RAPID CLINICAL ADVICE

The Use of Delamanid and Bedaquiline for Children with Drug-Resistant Tuberculosis

Sentinel Project
on pediatric drug-resistant tuberculosis

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Introduction

For the first time in almost 50 years, there are two new drugs—delamanid and bedaquiline—available to treat individuals with multidrug-resistant tuberculosis (MDR-TB). This rapid clinical advice document is meant to provide clinical recommendations on their use by providers in the field caring for children. The document builds on the current experience with bedaquiline and delamanid in adult populations, including data from clinical trials, expanded access/compassionate use, and programmatic implementation. It also considers the results of available data from clinical trials on delamanid in children, and the compassionate use of both delamanid and bedaquiline in children and adolescents.[1]

The World Health Organization (WHO) has issued interim guidelines on the use of bedaquiline and delamanid for the programmatic treatment of MDR-TB, and specifies that these medications should be used under the following five conditions: 1) there is careful selection of patients; 2) there is close clinical monitoring; 3) the drugs are used as a part of a combination regimen based on WHO principles; 4) there is a due process for and documentation of informed consent; and 5) there is active monitoring and management of adverse events.[2] These policies also apply to the use of new drugs in pediatric populations.

The target audience of this rapid clinical advice includes clinicians, nurses, lay health personnel and others working with children and adolescents with MDR-TB. This document could also be used by program managers, donors, and public health practitioners, as it represents the current state-of-the-art in the clinical management of children with MDR-TB. The goal of this document is to provide practical advice to persons on the frontlines of MDR-TB treatment. It attempts to level the playing field in the treatment of children with this disease and to ensure there is no longer a “double standard” in MDR-TB care, where adults have access to novel therapies but children do not benefit adequately yet. It advocates for careful assessment of the potential risks of using new MDR-TB drugs versus their benefits in children and adolescents.

Delamanid

Delamanid is recommended for the treatment of adults (aged 18 years and older) with MDR-TB and resistance or significant intolerance to second-line anti-TB medications, and for all adults with MDR-TB at high risk of treatment failure. Unlike most drugs used for MDR-TB in children, delamanid has been evaluated for its pharmacokinetic (PK) properties and safety in HIV-uninfected children: preliminary results are already available for children as young as six years of age[3,4] and studies are ongoing in younger children. These data, combined with the fact that delamanid will soon be available for procurement from the Global Drug Facility (GDF), means that the pediatric population will finally have access to a therapeutic innovation that could improve outcomes and decrease toxicity of regimens for children with MDR-TB.

In this setting, given the current lack of formal pediatric recommendations on the use of delamanid, the Sentinel Project issues the following rapid clinical advice on the use of delamanid in children with MDR-TB. As with the use of delamanid in adults, this drug should be given to children on an individualized basis or in settings where programmatic management of multidrug-resistant TB is being implemented according to international standards or care.

Treatment Recommendations for Delamanid in Children

1) Delamanid can be considered for a) children with confirmed MDR-TB and additional resistance to one or more of the second-line agents (based on Drug Susceptibility Testing - DST), for b) children with probable MDR-TB and additional resistance to one or more of the second-line agents (i.e. children exposed to a source case with such a drug resistance profile), or for c) children who are failing MDR-TB therapy. Delamanid should not be added as a single drug to a failing regimen and careful adherence support must be provided to the child and his or her family during treatment.

All children treated with delamanid should undergo close clinical monitoring (see monitoring recommendations below) and there should be careful documentation of the treatment experience and results.

Rationale: The WHO interim policy recommends that delamanid be given to adults with these indications, based on a careful review of phase IIb clinical trial data.[5] Adult efficacy data for anti-tuberculosis treatment should be extrapolated to the pediatric population,[6] and therefore these same indications should be followed in children. MDR-TB can be challenging to confirm bacteriologically in children,[7] so children with probable MDR-TB, diagnosed based on clinical evidence of TB and exposure to a source case that meets criteria to receive delamanid should also qualify to receive delamanid.

Children who have a known allergy to delamanid should not receive the drug. Delamanid may not be effective in children who have been previously treated with delamanid or another nitroimidazole agent (i.e. pretomanid), although there are likely to be few children who have experience with either of these medications.

2) Delamanid can be considered for any child on MDR-TB treatment who develops significant intolerance to one or more of the second-line drugs. The offending agent should be replaced with delamanid at the earliest sign of intolerance.

Rationale: The WHO recommends that delamanid be given to adults with these indications and this can be extrapolated to the pediatric population. Delamanid is an important therapeutic option for children with MDR-TB given the multiple and serious adverse effects associated with the current second-line agents, especially those associated with the injectable agents.[8] Although there is less clinical experience with delamanid than with most of the other second-line agents, the appearance of a significant adverse event should lead to cessation of the causative medication with delamanid then initiated in its place. Systematic monitoring for toxicity from all TB drugs should be a routine part of the care of children with MDR-TB.

3) Delamanid can be considered for any child on MDR-TB treatment who is at high risk of treatment failure. This would include children with co-morbidities such as HIV, diabetes, or malnutrition and also children with extensive disease (defined as pulmonary disease with the presence of bilateral involvement or the presence of cavities or those with severe forms of extrapulmonary disease). Delamanid should not be added as a single drug to a failing regimen and adherence support must be provided to the child and his or her family during treatment.

Rationale: The WHO recommends that delamanid be given to adults with these indications and this can be extrapolated to the pediatric population. Although children with MDR-TB usually have better outcomes than those seen in the adult population,[9] there are data showing that children with HIV, other immuncompromising conditions, and extensive disease are at higher risk of treatment failure.[10,11] Of note, there are currently only limited data on the use of delamanid in adults with HIV and limited PK data on drug-drug interactions with anti-retrovirals; however there do not appear to be any significant interactions with antiretroviral therapy. In adults, HIV infection is not a contraindication to receiving delamanid and no changes to antiretroviral therapy are currently recommended with delamanid treatment. There is no data on cerebrospinal fluid penetration of delamanid, but its high protein binding suggests it may have limited penetration; this should be considered when constructing a treatment regimen for persons with MDR-TB meningitis.

4) Delamanid can be given to children with MDR-TB and the indications specified above, if they are aged 6 years and above and their weight is 20kg or more, as PK and safety data to guide optimal dosing is available for this population

Rationale: The PK and safety studies of delamanid in children support the following dosing recommendations.[3,4]

Weight Range	Dose	Duration
20-34kg	50 mg twice daily	For 24 weeks
35 kg and above	100mg twice daily	For 24 weeks

5) Delamanid might be considered on a case-by-case basis in children with MDR-TB and limited treatment options who are under the age of 6 years or who weigh less than 20kg, if the likely benefit is considered to outweigh the risk

Rationale: Evaluation of the PK and safety of delamanid in younger children is ongoing and studies in children with MDR-TB and HIV co-infection are planned. Although there are currently no data on the PK of delamanid in young children and although a pediatric formulation is not available, but there is no reason to expect unique adverse events or toxicities in younger children. Dosing recommendations of second-line anti-tuberculous drugs in children have traditionally been extrapolated from the doses in adults while formal PK studies are pending in children. Despite these uncertainties, there may be children in this age group where the likely benefits of using delamanid outweigh the potential risks. It is recommended that the use of delamanid in children in this age group/weight range be considered on a case-by-case basis after a careful assessment of the benefits and risks and after consultation with clinical experts in pediatric MDR-TB. Expert opinion can be obtained from the Sentinel Project by contacting tbsentinelproject@gmail.com or by contacting the TB consilium at https://www.tbconsilium.org/ Both groups provide free, rapid expert advice on challenging pediatric TB cases.

6) Delamanid could be considered to replace the injectable agent in the initial MDR-TB treatment regimen for children greater than 6 years of age and who weigh 20kg or more

Rationale: Although there are currently no data to support the routine substitution of delamanid for a second-line injectable within the MDR-TB regimen, providers could consider using delamanid instead of the injectable drug in children with MDR-TB given the risk of permanent sensorineural hearing loss in children (reported in up to 25% of children)[8] and the pain, distress and requirements for hospitalization that are associated with daily intramuscular injections. Both drugs/categories of drug have only ever been assessed when given in combination with other agents;[12] it is therefore challenging to tease out the individual contribution of specific drugs in an MDR-TB regimen. However, there is higher quality evidence base for the inclusion of delamanid than there is for the inclusion of the injectable[13] given that delamanid has been assessed in randomized placebo-controlled clinical trials for MDR-TB while the injectables have not. There

also exists a substantial clinical experience treating children with non-severe MDR-TB disease with an injectable-sparing regimen, with good outcome[14] and injectable-free regimens for children with non-severe disease have been endorsed by the WHO in their most recent MDR-TB treatment guidelines.[15]

7) *Combination therapy with bedaquiline and delamanid in children might be considered* where other treatment options do not exist, after a careful assessment of the benefits and risks, and after consultation with clinical experts in pediatric MDR-TB.[16] The combined treatment should be administered in qualified clinical centers and after receiving expert opinion on the use of the two drugs in combination. Expert opinion can be obtained from the Sentinel Project by contacting tbsentinelproject@gmail.com or by contacting the TB consilium at https://www.tbconsilium.org/.

8) *The recommended course of delamanid is 24 weeks, but longer durations could be considered in children on a case-by-case basis where there are limited therapeutic options*

Rationale: A 24 week course of delamanid was chosen based on the ease of reaching a trial endpoint in adults with MDR-TB and not for clinical reasons. In the phase IIb trial of delamanid, a substantial number of patients were given delamanid for 8 months without any additional safety issues.[4] Prolongation of the 24 week course, in cases where other active drugs are not available/tolerated should be decided on a case-by-case basis after consultation with clinical experts either via the Sentinel Project (tbsentinelproject@gmail.com) or the TB consilium (https://www.tbconsilium.org/).

Safety Monitoring and Programmatic Recommendations for Delamanid in Children

1) ECG monitoring to assess for QTc prolongation should be carried out at baseline and then on monthly basis for children on delamanid

Rationale: Mild to moderate QTc prolongation was observed in the phase IIb clinical trials in adults, although no clinical cardiac complications were observed.[17] Children with a baseline QTc interval of greater than 500msec should not be started on delamanid until that QTc interval is below 500msec. Children on delamanid may be at risk for mild to moderate QTc prolongation, although the clinical significance of this finding, should it develop, is unclear. The use of other QTc prolonging TB medications (i.e. moxifloxacin, clofazimine, bedaquiline) should be limited where possible, although this may be challenging in the treatment of MDR-TB. Other baseline and follow-up tests for children on delamanid should follow guidelines for programmatic management of MDR-TB and include, at a minimum, clinical assessment for adverse events, dose re-evaluation, monthly liver function tests and potassium while the child is on delamanid.

2) Children with MDR-TB on delamanid would likely benefit from nutritional support and protein supplementation: appropriate nutritional support should be provided

Rationale: Delamanid is metabolized by albumin, and there may be a higher risk of adverse events in persons with low albumin.[18] Nutritional support should be considered for all children with MDR-TB, given the more severe disease and poorer treatment outcome in children with poor nutrition,[19] but in particular those on delamanid who have a low albumin would likely benefit from increased protein intake, which could be provided in the form of locally available foodstuffs such as beans, peas, other legumes, and eggs. Food, in particular high-fat meals, may improve delamanid absorption, and delamanid should be administered with meals as much as possible.

3) As is recommended for adults on delamanid, all children who receive delamanid should be carefully followed as a cohort and be included in active Drug Safety Monitoring and Management (aDSM) planning and implementation

Active Drug Safety Monitoring and Management is a strategy recommended by the WHO[20] to ensure any serious and severe adverse events experienced by persons on new TB drugs are reported to a centralized monitoring body within the country in order to continue building the safety database of these drugs.

Bedaquiline

Bedaquiline has been recommended by the WHO for programmatic use in adults since June 2013. Bedaquiline is recommended for adults with MDR-TB who have resistance or significant intolerance to an injectable agent, a fluoroquinolone or both, or in whom a WHO-recommended four-drug regimen cannot be constructed for reasons of resistance or intolerance.[21] There have been no formal studies to date on bedaquiline in children under the age of 18 years, although there is growing observational evidence of the safety and efficacy of bedaquiline in adolescents.[22] Currently, bedaquiline may be more widely available than delamanid, given its earlier regulatory approval by the US FDA in 2012 and the EMA in 2014 and might therefore be considered in children who are in settings where delamanid is not yet available.
The Sentinel Project issues the following clinical guidance on the use of bedaquiline in children with MDR-TB. As with the use of bedaquiline in adults, this drug should be given to children in settings where programmatic management of MDR-TB is being implemented according to international standards of care.

Treatment Recommendations for Bedaquiline in Children

1) Bedaquiline can be considered for children ages 12 years and above with resistance or significant intolerance to an injectable agent, a fluoroquinolone or both, for children who are failing MDR-TB therapy, or in whom a WHO-recommended four drug regimen cannot be constructed for reasons of resistance or intolerance. Bedaquiline should not be added as a single drug to a failing regimen and adherence support must be provided to the child and his or her family during treatment.

All children treated with bedaquiline should undergo close clinical monitoring (see monitoring recommendations below) and there should be careful documentation of the treatment experience and results

Rationale: Bedaquiline PK and safety has not been formally evaluated in children. Persons under the age of 18 years were not included in the phase IIb bedaquiline trials,[23] but part of this was due to the challenges of obtaining ethical approval and consent in this population.[24] Adolescents aged 12 years and above generally have similar PK parameters to adults for most medications, and even stringent regulatory agencies have agreed that adult dosing recommendations can be extrapolated to this population.[25] Multiple TB programs are already giving bedaquiline for adolescents as young as 12 years at the same doses as recommended for adults (400mg daily for 14 days followed by 200mg three times a week), after careful consideration of the risks and benefits.[26] These experiences are being considered for publication but, in general, studies in adolescents have found similar efficacy and safety as seen in the adult population. Children with an allergy to bedaquiline should not be given the drug, although it should be noted that allergies in the adult population are extremely rare.

2) Bedaquiline might be considered on a case-by-case basis in children with MDR-TB and limited treatment options who are under the age of 12 years and where delamanid is not available

Rationale: Studies of bedaquiline PK and safety in HIV-infected and uninfected children with MDR-TB are planned but are not yet open. There is currently no information on the appropriate dose in young children and no available pediatric formulation. However, dosing recommendations of second-line anti-tuberculosis drugs in children have traditionally been extrapolated from the doses used in adults while formal PK studies are pending in children. Despite these uncertainties, there may be cases in this age group in which the likely benefits of using bedaquiline may outweigh the potential risks. It is recommended that the use of bedaquiline in children less than 12 years of age only be considered after a careful assessment of the benefits and risks and after consultation with clinical experts in pediatric MDR-TB. Expert opinion can be obtained from the Sentinel Project by contacting tbsentinelproject@gmail.com or by contacting the TB consilium at https://www.tbconsilium.org/.

3) The recommended course of bedaquiline is 24 weeks, but longer durations could be considered in children on a case-by-case basis where there are limited therapeutic options

Rationale: A 24 week course of bedaquiline was chosen based on the ease of reaching a trial endpoint and not for clinical reasons, although bedaquiline does have prolonged terminal elimination half-life of 5.5 months.[27] Prolongation of the 24 week course should be decided on a case-by-case basis after consultation with clinical experts either via the Sentinel Project (tbsentinelproject@gmail.com) or the TB consilium (https://www.tbconsilium.org/)

4) Bedaquiline should not be used with efavirenz, as efavirenz lowers the effective concentration of bedaquiline

Children on antiretroviral therapy should not receive efavirenz while on bedaquiline and should instead receive nevirapine. Protease inhibitors also influence bedaquiline exposure. A regimen composed of triple nucleotide reverse transcriptase inhibitors is an option, however these regimens may not be as effective for viral load suppression. If a nevirapine-containing regimen is not appropriate for a patient, then a choice of antiretroviral regimen should be decided on a case-by-case basis after consultation with clinical experts either via the Sentinel Project (tbsentinelproject@gmail.com) or the TB consilium (https://www.tbconsilium.org/)

5) ***Combination therapy with bedaquiline and delamanid in children might be considered*** where other treatment options do not exist, after careful assessment of the benefits, and risks and after consultation with clinical experts in pediatric MDR-TB. The combined treatment should be administered in qualified clinical centers and after receiving expert opinion on the use of the two drugs in combination. Expert opinion can be obtained from the Sentinel Project by contacting tbsentinelproject@gmail.com or by contacting the TB consilium at https://www.tbconsilium.org/.

Safety Monitoring and Programmatic Recommendations for Bedaquiline in Children

1) Before starting bedaquiline, children should undergo baseline ECG and then, if bedaquiline is started, monthly ECG monitoring should be carried out to assess for QTc prolongation

Rationale: Moderate QTc prolongation was seen in the adult phase IIb trials of bedaquiline and has been reported in programmatic use. Although the clinical implications of this QTc prolongation are unclear, it is recommended all children being treated with bedaquiline have a baseline and monthly ECG to assess the QTc interval. Children with a baseline QTc interval of greater than 450msec should not be started on bedaquiline until that QTc interval is below 450msec. The use of other QTc prolonging medications (i.e. moxifloxacin, clofazimine, delamanid) should be limited where possible. Other baseline and follow-up tests for children on bedaquline should follow guidelines for programmatic management of MDR-TB and include, at a minimum, monthly liver function tests and potassium levels while the child is on bedaquiline.

2) ***As is recommended for adults on bedaquiline, all children who receive bedaquiline should be followed carefully as a cohort and be included in active Drug Safety Monitoring and Management (aDSM) planning and implementation***

Rationale: Active Drug Safety Monitoring and Management is a strategy recommended by the WHO[20] to ensure any serious and severe adverse events experienced by persons on new TB drugs are reported to a centralized monitoring body within the country in order to continue building the safety database of these drugs.

The Sentinel Project recognizes that this exciting time in the treatment of MDR-TB requires increased support and collaboration between clinical providers so that experience can be shared and developed in an expedited fashion. To this end, our clinical experts are available at any time to answer questions about the use of new drugs in children in general or about their use in specific patients. For questions, to review a case, or for more information, please contact the following email address and you will receive a reply within 24 hours:
tbsentinelproject@gmail.com

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