To: Dr. Tedros Adhanom Ghebreyesus, Director-General
    Dr. Tereza Kasaeva, Global TB Program Director
    World Health Organization
    Avenue Appia 20
    CH-1211 Geneva 27, Switzerland

1 February 2018

RE: World Health Organization Guidelines for the Treatment of Multidrug-resistant Tuberculosis

Dear Dr. Tedros,

As advocates, members and representatives of affected communities, and members of civil society invested in ensuring access to the best available and evidence-based treatments for tuberculosis (TB), we are writing to express our concerns regarding the existing World Health Organization (WHO) recommendations for the treatment of multidrug-resistant TB (MDR-TB), and to share our position for how they should be revised. We encourage the WHO to consolidate its guidance regarding the treatment for MDR-TB, and in the interim, as a matter of urgency, to recommend bedaquiline as part of the preferred regimen for patients with MDR-TB in place of the injectable agent.

The existing situation where WHO guidance is split across multiple documents is untenable. There are currently five different MDR-TB treatment guidance documents in circulation. These include: (1) WHO treatment guidelines for drug-resistant tuberculosis: 2016 update; (2) WHO interim guidance on the use of delamanid in the treatment of MDR-TB; (3) The use of delamanid in the treatment of MDR-TB in children and adolescents: Interim policy guidance; (4) Report of the guideline development group meeting on the use of bedaquiline in the treatment of MDR-TB: A review of the available evidence (2016); and (5) WHO best-practice statement on the off-label use of bedaquiline and delamanid for the treatment of MDR-TB. Additional guidance documents are anticipated in early 2018, including related to phase III and other observational data for delamanid and the shortened regimen.
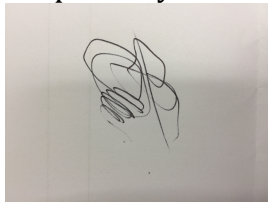
We recognize the importance of the WHO's response to and interpretation of evidence as it emerges, but any new recommendations issued by the WHO should always be contextualized alongside existing recommendations and evidence, including for other interventions. To rectify this current disparity, new, consolidated guidelines that consider all available data and provide clear guidance for when different interventions are indicated are necessary.

While there is a tremendous need for clear and consolidated WHO guidance, final data for the randomized clinical trial of the shortened regimen (STREAM stage I) is not expected until mid-2018. In the interim, an immediate need is to stop the unjustified subjection of MDR-TB patients to the risk of, and the actual, severe side effects associated with the injectable agents. These side-effects, including permanent hearing loss, lead to exactly the

sort of catastrophic economic consequences that the WHO's END TB Strategy aims to eliminate. In line with the attached position paper and evidence and rationale provided therein, we advise the WHO to urgently recommend bedaquiline as part of the preferred treatment regimen for MDR-TB and to relegate the injectables for use only in more complicated DR-TB 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.

To further discuss this position—which has been endorsed by over 21 individuals and 31 organizations—with the Global TB Community Advisory Board (TB CAB), please direct correspondence to Wim Vandevelde at wim@eatg.org.

Respectfully submitted,

Marcus Low
Technical Lead
Global TB Community Advisory Board (TB CAB)

On behalf of:

Organization endorsements:
AIDS and Rights Alliance for Southern Africa (ARASA)
AIDS-Free World, Canada
All-Ukrainian Association of People Who Recover from TB Stronger than TB, Ukraine
Americas TB Coalition
Asia Pacific Coalition of TB Activists (ACT AP), Thailand
Bihar Network of People Living with HIV (BNP PLUS), India
Drug Resistant Tuberculosis Scale Up Treatment Action Team (DR-TB STAT), Global
The Global TB Community Advisory Board (TB CAB)
Gujrat network of people living with HIV (GSNP PLUS), India
International Treatment Preparedness Coalition in Eastern Europe and Central Asia
   (ITPCru)
Kenya AIDS NGOs Consortium (KANCO)
Kenya Legal & Ethical Issues Network on HIV (KELIN)
KHANA, Cambodia
Kyrgyz Coalition to Combat Tuberculosis (Coalition against Tuberculosis), Kyrgyzstan
Madhya Pradesh Network of People Living with HIV (MPNP PLUS), India
National Coalition of People Living with HIV in India (NCPI plus)
National Empowerment Network of people living with HIV/AIDS in Kenya (NEPHAK)
Network of Maharashtra by People Living with HIV/AIDS (NMPPLUS), India

ONG GLOBE, Mauritania
Pamoja TB Group, Kenya
SECTION27, South Africa
The Sentinel Project on Drug-Resistant Tuberculosis, United States
Socios En Salud (SES), Peru
Spiritia Foundation, Indonesia
Stop TB Partnership Kenya
TBPeople, Georgia
TB Proof, South Africa
Treatment Action Campaign, South Africa
Treatment Action Group (TAG), United States
The Tunisian Center for Public Health, Tunisia
Uttar Pradesh Network of people living with HIV (UPNP PLUS), India

Individual endorsements:
Dr. Arne von Delft, School of Public Health and Family Medicine, University of Cape Town & TB Proof, South Africa
Begimai Tilek Kyzy, KNCV, Netherlands
Chernyshov Andrey, Public Association for the support of people living with HIV (KUAT), Kazakhstan
Chingiz Ramazanli, Towards Free Future, Public Union, Azerbaijan
Chris Dell, TB survivor and member of TBPeople, United Kingdom
Dr. Dalene von Delft, TB Proof, South Africa
Dilshat Haitov, TBpeople, Kyrgyzstan
Edwardo Z. Patac, TBpeople, TDF-(CKAT), Philippines
Elena Shastina, Autonomous Nonprofit Organization for Prevention of Socially Significant Diseases (NEW LIFE), Russian Federation
Dr. Helene-Mari van der Westhuizen, TB Proof, South Africa
Ingrid Schoeman, TB Proof, South Africa
Dr. Jennifer Furin, Harvard Medical School, United States
Kazieva Indira, Public Foundation, Kyrgyzstan
Mercedes Becerra, Harvard Medical School, United States
Roza Idrissova, The Public Foundation Sanat Alemi, Kazakhstan
Dr. Ruvandhi Nathavitharana, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, and TB Proof, South Africa
Tatyana Shumikhina, a patient of the TB regional hospital, Belarus
Timur Abdullaev, TBpeople, Uzbekistan
Vitali Morosan, Noncommercial Partnership (Medical-Social programs), Moldova
Dr. Vivian Cox, MDR Clinical Consultant, United States
Yahya Ould EL Eyil, ONG GLOBE, Mauritania

Additional endorsements:
Aydana Fedosik, Lawyer, AHO "New Life"
Dr. Eric Goemaere, Regional HIV/TB technical support coordinator, MSF South Africa, Honorary senior lecturer, School of Public Health, University of Cape Town

Global Coalition of TB Activists, Global
Global Health Advocates, France and India
Health and Development Alliance (HEAD), Cambodia
International Coalition of Women Living with HIV (ICWAP), Asia Pacific
Dr. Jonathan Stillo, Wayne State University, United States
Kagiso Norman Matiting, Lion Hunt Community Improvement Team, Botswana
RESIST-TB, Global
Results UK, United Kingdom
Samuel Getachew, Mizan-Tepi University, Ethiopia
South African Medical Unit, MSF South Africa, South Africa
TB Europe Coalition, Western and Eastern Europe, Caucasus and Central Asia
Wieda Human, TB Proof, South Africa

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).[34] 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.[67] 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/.

[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. IJTLD 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. IJTLD 2017; 21(1): 996–1001.

[17] Harausz E, Cox H, Rich M, et al. QTc prolongation and treatment of multidrug-resistant tuberculosis. IJTLD 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.