

*Please note this publication is outdated given recent and expected future updates to World Health Organization guidelines for drug-resistant TB treatment. All-oral regimens based on bedaquiline are now the preferred treatment option for most people with drug-resistant TB. Please see instead *An Activist's Guide To Bedaquiline*: <http://www.treatmentactiongroup.org/tb/publications/2013/activist-guide-bedaquiline>*

# IS SHORTER BETTER?

## UNDERSTANDING THE SHORTER REGIMEN FOR TREATING DRUG-RESISTANT TUBERCULOSIS

BY SAFIQA KHIMANI

Edited by Vivian Cox, Mike Frick, Jennifer Furin, Mark Harrington, Erica Lessem, and Marcus Low

### INTRODUCTION

To end the tuberculosis (TB) epidemic, we must address the rising threat of drug-resistant TB (DR-TB), which sickened half a million new people in 2016 alone.<sup>1</sup> TB is the leading infectious killer in the world, and DR-TB is the number one cause of death due to antimicrobial resistance.<sup>2</sup> DR-TB is preventable and curable, but many cases of DR-TB are not diagnosed, and treatment success rates for people who do receive treatment for DR-TB are unacceptably low, at about 50% globally.<sup>1</sup> DR-TB cannot be treated with the standard six-month TB treatment regimen for drug-sensitive TB containing isoniazid, rifampicin, ethambutol, and pyrazinamide. Instead, DR-TB requires longer regimens with more medications that tend to be less effective and more toxic.

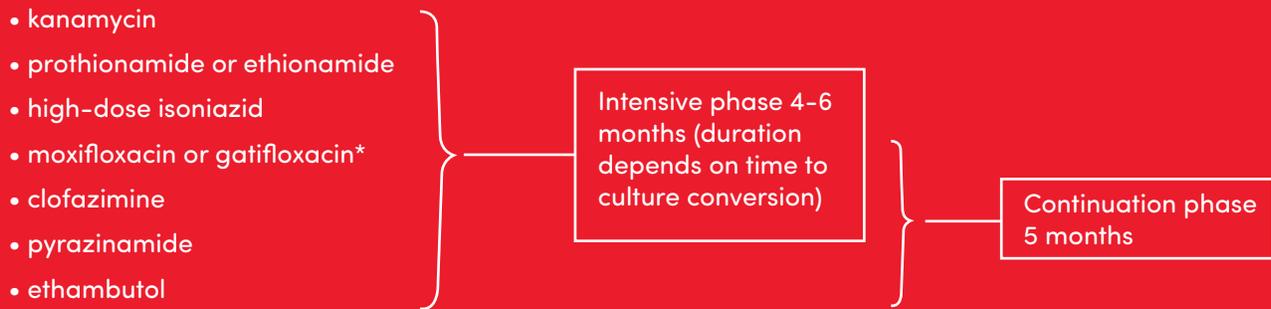
In 2016, the World Health Organization (WHO) issued guidance on the use of a shorter, standardized regimen to treat multidrug-resistant TB (MDR-TB), which is resistant to isoniazid and rifampicin.<sup>3</sup> Prior to the 2016 guidance, the WHO had recommended an individualized regimen of 18–24 months of treatment with at least five effective drugs. Evidence supporting the use of the shorter regimen came from observational studies rather than the gold standard of randomized, controlled clinical trials.<sup>4</sup> Several settings, mostly in Africa and Asia, have started using this shorter regimen to treat DR-TB more quickly and inexpensively.<sup>1</sup> Now, new data from a randomized controlled trial on the shorter regimen are available. This guide will explain what the shorter regimen is, who can receive it, and the evidence on how well it works.

*Evidence supporting the use of the shorter regimen came from observational studies rather than the gold standard of randomized, controlled clinical trials.*

### WHAT IS THE RECOMMENDED SHORTER TREATMENT REGIMEN FOR MDR-TB?

The shorter regimen—sometimes called the “modified Bangladesh regimen,” because a similar regimen was first studied in Bangladesh<sup>4</sup>—contains seven different drugs. The total length of treatment is 9–12 months (see Figure). The components of the regimen cannot be changed or substituted—if a patient cannot tolerate one or more of the drugs because of side effects, or because their TB is resistant to one or more of the medicines in the regimen (except isoniazid), they must switch to a longer, individualized regimen according to WHO guidance.

**FIGURE: THE WHO-RECOMMENDED SHORTER REGIMEN FOR MDR-TB<sup>5</sup>**



*\*Note that while either moxifloxacin or gatifloxacin can be used according to WHO guidance, gatifloxacin is not on the WHO Essential Medicines List and there is no quality-assured supplier of it, due to concerns about gatifloxacin’s safety, which led to its withdrawal from most markets.*

## ELIGIBILITY

The shorter regimen **cannot** be used in patients who:

- have TB that is resistant to a medicine in the shorter regimen (except for resistance to isoniazid, which in many cases can be overcome by giving higher doses of the drug);
- have previously taken any of the medicines included in the regimen for more than one month;
- have intolerance to one or more medicines in the regimen or increased risk of side effects (for example, they are taking other non-TB medicines that might increase their risk of a particular side effect, or are at risk of heart problems);
- have extrapulmonary TB (TB outside the lungs);
- are pregnant or may become pregnant (kanamycin and ethionamide may cause harm to the mother and the pregnancy).

Although this regimen has not been studied in children, WHO recommends that the shorter regimen can be used in children under 15 years of age, as similar medications have been used in previous MDR-TB pediatric treatment regimens.<sup>6</sup>

## TESTING AND MONITORING

Most people are diagnosed with drug-resistant TB upon receiving GeneXpert test results. Further drug susceptibility testing is necessary, since GeneXpert results can only give information on resistance to the drug rifampicin. This means people whose TB is resistant to rifampicin should receive testing using line probe assay (LPA) and liquid culture (or solid culture if liquid is not available) before starting the

shorter regimen, to make sure it will work for their strain of TB. People can start the shorter regimen while awaiting LPA results, which should be available in a couple of weeks. At a minimum, patients must receive susceptibility testing for isoniazid, rifampicin, fluoroquinolones (moxifloxacin), and injectables (kanamycin). If there is resistance to any of the drugs in the regimen (except isoniazid) the patient must switch to a longer, individualized regimen per WHO guidance. People unable to be treated with the shorter regimen should be offered treatment with at least one newer drug (bedaquiline, delamanid, or linezolid).

Patients on the shorter regimen should be tested monthly with both smear and culture to ensure that the treatment is working, and that resistance to additional drugs is not developing. Monitoring the patient's weight monthly is also important to check that the patient is improving on treatment. People who are not improving on the shorter regimen, or who are not cured by the shorter regimen, should be offered newer drugs as part of their therapy. Close monitoring is especially important given the one in five chance of a poor treatment outcome observed in the clinical trial (see below).<sup>7</sup> TB programs must follow up with patients after treatment completion to ensure that their TB has not relapsed.

***Patients on the shorter regimen should be tested monthly with both smear and culture to ensure that the treatment is working, and that resistance to additional drugs is not developing.***

## SIDE EFFECTS

The shorter regimen has many side effects, including gastrointestinal (stomach) upset and distress, hearing loss, damage to the kidneys and liver, and a potentially dangerous disturbance to the heart's electrical rhythm called QT prolongation.<sup>3</sup> One of the medications in the regimen, clofazimine, can cause a change in the color of the skin, making it darker or more orange. This problem is temporary and will usually go away within several months after completing treatment. While all DR-TB medicines have side effects, hearing loss is a common and particularly problematic feature of the kanamycin used in the shorter regimen. Hearing loss caused by kanamycin (or other injectable TB drugs) is irreversible and causes social, psychological, and economic suffering.<sup>8</sup> Children are especially vulnerable. Hearing loss is avoidable by using a newer drug (bedaquiline, delamanid, or linezolid) in place of kanamycin in a longer regimen.

Regular monitoring for side effects—and changing the regimen as needed—is essential. Important side effect monitoring includes:

- hearing tests (called audiometry) before starting the regimen and monthly afterwards;
- liver function tests before starting treatment, and regularly thereafter—especially if the patient has any liver issues or is living with HIV;
- an ECG (electrocardiogram) before starting treatment and monthly afterwards to check the heart;
- checking at every visit for signs of nerve damage (peripheral neuropathy), such as tingling, numbness, burning, or pain in the hands or feet;
- potassium checks (blood test). If levels appear low, the patient should receive potassium supplements.

## STREAM TRIAL PRELIMINARY RESULTS

WHO recommended the shorter regimen before data were available from controlled clinical trials testing the regimen’s safety and effectiveness. In October 2017, preliminary results from stage 1 of the STREAM trial became available. STREAM is the name of the phase III randomized, controlled trial to evaluate whether the shorter regimen described above was as effective as the longer WHO standard of care. Unfortunately, the trial failed to show that the shorter regimen was as effective as the longer individualized regimen. The number of people who had a poor outcome on the shorter regimen was up to 11% more compared with the longer regimen, although it could have been as much as 7% less.<sup>7</sup> The trial also showed similar kinds and amounts of side effects on the shorter and longer regimens overall. The trial included only 126 participants with HIV, but results suggested they were more likely to experience a serious side effect (44.7% versus 40.0%) and at twice the risk of death (hazard ratio: 2.21, 95% confidence interval 0.75-6.53) on the shorter regimen as compared to the longer regimen (though these results were not statistically significant).<sup>7</sup> The trial did show that the shorter regimen was less costly for both patients and TB programs, with the longer regimen costing four times as much as the shorter regimen.<sup>6,7</sup> WHO plans to review its guidelines in late 2018 when the full trial results become available.

**TABLE: ADVANTAGES AND DISADVANTAGES OF THE SHORTER REGIMEN**

Advantages	Disadvantages
<ul style="list-style-type: none"> <li>- Shorter duration of treatment</li> <li>- Inexpensive: medication costs for 9 months of treatment are between USD \$500-700 in most high-burden settings</li> <li>- Lower cost to patients and programs</li> <li>- Standardization may enable easier roll out for treatment programs</li> <li>- Drugs in the regimen are already widely available</li> </ul>	<ul style="list-style-type: none"> <li>- Painful injections have difficult side effects such as permanent hearing loss</li> <li>- Many drugs; each brings side effects and many have little evidence of effectiveness</li> <li>- High pill burden</li> <li>- Not tailored to individual susceptibility (people may be given drugs that are not effective for their TB but add side effects)</li> <li>- Excludes newer known effective drugs, such as bedaquiline and linezolid</li> <li>- May not be as effective as a longer regimen</li> <li>- May be associated with higher mortality among people living with HIV</li> </ul>

## CONCLUSIONS

### 1. Informed patient choice is crucial

The question, “is shorter better?” is really the patient’s to answer, in discussion with their doctor. The shorter regimen has both advantages and disadvantages (see Table). Patients deserve and indeed must be given an opportunity to make an informed choice about whether to take the shorter regimen or a longer individualized regimen. Some patients may choose the shorter regimen to finish treatment earlier and at a lower cost. Some may prefer to have a longer regimen to increase their chances of cure, to take fewer or different kinds of medicines, to avoid an injectable drug, or to take a newer drug known to be effective like bedaquiline or linezolid. Others may want to participate in a research study for the chance to receive other shorter regimens with newer drugs (to learn about trials that may be taking place near you, contact [tag@treatmentactiongroup.org](mailto:tag@treatmentactiongroup.org)).

### 2. Proper testing and regular monitoring is essential

Any setting using the shorter regimen must have timely access to drug susceptibility testing and treatment monitoring—including both line probe assays and liquid culture—to inform the best regimen choice. Monitoring for side effects, and adjusting treatment as soon as potentially harmful effects appear, is essential.

### 3. Better treatment options are needed

People living with DR-TB, their doctors, and treatment programs face important and difficult decisions because there is no clear evidence that one regimen is better than another. Both the shorter and longer regimen performed much better in the STREAM trial than the average MDR-TB treatment success rate of about 50% normally observed worldwide in regular treatment programs. Yet about one in five patients on either regimen had a bad treatment outcome even in the clinical trial.<sup>8</sup> More effective, safer regimens are clearly needed. Promising studies are ongoing, but greater investment in TB research and development is necessary to ensure better options.

## REFERENCES/ENDNOTES

- <sup>1</sup> World Health Organization. Global Tuberculosis Report 2017. Geneva: World Health Organization; 2017.
- <sup>2</sup> World Health Organization. The Shorter MDR-TB Regimen [Internet]. May 2016 (cited 20 November 2017). <http://www.who.int/mediacentre/factsheets/fs194/en/>
- <sup>3</sup> World Health Organization. WHO treatment guidelines for drug-resistant tuberculosis, 2016 update. Geneva: World Health Organization; October 2016.
- <sup>4</sup> Aung KJ, Van Deun A, Declercq E, et al. Successful ‘9-month Bangladesh regimen’ for multidrug-resistant tuberculosis among over 500 consecutive patients. *Int J Tuberc Lung Dis*. 2014 Oct;18(10):1180-7. doi: 10.5588/ijtld.14.0100.
- <sup>5</sup> McKenna L, Zhang A, & Lessem E. An Activist’s Guide to Tuberculosis Drugs. New York: Treatment Action Group; 2016. Figure 2, Shortened regimen for some forms of drug-resistant TB; p. 4.
- <sup>6</sup> World Health Organization. Frequently asked questions about the implementation of the new WHO recommendation on the use of the shorter MDR-TB regimen under programmatic conditions [Internet]. 20 December 2016. [http://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/FAQshorter\\_MDR\\_regimen.pdf](http://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/FAQshorter_MDR_regimen.pdf)
- <sup>7</sup> The Union & USAID. STREAM trial (Evaluation of a Standardised Treatment Regimen of Anti-tuberculosis Drugs for Patients with Multidrug-resistant Tuberculosis): preliminary stage 1 results. Presented at: 48th Union World Conference on Lung Health; 2017 October 12; Guadalajara, Mexico.
- <sup>8</sup> Reuter A, Tisile P, von Delft D, et al. The devil we know: is the use of injectable agents for the treatment of MDR-TB justified? *Int J Tuberc Lung Dis*. 2017 Nov 1;21(11):1114-1126. doi:10.5588/ijtld.17.0468.