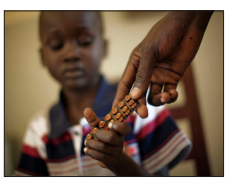
Children deserve simple, short, safe, and effective treatment for rifampicin-resistant tuberculosis



UNDP South Sudan/Brian Sokol

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Historically, treatment regimens for rifampicin-resistant tuberculosis were composed of five to seven older, second-line tuberculosis drugs, including injectable agents that resulted in frequent and sometimes permanent adverse effects in some patients, that were given for 18–24 months and were only modestly effective. The development of multiple novel and repurposed tuberculosis drugs has substantially changed the approach to rifampicin-resistant tuberculosis treatment, but children have not benefited equitably.

On the basis of emerging results from pivotal trials, in December 2022, WHO recommended a 6-month, once-per-day regimen of bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaLM) as a first-line treatment for individuals older than 14 years with rifampicin-resistant tuberculosis.[1] The inclusion of patients as young as 14 years in these pivotal trials, even though people aged 14–17 years were enrolled in small numbers, allowed WHO to extend their recommendation to this age group, thus avoiding unnecessary delays in access to this much-needed treatment innovation for older adolescents. Most older adolescents and adults aged 18 years or older treated for rifampicin-resistant tuberculosis can now expect to receive an effective, all-oral, once-per-day, four-drug regimen for 6 months.

Although extrapolating the efficacy of BPaLM to children aged 13 years or younger with rifampicin-resistant tuberculosis is reasonable, two crucial barriers prevent paediatric access to this regimen. First, although pretomanid was approved by the US Food and Drug Administration in 2019 for use in adults as part of the bedaquiline, pretomanid, and linezolid regimen, paediatric evaluation has been substantially delayed. The pharmacokinetics and safety of a single dose of pretomanid in children and adolescents will be evaluated in the IMPAACT 2034 trial (NCT05586230), which is expected to open in 2023. A subsequent multidose pretomanid paediatric trial will be needed to substantiate these doses and evaluate its safety long term. Pretomanid is thus unlikely to be available for children for several years. Second, although linezolid has potent antimycobacterial activity, its use for 6 months results in frequent adverse effects, including myelosuppression and neuropathies. These adverse events are associated with longer duration and increased exposure.[2] For adults with rifampicin-resistant tuberculosis who typically have severe disease and traditionally poor outcomes, the risk–benefit profile of 6 months of linezolid is favourable. However, for children who tend to have paucibacillary, less severe tuberculosis, and better outcomes, this risk–benefit profile is less acceptable. Shorter linezolid durations would substantially improve this risk–benefit profile, reducing the risk of developing severe anaemia, peripheral neuropathy, and optic neuropathy, which, while rare, might have long-term consequences.

Although some experts prescribe shorter, less intense regimens for rifampicin-resistant tuberculosis,[3] WHO still recommends a 9–11-month treatment regimen for children, composed of a 4–6-month intensive phase with seven drugs (ie, bedaquiline, levofloxacin, clofazimine, pyrazinamide, ethionamide, high-dose isoniazid, and ethambutol) and a 6-month continuation phase with four drugs (ie, levofloxacin, clofazimine, pyrazinamide, and ethambutol).[1] Children respond as well as, or better than, adults to tuberculosis treatment. However, compared with adults, this currently recommended paediatric rifampicin-resistant tuberculosis treatment regimen includes more drugs than BPaLM (ie, seven *vs* four) and older drugs that are less well tolerated and less likely to be effective for a longer duration than BPaLM (ie, 9–11 months *vs* 6 months). Currently recommended regimens, although generally safe, are not always well tolerated, with clofazimine-associated skin discoloration and ethionamide-associated nausea and vomiting frequently causing challenges for children and caregivers. Despite the current recommendation that injectable agents be avoided, they are still used in some countries and result in a high risk of permanent sensorineural hearing loss. As children overall respond well to treatment, ensuring the safety and tolerability of regimens, especially to avoid adverse effects with potentially long-term consequences, is imperative.

An attractive adaptation of the BPaLM regimen for children would substitute delamanid for pretomanid and shorten the duration of linezolid. Treatment

with 6 months of bedaquiline, delamanid, and a fluoroquinolone with 2 months of linezolid could allow children access to an efficacious, all-oral regimen similar to that used in adults. Delamanid and pretomanid are in the same class of drugs (ie, nitroimidazoles) with similar mechanisms of action. At exposures expected with current dosing of both compounds, there appears to be minimal difference in activity in preclinical evaluations.[4] There are no high-quality clinical data directly comparing the two drugs, but a reasonable assumption is that they will have similar activity. This assumption is further supported by preliminary results from the South African BEAT-Tuberculosis trial, which enrolled patients aged 6 years or older and showed that a 6-month delamanid-containing regimen was highly effective,[5] and from the BEAT-India trial.[6] Delamanid is now recommended by WHO for children of all ages and is available in a dispersible tablet formulation.

Furthermore, a shorter duration of linezolid would provide benefit while reducing the risk of adverse effects. The ZeNix trial showed that adults with rifampicin-resistant tuberculosis receiving regimens with 9 weeks of linezolid 600 mg once per day had excellent outcomes with less toxicity than higher doses and longer durations of linezolid.[2] This shorter linezolid duration would result in a more appropriate and favourable risk–benefit profile for most children with rifampicin-resistant tuberculosis.

Ease of preparation and administration of any such regimen is also essential to address current poor acceptability in children as a result of complex regimens; these factors can lead to imperfect adherence and increased risk of poor outcomes. Bedaquiline is recommended as thrice-per-week dosing after a 2-week, once-per-day dosing loading phase, and delamanid is recommended as twice-per-day dosing. Once-per-day dosing for both drugs has now been studied in adults and is increasingly used, but also needs to be evaluated in children.[7–10] Modelling and simulation with existing paediatric bedaquiline and delamanid pharmacokinetic data would enable selection of once-per-day dosing strategies for children for evaluation in a trial. Simple, once-per-day dosing strategies of the overall regimen would improve acceptability and adherence to this regimen.

A trial addressing these targeted questions of safety, pharmacokinetics, outcomes, and acceptability of a once-per-day, simple regimen for children with rifampicin-resistant tuberculosis is a crucial priority. Although currently not possible to fully implement the novel BPaLM regimen for children, children receiving longer, more toxic regimens with higher pill burden than adults is unacceptable. A pragmatic alternative is available that should be evaluated immediately. To wait would be unacceptable.

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Anthony J Garcia-Prats, Graeme Hoddinott, Pauline Howell, Jennifer Hughes, Patrick Jean-Philippe, Soyeon Kim, Megan Palmer, H Simon Schaaf, James A Seddon, Elin Svensson, Anneke C Hesseling
garciaprats@wisc.edu

Department of Pediatrics, School of Medicine and Public Health, University of Wisconsin-Madison, Madison, WI 53705, USA (AJG-P); Desmond Tutu TB Centre, Department of Paediatics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa (AJG-P, GH, JH, MP, HSS, JAS, ACH); Clinical HIV Research Unit, Sizwe Tropical Disease Hospital, Wits Health Consortium, Department of Internal Medicine, University of the Witwatersrand, Johannesburg, South Africa (PH); National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA (PJ-P); Department of Biostatistics, Frontier Science Foundation, Brookline, MA, USA (SK); Department of Infectious Disease, Imperial College London, London, UK (JAS); Department of Pharmacy, Uppsala University, Uppsala, Sweden (ES); Department of Pharmacy, Research Institute for Medical Innovation, Radboud University Medical Center, Radboud University, Nijmegen, Netherlands (ES)

1 WHO. WHO consolidated guidelines on tuberculosis. Module 4: treatment—drug-resistant tuberculosis treatment, 2022 update. 2022. https://www.who.int/publications/i/item/9789240063129 (accessed March 5, 2023).

2 Conradie F, Bagdasaryan TR, Borisov S, et al. Bedaquiline–pretomanid–linezolid regimens for drug-resistant tuberculosis. *N Engl J Med* 2022; **387:** 810–23.

3 The Sentinel Project on Pediatric Drug-Resistant Tuberculosis. Management of multidrug-resistant tuberculosis in children: a field guide. 2022. http://sentinel-project.org/2022/03/22/fifth-edition-of-management-of-multidrug-resistant-tuberculosis-in-children-a-field-guide-now-available/ (accessed May 22, 2023).

4 Mudde SE, Upton AM, Lenaerts A, Bax HI, De Steenwinkel JEM. Delamanid or pretomanid? A Solomonic judgement! *J Antimicrob Chemother* 2022; **77:** 880–902.

5 Conradie F. High rate of successful outcomes treating RR-TB with a delamanid–bedaquiline regimen in BEAT Tuberculosis: an interim analysis. Union World Conference on Lung Health 2022; Nov 8–11, 2022 (LBTB-2074-11).

6 Padmapriyadarsini C, Vohra V, Bhatnagar A, et al. Bedaquiline, delamanid, linezolid and clofazimine for treatment of pre-extensively drug-resistant tuberculosis. *Clin Infect Dis* 2022; **76:** e938–46.

7 Salinger DH, Nedelman JR, Mendel C, Spigelman M, Hermann DJ. Daily dosing for bedaquiline in patients with tuberculosis. *Antimicrob Agents Chemother* 2019; **63:** e00463-19.

8 von Groote-Bidlingmaier F, Patientia R, Sanchez E, et al. Efficacy and safety of delamanid in combination with an optimised background regimen for treatment of multidrug-resistant tuberculosis: a multicentre, randomised, double-blind, placebo-controlled, parallel group phase 3 trial. *Lancet Respir Med* 2019; **7:** 249–59.

9 Tanneau L, Karlsson MO, Rosenkranz SL, et al. Assessing prolongation of the corrected QT interval with bedaquiline and delamanid coadministration to predict the cardiac safety of simplified dosing regimens. *Clin Pharmacol Ther* 2022; **112:** 873–81.

10 Mallikaarjun S, Chapagain ML, Sasaki T, et al. Cumulative fraction of response for once- and twice-daily delamanid in patients with pulmonary multidrug-resistant tuberculosis. *Antimicrob Agents Chemother* 2020; **65:** e01207-20.