note, his 18 year-old sister is also diagnosed with RIF-resistant TB as well.

# Child 1 continued

- Because both children are close contacts of a person who died of XDR-TB, they are presumptively diagnosed with XDR-TB.
- TF's sister is started on a regimen that contains the new drug bedaquiline in addition to linezolid, clofazimine, PZA, ethionamide, and cycloserine.
- Because of his age, TF is given a regimen that does not contain any of the new drugs but instead is made up of LZD-CFZ-PZA-Ethio-CS and PAS.
- Although his sister improves quickly, TF continues to cough and lose weight and eventually dies because of massive hemoptysis

# Child 2

- RR is a 12 year-old female on MDR-TB treatment with a regimen of KM-Moxi-PZA-Ethio-CS-and PZA. Her 19 year-old sister is being treated with the same regimen.
- RR complains of buzzing in her ears at 6 weeks of treatment, and audiology confirms high-frequency hearing loss. Her KM is swicthed to thrice weekly, but she eventually becomes deaf.
- Her sister also develops hearing loss at month three at which time her KM is discontinued and she is started on BDQ as a replacement. She completes treatment but has to stop working so she can stay home and care for her deaf sister.



# Child 3

- RL is an 3 year-old child diagnosed with advanced HIV diagnosed with disseminated MDR-TB. On household screening, his HIV infected father (who also has advanced disease) is also found to have MDR-TB with severe, bilateral disease.
- Both individuals are deemed to be at high risk of treatment failure, and plans are made to start ART 2 weeks after initiating MDR-TB therapy.
- Because of the high risk of treatment failure, RL's father has delamanid added to his MDR-TB treatment regimen. RL receives the standard MDR-TB regimen.

# New Drugs and Children with MDR-TB

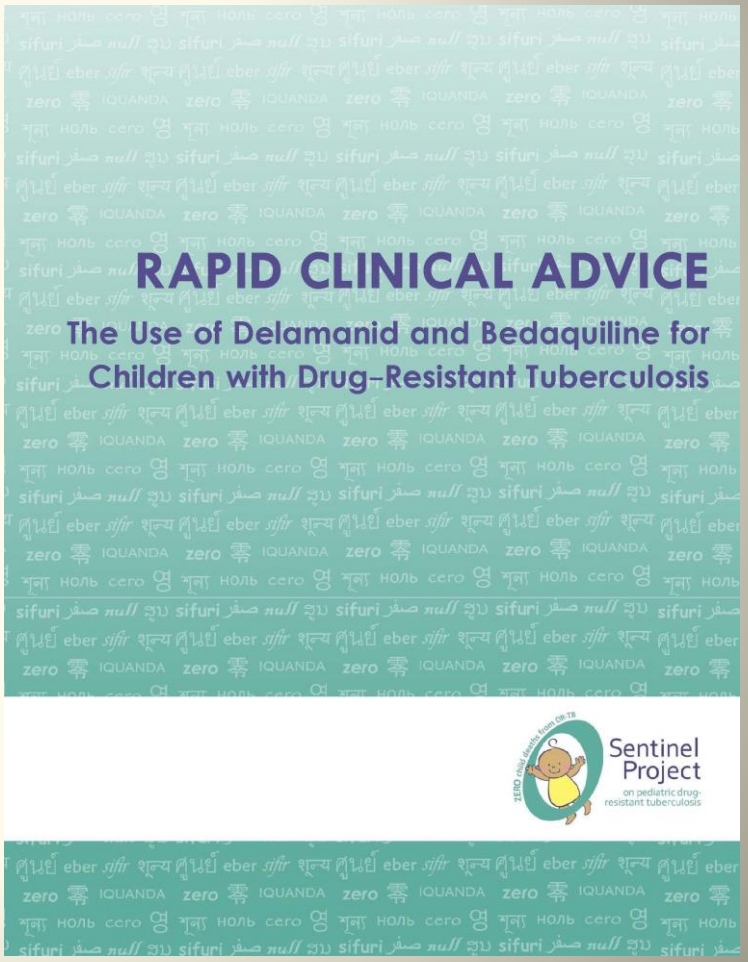
- Two novel agents—BDQ and DLM—have been approved by stringent regulatory agencies and recommended by the WHO for PMDT.
- The use of these agents have resulted in improved treatment outcomes for adults who have received them
- They have also been demonstrated to be viable therapeutic options for toxicity management, especially for hearing loss caused by the injectable agents
- There is currently a double standard when it comes to care of adults and children with MDR-TB, with adults able to access a higher standard of care than children.

# New Drugs for Children with MDR-TB

- Children under the age of 18 were not included in the efficacy trials.
- PK and safety studies have been started in the pediatric population, but there has been a reluctance to extrapolate dosing recommendations for the new drugs, even though this is the standard of care for many commonly used agents in children
- Data on safety and dosing of DLM is rapidly emerging, but there is no expedited process to review or incorporate these data into current WHO guidelines
- Current WHO guidance is a “No recommendation can be made” but not a “Do NOT use” .

# Sentinel Project Rapid Clinical Advice

- Developed to fill a gap in field management of children with MDR-TB
- Consensus reached by group of pediatric TB and MDR-TB experts after careful review of the literature
- Established a clinical guidance team to respond to questions about use, dosing, and safety of the new drugs in children (TBSentinelProject@gmail.com)



# Delamanid

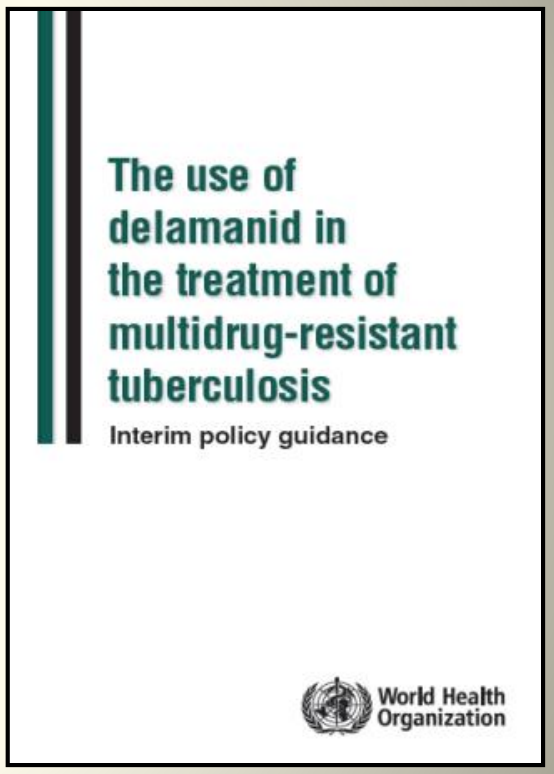
- Tablets come in 50mg form
- Adult dose is 100mg twice daily for 24 weeks
- Shelf-life: 4 years
- Half-life: 30-38 hours
- Cross-resistance with other nitroimidazoles (i.e. PA-824)
- Relatively low threshold to develop resistance
- Few drug-drug interactions

# DLM in Children

- PK and long-term safety in children ages 12-17 (Hafkin et al., 2015, ICAAC)
- PK and short-term safety in children ages 6-11 (Hafkin et al., 2015, Union)
- Enrolling in PK and safety studies of children ages 3-5 and 0-2
- Observational cohort of 19 children (mostly adolescents) with similar outcomes to adults (Tadolini et al., in press)

# WHO guidance on DLM (2014)

- Careful selection of patients
- Close monitoring
- Use in WHO approved regimen
- aDSM
- Due process of informed consent
- Broad recommendation for use in “high risk of treatment failure”



# DLM Recommendation 1

- Delamanid may be included in the treatment regimens of children aged 6 years and above and who weigh 20kg or more for the same indications as for adults: those with MDR-TB in whom a four drug-regimen plus pyrazinamide cannot be constructed due to resistance or significant intolerance *or* those with a high risk of treatment failure
- Applies to confirmed and probable MDR-TB in children

# DLM Recommendation 2

- Delamanid could be considered in children less than 6 years of age and who weigh less than 20kg if the child meets the criteria described above and no suitable alternatives are available and should be considered on a case-by-case basis.

# Dosing and duration

*Recommended dose:*

- >35kg: 100mg twice daily
- 20-34kg: 50 mg twice daily
- <20kg: consult with expert

Duration: 24 weeks; longer duration could be considered on a case-by-case basis (no alternative drug option).

# Contraindications for DLM

- Baseline QTc interval greater than 500 msecs that does not correct with medical management;
- Allergy to delamanid or metronidazole;
- Prior treatment with nitroimidazole agents (i.e. pretomanid/PA-824)
- Can be given with ARVs

# Monitoring for children on DLM

- Baseline: ECG to assess QTc interval and albumin in addition to standard MDR-TB assessments.

- Follow-Up: Monthly ECG to assess for QTc prolongation (although less frequent monitoring could be considered in children with a normal baseline QTc interval if access to electrocardiographic monitoring is a challenge) in addition to standard MDR-TB assessments.

# Can DLM be used instead of the injection?

- Could be considered in older children, especially given the high rates of morbidity and disability associated with the injectable agent.
- In children with severe disease, injectable should probably be continued unless there is evidence of resistance or toxicity

# Bedaquiline

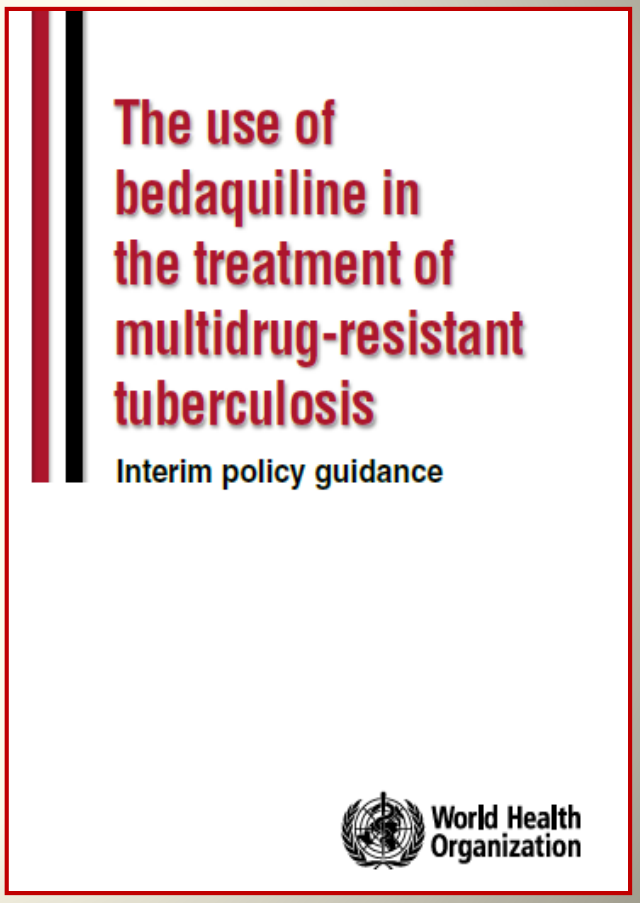
- Tablets come in 100mg form
- Two-year shelf-life, no cold chain required
- Adult dose is 400mg once daily for 2 weeks followed by 200 mg thrice weekly for 22 additional weeks
- Half life is 5.5 months
- Cross-resistance seen with CFZ
- Drug-drug interactions: avoid with efavirenz, cannot give with rifamycins

# BDQ in Children

- Formal PK and safety study in children ages 6-17 enrolling in Durban
- Programmatic use in adolescents as young as 12 years of age
- Individual patients with NTMs as young as 9 years of age

# WHO Guidance on BDQ (2013)

- Careful selection of patients
- Close monitoring
- Use in WHO approved regimen
- aDSM
- Due process of informed consent
- Use if resistance to intolerance to SLDs



# BDQ Recommendation 1

- Bedaquiline could be considered for the treatment of children aged 12 years and above in settings where delamanid is not available, for the same indications as for adults: those with MDR-TB in whom a four-drug regimen plus pyrazinamide cannot be constructed due to resistance or significant intolerance
- Applies to confirmed and probable MDR-TB in children

# BDQ Recommendation 2

- Bedaquiline could be considered on a case by case basis in children who are less than 12 years old if the child meets the criteria described above and no suitable alternatives are available.  Delamanid, however, would be the preferred novel agent in this population, given that there is some data on safety and dosing in children.

# Dosing and duration

*Recommended Dose:*

- Adolescents ≥12 years old: 400mg daily for 14 days followed by 200mg given thrice weekly for an additional 22 weeks

- Duration: 24 weeks; longer duration could be considered on a case-by-case basis.

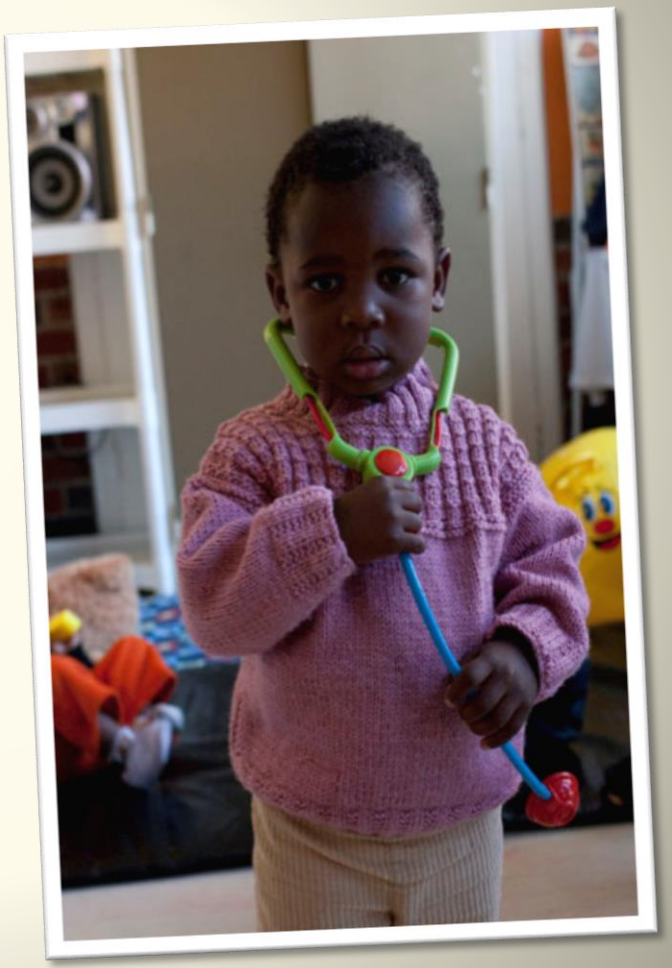
# Contraindications

- Baseline QTc interval greater than 450 msecs that does not correct with medical management;
- Allergy to bedaquiline.
- Avoid use with Efavirenz, rifamycins, other CYP3 inducers and inhibitors

# Monitoring for Children on BDQ

- Baseline: ECG to assess QTc interval in addition to standard MDR-TB assessments.

- Follow-Up: Monthly ECG to assess for QTc prolongation in addition to standard MDR-TB assessments.



# Combination BDQ and DLM

- Case reports of successful use of the combination of bedaquiline and delamanid in adults are emerging[7]. Treatment regimens containing both bedaquiline and delamanid in the pediatric population could be considered on a case-by-case basis, if no other treatment options exist, in consultation with expert clinicians.

# Consultation with Experts

- We are here to support you in the field
- Contact Sentinel Project at TBSentinelproject@gmail.com
- Contact ERS Consilium at https://www.tbconsilium.org/

# Cost and Availability of BDQ and DLM

- Both available from the GDF
- For Global Fund eligible countries, BDQ can be accessed through the USAID donation program free of charge.
- For Global Fund eligible countries, DLM can be accessed for USD 1700 for a 6 month course, and Global Fund monies can be used to pay for it.
- Free TA can be provided by USAID (ymukadi@usaid.gov) or the DR-TB STAT Task Force (jenniferfurin@gmail.com)

# Conclusions

- Children will benefit from the use of new drugs in much the same way adults have.
- PK and safety data is needed but children should not be denied these medications while waiting for these data.
- Close follow up and assessment of cohorts of children on these drugs can contribute to the growing body of evidence on their safety.
- Children deserve access to the best available treatments

# Contact/Information

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# Thank you!