Treatment of drug-susceptible tuberculosis: rapid communication

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Background

The current World Health Organization (WHO) recommendations for treating people suffering from drug-susceptible TB are defined in the *WHO Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update*. A 6-month treatment regimen composed of four first-line TB medicines, namely isoniazid, rifampicin, ethambutol and pyrazinamide, is recommended for treatment of drug-susceptible TB (1). This regimen is well known and has been widely adopted worldwide for decades, and while using it, approximately 85% of patients will have a successful treatment outcome. This regimen is based on seminal TB treatment studies conducted by the British Medical Research Council in the second half of 20th century (2).

Long treatment regimens present serious challenges to the programmatic management of TB globally. Since the discovery of first-line anti-TB medicines and treatment regimens, the TB community has been in search of shorter and more effective treatments for TB disease. Shortened treatment has the potential to improve adherence and reduce patient and health system costs. There has been particularly strong research interest in shortening the duration of treatment over the last few decades and a recent randomized controlled trial (TBTC[1] study 31/ACTG[2] A5349, or S31/A5349, referred to as "Study 31") assessed the safety and effectiveness of two 4-month regimens for the treatment of drug-susceptible TB (3).

In 2021, the WHO Global TB Programme received data from the Study 31 investigators and convened a Guideline Development Group (GDG) to review study results. The GDG meeting took place as an online meeting from 27-30 April 2021. Detailed results from Study 31 were published on 6 May 2021 (4).

The objectives of the GDG meeting were to review the evidence on the efficacy and safety of a 4-month regimen for the treatment of drug-susceptible TB and update evidence-informed recommendations on the optimal use of regimens for the treatment of drug-susceptible TB. Based on the outcomes of the GDG meeting, detailed recommendations will be presented in the 2021 update of the *WHO consolidated guidelines on tuberculosis. Module 4: Treatment - Drug-Susceptible Tuberculosis Treatment.*

This rapid communication aims to inform national TB programmes, technical partners and other stakeholders about the key findings and considerations on the use of the 4-month regimen following the assessment of new evidence, in order to allow for planning at the country level.

[1] TBTC stands for Tuberculosis Clinical Trials Consortium, which is "a collaboration of researchers from the CDC, domestic and international public health departments, academic medical centers, and selected Veterans Administration medical centers whose mission is to conduct programmatically relevant research concerning the diagnosis, clinical management, and prevention of tuberculosis (TB) infection and disease." Information on TBTC is available at: https://www.cdc.gov/tb/topic/research/tbtc/default.htm

[2] ACTG stands for the AIDS Clinical Trials Research Group, is the "the world's largest and longest running HIV clinical trials network. The ACTG conducts groundbreaking research to improve the treatment of HIV and its co-infections, including tuberculosis and viral hepatitis, as well as its co-morbidities. The ACTG also seeks to advance approaches to ultimately cure HIV. ACTG clinical trial units in 12 countries serve as major resources for HIV/AIDS research and training/education in their communities." Information on ACTG is available at: https://actgnetwork.org

Key findings

Study 31 was a randomized, multi-national, open-label, controlled phase 3 trial comparing two 4-month rifapentine-containing regimens to the standard 6-month control regimen. The intervention considered by the WHO convened GDG was a 4-month regimen composed of rifapentine, isoniazid, pyrazinamide and moxifloxacin. The other 4-month regimen composed of rifapentine, isoniazid, ethambutol and pyrazinamide did not meet non-inferiority criteria and therefore was not reviewed by the GDG. The trial enrolled participants who were 12 years or older with newly diagnosed pulmonary tuberculosis confirmed by a WHO recommended diagnostic test and who were susceptible to isoniazid, rifampicin and the fluoroquinolones. The primary efficacy outcome was tuberculosis disease-free survival at 12 months after randomization. The efficacy of the 4-month rifapentine-based regimen containing moxifloxacin was noninferior to the standard 6-month regimen for the treatment of drug susceptible pulmonary tuberculosis and the regimen was equally well tolerated.

Conclusions/Summary

The available evidence reviewed by the GDG on the 4-month regimen for treatment of drug-susceptible pulmonary TB supports the use of this regimen as a possible alternative to the current standard 6-month regimen. The shorter regimen has showed similar performance to the current standard regimen, both in terms of efficacy and safety. The 4-month regimen, which is shorter, effective and all-oral, would be a preference for many patients and also national TB programmes, allowing faster cure and easing the burden on both patients and the healthcare system. However, implementation and uptake of the new regimen in the short to medium term will be more feasible if the cost of rifapentine is reduced and availability improved. It will also require rigorous antibacterial stewardship to ensure the appropriate use of the first-line regimen given that it contains moxifloxacin, an antibiotic usually used for the treatment of drug-resistant TB.

Next steps

- The updated policy guidelines will be released later in 2021, as part of the 2021 update of the *WHO consolidated guidelines on tuberculosis. Module 4: Treatment - Drug-Susceptible Tuberculosis Treatment.* The guidelines will incorporate all current recommendations on the treatment of drug-susceptible TB.
- The release of the guidelines will be accompanied by operational guidance in the form or the *WHO Operational Handbook on Tuberculosis, Module 4: Treatment - Drug-Susceptible Tuberculosis Treatment*
- WHO will also convene a series of the global and regional webinars in 2021 to inform Member States, technical partners, donors and civil society on the key changes in the updated guidelines. These webinars will aim to support countries to update their national guidelines, inform programme budgets and enable monitoring systems to be adapted to facilitate adoption and implementation of the new treatment regimen.

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References

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