Frequently asked questions about the shorter MDR-TB regimen
Version: 12 May 2016

These notes are to be read alongside the WHO treatment guidelines for drug-resistant tuberculosis, 2016 update (WHO/HTM/TB/2016.04) released by the Global TB Programme of the World Health Organization (WHO) in 2016 (see references under Further Reading at the end of these FAQs).

Why is multidrug-resistant TB (MDR-TB) important?
Multidrug-resistant TB, or MDR-TB, is caused by TB bacteria resistant to at least rifampicin and isoniazid, the two most effective TB drugs. About half a million fresh cases of MDR-TB emerge each year. This form of TB cannot be treated with the standard 6-month course of medication which is so effective in most TB patients. Patients with MDR-TB are treated with a different combination of drugs and usually for 18 months or more; this treatment is nonetheless not as effective as the one for non MDR-TB. All patients with confirmed rifampicin-resistant disease (e.g. from Xpert MTB/RIF testing) need to be treated as for MDR-TB.

What is the shorter MDR-TB regimen?
The long duration of MDR-TB treatment and the toxicity of certain drugs discourage many patients from completing the treatment as required, and when associated with its high costs, pose a major challenge to the health system. Attempts to reduce the length of treatment of MDR-TB and to use a combination of drugs which is more tolerable and more effective have been ongoing for several years. More recently, a fairly standardised treatment regimen lasting 9-12 months has been studied in a number of countries and shown to result in high rates of relapse-free cure in selected MDR-TB patients with an acceptable safety profile.

Are there different shorter MDR-TB regimens? Which is the one that WHO-recommends?
Over the years several combinations of drugs and duration of treatment have been studied, with the intention of reducing the number of drugs and length of treatment as much as possible without losing effectiveness. The regimen which has been studied most widely contains kanamycin (an injectable), moxifloxacin, prothionamide, clofazimine, high-dose isoniazid, pyrazinamide and ethambutol, given together in an initial phase of 4 months, and followed by 5 months of treatment with four of the drugs (moxifloxacin, clofazimine, pyrazinamide, and ethambutol). In summary:

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Why is WHO releasing its recommendations on the shorter MDR-TB regimen only now?
To formulate treatment recommendations, WHO follows a rigorous process whereby evidence is reviewed systematically, summarised and used to inform the new policies, using the GRADE approach. The evidence on the of the shorter MDR-TB regimen is developing gradually, and it was only until recently that a fair amount of observational data on both effectiveness and safety became available from different settings. In May 2016, following a review of published and unpublished data, WHO updated its treatment guidelines for MDR-TB and included a recommendation on the use of a standardised shorter MDR-TB regimen. Before the current recommendation, the WHO position on shorter MDR-TB regimens from 2012 was based on the limited evidence available then and required that treatment be carried out under operational research conditions to assess safety and effectiveness, and that such projects be approved by a national ethics review committee.
**Why is WHO recommending the use of the shorter MDR-TB regimen if the evidence is considered to be of low quality?**
The WHO recommendation on the use of the shorter MDR-TB regimen is conditional and based on very low certainty in the evidence, according to the terminology of the GRADE approach. Until such time as trial data become available - the STREAM trial results are not expected before 2018 - the quality of the evidence is likely to remain low. The recommendation will be reviewed once these data become available. Nonetheless, mindful of the considerable benefits which both patients and health systems stand to gain with the increased use of the shorter MDR-TB regimen in the place of the longer treatment options, WHO already advises national TB programmes to introduce the shorter MDR-TB regimen within the conditions specified in the guidelines.

**What was the success rate among patients on shorter MDR-TB regimens? Were all patients followed up to check for relapse?**
The evidence review for the Guidelines considered observational study data from a pool of 1,205 patients treated with shorter MDR-TB regimens in African and Asian sites (Bangladesh, Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, DR Congo, Niger, Swaziland, and Uzbekistan). Treatment success versus all other outcomes was reported in 84% (95%CLs: 79%-87%) of these patients [a comparable selection of MDR-TB patients treated with a variety of individualised regimens of longer duration had a pooled treatment success of 62% (95%CLs: 53%-70%)]. Amongst patients who did not complete treatment successfully, 7% died, 6% were lost to follow up, and 3% had a treatment failure. Relapse in patients with successful outcomes was incompletely assessed in the studies reviewed: in two of the country series it was assessed at 24 months after treatment and in another at 12 months. Relapse was only observed in 3 patients and occurred in less than 1% of those completing treatment successfully. So while relapse appears to be rare, it will be important to continue following up patients who complete the shorter MDR-TB regimen closely and to await the definitive findings of the STREAM trial on this outcome.

**Can all MDR-TB patients be treated with the shorter MDR-TB regimen?**
Not all MDR-TB patients are eligible for the shorter MDR-TB regimen. If any of the following conditions are present then *it is not recommended* to use the shorter MDR-TB regimen:

- Confirmed resistance or suspected ineffectiveness to a medicine in the shorter MDR-TB regimen (except isoniazid resistance)
- Exposure to a second-line medicine in the shorter MDR-TB regimen for >1 month
- Intolerance to one or more medicines in the shorter MDR-TB regimen or risk of toxicity (e.g. drug-drug interactions, cardiotoxicity)
- Pregnancy
- Extrapulmonary disease
- A medicine in the shorter MDR-TB regimen is not available to the programme

There may be other contraindications to the treatment decided by the clinician on a case-by-case basis. If the shorter MDR-TB regimen cannot be used the patient needs to be reassessed with a view to the start of an individualised (“conventional”) MDR-TB treatment.

While shorter MDR-TB regimens have as yet been used on a limited number and variety of patients, children and people with HIV on antiretroviral therapy may receive the shorter MDR-TB regimen. Given that all patients with confirmed rifampicin-resistant disease are treated as for MDR-TB, the shorter MDR-TB regimen may be used in these patients unless they have other exclusion criteria. The shorter MDR-TB regimen should not be used in patients in whom the diagnosis of RR-/MDR-TB has not been reliably confirmed using an approved molecular (e.g. Xpert MTB/RIF) or conventional diagnostic.
Can the shorter MDR-TB regimen be used everywhere in the world?
Yes. There are about 20 countries in Africa and Asia where shorter MDR-TB regimens have been used under different settings, and the experience keeps increasing. In the African countries, several patients treated were HIV infected and performed well on the shorter MDR-TB regimen. Special care is needed when the shorter MDR-TB regimen is used in settings where the level of resistance to the second-line drugs is known to be high. Nonetheless, the regimen has been used successfully among carefully-selected patients in Uzbekistan, a former Soviet Union country.

Should all patients placed on the shorter MDR-TB regimen be tested for resistance to second-line drugs?
Yes, ideally, all MDR-TB patients should be tested for resistance to fluoroquinolones and second-line injectable drugs before starting any MDR-TB treatment. This is particularly important for shorter MDR-TB regimens because the regimen is not recommended in patients resistant to any of these drugs or who have extensively drug-resistant TB (or XDR-TB; MDR-TB with additional resistance to a fluoroquinolone and a second-line injectable). In these patients the shorter MDR-TB regimen may not provide adequate protection from the acquisition of additional resistance. The capacity to undertake these tests is expected to increase in the near future as countries implement rapid molecular testing using line probe assay. These tests have been approved for use by WHO in 2016. In places where the capacity for drug-susceptibility testing for fluoroquinolones and second-line injectable drugs is as yet unavailable, treatment decisions have to be based on the likelihood of resistance to these medicines, informed by the patient’s clinical history and recent representative surveillance data from the area.

Can changes be made to the shorter MDR-TB regimen?
Only some changes are allowed. The shorter MDR-TB regimen has been studied as a fairly standardised intervention; the effect of drastic changes to its composition is unknown but some changes are allowed. If the patient’s sputum does not become negative in the first four months the initial phase may be prolonged by two months. Kanamycin can be switched with amikacin; ethionamide can be used instead of prothionamide. The original fluoroquinolone used in the shorter MDR-TB regimens – gatifloxacin – has more recently been replaced by moxifloxacin due to shortages in the supplies of the drug. Until further experience is acquired it is not recommended to make any substantial changes to the form and duration of the shorter MDR-TB regimen from the one which has been studied.

Can the regimen be used with new drugs (bedaquiline or delamanid)?
There are as yet no published reports of the experience of use of shorter MDR-TB regimens with bedaquiline or delamanid, but one of the STREAM Trial arms will study the effect of replacing kanamycin with bedaquiline. Until further evidence becomes available it is not recommended to add or remove any of the components of the shorter MDR-TB regimen from those recommended, or to replace them with bedaquiline or delamanid.

What happens to MDR-TB patients who do not respond to the shorter MDR-TB regimen or who interrupt treatment?
Patients on the shorter MDR-TB regimen who do not respond (remain sick or sputum smear positive) need to be assessed to decide whether they should be switched to an individualised treatment MDR-TB regimen. No changes should be made to the shorter MDR-TB regimen composition to forestall treatment failure. Likewise, patients who develop a condition which is one of the exclusion criteria (e.g. extrapulmonary disease or pregnancy) during treatment need a reassessment with a view to the change of regimen. If patients miss 2 consecutive months or more of shorter MDR-TB treatment then the episode is classified as “Loss to follow up” and if returning for treatment they are not restarted on a shorter MDR-TB regimen. If there are interruptions...
of less than two months then the shorter MDR-TB treatment is usually continued and the missed doses added to the rest of the treatment.

**Can I start using the shorter MDR-TB regimen immediately in my programme?**
Yes, national TB programmes can introduce the shorter MDR-TB regimen from now. There is no need to wait until the results of the randomised controlled trial are published. The conditions for use (inclusion and exclusion criteria detailed in the guidance) need to be respected and reflected in the national TB treatment guidelines documents.

**How much does one treatment with the shorter MDR-TB regimen cost?**
Large scale implementation of the shorter MDR-TB regimen is expected to make savings which can be turned back into the programme to support other functions. In MSF-supported sites in 2015, the cost of medicines for the shorter MDR-TB regimen typically totalled about USD450 per patient treated under programmatic conditions, one third of which due to clofazimine alone. The medicines needed for a full course of treatment with individualised MDR-TB regimens lasting about 20 months typically cost four times as much.

**Where can I get clofazimine and other medicines needed for the shorter MDR-TB regimen?**
The Global Drug Facility can supply the medicines needed for the shorter MDR-TB regimen (www.stoptb.org/gdf/drugsupply/drugs_available.asp).

**Is the shorter MDR-TB regimen supported by my Global Fund grant to treat MDR-TB patients?**
Yes, the Global Fund grant may be used to purchase medicines for the shorter MDR-TB regimen. Please contact your Fund Portfolio Manager to discuss the ways to do this.

**How are patients on the shorter MDR-TB regimen monitored?**
The treatment outcome definitions and reporting framework for patients on the shorter MDR-TB regimen are similar to those for the individualised MDR-TB regimens. The cohort outcomes may be reported to WHO combined with the ones for patients on other longer MDR-TB regimens, and the national TB programme may wish to analyse the two cohorts separately.

Active TB drug safety monitoring and management (aDSM) is recommended when patients are treated with the shorter MDR-TB regimen. A schedule of patient monitoring is thus recommended for the whole duration of treatment, as well as to check for relapse after the end of treatment. Schedules have been developed for this purpose by stakeholders (e.g. Médecins Sans Frontières [MSF], UNION, Global Drug-Resistant TB Initiative[GDI]).

To date, the most frequent drug-toxicities reported in patients on the shorter MDR-TB regimen have been those which are well-established with the medicines used, such as hearing impairment linked to the injectable agents and gastro-intestinal disturbances related to prothionamide. Given the concomitant use of clofazimine and moxifloxacin, both of which prolong the QT interval, the safety profile for the shorter regimen may be different from those of individualised MDR-TB regimens, even if its length is shorter.

**Do I need to have aDSM (active TB drug safety monitoring and management) up and running before I start patients on the shorter MDR-TB regimen?**
No, a fully functional aDSM is not required up front at the time of ordering the drugs or starting
patients on the shorter MDR-TB regimen. However, two key elements need to be in place so that the essential safety data are collected for all patients from the moment that they are started on treatment: preparations for the collection of data (e.g. paper or electronic forms) and staff properly trained to collect these data. The NTP needs to assign someone from the start to coordinate the process, to ensure that the two minimum elements are in place.

Is ethics clearance needed before introducing the shorter MDR-TB regimen?
The shorter MDR-TB regimen is now being recommended for use as a standard of care and not as part of operational research. Ethical clearance is therefore not needed.

Is informed consent required to use the shorter MDR-TB regimen?
No. If the patient is treated within the national TB programme under routine conditions of care then there is no need for additional measures to those taken for other patients treated for MDR-TB. Patients on the shorter MDR-TB regimen should be made aware that if they discontinue their treatment for 2 months or more they will not be able to continue the shorter regimen and can only be offered the longer conventional MDR-TB treatment thereafter.

Further reading


Research Protocol - Effectiveness of a simplified short regimen for Multidrug Resistant Tuberculosis treatment in Karakalpakstan, Uzbekistan - MSF Field Research. Available from:
http://fieldresearch.msf.org/msf/handle/10144/32296


www.who.int/iris/bitstream/10665/79199/1/9789241505345_eng.pdf


The evaluation of a standardised treatment regimen of anti-tuberculosis drugs for patients with multi-drug-resistant tuberculosis (MDR-TB) [STREAM-TRIAL]. Available from:
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4164715/

Stop TB Partnership | Global Drug Facility (GDF) - GDF Products List. Available from:
http://www.stoptb.org/gdf/drugsupply/drugs_available.asp