Brussels, June 13th, 2019

Ref. [a]Open letters:

- *Serious concerns about errors in the WHO Guidance for the Treatment of Rifampicin Resistant and Multidrug-Resistant Tuberculosis (RR-/MDR-TB)*
- *Crisis of Confidence in the WHO's Ability to Issue Recommendations for the Treatment of Rifampicin-Resistant and Multidrug-Resistant Tuberculosis (RR-/MDR-TB)*

Dear Dr Tedros,

Through this letter we would like to express our sincere appreciation for WHO's efforts to improve the management of MDR-TB. We believe that WHO has managed to do so also in the latest 2019 updated guidelines, leaving the choice between the hitherto recommended and well documented so-called shorter treatment regimen (STR) and a newly devised All-Oral long regimen of 18-20 months duration[1]. We are aware of the concerns brought up by certain groups of experts and activists regarding the new recommendations of the MDR-TB Guidelines, protesting the choice left between these two regimens [a]. After close to 15 years implementation, we dare to claim that STR has proven its worth and kept its initial promise of very high bacteriological effectiveness, safety and operational simplicity.

Here we summarize the main features of STR balancing its merits and shortcomings.

Why and for whom was STR developed

STR was developed as an attempt to provide an effective service for MDR-TB patients at a time (1997) and in a setting (Bangladesh) when programmatic standardized management of MDR-TB was still discouraged by WHO and The Union. The regimen was conceived for low-income countries in the pre-Global Fund era, when cost was a huge concern and public health principles prevailed. The regimen had to make MDR-TB control possible through its adequate power and ease of administration and tolerability, without striving for perfection. Standardised to avoid excessive delays waiting for susceptibility testing results, avoiding weak but toxic drugs and excessively long treatment to promote optimal adherence and minimise adverse events. Of prime concern was also the preservation of the efficacy of the driving drugs, fluoroquinolones, to assure that their status of driving drug would last long. On these terms, the regimen was meant to provide maximal coverage of populations, administered through a highly accessible service of adequate quality, with great promise for durability and long-term sustainability.

[a] Signed on April 23rd and June 6th, 2019 by representatives of Partners in Health, MSF, Treatment Action Group, Drug-Resistant TB Scale-Up Treatment Action Team, Project on Paediatric Drug-Resistant Tuberculosis and Global Tuberculosis Community Advisory Board.

Why STR is highly effective and efficient

The original STR used gatifloxacin high dose as the driving drug with excellent results in Bangladesh[2], Cameroon[3] and Niger[4]: **84-89% relapse-free cure rate**, 0-2.2% recurrence (either failure or relapse) 24 months after cure, and not a single case of acquired fluoroquinolone resistance among 859 patients at risk. Unfortunately, gatifloxacin was banned from the market, therefore subsequent STR cohorts had to be treated with the less powerful moxifloxacin or high-dose levofloxacin. In a study using moxifloxacin involving nine West and Central African countries, very good cure rates (82%) were observed but rates of failure, relapse and acquired resistance were slightly higher[5].

Since the endorsement of STR by WHO[6], the STR is being implemented by 62 countries. In 2015, Bangladesh, Benin, Burundi, Cameroon, Democratic Republic of the Congo and Niger, the countries that pioneered STR, achieved an average success rate ranging from 78 to 100%, compared to 55% achieved globally with the conventional long regimen[7]. Central and West African countries having participated in the study led by The Union in 2013-2014 were able to maintain high cure rates even after the completion of the study.

In addition, Bangladesh, Niger and Cameroon maintain high cure rates (>80%) for more than 10 years using the STR at programmatic national level. Also, in settings with higher prevalence of second line resistance the STR has been successfully used after exclusion of such second line drug resistance.

Finally, STREAM, the only multicentre randomised clinical trial of a standardised regimen for MDR-TB, showed non-inferiority of STR compared to the conventional long regimen [8].

When is STR not going to work well?

In the original STR, only high-level fluoroquinolone resistance carried a high risk for failure or relapse[9], in settings where injectable resistance rates were low. However, drug resistance was not amplified, avoiding an even bigger future problem. Rare failure and relapse cases from primary XDR-TB were easily cured with regimens based on a driving drug from the next generation, following the cascade of regimens strategy [10,11]. Directly providing a regimen based on the next-generation driving drug for (pre)XDR TB is indeed preferable, and preliminary experience suggests that this can be done effectively and efficiently within the same background regimen. There is no scientific basis for the restrictions proposed by other organizations on STR eligibility, i.e. absence of resistance to any of the drugs used, since the success of STR depends entirely on the activity of the main drugs in the regimen.

What is the strategy of prevention and management of adverse events in STR?

Adverse drug reactions in STR occur but remain readily manageable and have not led to interruption of treatment[2,4,9,12]. Severe hearing loss was more frequent in the past because of previous treatment with streptomycin, now being phased out. Audiometry monitoring has become routine also in resource-limited settings. Niger did not report any severe hearing loss since 2016, after implementation of monthly audiometry, replacing the injectable by linezolid if audiometry showed any deterioration in around 10% of cases.

We all look forward to the era when injectables are no longer needed to cure MDR-TB given the serious morbidity associated with irreversible ototoxicity, and painful injections especially with amikacin, yet evidence for the efficacy of injection free regimens is currently very weak, pending results of ongoing studies.

Moreover, the new long regimen aims to avoid injectable ototoxicity[1], yet relies itself on drugs with potentially more serious, more frequent and more difficult to monitor toxicity, risking increased mortality (cardiotoxicity and haematological toxicity) rather than morbidity. The predictably high rates of interruptions of treatment and stopping of essential drugs thus risk to offset the expected gains

offered by these most effective drugs, while the excessively long duration of two years will unavoidably lead to inacceptable rates of premature absconding from treatment.

Why are countries hesitating to go for an all-oral long regimen?
As illustrated above, STR is highly effective and efficient for MDR patients without resistance to fluoroquinolones and second line injectables in all settings where it has been implemented. Moreover, population-wide TB treatment will unavoidably result in a few cases failing or relapsing that need the next level driving drug to be cured. Following the cascade of regimens strategy, this drug is most likely bedaquiline. Combining bedaquiline systematically with a fluoroquinolone for the sake of avoiding ototoxicity thus mortgages the possibly needed next treatment course, given that failure cases will have an increased risk of resistance to bedaquiline.

Moreover, results of a small cohort treated with regimens similar to the new long regimen show high rates of acquired drug resistance to new drugs, which decreases confidence that the new long regimen will be effective[13].

In its 2019 recommendations, WHO has wisely left the choice to countries to choose between the two regimens. Considering the above, if countries are not inclined to change to the new long regimen[1], they may simply not see the need for it in view of the results they obtain with STR. Others may not have used the shorter regimen yet, but prefer the STR, understanding that the challenges associated with implementation of the new long regimen, including the advanced monitoring needs, will be hard to overcome in their setting and that their levels of second-line resistance do not require it.

To conclude, we hope WHO will follow its prior mandate of providing guidance based on a sound rationale and the justification for the recommendations, i.e. giving the countries a sense of ownership rather than simply imposing. The guidelines should consider differences in settings by offering countries options to choose from. We thus disagree with the objection voiced in the letters [a] against the choice left between these two regimens. As results from ongoing studies become available, we hope that the next WHO guidelines can provide evidence-based suggestions for effective injection free short regimens that avoid acquired resistance. In the absence of such evidence base, we deem the statement that the STR is obsolete as premature[14].

Sincerely,

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