Bedaquiline Bulletin: WHO Updates Bedaquiline Recommendations for the Treatment of MDR-TB

Understanding the 2017 WHO Meeting Report on recommendations for bedaquiline in the treatment of 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 (available here: 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 shortened MDR-TB regimen.

This report 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. Of note, while 4.7% of patients had a QTcF interval that was greater than 500 msec, no cases of fatal cardiac arrhythmia occurred.

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

- Recommending bedaquiline for persons who do not qualify for the short course regimen (i.e., whose TB is resistant to a medicine in the shorter regimen excluding isoniazid; with previous exposure for >1 month to a second-line medicine included in the shorter regimen; intolerance to one or more medicines in the shorter MDR-TB regimen or increased risk of toxicity);
- 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 only “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.

Although no changes were made in the official WHO recommendations on specific patient populations, DR-TB STAT reports that the following groups were included in the cohorts reviewed, and no additional specific safety concerns were noted by the expert panel:

- ***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 7% of persons in 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 and monitoring (ADSM) and management—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 calls on:

- Countries to allow in their guidance for the possibility of prolonging bedaquiline beyond 24 weeks in persons who have insufficient medications in their regimen, provided the risk/benefit ratio favors the use of bedaquiline in this way and to also allow in their guidance the inclusion of persons with HIV and adolescents. No negative recommendations on the use of bedaquiline were made in the Meeting Report following analysis of the use of bedaquiline in these populations or for extended duration;

- WHO to include bedaquiline and delamanid along with MDR-TB treatment in consolidated guidelines, and ensure consistency across products and regimens in the use of observational cohort data. This will provide national programmes and treatment providers with a unified guideline based on the latest evidence for the treatment of MDR-TB. 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). We also call upon WHO to update formal MDR-TB guidance regularly and routinely as soon as new data are available, including a review of the more than 8,000 patients who have been treated with bedaquiline rather than waiting for the results of Phase III trials.

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