

The World Health Organization (WHO) must recommend bedaquiline as part of the preferred regimen for multidrug-resistant tuberculosis (MDR-TB): A position statement from the Global TB Community Advisory Board (TB CAB)

The Global Tuberculosis Community Advisory Board (TB CAB) is a group of research-literate treatment activists from around the world who work in an advisory capacity to researchers and product developers conducting trials of new and repurposed tuberculosis (TB) drugs, regimens, and diagnostic technologies, and provide input on study designs, early access, regulatory, post marketing, implementation, and access strategies.

In recent months, the TB CAB has had in-depth discussions on the appropriateness of the current drugs frequently used to treat multidrug-resistant TB (MDR-TB). The urgency of these discussions is driven by the experiences of patients and clinicians and the accumulating evidence on the safety and efficacy of the newer TB drugs – especially bedaquiline – and whether an evidentiary threshold has been crossed where the use of newer TB drugs should be expanded and placed ahead of certain older drugs with well-known toxicities.

Recently announced findings from stage I of the STREAM trial (a phase III study conducted by the Union comparing a 9-12 month standardized regimen to 18-24 months of individualized treatment for MDR-TB, both of which are recommended by the WHO under certain conditions) have also created uncertainty regarding the optimal treatment for MDR-TB based on existing evidence. The STREAM trial did not show that the new shorter regimen is non-inferior to the previous 18–24 month standard of care for MDR-TB.¹ Under the conditions of a randomized, controlled clinical trial (RCT), both regimens achieved around 80 percent treatment success. While the shorter regimen performed similarly in the RCT (78 percent treatment success) to previously conducted cohort studies,² the control (the 18-24 month regimen) performed better in the RCT than commonly reported in program settings (80.6 vs. 54 percent treatment success).^{3,4} Still, we consider unfavourable outcomes in one of every five patients to be unacceptable, especially given that rates of treatment success are lower in non-trial settings. Furthermore, the shorter regimen offered no advantage in terms of adverse effects or mortality compared to 18-24 months of treatment.⁵ The TB CAB believes a case can be made for moving beyond the false dichotomy of choosing between two sub-optimally performing regimens to a third possibility: a regimen that includes one of the newer TB drugs.

The current WHO guidelines for the treatment of MDR-TB place patients at substantial risk of severe side-effects and drug-related toxicities, including dangerous kidney toxicity, electrolyte abnormalities, and hearing loss. The group of drugs that cause hearing loss in as many as 50 percent of patients are called aminoglycosides or injectable agents.^{6,7} They include amikacin, capreomycin, and kanamycin. Apart from hearing loss, patients also report that the injections are often very painful. According to current WHO guidelines, people with MDR-TB must receive an injectable unless they are tested for and show resistance or signs of hearing loss—in other words, only once

some hearing loss is acquired are patients offered another drug in place of the injectable. Based on anecdotal evidence, in most resource-limited, high TB burden settings, audiometry testing to monitor for hearing loss is not implemented. As a result, patients are allowed to go deaf, even though alternative treatment options exist.

The evidence for the effectiveness of injectables is unclear—one review recently published in *The International Journal of Tuberculosis and Lung Disease* stated “even though injectable agents have been recommended as core agents for treating MDR-TB for almost 20 years, the evidence base for the use of injectable agents is weak at best.”⁸ That review also points out the complete lack of RCTs evaluating the injectables for the treatment of MDR-TB. While evidence demonstrating the efficacy of the injectable agents is lacking, the evidence of hearing loss is undisputed.

In recent years, evidence of the safety and efficacy of bedaquiline has been accumulating. While a hard-to-explain imbalance in deaths in an earlier phase IIb trial of the drug raised concern,⁹ wide use of the drug since then suggests that the drug actually provides a mortality benefit.¹⁰ Accumulating evidence also strongly suggests that the drug is effective against MDR-TB, including as a substitute for the injectable agent.^{11,12,13,14,15}

When the safety profile of bedaquiline is compared to that of the most widely used injectables, bedaquiline is much safer and better tolerated, posing no risk of hearing loss and not requiring any injections. The main concern regarding bedaquiline is the drug’s effect on the heart’s rhythm (also known as QT-prolonging effects), although this effect has not appeared to have clinical significance to date.¹⁶ It is also important to acknowledge that other TB drugs also have QT-prolonging effects, including two used in the shorter regimen, moxifloxacin and clofazimine.¹⁷

Regarding efficacy, there is more rigorous randomized trial evidence of activity against TB available for bedaquiline than for any of the injectable agents. While we acknowledge that with the phase III trial underway, there is still some uncertainty about how bedaquiline’s efficacy will fare in a clinical trial with long-term outcomes, there is a growing body of evidence from the use of the drug in over 8,000 patients with DR-TB.¹⁸ A balanced consideration of all the evidence leaves us with no reason to prefer the use of injectables. The efficacy of bedaquiline is much clearer than that of the injectable agents, and its toxicity appears to be less common and less serious than that of the injectable agents.

We are aware that several important trials are currently underway that will more clearly address the QTc prolongation issue while using multiple newer drugs, and evaluate whether new drugs can replace the injectable agents in regimens to shorten treatment for MDR-TB (e.g. NEXT-TB, TB-Practecal, endTB, STREAM stage II, MDR-END, etc.).¹⁹ These trials will be critically important to providing a stronger evidence-base necessary to inform future decision-making.

However, even based on the current, admittedly incomplete evidence, the case to replace the injectables with bedaquiline is compelling and in our view scientifically sound. We are in no doubt that each of us, given the choice, would prefer a regimen with

bedaquiline to a regimen containing an injectable. We are also confident that most experts in the field would have the same preference should they be diagnosed with MDR-TB. We thus see no justification whatsoever as to why anyone with MDR-TB should still be subjected to the risk of, and the actual, severe side effects associated with the injectable agents.

Thus, as a matter of urgency, we urge the WHO to recommend bedaquiline as part of the preferred regimen for MDR-TB and to relegate the injectables for use only in more complicated cases, and with absolute requirement and assurance of monitoring for hearing loss. For children under 12 (in whom safety and dosing data on bedaquiline are not yet available) and others who do not qualify for bedaquiline, other newer drugs (i.e. delamanid or linezolid) should replace the injectable in bedaquiline's stead.

¹ Rusen ID, Nunn A, Phillips P, Bertel Squire S. STREAM trial (Evaluation of a Standardised Treatment Regimen of Anti-tuberculosis Drugs for Patients with Multidrug-resistant Tuberculosis): preliminary stage 1 results. Satellite session at: 48th Union World Conference on Lung Health, Guadalajara, Mexico; 12 October 2017.

² Trébucq A, Schwoebel V, Kashongwe Z, et al. Treatment outcome with a short multidrug-resistant tuberculosis regimen in nine African countries. *IJTD* 2017; 22(1): 17–25.

³ Rusen ID, Nunn A, Phillips P, Bertel Squire S. STREAM trial (Evaluation of a Standardised Treatment Regimen of Anti-tuberculosis Drugs for Patients with Multidrug-resistant Tuberculosis): preliminary stage 1 results. Satellite session at: 48th Union World Conference on Lung Health, Guadalajara, Mexico; 12 October 2017.

⁴ Global Tuberculosis Report 2017. Geneva: World Health Organization: 2017. Available from: http://www.who.int/tb/publications/global_report/en/.

⁵ Rusen ID, Nunn A, Phillips P, Bertel Squire S. STREAM trial (Evaluation of a Standardised Treatment Regimen of Anti-tuberculosis Drugs for Patients with Multidrug-resistant Tuberculosis): preliminary stage 1 results. Satellite session at: 48th Union World Conference on Lung Health, Guadalajara, Mexico; 12 October 2017.

⁶ Shin S S, Pasechnikov A D, Gelmanova I Y, et al. Adverse reactions among patients being treated for MDR-TB in Tomsk, Russia. *IJTLD* 2007; 11: 1314–1320.

⁷ Torun T, Gungor G, Ozmen I, et al. Side effects associated with the treatment of multidrug-resistant tuberculosis. *IJTLD* 2005; 9: 1373–1377.

⁸ Reuter A, Tisile P, von Delft D, et al. The devil we know: is the use of injectable agents for the treatment of MDR-TB justified? *IJTLD* 2017; 21(11): 1114–1126.

⁹ Food and Drug Administration (U.S). Anti-infective drugs advisory committee meeting briefing document TMC207 (bedaquiline). Treatment of patients with MDR-TB. NDA 204-384. 2012 November 28.

¹⁰ A 2016 review of available evidence on the use of bedaquiline in the treatment of multidrug-resistant tuberculosis. Geneva: World Health Organization: 2017. Available from: http://www.who.int/tb/publications/2017/GDGreport_Bedaquiline/en/

¹¹ Report of the guideline development group meeting on the use of bedaquiline in the treatment of multidrug-resistant tuberculosis. Geneva: World Health Organization: 2016. Available from:

http://www.who.int/tb/publications/2017/GDGreport_Bedaquiline/en/.

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- ¹² A 2016 review of available evidence on the use of bedaquiline in the treatment of multidrug-resistant tuberculosis. Geneva: World Health Organization: 2017. Available from: http://www.who.int/tb/publications/2017/GDGreport_Bedaquiline/en/
- ¹³ Gugliemetti L, Jaspard M, Le Du D, et al. Long-term outcome and safety of prolonged bedaquiline treatment for multidrug-resistant tuberculosis. *Eur Respir J* 2017; 49: 1601799.
- ¹⁴ Ndjeka N, Conradie F, Schnippel K, et al. Treatment of drug-resistant tuberculosis with bedaquiline in a high HIV prevalence setting: an interim cohort analysis. *IJTL D* 2015;19:979–985.
- ¹⁵ Borisov SE, Dheda K, Enwerem M, et al. Effectiveness and safety of bedaquiline-containing regimens in the treatment of MDR- and XDR-TB: a multicentre study. *Eur Respir J* 2017; 49: 1700387.
- ¹⁶ Yoon H-Y, Jo K-W, Nam GB, Shim TS. Clinical significance of QT-prolonging drug use in patients with MDR-TB or NTM disease. *IJTL D* 2017; 21(1): 996–1001.
- ¹⁷ Harausz E, Cox H, Rich M, et al. QTc prolongation and treatment of multidrug-resistant tuberculosis. *IJTL D* 2015; 19(4): 385–391.
- ¹⁸ Pai M, Furin J. Tuberculosis innovations mean little if they cannot save lives. *eLife* 2017; 6: e25956.
- ¹⁹ Low M. The tuberculosis treatment pipeline: A breakthrough year for the treatment of XDR-TB. In: 2017 pipeline report. New York: Treatment Action Group; 2017.