Global TB CAB welcomes introduction of safer drug for most South Africans with rifampicin-resistant TB

Other countries and the World Health Organization must now follow

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The Global Tuberculosis Advisory Board (Global TB CAB) welcomes the announcement by the South African Department of Health that bedaquiline will become part of its standard recommended treatment regimen for rifampicin-resistant tuberculosis (RR-TB). Over 15,000 South Africans with RR-TB have already received bedaquiline, and this new recommendation paves the way for many more patients to receive this life-saving drug. Bedaquiline will replace the injectable medicines that currently form part of the country's standard treatment regimen. The injectables are associated with a number of serious side effects, including irreversible hearing loss, and their efficacy against drug-resistant TB has not been validated in a clinical trial.

Bedaquiline is one of only two new drugs approved to treat multidrug-resistant TB (MDR-TB) in the last half a century. It appears to be a much safer drug than any of the injectables and available evidence strongly suggests that it is at least as effective as the injectables, and probably more effective. It thus seems likely that the decision by South Africa's Department of Health will both save lives and prevent hearing loss. Indeed, a retrospective cohort analysis of all patients with RR-TB treated with bedaquiline in South Africa showed bedaquiline's inclusion in a treatment regimen was associated with a 41 percent increase in treatment success and a three-fold reduction in mortality compared with regimens that did not contain bedaquiline.

The Global TB CAB and various other organisations and individuals have previously argued in favour of replacing the injectables with bedaquiline. In February 2018, the Global TB CAB and over 30 other organisations wrote a letter to the World Health Organization (WHO) urging it "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." That letter and an accompanying position paper can be read here: http://www.tbonline.info/media/uploads/documents/letter_to_who_re_mdr_guidelines_final_2.1.18.pdf

While the WHO has acknowledged our letter, WHO guidelines have not yet been updated and the WHO still recommends that most people with MDR-TB should be given injectables. The injectables, also called aminoglycosides or injectable agents, cause hearing loss in as many as 50 percent of patients. Drugs in this class 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.

We congratulate the South African government for having weighed the evidence and having come to a decision that we believe is best for patients. We urge the WHO and other countries to follow the example set by South Africa by including bedaquiline in the standard recommended regimen for RR-TB, in place of an injectable. It is unconscionable to continue to subject patients to the avoidable pain and serious risks associated with the injectables. In advance of the United Nations High-Level Meeting on TB, we urge other governments to follow South Africa's leadership to take demonstrative measures, decisive actions, and commit to implementing the latest tools such as GeneXpert MTB/RIF Ultra to diagnose RR-TB and bedaquiline to treat it, and ensure measures that expand access are featured in ongoing negotiations.

We note with regret that this broader access to bedaquiline will likely not extend to children under 12 years of age, for whom appropriate dosing of bedaquiline is not yet known due to unconscionable delays in initiating pediatric research on behalf of its makers, Janssen Pharmaceuticals—a division of Johnson & Johnson. Pediatric studies of bedaquiline are now underway, and while we await their results, we urge the South African Department of Health and other countries and the WHO to determine an adequate injectable-sparing regimen for children, who are particularly vulnerable to hearing loss. For children under 12 years old with less severe disease, programs should drop the injectable without replacement in line with 2016 WHO recommendations for children. For children under 12 years old with more severe forms of disease, programs should consider replacing the injectable with other TB drugs, such as delamanid, which has been shown to be very safe in clinical trials and for which pediatric dosing and safety data, and WHO guidance, have been published for children down to six years old. We urge Otsuka and Janssen to submit all available pediatric dosing and safety data to the WHO and regulatory authorities as soon as they are available, especially for younger age cohorts. Speeding the availability of these data will inform bedaquiline use in children ages 6-12 years old, and subsequently younger children, and delamanid use in children younger than 6 years old.

We also urge Janssen to drop the price of bedaquiline to levels that would allow wider uptake of the drug. Researchers from the University of Liverpool have calculated that bedaquiline could be produced and sold at a profit at a price of US$16 per month if nearly all patients currently started on RR-TB treatment were given bedaquiline. Currently, many countries are eligible to receive bedaquiline for free via a donation programme arranged by USAID and Janssen; however, this programme is ending March 2019. Outside of the donation program, Janssen offers the drug at different prices to different countries, with the lowest price being US$150 per month. While we do not expect Janssen to drop the price to US$16 immediately given current order volumes of the drug, we will be writing to Janssen asking them to drop the price to a level no higher than US$32 per month, in keeping with Médecins Sans Frontières target price of a $500 total RR-TB treatment course.

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About the TB CAB: The Global Tuberculosis Community Advisory Board (TB CAB) is a group of strong, research-literate community activists from HIV and TB networks in Asia, Europe, Africa, and North and South America. Founded in 2011, the TB CAB acts in an advisory capacity to: product developers and institutions conducting clinical trials of new TB drugs, regimens, diagnostics and vaccines; and provide input on study design, early access, regulatory approval, post marketing, and implementation strategies. The TB CAB is dedicated to increasing community involvement in TB research and access to tools to fight TB and mobilizing political will. For more information, please see http://tbonline.info/tbcab/