

Frequently asked questions about the implementation of the new WHO recommendation on the use of the shorter MDR-TB regimen under programmatic conditions

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These FAQs 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 May 2016(1). The 2016 guidelines and their online appendices provide more background about the updated WHO recommendation on the shorter MDR-TB regimen since the previous guidelines of 2011(2).

Why are shorter MDR-TB regimens needed?

About half a million new cases of rifampicin-resistant (RR-TB) and multidrug-resistant (MDR-TB; RR-TB with additional resistance to isoniazid) emerge each year globally(3). RR-/MDR-TB cannot be treated with the recommended 6-month standard course of medication which is effective in most TB patients(4). Patients with MDR-TB are typically treated with more medicines and for much longer (conventionally 20 months or more(2)). Despite this, these regimens are not as effective as standard first-line regimens for drug-susceptible TB.

The duration of the longer MDR-TB treatment regimens and the toxicity of certain agents composing them discourage many patients from completing the treatment as intended. In addition, the high cost associated with the implementation of the regimens poses a significant challenge to health systems. Attempts to reduce the length of treatment and to use a combination of medicines which is more tolerable, more effective and less expensive have been ongoing for several years(5). More recently, a fairly standardised treatment regimen lasting 9-12 months has been reported to give relapse-free cure in >85% of selected MDR-TB patients, with adverse reactions typical of those expected when using these second-line TB medicines (1),(6),(7),(8).

Which is the shorter MDR-TB regimen that WHO-recommends?

The regimen recommended by WHO is the one which has been used more recently in different geographical sites and in the STREAM trial¹(9). The regimen contains kanamycin (an injectable agent), moxifloxacin, prothionamide, clofazimine, isoniazid, pyrazinamide and ethambutol, given together in an initial phase of 4 months (with the possibility to extend to six months if they remain sputum smear positive at the end of month 4), and followed by 5 months of treatment with four of the medicines (moxifloxacin, clofazimine, pyrazinamide, and ethambutol). Earlier cohorts used gatifloxacin instead of moxifloxacin when this medicine was still available on the market. In summary:

4-6 Km-Mfx-Pto-Cfz-Z-H_{high-dose}-E / 5 Mfx-Cfz-Z-E

What is the dosage of medicines to use in the WHO-recommended shorter MDR-TB regimen?

The recommended dosage by weight is the one which has been published earlier by the Global Drug-resistant TB Initiative (GDI) in 2015 and the STREAM trial(9),(10) (see below). The multicentre African cohorts supported by the UNION used a different schedule with lower dosing of moxifloxacin(11)(for paediatric doses see Annex 3 of (4)).

¹ STREAM is a clinical trial comparing outcomes in MDR-TB patients on a nine-month regimen with those of the longer treatment regimen. The first stage of the trial completed enrolment in mid-2015 (424 patients in 4 countries) and results are expected in 2018

Drug	Weight group		
	Less than 30 kg	30 kg to 50 kg	More than 50 kg
Gatifloxacin	400 mg	600 mg	800 mg
Moxifloxacin	400 mg	600 mg	800 mg
Clofazimine	50 mg	100 mg	100 mg
Ethambutol	800 mg	800 mg	1200 mg
Pyrazinamide	1000 mg	1500 mg	2000 mg
Isoniazid	300 mg	400 mg	600 mg
Prothionamide	250 mg	500 mg	750 mg
Kanamycin [†]	15 mg per kilogram body weight (maximum 1 g)		

†For adults over 59 years of age, the dose will be reduced to 10 mg/kg (max dose 750 mg).

Gatifloxacin is currently unavailable in most countries

What was the success rate among patients on shorter MDR-TB regimens?

The evidence review for the 2016 update of the WHO 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) (see Online Appendix 4, Section I of (1)). 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.

Were all patients on the shorter MDR-TB regimens followed up to check for relapse?

In the studies included in the evidence review for the 2016 update of the WHO guidelines, relapse in patients with successful outcomes was assessed incompletely and for a variable duration between projects: in two of the countries it was assessed at 24 months after treatment and in another at 12 months. Just over 600 patients with a successful outcome who were followed up; among them, relapse was observed in less than 1%. While it appears to be rare, it will be important to monitor closely for relapse in patients who complete the shorter MDR-TB regimen successfully and to await the findings of the STREAM trial on this outcome(9).

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 - using the GRADE approach - before policy is changed(12),(13). The evidence on the use of the shorter MDR-TB regimen is developing gradually, and it was not until very recently that observational data on both its effectiveness *and* safety became available from different settings. In May 2016, following a review of published and unpublished data by an expert panel convened for this purpose, WHO updated its treatment guidelines for MDR-TB and included a recommendation on the use of a standardised shorter MDR-TB regimen(1). 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 certainty in the evidence is very low?

There are considerable benefits to both the patients and to the health systems if the shorter MDR-TB regimen is used instead of longer treatment options. Although the evidence for the effectiveness of the shorter MDR-TB regimen is still considered of very low quality, the outcomes from the observational studies assessed to date do show high levels of success in selected patients treated in different settings. WHO is thus advising national TB programmes to initiate patients on the shorter MDR-TB regimen only under specific conditions(1). The recommendation may be revised once the results of the STREAM trial become available (expected in 2018)(9).

Can all MDR-TB patients be treated with the WHO-recommended shorter MDR-TB regimen?

No. The shorter MDR-TB regimen may be used in MDR-TB patients who do not have the following conditions:

- Confirmed resistance, or suspected ineffectiveness, to a medicine in the shorter MDR-TB regimen (excluding resistance to isoniazid)
- Previous exposure for >1 month to a second-line medicine included in the shorter MDR-TB regimen
- Intolerance to one or more medicines in the shorter MDR-TB regimen or increased risk of toxicity (e.g. drug-drug interactions, cardiotoxicity)
- Pregnancy
- Extrapulmonary disease

Previous exposure for >1 month to a fluoroquinolone or a second-line injectable medicine which is not in the shorter regimen but which may generate cross-resistance is considered an exclusion criterion. However, if resistance to both of these two agents has been excluded by a reliable drug-susceptibility test (DST), then the shorter MDR-TB regimen can be used. Resistance to pyrazinamide at the start of treatment, when determined using a reliable DST, may also be considered a criterion for exclusion. It is not recommended to base treatment decisions on the DST for ethambutol or any other drug in the regimen apart from those mentioned, owing to the unreliable nature of the tests(14).

In addition to these criteria, the clinician may use a longer treatment based on the individual circumstances (e.g. uncertainty about drug susceptibility; there is no access to 2nd line LPA; unavailability of one or more medicines; or the patient condition requires immediate start of treatment). If the shorter MDR-TB regimen cannot be used the patient needs to be reassessed with a view to starting a longer MDR-TB treatment.

The shorter MDR-TB regimen is recommended for patients in whom the diagnosis of RR-/MDR-TB has been reliably confirmed by an approved molecular (e.g. Xpert MTB/RIF) or phenotypic DST method. All patients with confirmed rifampicin-resistant disease are treated as for MDR-TB, and the shorter MDR-TB regimen could be used in these patients too. Children and people with HIV on antiretroviral therapy could receive the shorter MDR-TB regimen.

Should patients be tested for pyrazinamide resistance before starting treatment? What if there is resistance?

DST to pyrazinamide is not an essential pre-requisite before starting the shorter MDR-TB regimen. There is no approved rapid test for pyrazinamide susceptibility at this point in time and testing may require several weeks to produce a reliable result. If, however, there is a result from reliable DST which shows resistance to pyrazinamide before the start of treatment the health care provider may decide to put the patient on a longer MDR-TB regimen. The clinician may still decide to use the shorter MDR-TB regimen in the presence of pyrazinamide resistance². If a test result showing resistance becomes available after the shorter MDR-TB regimen has been started, the clinician may decide whether to continue the shorter treatment or to switch to a longer MDR-TB regimen, based on the patient's response to treatment and other considerations.

Should patients also be tested for resistance to ethambutol, clofazimine or prothionamide before starting treatment?

It is not recommended to base treatment decisions on the DST for ethambutol owing to the unreliable nature of this test(14). There are no reliable methods available to test for the susceptibility of TB strains to clofazimine or to prothionamide.

Can the WHO-recommended shorter MDR-TB regimen be used everywhere in the world?

Yes. There are more than 20 countries in Africa and Asia where shorter MDR-TB regimens are being used, and the experience keeps accumulating. In the African countries, several patients treated were HIV infected and performed well on the shorter MDR-TB regimen. When the shorter MDR-TB regimen is used in settings where the level of resistance to the second-line medicines is known to be high, careful evaluation is needed (in addition to rapid testing for fluoroquinolones and second-line injectable agents) to avoid treating patients with resistance to medicines in the regimen for which no reliable DST exists. Nonetheless, the regimen is showing good results in patients who fit the inclusion criteria in one Central Asian setting where TB strains with advanced patterns of resistance are very common.

Can the WHO-recommended shorter MDR-TB regimen be used in people with HIV?

Yes. The shorter MDR-TB regimen can be used in people living with HIV, including those who are receiving antiretroviral treatment. People living with HIV need to be given the same consideration for treatment with the shorter MDR-TB treatment regimen as people who are HIV seronegative. There may be a potential for overlapping, additive toxicities or for drug-drug interactions between some antiretroviral medicines and the injectable medicines, moxifloxacin and clofazimine³: however no studies are available to warrant modifications of the MDR-TB or the ARV regimens. Close monitoring of people on the two regimens is advised given that the data in this area remains limited.

Can the shorter MDR-TB regimen be used in children?

Shorter MDR-TB regimens have largely been used in patients older than 14 years of age. However, the medicines which compose these regimens have formed part of MDR-TB regimens for many years, in similar combinations, for both adults and children. The associated adverse drug reactions have been widely described and the drug dosages established(4). The WHO recommendation is that the regimen can be used in children under 15 years. However, given the incomplete information about the safety profile of the regimen as a whole, close monitoring– including aDSM – is recommended during its use in both children and adults.

² In the data reviewed for the 2016 guidelines, treatment success decreased under such conditions but the experience was limited to less than 200 cases (in these patients pyrazinamide was retained in the regimen)

³ http://liverpool-web-production.s3.amazonaws.com/treatment_selectors/pdfs/000/000/012/original/TS_TB_2016_Mar.pdf

Should all patients placed on the WHO-recommended shorter MDR-TB regimen be tested for resistance to second-line medicines? Can patients be placed on the shorter MDR-TB regimen without testing for resistance to second-line medicines?

Ideally, all MDR-TB patients are to be tested for resistance to fluoroquinolones and second-line injectable agents before starting any MDR-TB treatment. This is particularly important for the shorter MDR-TB regimen. This regimen is not recommended in patients with resistance to any of these two drug classes, or who have extensively drug-resistant TB (XDR-TB; MDR-TB plus 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 of programmes to test for resistance to fluoroquinolones and to second-line injectable agents is expected to increase in the near future as countries implement rapid molecular testing using line probe assay. All efforts should be made to ensure patients can get access to these tests, which have now been approved for use by WHO(15). Until the capacity for second-line DST is available, treatment decisions have to be guided by the likelihood of resistance to these medicines, informed by the patient's clinical history and recent representative surveillance data from the area.

Will culture-based tests for fluoroquinolones and second-line injectable agents have any role once the WHO-recommended line probe assay for second-line agents becomes available?

There may be less demand for culture-based techniques to perform diagnostic second-line DST (on solid or liquid media) once molecular tests such as line probe assay (LPA) become more easily available to the clinicians(15). However, culture-based techniques retain their role for the follow-up of patients on MDR-TB treatment. It is likely that these tests will still be needed in the coming years in many settings where LPA is not yet available or as a backup in case LPA is temporarily unavailable. Culture-based test results for fluoroquinolones and second-line injectable drugs have the same diagnostic value as the line probe assay for these medicines.

Can changes be made to the duration and composition of the shorter MDR-TB regimen?

Unlike the longer MDR-TB regimen the shorter MDR-TB regimen has been studied as a fairly standardised intervention. It is not advised to shorten the duration of the intensive or continuation phase, or to prolong them in case of lack of response. Likewise, changes to the regimen composition other than those which were allowed in the studies may have an unpredictable impact on its effectiveness and are therefore not recommended. The following modifications can thus be done:

- If sputum smear does not become microscopy negative by the fourth month the initial phase is prolonged until sputum smear converts; however the initial phase is not prolonged for more than six months in total (the duration of the continuation phase remains fixed at 5 months regardless)
- Moxifloxacin can be replaced with gatifloxacin, the fluoroquinolone used in the earlier studies of shorter MDR-TB regimens. However, no quality-assured brand of gatifloxacin is currently available. Moxifloxacin is not to be replaced by levofloxacin
- Ethionamide can be used instead of prothionamide
- Amikacin can be used instead of kanamycin. In two studies, capreomycin was used when kanamycin resistance was detected

What happens if the health care provider does not have one of the medicines or else there is a stockout while patients are on treatment? Can some medicines be replaced if there is no other option (e.g. clofazimine with linezolid)?

There is no experience with the replacement of medicines in the shorter MDR-TB regimen beyond the adjustments that have been mentioned in a previous answer above. The health care provider thus needs to ensure that the doses needed for a patient on the shorter MDR-TB regimen are secured for the time during which the treatment will last. This requires a careful quantification of needs when ordering medical supplies to avoid stock outs or the expiry of any medicine in the regimen, but also to prevent wasteful over-stocking.

Can the regimen be used with new medicines (bedaquiline or delamanid)?

WHO has released policy on the use of these new medicines in recent years and at the time of the release of these FAQs this policy had not changed(16),(17). There are as yet no 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.

When should one consider switching a patient from the shorter MDR-TB regimen to a longer MDR-TB regimen?

All the care needs to be taken to select the right patients to receive the shorter MDR-TB regimen. However, fresh information or developments while the patient is on treatment may require that the shorter MDR-TB regimen is stopped and a longer, individualised MDR-TB regimen or other treatment is started. This is most likely to happen if:

- DST results taken after start of treatment fail to confirm resistance to rifampicin or even tuberculosis (i.e. initial results were not valid);
- DST results show resistance to medicines in the shorter MDR-TB regimen: this may be reflect the actual situation at start of treatment which was unknown at that time, or else the acquisition of additional resistance during treatment;
- Lack of response to treatment (e.g. no sputum smear conversion by 6 months or deterioration of clinical condition despite treatment);
- Patient is treated for more than one month, interrupts treatment and returns after an interval ≥ 2 months (i.e. fulfils another exclusion criterion);
- Emergence of another exclusion criterion (e.g. extrapulmonary disease, pregnancy, intolerance to a medicine in the regimen).

If the patient is assessed for a longer MDR-TB regimen, the treatment should be designed on the basis of established algorithms(4).

What should be offered 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 need to be assessed to decide whether they need to be switched to a longer MDR-TB regimen. No changes should be made to the shorter MDR-TB regimen composition if there are signs of impending treatment failure (e.g. no sputum smear conversion by 6 months or deterioration of clinical condition despite treatment). If patients miss 2 consecutive months or more of shorter MDR-TB treatment then the episode is classified as “Loss to follow up”. If a patient has received the shorter MDR-TB regimen for more than one month, and returns for treatment after an interruption of 2 consecutive months or more, s/he is not restarted on a shorter MDR-TB regimen but on a longer MDR-TB regimen which may have to be individualized based on the medicines most likely to be effective. Patients need to be made aware of this. If there

are interruptions of less than two months (e.g. medical indication in the case of adverse events, patient decision) then the shorter MDR-TB regimen can be continued and the missed doses added to the rest of the treatment.

Can the health care provider start using the shorter MDR-TB regimen immediately?

Yes, national TB programmes can introduce the shorter MDR-TB regimen from now. The conditions for use - see elsewhere in these FAQs and in the 2016 update of the guideline - need to be respected and reflected in the national TB treatment guidelines documents.

What are the key steps for the health care provider to take when introducing the WHO-recommended shorter MDR-TB regimen?

Introducing the shorter MDR-TB regimen entails a series of steps, which are in common with those necessary when a new MDR-TB treatment component is introduced in the TB programme.

- i. The main policy and operational documents which govern the main components of the programme, such as the national strategic plan for TB, treatment guidelines and algorithms, regulations (e.g. importation of clofazimine), drug orders, and training material would need to be revised, as well as the diagnostic algorithm if there is a concomitant introduction of LPA for 2nd line medicines;
- ii. The MDR-TB council of experts (the *consilium* or its equivalent structure within the national TB programme (NTP)) will assist the health care provider to coordinate policy changes and activities related to the introduction of the shorter MDR-TB regimen, training, communication, establishing the patient eligibility for shorter MDR-TB regimen; train staff in the clinical aspects of the active TB drug safety monitoring and management (aDSM) component; and provide technical, clinical advice. This needs to take into account any phased implementation process, such as the introduction in one or a few centres or if it is also being done in the private sector;
- iii. The NTP and other health care providers need to estimate the number of MDR-TB patients eligible for the shorter regimen, budget accordingly, and submit the corresponding drug request after taking into account the existing stock of medicines. Of note, the reduction in the cost of the shorter regimen may enable the health care provider to accelerate scale up of treatment. However, estimated costs for enrolment of increased number of patients and allocation of sufficient resources, both human and financial, should be considered beforehand.
- iv. As it is in the case of the longer MDR-TB regimen the supply chain management has to be reviewed to ensure that drug orders are made in good time and correctly quantified to avert overstocking or shortages. Likewise, other consumables (e.g. medicines for symptomatic relief and adverse reactions, syringes, kits for LPA, medication for management of adverse effects, masks, N95 respirators) will be needed to ensure that the intervention is delivered as per internationally recommended standards(18);
- v. No changes are usually needed to the *Second-line TB treatment register* or the *Annual treatment outcomes report for RR-TB/MDR-TB*. The *TB treatment card* may be changed to allow the tabulation of results of periodic testing for response and adverse events (this may have already been done for the purposes of aDSM(19)); and
- vi. Electronic recording and reporting: if it does not yet exist it is important that the management considers its introduction(20). If it exists, changes may be needed in the electronic recording and reporting system to allow individuals belonging to the shorter MDR-TB regimen cohorts to be identifiable and for certain options to be included in their monitoring framework (e.g. addition of clofazimine, registration of ECG findings).

How much does the WHO-recommended shorter MDR-TB regimen cost?

With current GDF prices for quality-assured medication, the medicines needed for 9 months treatment with the shorter MDR-TB regimen cost between approximately USD500 and USD700 (ex-works). About 40-60% of the overall cost is due to clofazimine alone. The medicines needed for a full course of treatment with longer MDR-TB regimens typically cost four times as much or more, depending on composition and duration(21). Associated programme and patient costs other than the medicines themselves are also expected to decrease given the shorter duration of treatment.

What are the critical budget items to consider when introducing the WHO-recommended shorter MDR-TB regimen?

Large scale implementation of the shorter MDR-TB regimen is expected to make savings which can be reinserted into the programme to support other functions. The WHO Global TB Programme is revising its budgeting tool to provide a more systematic manner for implementers to quantify their main costs(22). The costs that health care providers need to consider when introducing the shorter MDR-TB regimen include the following: revision of the normative and regulatory documents, upgrades to the laboratory diagnostic services (2nd line LPA, testing for adverse events), enhancements to the information systems (paper or electronic), retraining of staff, aDSM component which include the costs of functional tests (e.g. ECG). Other recurrent costs of the TB patient-centred care and support are not different when using shorter MDR-TB regimen (e.g. treatment of adverse events, hospitalisation, diagnostic consumables, other clinical care, and social support). These costs may total to several times the costs of the medicines themselves, as is the case for the longer MDR-TB regimens although they are expected to be lower given the shorter duration of treatment.

Can the recommended WHO shorter regimen be used by all health care providers?

Yes, all health care providers which treat tuberculosis are invited to follow the WHO recommendations for TB treatment, including the current one on the shorter MDR-TB regimen. WHO has also produced guidance for the engagement of all health care providers in the treatment of drug-resistant TB(23).

How can the health care provider estimate the number of patients to place on the WHO-recommended shorter MDR-TB regimen?

Estimating the number of RR-/MDR-TB cases who are eligible for treatment with the shorter MDR-TB regimen forms part of the overall planning for MDR-TB treatment. The programme first establishes the number of MDR-TB enrolments expected in the coming years, depending upon the future increase in programme capacity (e.g. as part of a Global Fund-supported project). Then, based on surveillance and other data, two patient groups are defined: those who will be eligible for the shorter MDR-TB regimen and those who are not and who will need a longer MDR-TB regimen (the exclusion criteria are listed in one of the replies to an earlier question above and also in the factsheet at (24)). When estimating the caseload to put on treatment, in addition to considerations of eligibility, one needs to factor in what would be feasible to achieve within a given time to ensure that all elements are in place to be able to start and maintain patients on treatment, such as training and provision of an adequate framework for patient monitoring and support.

How can the volumes of medicines needed to treat patients with the WHO-recommended shorter MDR-TB regimen be calculated?

The principles for the quantification of medicines needed for the shorter MDR-TB regimen are similar to those for any other TB treatment component. The health care provider needs to have some basic details about how many patients will be treated and when they will start; what is the expected increment in caseload over successive years; what is the average body weight of the patients;

whether children will also be enrolled; what are the expected losses (from interruptions, deaths and transfers to another regimen); current stock on hand including expiry dates and orders of medicines already in the pipeline and not yet delivered; and whether some medicines will be exchanged during the period (e.g. Eto for Pto; Am for Km). It is best to split an order of medicines, the first part for the patients expected to be started within 6 months, and then adjusting the second part of the order based on the actual enrolments.

As for any TB treatment, the NTP must ensure an uninterrupted supply of TB medicines through proper quantification, supply planning, and rigorous quarterly monitoring with a functional early warning system to avoid treatment interruptions. The calculations of volumes of medicine can be done automatically using QuanTB, an application available for download free-of-charge (siapsprogram.org/tools-and-guidance/quantb/). QuanTB was created by the USAID-funded Systems for Improved Access to Pharmaceutical and Services (SIAPS) Programme to support quantification, order planning and budget/cost and early warning. Moreover the tool allows the generation of alerts on potential stock-outs, overstocks and risk of medicines expiry. More details on technical assistance or trainings linked to QuanTB can be obtained from the Global Drug Facility (GDF; email gdfprs@stoptb.org). Technical assistance to strengthen the procurement and supply and to establish an early warning system can be accessed via GDF, regional GLCs, WHO offices, or USAID bi-lateral field projects.

Where can the health care provider access clofazimine and other medicines needed for the WHO-recommended shorter MDR-TB regimen?

The Global Drug Facility (GDF) of Stop TB Partnership supplies a full gamut of quality-assured TB medicines recommended by WHO, including those required for the shorter MDR-TB regimen (www.stoptb.org/gdf/drugsupply/drugs_available.asp). Health care providers planning to order medicines for the shorter MDR-TB regimen should contact GDF early on to discuss details, such as quantification, order planning, preferred delivery dates and required funding. The Procurement Request Form with all information needed is accessible at www.stoptb.org/gdf/drugsupply/procurement_forms.asp and more queries can be sent to GDF via email (gdfprs@stoptb.org).

How can a health care provider access clofazimine if the medicine is not registered in country?

The new WHO recommendation provides an authoritative position on the role of clofazimine in MDR-TB treatment. An application will be made to have clofazimine included in the WHO Model List of Essential Medicines in 2017. These measures are expected to make it easier for country authorities to effect the necessary changes to their regulations in order to facilitate importation of the medicine. In some countries a waiver procedure is used to allow the importation of the medicine on a named-patient basis.

Does the health care provider need to report adverse events to clofazimine to GDF?

Any adverse events for patients on treatment such as clofazimine need to be reported primarily to the national agency responsible for pharmacovigilance, within the framework of aDSM described elsewhere in these FAQ(25). A mechanism for reporting of aDSM to a WHO global database is being created at this point. There is no special form or requirement to report the event to GDF.

Should a health care provider introduce the shorter MDR-TB regimen only when the current stock of medicines for treatment with longer MDR-TB regimens is exhausted?

This is an important consideration from the side of programme resources. However it should not prevent the health care provider from starting to plan for the introduction of the shorter MDR-TB

regimen early on. Most of the medicines composing the shorter MDR-TB regimen are also used for the longer MDR-TB regimens and therefore the available stocks may actually facilitate the introduction of the shorter MDR-TB regimen, when complemented by clofazimine. It is also important to keep in mind that a substantial proportion of the patients will still need a longer MDR-TB regimen which is individualized to the patient. When planning medicine orders it is therefore necessary to quantify carefully for both types of regimens to cover a specific forecasting period (1 year is recommended), in order to avoid waste of medicines which are used only in the longer regimens (e.g. linezolid, cycloserine, levofloxacin). QuantTB (siapsprogram.org/tools-and-guidance/quantb/) allows the quantification of medicines both regimens.

Is the WHO-recommended shorter MDR-TB regimen supported by the Global Fund grant?

Yes, a Global Fund grant could be used to purchase medicines for the shorter MDR-TB regimen. The Global Fund Country Team can provide more assistance on the ways to do this and how to undertake the transition plan. Moreover the health care providers can request technical assistance from other local and international funding agencies which have experience in MDR-TB care.

Who can provide technical assistance to national programmes on the shorter MDR-TB regimen?

A number of technical agencies have now acquired direct experience on the shorter MDR-TB regimen from programmes that they are supporting. These include Action Damien, Médecins sans Frontières, and the UNION. Programmes may contact WHO Global TB Programme or the regional Green Light Committee to access help in this respect.

Should the Global Fund supported projects on shorter MDR-TB regimens under operational research conditions be stopped and patients continued on the shorter MDR-TB regimen under normal programmatic conditions?

Patients being treated under operational research conditions need to be followed through according to the treatment plan they started. However, patients newly enrolled on the shorter MDR-TB regimen are treated under routine programmatic conditions. Nonetheless, even under the normal conditions, regular monitoring is needed to ensure the required standard of care and for aDSM(25). This will be important to ensure the best possible outcomes for patients and to safeguard their health. The direct observation of treatment (DOT) and other adherence support is advised for patients on the shorter MDR-TB regimen. Further evidence is needed about the effectiveness and safety of the shorter MDR-TB regimen under different settings, and about best practices in addressing challenges met when implementing the regimen.

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 the same as those for longer MDR-TB regimens. Response to treatment is monitored on the basis of monthly sputum smear microscopy, as well as culture ideally at the same frequency. This is similar to the schedule used in patients on the longer MDR-TB regimen. The cohort outcomes may be reported to WHO combined with the ones for patients on other longer MDR-TB regimens, although 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](26), UNION, Global Drug-Resistant TB Initiative[GDI](10)).

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. Even with its shorter length, the safety profile of this regimen may differ from the one of longer MDR-TB regimens and present its own concerns. Thus, for instance, concomitant use of clofazimine and moxifloxacin - both of which prolong the QT interval – may make it more important to undertake electrocardiography than for other regimens.

When using the shorter MDR-TB regimen, can the same interim results and final treatment outcome definitions be used as for the longer MDR-TB regimens? Does the health care provider need to modify the data collection forms to report on treatment outcomes of shorter regimen?

The 2013 revisions of the TB definitions and reporting framework took into account the eventuality that shorter MDR-TB regimens would be used more widely and they are therefore applicable to patients on these treatments(4),(27). The definitions of “Cured” and “Treatment Failed” can be equally applied to treatment lasting less than 18 months. The proportion of confirmed pulmonary RR-/MDR-TB cases registered and started on a shorter MDR-TB treatment with negative results for culture in month six of their treatment can also indicate early response for the purposes of the “Interim results” although it is of less value than for the longer regimens. There is no need to change the *Second-line TB treatment register* or the *Annual treatment outcomes report for RR-TB/MDR-TB* when monitoring patients on the shorter MDR-TB regimen. The *TB treatment card* may be changed to allow the tabulation of results of periodic testing for response and adverse events (this may have already been done for the purposes of aDSM(17)). Moreover, programmes are advised to organise their data management electronically for patients on MDR-TB treatment(20), to permit closer monitoring.

Does the national TB programme need to have a functional aDSM (active TB drug safety monitoring and management) before patients are started on the WHO-recommended shorter MDR-TB regimen?

No, a fully functional aDSM is not required up front at the time of ordering the medicines or starting patients on the shorter MDR-TB regimen(19). 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 or written informed consent needed before introducing the WHO-recommended shorter MDR-TB regimen?

No. 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. If the patient is treated within the national TB programme under routine conditions of care 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 MDR-TB treatment thereafter.

Which are the new skills that health care workers need to develop specifically for managing the shorter MDR-TB regimen?

There are actually very few additional skills needed specifically for the shorter MDR-TB regimen. Knowledge about the component medicines is important: clofazimine is probably the one medicine that may not be very familiar to the TB health worker. Health care workers in both the public and private sector need to be familiarised with the dosages and adverse reactions associated with this medicine and on the principles of aDSM (collecting and reporting data on serious adverse events; managing harms associated with the regimen)(4),(25). The direct observation of treatment (DOT) and other adherence support is advised for patients on the shorter MDR-TB regimen.

In view of the high cure rates, low mortality and low loss to follow-up observed in countries that have introduced shorter MDR-TB regimens, can the NTP stop investing in social support and enablers to enable adherence to treatment?

The shorter MDR-TB regimen is still long and requires seven agents – including an injectable agent - to be taken together for up to 6 months and four medicines for another five months. All sites reporting satisfactory treatment outcomes using the shorter MDR-TB regimen relied on some forms of social support, as part of a patient-centred approach to enable direct observation of treatment. Cohorts have also tended to be small and managed under operational research conditions with a level of individual attention that may be challenging to replicate when scaling up and decentralising. Therefore, patients will need social support to help them overcome the hardships associated with TB and its treatment, including daily adherence, adverse drug reactions, indirect costs, stigma and discrimination.

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