**Reliable inference about the efficacy and safety of regimens for drug-resistant tuberculosis requires randomised controlled trials**

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In marked contrast to drug sensitive tuberculosis, multi drug-resistant disease (MDR-TB) has received little attention until recently. The MDR-TB regimen of at least 20 months’ duration recommended by the World Health Organisation (WHO) in 2011(1), on the basis of very limited evidence, is successfully completed by only 50% of patients(2). This global average disguises substantial variation in treatment success between countries(2). However, a shorter, more effective regimen with fewer side effects is clearly needed.

In May 2016, the WHO made a conditional recommendation that the 9-11 month regimen developed in Bangladesh could be used as an alternative for isolates sensitive to fluoroquinolones and aminoglyclosides(3,4). This recommendation was based on a meta-analysis of data from cohorts of patients in ten countries who had received Bangladesh-style regimens. Treatment outcomes in 1205 patients given these shorter regimens were compared to those in 7,665 MDR-TB patients with similar treatment histories who had been treated with regimens of longer duration(3).

How comparable are the two groups? There is substantial heterogeneity in outcomes between MDR-TB treatment cohorts using the longer regimen(5,6). This may be explained as much by patient and programme characteristics as by the regimens used(6). Recruitment to several of the shorter regimen cohorts was selective. In some(7,8), patients had to agree to prolonged hospitalisation. In Cameroon, patients in ‘very poor clinical condition’ were excluded(8). Using composite outcomes that include treatment completion is likely have to favoured shorter regimens. The comparator patients are unlikely to have been as closely monitored as were the cohorts, almost certainly resulting in a bias in favour of the shorter regimen. Finally, in only three of the ten cohorts was there follow up data on relapse(4).

It seems reasonable to suppose that good outcomes are possible using either a longer or a shorter regimen and, consequently, based on the data available to date, to allow cautious use of the 9-11 month regimen. However, given considerable uncertainty about the comparability of the groups, we will not truly know whether the shorter regimen is as effective as the longer regimen until early 2018 when the results of Stage 1 of the STREAM randomised trial are reported(9). WHO rightly acknowledge the ‘very low certainty in the evidence’(3).

Treatment programmes now face a difficult choice regarding whether or not to adopt the shorter regimen. Where resources are limited, the shorter regimen may be preferred because it is more easily and cheaply delivered(10). Where there is political instability, where populations are mobile, or where many patients, despite adequate treatment support, fail to complete 20 months or more of treatment, a shorter regimen may increase chances of treatment completion(10). However, in settings where adherence may be poor, an untested shorter regimen should perhaps only be adopted once adherence has been improved. Programmes treating large numbers of patients co-infected with HIV and MDR-TB should note that there are very limited data in this population; this will be provided by STREAM(9). Where there are no data on the prevalence of pyrazinamide resistance, programmes should also proceed with caution given recent data describing widespread genotypic resistance to pyrazinamide in MDR-TB patients in a number of countries(11)

An important safety consideration is the recommended dose of moxifloxacin; in contrast to the cohorts, which used either gatifloxacin or the standard dose of moxifloxacin, WHO are recommending higher weight-adjusted doses(4) about which there are very limited data. The STREAM trial(9) will provide that information, including an assessment of the likelihood of QT prolongation and cardiac events. These data are not expected to be available until early 2018. Meanwhile, it is important that patients prescribed the higher doses are carefully monitored to reduce the risk of life threatening toxicity. The WHO recommendations make only passing reference to such monitoring stating, in an accompanying document, that active TB drug safety monitoring ‘is not required up front at the time of ordering the medicines or starting patients on the shorter MDR-TB regimen’(4).

Randomised Controlled Trials (RCTs) remain the gold standard for assessing new treatments. Cohorts can provide useful supplementary data but, as a means of estimating efficacy, safety or comparative toxicity, they cannot replace well-conducted randomised trials. The availability of new and repurposed drugs with activity against MDR-TB means a large number of potential regimens are now available. However, there needs to be substantial investment in RCTs in drug resistant tuberculosis. It would be unforgivable if, when future guidelines are written, untested regimens are still being recommended in a disease carrying such a poor prognosis, affecting half a million people each year(2).

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1. World Health Organization. Guidelines for the programmatic management of Multidrug-resistant Tuberculosis. World Health Organization. Geneva; 2011.

2. World Health Organization. Global tuberculosis report 2015. Geneva; 2015.

3. World Health Organization (WHO). WHO treatment guidelines for drug-resistant tuberculosis, 2016 update. Geneva; 2016.

4. World Health Organization (WHO). Frequently asked questions about the implementation of the new WHO recommendation on the use of the shorter MDR-TB regimen under programmatic conditions. Geneva; 2016.

5. Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, et al. Multidrug Resistant Pulmonary Tuberculosis Treatment Regimens and Patient Outcomes: An Individual Patient Data Meta-analysis of 9,153 Patients. PLoS Med. 2012;9(8).

6. Toczek A, Cox H, Du Cros P, Cooke G, Ford N. Strategies for reducing treatment default in drug-resistant tuberculosis: Systematic review and meta-analysis. Int J Tuberc Lung Dis. 2013;17(3):299–307.

7. Aung KJM, Van Deun A, Declercq E, Sarker MR, Das PK, Hossain MA, et al. Successful “9-month Bangladesh regimen” for multidrugresistant tuberculosis among over 500 consecutive patients. Int J Tuberc Lung Dis. 2014;18(10):1180–7.

8. Kuaban C, Noeske J, Rieder HL, Aït-Khaled N, Abena Foe JL, Trébucq A. High effectiveness of a 12-month regimen for MDR-TB patients in Cameroon. Int J Tuberc Lung Dis. 2015;19(5):517–24.

9. Nunn AJ, Rusen ID, Van Deun A, Torrea G, Phillips PPJ, Chiang C-Y, et al. Evaluation of a standardized treatment regimen of anti-tuberculosis drugs for patients with multi-drug-resistant tuberculosis (STREAM): study protocol for a randomized controlled trial. Trials. 2014;15(1):353.

10. du Cros P. This house believes the 9-month Bangladesh regimen should be the new standard of care for MDR-TB treatment [Internet]. UCL TB. 2016 [cited 2016 Jul 12]. Available from: http://www.ucl.ac.uk/tb/wtbd2016

11. Zignol M, Dean AS, Alikhanova N, Andres S, Cabibbe AM, Cirillo DM, et al. Population-based resistance of Mycobacterium tuberculosis isolates to pyrazinamide and fluoroquinolones: results from a multicountry surveillance project. Lancet Infect Dis. 2016;3099(16):1–8.