



# Recommending prolonged bedaquiline use for the treatment of highly resistant strains of tuberculosis

*To the Editor:*

We read with interest the article by CAMINERO *et al.* [1] proposing a standardised approach to treating both pre-extensively drug-resistant tuberculosis (pre-XDR-TB) and extensively drug-resistant tuberculosis (XDR-TB). This proposal is welcome considering the dearth of evidence-based recommendations on the optimal management of highly resistant tuberculosis (TB) [2]. Given the increasing recognition of the prevalence, morbidity and mortality associated with pre-XDR and XDR-TB, as well as the significant improvement in treatment outcomes with the use of novel and repurposed drugs [3], a clear policy for optimal management of these forms of TB is urgently needed.

We note that the article emphasises the use of one or both newer TB drugs, bedaquiline or delamanid, and the necessity to include them throughout the treatment or for a minimum of 13–15 months. Global discussion about the prolonged use of bedaquiline beyond 6 months for the treatment of some individuals with multidrug-resistant TB (MDR-TB) has increased [4]. Indeed, in 2017 the World Health Organization (WHO) Guidelines Development Group Meeting Report on the use of bedaquiline for the treatment of MDR-TB noted that bedaquiline has been used for longer than 6 months in some populations of limited size with no additional safety concerns being seen [5]. The accompanying frequently asked questions (FAQ) file noted that bedaquiline use beyond the 24-week recommendation in the 2013 guidelines can be considered at “...*the discretion of the treating clinician...*” [6]. Despite these statements, uncertainty about the prolonged use of bedaquiline has arisen amongst clinicians, technical assistance partners and national TB programmes, all of whom rely on WHO guideline updates to inform local practices and recommendations. Until additional clinical and programmatic evidence is gathered and analysed, prolonged use of bedaquiline is supported for selected individuals with MDR-TB for the following reasons: 1) The 24-week duration for bedaquiline administration was chosen to facilitate timely completion of Phase-IIb clinical trials. Additionally, extension of the corrected QT interval (QTc), the primary safety concern with bedaquiline, peaks between weeks 8 and 12 of treatment. 2) Clinical trial protocols approved by stringent regulatory authorities also allow for prolonged use of bedaquiline, even in patients without highly resistant forms of disease [7]. 3) Evidence from a cohort of people living with pre-XDR and XDR supports the efficacy and safety of prolonged bedaquiline use, suggesting a benefit in populations who have highly resistant TB or delayed culture conversion. Extension of bedaquiline use was associated with culture conversion in most subjects who received the drug for an extended period (median 361 days) with safety parameters comparable to those who received only 24 weeks of bedaquiline [8]. 4) There are a limited number of options available for treatment of patients with highly-resistant TB. Thus, halting a drug with both bactericidal and sterilising characteristics without having similar core drugs in the regimen to achieve a non-relapsing cure is risky. This is especially true in the case of bedaquiline, which has a prolonged terminal elimination half-life of almost 6 months. If this medication is stopped and there are not sufficient active agents left in the regimen, mycobacteria may multiply, which, in the setting of low levels of bedaquiline, could lead to the development of resistance. For patients already at high risk of treatment failure or relapse, this could leave them with few or potentially no efficacious therapeutic options. 5) The “off-label” use of medication to treat MDR-TB is common. Many types of medication, such as fluoroquinolones, linezolid and clofazimine, are recommended for use in MDR-TB without a registered indication for TB [9]. As MDR-TB is a public health emergency, such off-label use is not only clinically

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**Treatment of XDR-TB by prolonged use of bedaquiline is appropriate for some individuals**

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justified but essential from a public health and ethical perspective, and as such is supported by donor funding. These same considerations must be extended to the newer TB drugs, provided the experiences and outcomes of individuals receiving them in an off-label manner are carefully documented.

This is an exciting time in the treatment of people living with MDR-TB, especially for individuals with highly resistant forms of disease. While awaiting evidence from randomised clinical trials, clinicians, policy makers and people with TB must make choices about optimal use of the newer drugs. This requires a careful analysis of risks and benefits; however, in the case of bedaquiline use beyond 24 weeks, the potential benefits will outweigh the risks for many. As always, thoughtful discussions between providers and people receiving treatment should guide choices [10]; however, it is imperative that global and national policy makers and donors support the need for prolonged use of bedaquiline in patients with MDR-TB by allowing the decision about off-label use to be made by clinicians and people receiving treatment. Such use would be facilitated by unified but flexible guidelines on MDR-TB treatment. Implementation of such comprehensive guidelines would be further strengthened by having the donor community support innovation and operational research around prolonged bedaquiline administration.

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## Bedaquiline: how better to use it

*From the authors:*

We read with interest the correspondence by J. Furin and co-workers and we wish to thank them for their useful comments on our editorial proposing a rationale for a standardised regimen to manage difficult-to-treat cases affected by extensively drug-resistant tuberculosis (XDR-TB) or by so-called pre-extensively drug-resistant tuberculosis (pre-XDR; multidrug-resistant tuberculosis (MDR-TB) cases with additional resistance to fluoroquinolones or second-line injectable drugs) [1]. We agree with the comments by Furin and co-workers and the arguments discussing the possible use of the new drugs





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