M E M O R A N D U M

From:	Director, GTB	**To:**	Director, HPS	**Date: 26 May 2021**
Our ref:		**Attention:**	Secretary of the Expert Committee on Selection and Use of Essential Medicines	
Your ref:		**Through:**		
Originator:	MZ/FM/TM/js	**Subject:**	**REQUEST FOR EXCEPTIONAL CONSIDERATION BY THE EXPERT COMMITTEE OF THE INCLUSION OF RIFAPENTINE AND MOXIFLOXACIN ON THE EML FOR THE TREATMENT OF DRUG-SUSCEPTIBLE TB**	

We would like to request exceptional consideration by the 2021 Expert Committee on Selection and Use of Essential Medicines of the inclusion of rifapentine (150 mg and 300 mg tablets) and moxifloxacin (400 mg tablets) on the EML for the new indication of treatment of drug-susceptible tuberculosis.

The WHO Global Tuberculosis Programme convened a Guideline Development Group (GDG) meeting from 27 to 30 April 2021 to review results received from the study[1] A5349, or S31/A5349, here referred to as "Study 31") that assessed the safety and effectiveness of two 4-month regimens for the treatment of drug-susceptible tuberculosis[2]. Detailed results from Study 31 were published on 6 May 2021.[3]

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 for the treatment of drug-susceptible tuberculosis (TB). The intervention considered by the WHO-convened GDG was a 4-month regimen composed of rifapentine (1200 mg daily dose), isoniazid, pyrazinamide and moxifloxacin. The available evidence reviewed by the GDG on the 4-month regimen for treatment of drug-susceptible pulmonary TB (DS-TB) supports the use of this regimen as a possible alternative to the current standard 6-month regimen (additional details in the attached summary of the study 31).

A Rapid Communication (final draft attached) to inform the public about the new WHO recommendations will be launched in May 2021, in anticipation of the updated policy guidelines to be released later in 2021, as part of the updated *WHO consolidated guidelines on tuberculosis. Module 4: Treatment - Drug-Susceptible Tuberculosis Treatment*.

Therefore, in addition to the current strong recommendation for the 6-month regimen, the updated WHO guidelines will include a conditional recommendation for the use of the alternative, new, 4-month regimen composed of rifapentine (1200 mg daily dose), isoniazid, pyrazinamide and moxifloxacin for the treatment of DS-TB in both children (>12) and adults.

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[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] Dorman SE, Nahid P, Kurbatova EV, Goldberg SV, Bozeman L, Burman WJ, et al. High-dose rifapentine with or without moxifloxacin for shortening treatment of pulmonary tuberculosis: Study protocol for TBTC study 31/ACTG A5349 phase 3 clinical trial. Contemp Clin Trials. 2020 Mar 1;90:105938.

[3] Dorman SE, Nahid P, Kurbatova EV, Phillips PPJ, Bryant K, Dooley KE, et al. Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis. N Engl J Med. 2021 May 6;384(18):1705–18.

Isoniazid and pyrazinamide are already included on the EML for treatment of DS-TB. Rifapentine (150 mg tablets) is currently included on the EML only for the indication of TB-preventive treatment (TPT). (A separate application to the 2021 Expert Committee requests addition of a 300 mg strength formulation of rifapentine for TPT[4]). Moxifloxacin (400 mg tablets) is currently included on the EML for treatment of drug-resistant TB.

We acknowledge that the timing of this request falls outside the deadline for EML applications. However, we would request exceptional consideration by the Expert Committee to avoid potential misalignment between the EML and the WHO guidelines on TB treatment until the next EML update in 2023.

We thank you in advance for considering this request.

Dr Tereza Kasaeva

[4] https://www.who.int/groups/expert-committee-on-selection-and-use-of-essential-medicines/23rd-expert-committee/f12-rifapentine

Short summary of the Study 31/A5349

BACKGROUND

Treatment of drug-susceptible pulmonary tuberculosis is a standard six-month daily regimen, composed of two months of isoniazid, rifampin, ethambutol, and pyrazinamide followed by four months of isoniazid and rifampin (2HREZ/4HR). The standard six-month regimen is well- known and widely implemented worldwide. However, rifapentine-based regimens have potent antimycobacterial activity allowing shortening of a treatment course in patients with drug-susceptible pulmonary tuberculosis.

The Tuberculosis Trials Consortium Study 31/AIDS Clinical Trials Group A5349 (Study 31/A5349) was an international, multicenter, randomized, open-label, phase 3, noninferiority trial conducted at sites of the Centers for Disease Control and Prevention (CDC) Tuberculosis Trials Consortium and the National Institutes of Health AIDS Clinical Trials Group[1]. The aim of the trail was to determine whether treatment regimens that included rifapentine, at a once-daily dose of 1200 mg, with or without moxifloxacin, at a once-daily dose of 400 mg, can provide a durable cure in participants with drug-susceptible pulmonary tuberculosis in 4 months, as compared with the standard 6-month regimen.

METHODS

The Study 31/A5349 trial involved persons with newly diagnosed pulmonary tuberculosis patients of 12 years of age or older and has been implemented in 34 clinical research sites of 13 countries (Brazil, China Haiti, India, Kenya, Malawi, Peru, South Africa, Thailand, USA, Uganda, Vietnam, Zimbabwe), across 4 continents.

Two shorter regimens were assessed: i) the first short regimen including two months of isoniazid (H), rifapentine (P), ethambutol (E), and pyrazinamide (Z), followed by two months of isoniazid and rifapentine (2PHZE/2PH) and the ii) the second short regimen with a double substitution of rifapentine for rifampin and moxifloxacin for ethambutol: two months of isoniazid, rifapentine, moxifloxacin (M), and pyrazinamide, followed by two months of isoniazid, rifapentine, and moxifloxacin (2PHZM/2PHM).

Rifapentine and moxifloxacin doses were 1200mg and 400mg, respectively. Other drugs were administered at standard doses adjusted for body weight (Table 1). Because food affects the absorption of rifapentine and rifampin differently, rifapentine was administered within one hour after ingesting food and rifampin was administered on an empty stomach. All regimens were administered 7 days/week, including at least 5 days/week by in-person directly observed therapy (DOT). All drugs were administered orally, and only individual drugs were used.

[1] Study 31/A5349 ClinicalTrials.gov number, NCT02410772. opens in new tab.

These two 4-month rifapentine-based regimens were compared with a standard 6-month regimen consisting of rifampin (R), isoniazid (H), pyrazinamide (Z), and ethambutol (E), followed by eighteen weeks of once daily rifampin and isoniazid (2RHZE/4RH) using a noninferiority margin of 6.6 percentage points.

The primary efficacy outcome was survival free of tuberculosis at 12 months after randomization, and safety was assessed through day 14 after the last dose of a trial drug.

Table 1. Doses of study medications by body weight

DRUG	DOSE
RIFAPENTINE	**1200MG**
MOXIFLOXACIN	**400MG**
RIFAMPIN	**600MG**
ISONIAZID	**300MG**
PYRAZINAMIDE	
< 55KG	**1000MG**
≥ 55-75KG	**1500MG**
>75KG	**2000MG**
ETHAMBUTOL	
< 55KG	**800MG**
≥ 55-75KG	**1200MG**
>75KG	**1600MG**

RESULTS

Study population

Between 25 January 2016 and 30 October 2018, 5124 patients were screened and 2516 underwent randomization at 34 sites in Brazil, China (Hong Kong), Haiti, India, Kenya, Malawi, Peru, South Africa, Thailand, Uganda, the United States, Vietnam, and Zimbabwe. Among those randomized, 173 were excluded from the microbiologically eligible primary analysis population, comprised of 2343 participants. Retention in follow-up was high -- 728 (94.8%), 759 (96.0%), and 754 (96.2%) of participants in the microbiologically eligible analysis population were seen at month 12 or were known to have died previously in the control, rifapentine-moxifloxacin, and rifapentine regimens, respectively.

Primary outcome

Among 2516 participants who had undergone randomization, 2343 had a culture positive for Mycobacterium tuberculosis that was not resistant to isoniazid, rifampin, or fluoroquinolones, of whom 194 were coinfected with human immunodeficiency virus and 1703 had cavitation on chest radiography. A total of 2234 participants could be assessed for the primary outcome. Rifapentine-moxifloxacin regimen was noninferior to the control in the microbiologically eligible population (15.5% vs. 14.6% had an unfavorable outcome; difference, 1.0 percentage point; 95% confidence interval [CI], −2.6

to 4.5) and in the assessable population (11.6% vs. 9.6%; difference, 2.0 percentage points; 95% CI, −1.1 to 5.1). Noninferiority was shown in the secondary and sensitivity analyses. Rifapentine without moxifloxacin regimen was not shown to be noninferior to the control in either population (17.7% vs. 14.6% with an unfavorable outcome in the microbiologically eligible population; difference, 3.0 percentage points [95% CI, −0.6 to 6.6]; and 14.2% vs. 9.6% in the assessable population; difference, 4.4 percentage points [95% CI, 1.2 to 7.7]).

Safety and Tolerability

There was no evidence of a difference between the rifapentine-moxifloxacin and control regimens in the primary safety outcome, percentages of participants with on-treatment grade 3 or higher adverse events, which were reported for 159 (18.8%) participants in the rifapentine-moxifloxacin regimen and 159 (19.3%) in the control regimen (adjusted difference vs. control of -0.6 [-4.3, +3.2]). The percentage of participants with on-treatment grade 3 or higher adverse events was lower in the rifapentine regimen (119 [14.3%]) compared with the control regimen (adjusted difference vs. control of -5.1 [95%CI -8.7, -1.5]). In addition to that, all-cause mortality during treatment was low and similar across treatment regimens (7 [0.8%], 3 [0.4%], and 4 [0.5%], in the control, rifapentine-moxifloxacin, and rifapentine regimens, respectively).

There was no evidence for a difference in tolerability between the rifapentine-moxifloxacin regimen and the control regimen (risk difference -1.0, 95%CI -3.6, +1.6). The rifapentine regimen was better tolerated than the control regimen (-3.3, 95%CI -5.7, -0.9).

CONCLUSIONS

The results of the Study 31/A53492 demonstrated the efficacy of a 4-month rifapentine-based regimen containing moxifloxacin was noninferior to the standard 6-month regimen in the treatment of drug-susceptible tuberculosis.

These findings were reviewed by the Guideline Development Group meeting organized by WHO and supported the use of it as a possible alternative to the current standard 6-month regimen. The updated WHO policy guidelines will be released later in 2021, as part of the 2021 update of the WHO consolidated guidelines on tuberculosis.

[2] Dorman SE, Nahid P, Kurbatova EV, Phillips PPJ, Bryant K, Dooley KE, et al. Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis. N Engl J Med. 2021 May 6;384(18):1705–18.

Treatment of drug-susceptible tuberculosis: rapid communication

June 2021

World Health Organization

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.

Acknowledgements

We gratefully acknowledge the work of the GDG members, the evidence reviewers, national TB and HIV programmes, WHO colleagues, technical and funding partners, civil society, patients and Study 31 investigators who contributed data that were used to inform this guidelines update.

References

1. WHO | Guidelines for treatment of drug-susceptible tuberculosis and patient care (2017 update) [Internet]. WHO. World Health Organization; [cited 2021 May 7]. Available from: http://www.who.int/tb/publications/2017/dstb_guidance_2017/en/

2. Fox W, Ellard GA, Mitchison DA. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council tuberculosis units, 1946-1986, with relevant subsequent publications. Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis. 1999 Oct;3(10 Suppl 2):S231-279.

3. Dorman SE, Nahid P, Kurbatova EV, Goldberg SV, Bozeman L, Burman WJ, et al. High-dose rifapentine with or without moxifloxacin for shortening treatment of pulmonary tuberculosis: Study protocol for TBTC study 31/ACTG A5349 phase 3 clinical trial. Contemp Clin Trials. 2020 Mar 1;90:105938.

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ISBN 978-92-4-002867-8 (electronic version)