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Cc: Dr. Soumya Swaminathan, Chief Scientist, World Health Organization

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Ms. Susan Norris, Guideline Review Committee Secretariat, World Health Organization

Mr. Nathan Ford, Guideline Review Committee Chair, World Health Organization

Mr. Andreas Mlitzke, Director, Office of Compliance, Risk Management and Ethics, World Health Organization

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Members of the WHO Civil Society Task Force

Open Letter: Serious concerns about errors in the WHO Guidance for the Treatment of Rifampicin-Resistant and Multidrug-Resistant Tuberculosis (RR-/MDR-TB)

April 23, 2019

Dear Dr. Tedros:

In the interest of honoring your commitment on behalf of the World Health Organization (WHO) to a more open and collaborative relationship with stakeholders, we write to you to express serious concerns about the WHO Global TB Program's ability to issue evidence-based guidelines for the treatment of drug-resistant tuberculosis (DR-TB). While much of the guidance is technically sound and reflects the discussions of the Guideline Development Group (GDG), there are urgent and specific technical errors in the 2019 *WHO consolidated guidelines on drug resistant tuberculosis treatment*¹ and the 2018 *WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis (MDR-/RR-TB)*² that require immediate action and correction.

We note with alarm and frustration that the undersigned organizations have separately raised these errors—described in more detail with potential solutions at the end of this letter— with Dr. Kasaeva and her team on multiple occasions following the conclusion of the GDG meeting in July of 2018. We remain disappointed by the lack of appropriate action and feel it is our obligation to clearly document and share these concerns with the highest levels of WHO leadership.

The problems discussed in this correspondence demonstrate how shortcomings of the guideline development process—originally raised in an open letter dated May 8, 2018³—have again manifested gross errors in the guidelines, many of which have the potential to cause harm to the very people affected by TB that guidelines aspire to protect. Without addressing the underlying guideline development process issues, we feel these types of technical and scientific errors will be repeated in future guidelines.

We reiterate our call for WHO leadership to resolve the persistent issues in its guideline development process, which include 1) transparency regarding the process and criteria by which the WHO selects GDG members; 2) the need for increased GDG member capacitation to allow for optimal participation in GDG

meetings; 3) reforms to the WHO's conflict of interest policy; 4) the establishment of a mechanism for public comment on the selection and framing of the questions that inform what data are collected and how they are analyzed (PICO questions); 5) the speed and regularity at which guidelines are updated, especially in response to emerging evidence, and how to best integrate updates; 6) the inconsistent and undue consideration of cost in forming recommendations; 7) the need for more regular and independent evaluations of WHO guidance documents via end-user surveys; and 8) harmonization of the expectations of the WHO and stringent regulatory authorities regarding quality and outcomes of interest for phase III TB trials.

We read with disappointment the *Information note on developing policy guidance for drug-resistant tuberculosis* published in October, 2018,⁴ and would like to make clear that despite the document's conclusion that "from the perspectives of the internal bodies governing and overseeing WHO guideline development the processes followed by GTP [Global TB Program] is regarded as fully transparent, high-quality, inclusive, and respectful of the rules of the Organization," serious changes are necessary to restore our faith in the WHO guideline development process.

The WHO's core function is to set normative guidance. Although the organization has publicly committed to a more open and collaborative process for the development of such guidelines, the experience that has produced the 2019 RR-/MDR-TB treatment guidelines highlights the need to prioritize changes to the process through which the Global TB Program develops TB guidelines. The urgency of these changes is exacerbated by the fact that new data on the treatment of DR-TB are expected to emerge more frequently in the coming years.

In the meantime, we ask you to treat the specific technical concerns described in detail below the signature line with urgency. **Before May 14th, we look forward to your comprehensive written response, and to hearing how the WHO plans to: (1) support the Global TB Program to address the errors in its current 2018/2019 MDR-/RR-TB treatment guidelines, and (2) improve the guideline development process so that future errors of this nature can be avoided.**

Sincerely,



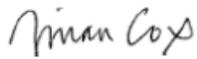
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SPECIFIC TECHNICAL CONCERNS

1) False equivalence between shorter and new longer, all-oral regimens

Recommendation 4.1 for the shorter regimen is based on a comparison between the shorter regimen (also referred to as the 9-12 month regimen or the modified Bangladesh regimen) and longer, injectable-containing regimens, which are no longer considered the best available standard of care for MDR-/RR-TB.

Currently, recommendation 4.1 states, “a shorter MDR-TB regimen of 9–12 months may be used instead of the longer regimens.” This is misleading given that there has not been any formal evaluation of how the shorter regimen compares to the new all-oral, longer regimens endorsed and described in the 2018/2019 guidance document.

Given the lack of available evidence to support whether the shorter regimen can safely replace the newly recommended, all-oral longer regimens, recommending continued use of the shorter regimen in the absence of its comparison to the new best available standard of care promotes a false equivalent between the shorter regimen and new, all-oral longer regimens.

We request a formal erratum be issued immediately to communicate that it is unknown how the shorter regimen compares to the newly recommended, all-oral longer regimens.

2) The recommendation for the shorter regimen fails to emphasize that it should not be used in patients with confirmed or suspected drug resistance to any of the drugs in the regimen, except isoniazid

All studies to evaluate the shorter regimen excluded persons whose strains of *M. tuberculosis* had resistance to an injectable or a fluoroquinolone. Additionally, the individual patient data (IPD) meta-analysis that informed the 2018/2019 guidance documents showed that resistance to ethionamide or pyrazinamide was associated with higher rates of treatment failure and relapse, although we acknowledge the possible biases of the IPD with regard to the small number of patients treated with the shorter regimen.

Currently, recommendation 4.1 states that the shorter regimen may be used in MDR-/RR-TB patients, “who have not been previously treated for more than 1 month with second-line medicines used in the shorter MDR-TB regimen **or** in whom resistance to fluoroquinolones and second-line injectable agents has been excluded.” Recommending the shorter regimen may be used in anyone with no history of previous treatment with second-line medicines ignores the spread of MDR-TB through primary infection.

We suggest recommendation 4.1 be revised to make clear that drug-susceptibility testing for the fluoroquinolones and the second-line injectable agents (at minimum) is required prior to the initiation of the shorter regimen, and that the shorter regimen should not be used when there is confirmed resistance to, or suspected ineffectiveness of a medicine in the shorter regimen (except isoniazid).

3) *Minimizing the benefits of shorter, all-oral regimens under operational research conditions.*

The use of shorter, all-oral treatment regimens under operational research conditions would help address the practical concerns of implementing longer regimens (especially in settings of conflicts or with mobile populations, where implementation of a longer regimen can be extremely challenging), while reducing unnecessary risks of toxicity and poor outcomes associated with the injectable-agents, and generating evidence that can be used to inform future updates to the WHO treatment guidelines for MDR-/RR-TB.

We request that support for the use of shorter, all-oral treatment regimens under operational research conditions be made more explicit in the guidelines and supporting documents.

4) *The recommendation that bedaquiline be routinely stopped after six months lacks evidence and is inconsistent with the evaluation methods for other medications.*

Recommendation 2.1 states, “in MDR/RR-TB patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of the treatment after bedaquiline is stopped.” The narrative in section 2 further reinforces this point by stating, “it is expected that most patients can be treated with four effective agents at start, of which one – usually bedaquiline – would be stopped at month 6. Given that the regimen needs to have at least three effective agents after bedaquiline is stopped at 6 months [...]”

No PICO question evaluated whether it is beneficial or not to routinely stop bedaquiline after six months of treatment; the recommendation that bedaquiline be routinely stopped after six months is not evidence-based.

Small cohorts provide evidence supporting the safe use of bedaquiline for longer than six months^{5,6} and limited indirect evidence suggests that stopping bedaquiline routinely at six months could result in poor outcomes.⁷ These data were presented to the GDG in July 2018.

Recommendation 2.1, the section 2 narrative, and the emphasis that the use of bedaquiline and delamanid for longer than six months is “off-label use” (see table 2.1, footnote 2) exceptionalizes bedaquiline and delamanid and risks creating further access barriers to these life-saving drugs.

We request that the reference to routinely stop bedaquiline in Recommendation 2.1 be removed and the narrative text in section 2 be revised to reflect the availability of cohort data supporting the safe use of bedaquiline for longer than six months.

We are also troubled by the guidelines’ silence on a number of topics of urgent public health and clinical importance. Specifically, we call your attention to:

- 5) *The lack of a definitive and consistent requirement for high-quality audiometry testing to monitor for hearing loss among MDR-/RR-TB patients treated with amikacin-containing regimens (see recommendation 2.11 and section 4).*

We acknowledge that high-quality audiometry monitoring is recommended in the narrative; however, we request that this requirement be included in recommendation 2.11 and repeated in the recommendations listed under section 4 regarding use of the shorter regimen.

- 6) *The lack of recommendation to use culture to monitor response to treatment among people on the shorter regimen (see section 5).*

The data reviewed by the GDG showed people on the shorter regimen were more likely to have worse bacteriologic outcomes.

We acknowledge that more frequent culture testing to monitor response to treatment among people treated with the shorter regimen is encouraged in the narrative; however, the claim that, “programs may thus consider that patients on a shorter MDR-TB regimen may need less frequent or no culture to monitor treatment,” is not evidence-based.

We suggest the following:

- **The guidance should make clear that persons treated with the shorter regimen should receive culture testing to monitor response to treatment at the same, if not more frequent intervals as persons treated with longer regimens.**
- **A schedule of relevant clinical and laboratory testing for the shorter regimen should be added to the new 2019 guidelines.**

- **Proper emphasis on smear and culture as well as regular high-quality audiometry, renal and electrolyte monitoring is needed.**

7) *The lack of recommendation regarding the use of bedaquiline and delamanid in combination.*

Preliminary data from ACTG 5343 were presented to the GDG in July 2018. These data, presented publicly at the 2019 Conference on Retroviruses and Opportunistic Infections (CROI), support the safe use of bedaquiline and delamanid in combination for RR-/MDR-TB.⁸

We suggest that the guidelines include advice on the concomitant use of bedaquiline and delamanid given the definitive safety results of the ACTG 5343 study.

8) *The exclusion of pregnant women from the potential benefits of bedaquiline.*

Currently, section 2 on the composition of longer MDR-TB regimens says, “knowledge about the safety of bedaquiline and delamanid in pregnancy and while breastfeeding is sparse. It is recommended that in such cases, a longer regimen be individualized to include components with a safety profile that is better established.”

Knowledge about the safety of all second-line TB medicines in pregnancy and while breastfeeding is limited; still, it is important to evaluate the evidence that is available, to consult experts, and to make recommendations accordingly. We note that bedaquiline is considered to be among the safer second-line TB agents for use in pregnancy based on animal models.

We further note that no experts in the management of MDR-/RR-TB in pregnant women were part of the GDG discussions in July 2018 despite the inclusion of pregnant women as a key population listed for each PICO question addressed by the 2018/2019 MDR-/RR-TB treatment guidelines.

We request the guidelines include more comprehensive advice assessed by RR-TB and pregnancy experts on use of second-line TB drugs in pregnancy with uniform criteria to describe risks and benefits of each drug.

References

¹ World Health Organization. WHO Consolidated guidelines on drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2019. Available from: <https://www.who.int/tb/publications/2019/consolidated-guidelines-drug-resistant-TB-treatment/en/>.

² World Health Organization. WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis: Pre-final text. Geneva: World Health Organization; 2018. Available from: <https://www.who.int/tb/publications/2018/WHO.2018.MDR-TB.Rx.Guidelines.prefinal.text.pdf>

³ Open letter re: Urgent reforms required for World Health Organization guidelines for the diagnosis and treatment of tuberculosis. 8 May 2018. Available from: www.tbonline.info/.../guidelines_letter_to_who_final_for_submission.pdf.

⁴ World Health Organization. WHO information note on developing policy guidance for drug-resistant tuberculosis. World Health Organization. Geneva: World Health Organization; 2018. Available from: <https://apps.who.int/iris/handle/10665/275010>.

⁵ Guglielmetti L, Jaspard M, Le Dû D, Lachâtre M, Marigot-Outtandy D, Bernard C, Veziris N, Robert J, Yazdanpanah Y, Caumes E, Fréchet-Jachym M; French MDR-TB Management Group. Long-term outcome and safety of prolonged bedaquiline treatment for multidrug-resistant tuberculosis. *Eur Respir J*. 2017;49(3).

⁶ Bedaquiline- and delamanid-containing regimens achieve excellent interim treatment response without safety concerns: endTB interim analysis. 2018. endTB: Boston, MA.

⁷ Hewison C, Bastard M, Khachatryan N, Kotrikadze T, Hayrapetyan A, Avaliani Z, et al. Is 6 months of bedaquiline enough? Results from the compassionate use of bedaquiline in Armenia and Georgia. 2018;22:766–72.

⁸ Dooley KE, Rosenkranz SL, Conradie F, Moran LE, Hafner R, von Groote-Bidlingmaier F, et al. QT effects of bedaquiline, delamanid or both in MDR-TB patients: the DELIBERATE trial (Abstract 84). Presented at: 2019 Conference on Retroviruses and Opportunistic Infections; 2019 March 6; Seattle, WA. Available from: <http://www.croiconference.org/sessions/qt-effects-bedaquiline-delamanid-or-both-mdr-tb-patients-deliberate-trial>.