



## **Bedaquiline bulletin: understanding the 2017 WHO Meeting Report on the use of bedaquiline for multidrug-resistant TB**

The DR-TB Scale-Up Treatment Action Team (DR-TB STAT) welcomes the recent announcement from the World Health Organization (WHO) renewing its 2013 conditional recommendation on the use of bedaquiline in people with multidrug-resistant tuberculosis (MDR-TB) for whom an effective regimen cannot be constructed due to resistance or intolerance. The Meeting Report ([www.who.int/tb/publications/2017/GDGreport\\_Bedaquiline/en/](http://www.who.int/tb/publications/2017/GDGreport_Bedaquiline/en/)) makes it clear that bedaquiline should be used for treating MDR-TB in people not eligible for the shorter MDR-TB regimen.

This support is based on expert meetings held in late June and early September 2016 in which data from cohorts including 537 patients receiving bedaquiline through compassionate use and expanded access programmes from a variety of countries—including South Africa, France, Armenia, and Georgia—were reviewed. Despite high proportions of extremely ill patients in these programmes, combined treatment success was 69.3% and serious adverse events were seen in only 7.4% of patients. 4.7% of patients had a QTcF interval that was greater than 500 msec.

Although the conditions for bedaquiline use remain the same as those issued in the 2013 interim guidance, some notable updates were made, including:

- Recommending bedaquiline for persons who do not qualify for the shorter regimen (patients whose TB is resistant to a medicine in the shorter regimen excluding isoniazid; with previous exposure for more than one month to a second line medicine included in the shorter regimen; or intolerance/increased risk of toxicity to one or more medicines in the shorter regimen);
- Continuing to recommend bedaquiline for persons with MDR-TB in whom a five drug regimen cannot be constructed for reasons of resistance or intolerance;
- Downgrading safety concerns, with potential risks now being deemed “moderate” instead of “large”;
- Acknowledging that while the certainty of the evidence reviewed is low, the impact of bedaquiline on culture conversion and mortality was large enough to outweigh the harms for most patients.

No changes were made in the official WHO recommendations on specific patient populations due to insufficient evidence to make a recommendation. However, it is important to note that the following groups were included in the cohorts reviewed:

- ***HIV co-infected persons receiving antiretroviral therapy***, who accounted for a quarter of patients;
- ***Adolescents***, who made up 7% of the persons who received bedaquiline, although the numbers are small (39 adolescents);
- ***Persons who had an extension of bedaquiline beyond 24 weeks***, who represented 5.9% of persons in the analysis.

DR-TB STAT also notes the following helpful clarifications in the language of the 2017 Meeting Report:

- Bedaquiline should be used with caution in patients receiving efavirenz (due to drug-drug interactions) or lopinavir/ritonavir (due to QT prolongation effects), while noting that bedaquiline has been safely used in large cohorts of people with HIV receiving antiretrovirals;
- Active drug safety monitoring and management (aDSM) – as opposed to the more onerous Cohort Event Monitoring – should be used to ensure reporting of adverse drug reactions;
- Informed consent policies should follow local practice for MDR-TB treatment in general.

*Based on the above, DR-TB STAT advocates for:*

- Countries to consider inclusion of HIV positive patients, adolescents, and persons requiring prolongation of bedaquiline beyond 24 weeks in national DR-TB treatment guidelines, provided the risk/benefit ratio favors the use of bedaquiline in this way. WHO cannot make a recommendation for extended use of bedaquiline beyond six months or use in adolescents given limited data, but there may be individuals in whom the potential benefits outweigh the risks;
- WHO to continue to lead the process of consolidating and finalizing the TB treatment guidelines, including updates on MDR-TB treatment and the use of bedaquiline and delamanid. This will provide national programmes and treatment providers with a unified guideline based on the latest evidence for the treatment of MDR-TB, as well as ensure consistency across products and regimens in the use of observational cohort data. Due to historically limited funding for TB research, current WHO recommendations on the treatment of MDR-TB are based on observational data alone without randomized, placebo-controlled clinical trials to support any of the drugs or regimens that are routinely recommended (except bedaquiline and delamanid);

- WHO to update guidance regularly and routinely as soon as new data are available, including a review of the more than 8000 patients who have been treated with bedaquiline, rather than waiting for the results of Phase III trials.

For questions or comments on the WHO Meeting Report or this bulletin, please contact DR-TB STAT via Ms. Natasha Morozova ([nmorozova@pih.org](mailto:nmorozova@pih.org)), Dr. Vivian Cox ([vivian.cox@me.com](mailto:vivian.cox@me.com)), or Dr. Jennifer Furin ([jenniferfurin@gmail.com](mailto:jenniferfurin@gmail.com)). Additional information on DR-TB STAT can be found at <http://drtb-stat.org/about/>.