



Every breath counts



Sentinel Project
on pediatric drug-resistant tuberculosis

TAG

Treatment Action Group

Statement on Injectable-Free Regimens for Children under the Age of 12 Years with Rifampicin-Resistant Tuberculosis

We applaud the announcement from the South African National Department of Health in June 2018 that bedaquiline will now be used to replace the injectable agent in the routine treatment of rifampin-resistant/multidrug-resistant tuberculosis (RR/MDR-TB) in patients 12 years of age and older, and congratulate the leadership of the South African National TB Program for being the first country to recommend all-oral regimens for RR/MDR-TB treatment. The accumulating data on decreased mortality and excellent safety with the drug bedaquiline for the treatment of patients with RR/MDR-TB tuberculosis provides compelling evidence to support this change. We note with concern, however, that the lack of data available to inform bedaquiline dosing and safety in children may preclude children under the age of 12 years from accessing the benefits of all-oral RR/MDR-TB treatment in the near future.

Because as many as 1 in 4 children develop hearing loss with injectable therapy and because hearing loss has a more significant impact on younger children who are developing language and social skills, we call for policies that support all-oral regimens for the treatment of persons less than 12 years of age both in South Africa and globally. The World Health Organization's 2016 drug-resistant (DR)-TB treatment guidelines explicitly recommend that children with non-severe disease can be treated with injectable-free regimens. For the purposes of this recommendation, "non-severe" was defined as an absence of bacteriological confirmation, unilateral, or non-cavitary pulmonary TB disease.

For children with "severe" forms of TB (including those with bacteriological confirmation, bilateral pulmonary disease, cavitary disease, disseminated TB, TB meningitis, and osteoarticular TB) there are multiple options for replacing the injectable agent in children. One or more of the following drugs could be considered depending on the child's individual circumstances¹:

1) Bedaquiline: Phase 1/2 pediatric trials are finally ongoing and are enrolling children as young as six years of age; initial dosing and safety data should be available by the end of 2018. Once dosing and safety are established in younger age groups, bedaquiline should be the drug of

choice to replace the injectable agents (given good efficacy data in adults). A pediatric formulation is in development and the adult 100 mg bedaquiline tablet can be dissolved in water without altering its bio-availability in healthy adult volunteers, paving its way for use in young children until the pediatric formulation becomes available. The TB community must call on Janssen to urgently release any existing safety and dosing data as it becomes available, to inform its use in children <12 years of age, especially those <6yrs of age who have not been studied to date.

2) Delamanid: this drug has been tested in children of all ages and has shown to be safe in children age 3 years and above (data on the 0-2 years cohort are currently being assessed) with available dosing guidance. A pediatric formulation is used in the ongoing trials, but will not be commercially available for some time. *Delamanid is the currently recommended candidate to replace injectable agents in children with severe RR/MDR-TB down to age 3 years. Delamanid could be considered in children under the age of 3 years, once new safety and dosing data becomes available.* The availability of delamanid is a serious challenge, and urgent action is needed to improve access to this medication for children. The TB community must call on Otsuka to urgently release any existing safety and dosing data not yet in the public domain, to inform the use of delamanid in children.

3) PAS: There is extensive experience with the use of PAS in children of all ages. As for other drugs there are limited data to support its specific role in RR/MDR-TB treatment; however, resistance to PAS is low and older studies in the literature suggest it is effective and may protect other drugs from developing resistance. PAS is available as granules and can be given with a dosing spoon in children. Children on PAS need to have their thyroid function assessed monthly. There is accumulating experience with using PAS as a substitute for the injectable in children with non-severe RR/MDR-TB.

4) Linezolid: this drug has been given to children of all ages with bacterial infections for short durations and is increasingly being used in children with RR/MDR-TB. Dosing could be extrapolated from adults—although optimal linezolid dosing even in adult populations is still being determined—and there are challenges obtaining the granule/syrup formulation. A pediatric water dispersible tablet is in development. There is a substantial risk of serious adverse effects with longer term usage, including bone marrow suppression (anaemia, neutropaenia, thrombocytopaenia), peripheral neuropathy, and more rarely optic neuropathy or other adverse effects. Children on linezolid must have full blood count monitored monthly, should be assessed for peripheral neuropathy monthly and should have regular visual assessments. It is acknowledged that performing these assessments in young children can be challenging. Linezolid may be a good substitute for the injectable among patients with extensive, severe disease and those with TB meningitis (good cerebrospinal fluid [CSF] concentrations achieved); however, there should be access to careful safety monitoring. Short-term (i.e. 8-12 weeks) of linezolid could be used followed by delamanid or PAS as a strategy for reducing toxicity, as long as single drugs are not added to a failing regimen.

Some children with severe RR/MDR-TB disease may still need an injectable, but the risk and benefits should be considered on an individual basis. In general, all attempts to provide an all-oral regimen should be pursued. In such situations where a child needs an injectable agent, all steps should be taken to minimize toxicity (including therapeutic drug monitoring by checking a single serum trough level) and ongoing monitoring of hearing. The injectable should be discontinued at the first sign of ototoxicity developing and replacement considered, depending on the individual circumstances and availability of other options.

Children with central nervous system RR/MDR-TB (TB meningitis and miliary TB) need special consideration drugs penetrating the CSF should be prioritized. Linezolid has excellent CSF penetration and should be given to all children with TB meningitis.

These are exciting times in the treatment of RR/MDR-TB and the landscape is changing rapidly. It is important that all new TB drugs should have a pediatric development plan and that new data are made available as rapidly as possible. There is no need to repeat efficacy trials in children, but there is an imperative to establish safety and optimal dosing options in children, as soon as efficacy in adult trials has been established. It is also vital that guidelines are updated frequently so that children can benefit from the most up-to-date information. This changing landscape can be challenging for healthcare providers who are looking after children with RR/MDR-TB. However, there is a supportive community that can assist in complex and difficult cases. Expert opinion can be obtained from the Sentinel Project by contacting tb sentinelproject@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.

¹ Of note, children with RR-TB that has additional resistance to the fluoroquinolones may need more than one of these agents. Those with fluoroquinolone resistance and severe disease should still receive an injectable in most cases, and when the injectable is used, age-appropriate baseline and monthly audiology assessments are required.