

Frequently Asked Questions on the WHO Rapid Communication: key changes to the treatment of multidrug- and rifampicin-resistant TB

Version: 2.0

Prepared by the WHO Task Force to support country transition towards new recommendations for the treatment of MDR-TB

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ABBREVIATIONS

aDSM	active TB drug safety monitoring and management
AIDS	acquired immunodeficiency syndrome
ARV	antiretrovirals
CNS-TB	tuberculosis of the central nervous system
DST	drug susceptibility testing
FPM	Fund Portfolio Manager
GDF	Global Drug Facility
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GTB	WHO Global TB Programme
HIV	human immunodeficiency virus
LPA	line probe assay
MDR-TB	multidrug-resistant tuberculosis
MDR/RR-TB	multidrug-/rifampicin-resistant tuberculosis
NTP	national TB programme
PICO	Population, Intervention, Comparator and Outcomes
PK/PD	pharmacokinetics/pharmacodynamics
RCT	randomized controlled trial
RR-TB	rifampicin-resistant TB
SRL	supranational TB reference laboratory
STP	Stop TB Partnership
TB	tuberculosis
USAID	United States Agency for International Development
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

In these FAQs, and unless otherwise specified:

- *shorter MDR-TB regimen* refers to the standardized shorter regimen lasting 9-11 months composed according to the WHO recommendation in 2016
 - *injectable agent* refers to amikacin, capreomycin, kanamycin or streptomycin, previously considered to be key MDR-TB regimen components (the term as used here does not include the second-line TB drugs imipenem and meropenem that are also given by injection)
 - *WHO Task Force* refers to the newly appointed WHO Task Force to support country transition towards new recommendations for the treatment of MDR-TB.
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POLICY-RELATED QUESTIONS

1.01 - Why are changes expected to the World Health Organization guidelines on MDR-TB treatment?

In response to fresh results from trials and other studies on the effectiveness and safety of treatment regimens for multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB), the World Health Organization (WHO) convened an independent Guideline Development Group meeting on 16-20 July 2018 to assess the evidence and advise WHO on necessary changes to its WHO policy guidelines. The new treatment guidelines along with summaries of the evidence on which they are based will be released by December 2018 and will replace all previous WHO evidence-based recommendations on the treatment of MDR/RR-TB. The pace with which new MDR-TB studies and other patient data have been released has increased in recent years, requiring repeated changes in global treatment policies. It is expected that further studies will be completed in the coming few years requiring further updates to WHO treatment policy to allow readers to improve therapeutic options for patients.

1.02 - Why was the Rapid Communication released by WHO?

The Rapid Communication was released by WHO in advance of the detailed updated policy guidelines to alert national TB programmes and other stakeholders early-on to key changes that will have major implications on future MDR-TB treatment. The Rapid Communication does not include basic information such as detailed guidance on patient selection criteria, number of effective medicines to include, duration of treatment, and adult and paediatric dosing. These additional details, important for national policy revisions and planning, will be available in the detailed guidelines and accompanying implementation aids.

1.03 How is the Rapid Communication to be interpreted in view of the forthcoming WHO guidelines?

The Rapid Communication is not a WHO guidelines; however the changes announced will be conveyed in the forthcoming revised MDR/RR-TB treatment guidelines to be issued later in 2018. WHO guidelines are produced following a rigorous process to assess the latest available evidence ([GRADE](#)), manage potential conflict of experts involved in the process and provide transparency on how decisions are reached on recommendations. In addition to the guidelines themselves, WHO produces other derivative documents, such as implementation frameworks, “how to” documents and FAQs to help end-users put in place recommended policies and practices (see [WHO Information Note on developing policy guidance for drug-resistant tuberculosis](#)).

1.04 - What are the main changes signalled by the Rapid Communication?

Amongst the most important changes signalled by the Rapid Communication are the following:

- An all-oral regimen of 18-20 months’ duration is the preferred option for most patients and the injectable agents kanamycin and capreomycin are no longer recommended for use in treatment;
- Based on the latest evidence, the priority ranking of medicines to design a longer regimen has changed substantially, with bedaquiline, linezolid and clofazimine rising in importance and ethionamide and prothionamide and the injectable agents - amikacin and streptomycin - becoming less important. Inclusion of drugs is decided upon a balance of benefits to harms and guided by drug-susceptibility testing (DST);
- The 9-month shorter MDR-TB regimen recommended by WHO since 2016 may still be used but its role is now impacted by additional requirements for DST and close monitoring of patients’ response to treatment. Kanamycin is systematically replaced by amikacin in the shorter MDR-TB regimen;

- More emphasis is placed upon DST, active TB drug safety monitoring and management (aDSM), monitoring for treatment response, operational research and continued data collection and sharing, and support to all patients to complete therapy.

It is important that no changes are made to a patient's regimen unless a better alternative is available (e.g. replacing kanamycin with amikacin or another drug to ensure sufficient effective agents).

1.05 - Should countries stop using the shorter MDR-TB regimen recommended by WHO in 2016?

No. The relative advantages and challenges need to be considered in the context in which the treatment will be given. The shorter MDR-TB regimen still has a role in the treatment of eligible MDR/RR-TB patients, particularly those in whom resistance to fluoroquinolones and second-line injectable agents has been excluded by laboratory testing (see also related FAQ 2.07). The decision about which regimen to use should be an informed decision. The patient and the clinician need to be aware that in eligible patients under trial conditions the shorter MDR-TB regimen showed similar efficacy to longer MDR-TB regimens without new drugs, but had the advantage of a much shorter duration and a lower likelihood of loss to follow-up. However, evidence from observational studies indicates that patients who adhere to longer regimens lasting 18-20 months have a lower risk of treatment failure, relapse and death, particularly when bedaquiline and linezolid are included.

Where the shorter MDR-TB regimen is already being used or its introduction is being planned, audiometry needs to be made available to all patients to monitor for early hearing loss given that this regimen includes an injectable agent. Programmes using the shorter MDR-TB regimen with good results and adequate capacity for monitoring drug safety can opt to continue using it in eligible patients, but should plan to replace kanamycin with amikacin as soon as possible. Programmes considering the replacement of the injectable agent with bedaquiline or making other modifications to the standardized composition and duration of the shorter MDR-TB regimen or using it outside the usual eligibility criteria should do so only under operational research conditions.

1.06 - Can the shorter MDR-TB regimen be used in extrapulmonary patients?

Sometimes. The shorter MDR-TB regimen may be used for extrapulmonary TB other than severe forms (disseminated, meningeal or CNS-TB) and in people living with HIV/AIDS who have any form of extrapulmonary TB. This is because of the limited evidence for effectiveness in these situations.. In such cases specialist opinion would help to assess if other medicines or regimens would be better suited.

1.07 - Why are many of the medicines used in the shorter MDR-TB regimen positioned so low in the revised table of drugs to use in MDR-TB treatment?

The table in the Rapid Communication shows the positioning of medicines primarily ranked in terms of the balance between benefits and harms as used in longer MDR-TB regimens. This may partially explain why amikacin and ethionamide / prothionamide - two of the seven agents in the intensive phase of the shorter MDR-TB regimen - are ranked lower in the priority listing compared to their position in the 2016 guidelines. The shorter MDR-TB regimen was considered as a standardized "package" in the STREAM trial, observational studies, and in the analysis performed ahead of the 2018 WHO Guideline Development Group meeting. The individual contribution of each component of the shorter MDR-TB regimen to its effectiveness has not been evaluated. Some changes have been allowed in studies of the shorter MDR-TB regimen and these are permitted: for example, replacing kanamycin with amikacin; extending the intensive phase from 4 months up to 6; replacing ethionamide with prothionamide; and replacing gatifloxacin with moxifloxacin).

1.08 - Why is there no WHO recommendation for a shorter regimen with bedaquiline as used in South Africa?

The Department of Health in South Africa has implemented a 9-month regimen in which the injectable agent is replaced by bedaquiline. Data on the performance of this regimen are not yet available, but are expected to be reported to WHO in 2019. Additionally, STREAM stage 2, a randomized controlled trial (RCT) to evaluate a shorter MDR-TB regimen with bedaquiline in place of the injectable agent will finish enrolling new patients in late 2019. Other trials to evaluate 6-9 month all-oral regimens are also ongoing. The WHO recommendations will be updated as results from these studies become available. National programmes that intend to replace injectable agents with bedaquiline/linezolid/delamanid or make any other change to the regimen beyond current WHO recommendations, are advised to implement any modifications to the shorter regimen under operational research conditions and are encouraged to collect and validate these data rigorously so that they may help inform future updates to the WHO guidelines.

1.09 - Is it still useful to diagnose MDR-TB and other resistance patterns given that new, more powerful drugs will be used?

Yes, it is even more important to strengthen and rapidly increase coverage of DST for at least rifampicin, isoniazid, levofloxacin/moxifloxacin and amikacin. This is useful in order to confirm MDR/RR-TB, to identify eligible patients for the shorter MDR-TB regimen and to select the agents likely to be effective in an individualised longer regimen. National programmes should also plan for the implementation of DST for the drugs that they intend to use in longer regimen, especially those in Group A. Phenotypic DST (on MGIT) to bedaquiline, linezolid, clofazimine, pyrazinamide and delamanid is now possible. Many high burden countries may currently lack the ability to implement widespread DST for these agents but capacity to test for at least bedaquiline and linezolid should be established as a priority, but regimen changes can and should proceed while this DST capacity is being established. WHO guidance will be forthcoming by the end of 2018 to guide countries in the necessary expansion and changes to country DST capacity that result from the new treatment guidelines.

The characterisation of the mutations conferring resistance using molecular tests is becoming increasingly important given that it can rapidly determine the likelihood of effectiveness of specific medicines. WHO and FIND will publish a "Technical guide: The use of next-generation sequencing technologies for the detection of mutations associated with drug resistance in Mycobacterium tuberculosis complex", including a list of 'high-confidence mutations' later this year. Some of these mutations are detectable by commercially available LPA currently recommended by WHO.

1.10 - Should everyone on treatment immediately receive bedaquiline instead of the injectable agent? Why is an all-oral regimen preferred when injectable-containing treatment can achieve such good outcomes?

The possibility to switch patients from an injectable agent to bedaquiline in a longer regimen is not systematic and will depend on several factors, including the availability of the drug, any contraindications to it, the stage of treatment and whether patients are responding well to their current regimen. Replacement of the injectable agent with bedaquiline in the shorter MDR-TB regimen is not routinely recommended and should be done only under operational research conditions. In the new grouping of TB medicines bedaquiline is positioned higher (Group A) than amikacin, while kanamycin and capreomycin are no longer recommended and should be phased out as soon as possible. The use of bedaquiline, along with other Group A and Group B medicines, is preferred and should be prioritized over the use of amikacin in longer regimens. An all-oral treatment is preferred because apart from the discomfort of intramuscular injections and health problems (e.g. abscesses, hearing loss, nephrotoxicity) that they cause the patient they also incur additional programmatic resources to administer daily injection.

Patients should be consulted regarding treatment decisions, and provided with updated information necessary to make an informed choice about whether they prefer the injectable-containing shorter MDR-TB regimen or an 18-20 month all-oral regimen. The selected regimen and medicines included in it determine what monitoring is needed (e.g. audiometry in case of amikacin or streptomycin; clinical and biochemical assessment for linezolid; electrocardiography particularly when the regimen contains multiple QT-interval prolonging agents such as bedaquiline, delamanid, moxifloxacin and clofazimine).

1.11 - Can the same drugs be used in children? What dosages should be used?

The principles for designing a treatment regimen in adults apply to children too. The shorter MDR-TB regimen can be used in eligible children unless an all-oral longer regimen is feasible and preferred. The use of bedaquiline in patients younger than 18 years and delamanid in children younger than 6 years will be discussed in the upcoming guidelines. Revised dosages for use of all medicines in children and adults will also be published with the new guidelines. Quality-assured paediatric formulations of levofloxacin, moxifloxacin, cycloserine, ethionamide, ethambutol, and pyrazinamide are available through the Global Drug Facility (paediatric formulations of clofazimine and linezolid are under review by the WHO Pre-Qualification Programme).

1.12 - How many effective agents do we need in a regimen?

The 2016 WHO guidelines recommended 4 second-line agents likely to be effective plus pyrazinamide in the longer MDR-TB regimens. One of these agents would usually be an injectable agent (amikacin, capreomycin, kanamycin or streptomycin). The new WHO guidelines will also provide details on the number of effective agents, which will depend on the combination and the individual medicines selected for the regimen. No changes to the number of agents in the intensive and continuation phases of the shorter MDR-TB regimen are being made.

1.13 - For how long should the treatment be given?

The analysis for the new guidelines has looked at three different durations for the longer MDR-TB regimens: the length of the intensive phase, the duration from culture conversion till the end and the total treatment duration. Separate recommendations will be made about these in the forthcoming guidelines.

1.14 - Can we still refer to an intensive phase in a fully oral longer regimen or will this concept no longer apply?

The intensive phase of second-line MDR-TB regimens has been determined up to now by the initial period during which the injectable agent was included in the regimen. The patient is usually bacteriologically positive well before the end of the intensive phase, when the number of effective agents in the regimen is usually reduced from a minimum of 5 to 4 upon stopping the injectable agent. An intensive phase thus still applies to the shorter MDR-TB regimen. In all-oral regimens, however, no intensive phase applies. The duration of use of different drugs will depend upon their clinical indication (e.g. bedaquiline and delamanid have been marketed for use for 6 months), patient tolerability (e.g. linezolid used for as long as no SAE emerges) and individual treatment response (e.g. culture negativity), up until the expected total duration of treatment or time after culture conversion are completed. The duration and composition of an intensive phase will henceforth only apply to patients receiving amikacin (or streptomycin) and is likely to apply to a decreasing number of patients into the future as oral-only longer regimens will be increasingly employed. More details will be provided in the full guidelines and the Companion handbook.

1.15 - The Rapid Communication indicates that kanamycin and capreomycin should no longer be used. Does this apply in all situations?

Kanamycin and capreomycin are no longer recommended for use in any MDR-TB regimen. In longer MDR-TB regimens, there was an increased risk of treatment failure or relapse and death associated with their use when compared with regimens without them. The use of amikacin or streptomycin showed an association with lower treatment failure or relapse and death when used in people with susceptible strains (although they share the other disadvantages and toxicity of injectable agents). Amikacin and streptomycin use is conditional upon having a DST result confirming susceptibility and close monitoring with audiometry for early hearing loss. The use of amikacin and streptomycin in longer MDR-TB regimens should be avoided when it is possible to have an alternative, all-oral regimen.

1.16 - What do we do with patients who are already on kanamycin and capreomycin? Should they stop the injectable and continue with the rest of the medicines?

If patients are on the longer MDR-TB regimen, if better alternatives to kanamycin and capreomycin can be provided, these medicines should be replaced without compromising the effectiveness of the regimen (i.e. the regimen should still contain sufficient agents likely to be effective). If amikacin is available it should replace kanamycin in the shorter MDR-TB regimen and, in the absence of a better alternative, in the longer regimens too.

If kanamycin and capreomycin cannot be replaced in longer or shorter regimens and the patient is responding well to treatment without showing evidence of toxicity, then kanamycin or capreomycin may be continued for the planned duration. Monitoring with audiometry is mandatory at baseline and throughout the duration of injectable use.

1.17 - Are there any changes in the management of MDR-TB HIV infection?

The new guidelines will not have specific recommendations on the use of antiretrovirals (ARVs) in patients on MDR-TB treatment. Previous recommendations on the timing of initiation of ARVs continue to apply. There will be an updated chapter on MDR-TB regimen design and on use of ARVs in patients with HIV in the Companion handbook

1.18 - Are there any new recommendations on the management of MDR-TB in patients with hepatitis C infection?

The analysis prepared for the guidelines could not support specific recommendations for the adaptation of MDR-TB regimens in patients with hepatitis C infection in MDR-TB.

ADDENDUM

The questions 1.19 through 1.34 below were added in June 2019.

1.19 - Why the revised dosages of some TB drugs are higher than previously recommended? Is there evidence on the safety of these new dosages?

Dosages in the lasted WHO treatment guidelines are based on the most recent reviews and known practices in the treatment of MDR/RR-TB presented in the [Technical report on the pharmacokinetics and pharmacodynamics \(PK/PD\) of medicines used in the treatment of drug-resistant tuberculosis](#). For certain agents the dosages were informed by pharmacokinetic modelling results based on the principle of allometric scaling. Due to the pharmacokinetic properties of certain medicines the doses proposed may exceed the usual mg/kg/day ranges in order to achieve blood concentrations similar to target levels in an average adult patient. The MDR-TB treatment recommendations, with the corresponding drug-dosages should be implemented under strict aDSM, and therapeutic drug monitoring is advisable to minimize the

adverse therapeutic consequences of over- and under-exposure, especially for certain agents like linezolid and fluoroquinolones.

1.20 - Should DST for moxifloxacin be based on genotypic or phenotypic results?

As indicated in [The use of molecular line probe assays for the detection of resistance to second-line anti-tuberculosis drugs: policy guidance](#), rapid molecular detection of mutations associated with increased MICs for moxifloxacin using line probe assays should be performed as the initial test for all patients with rifampicin-resistant TB to guide the initiation of an appropriate treatment regimen. Culture based DST is the reference method for the detection of moxifloxacin resistance and should be performed to confirm or exclude resistance.

1.21 - How to construct all oral longer regimen in children?

The design of longer regimens in children largely follows the same principles as in adults. See the guidelines and forthcoming [Companion Handbook to the WHO Guidelines for the Programmatic Management of drug-resistant tuberculosis](#) for more details.

1.22 - Given the limited evidence and the restricted recommendations, can some further guidance be offered on how to construct an effective regimen for children?

Further detail on the design of paediatric regimens will be provided in the forthcoming [Companion Handbook to the WHO Guidelines for the programmatic management of drug-resistant tuberculosis](#).

1.23 - What is the Group C agent that WHO recommends as the first choice for most patients?

Generally, the choice follows the order in which the individual agents are positioned in the Table 2.1 of the [Consolidated Guidelines on drug-resistant tuberculosis treatment](#), but this is also determined by the individual circumstances of the patient, drug-resistance and the toxicity profile of the medicines used, e.g. hepatotoxicity of pyrazinamide in patients with liver disease; ototoxicity of aminoglycosides in patients with renal impairment; gastrointestinal tolerability of thioamides, PAS; or likelihood of additive QT-interval prolongation of delamanid.

1.24 - A significant proportion of the data on standardized shorter regimen is originated from Low income Countries and Low-Middle Income Countries. Was the propensity score used even on this key point?

All records for the standardized shorter regimens and 80% of longer regimens used as comparators in analysis for the 2018 guidelines were from patients in low or middle-income countries. The basic analysis adjusted for age, sex, HIV, ART if HIV, AFB, prior treatment with first line drugs. Adjustment for confounders using either propensity-score matching, or multivariable meta-regression followed the same methods used elsewhere in the 2018 analysis.

1.25 - Should WHO have abstained to make any recommendation on the standardized shorter regimen?

In 2016, when WHO first made its recommendation on the use of a 9-12-month standardized shorter MDR-TB regimen the evidence base was entirely drawn from observational study data from different settings that attested to its effectiveness. These findings were confirmed once more by higher-quality evidence from the STREAM trial and the review of data from further observational studies in different settings in 2018. The latest available evidence support the decision made in 2016 to continue to recommend this regimen, subject to eligibility criteria and within the context of

other treatment options lasting 18 months or more that have been recommended since 2018 to optimize treatment outcomes (see other explanations in the answers below).

1.26 - Should it be understood that shorter and new longer all-oral regimens are equivalent?

The 2018 recommendations for designing longer regimens are based on an evaluation of the contribution of individual drugs to treatment outcomes. This was done using an individual patient data meta-analysis (IPDMA) from patients receiving diverse, individualized regimens rather than single, standardised regimen. Importantly, few individuals have yet been treated with the new all-oral longer regimen in its recommended form, resulting in a lack of direct evidence to inform comparisons with the standardized shorter regimen. As part of the IPDMA, the GDG attempted to compare the standardized shorter regimen with longer regimens containing bedaquiline, linezolid and delamanid but interpretation of this comparison was limited by small numbers of patients, the routine inclusion of aminoglycosides in the longer regimens, differences in eligibility criteria for the shorter and longer regimens (see page 36) and an inability to account for the impact of losses to follow-up – which were higher in the longer regimens (see pages 5 and 6 in [Annexes 8-10](#)). This subgroup analysis was based on indirect and imprecise evidence that provided very low certainty about better health outcomes with longer regimens containing one or more highly effective medicines. Until new data become available to permit a more direct comparison caution is advised when interpreting this analysis.

1.27 - Why is the standardized shorter regimen still recommended when the new all-oral, longer regimens seem to show better treatment outcomes, except for treatment completion?

The indirect evidence from comparisons of longer and standardized shorter regimen was considered in light of the imprecision and possible biases/confounders (see above), as well as the direct moderate certainty evidence from the STREAM trial, in which the standardized shorter regimen was judged to be non-inferior to the previously recommended longer regimens that did not contain bedaquiline or linezolid. Acknowledging these limitations of the newly available data and responding to the need for timely review of the existing guidance on the standardized shorter regimen, the GDG issued a conditional recommendation that use of the shorter regimen should remain an option, depending on patient and programme circumstances, until the IPDMA can be further updated. The Consolidated Guidelines do not however present the shorter regimen as equivalent to the 2018 longer regimens, stating that “Fully oral regimens should be prioritized and become the preferred option for most patients, and injectable agents are no longer among the priority medicines to consider when designing longer MDR-TB regimens” (Page 28).

1.28 - Is drug-susceptibility testing for the fluoroquinolones and the second-line injectable agents (at minimum) required prior to the initiation of the standard standardized shorter regimen or the longer regimens?

The need to rule out resistance to drugs applies to standardized shorter and to longer regimens. The availability of reliable and rapid molecular tests such as lineprobe assays to identify resistance to isoniazid, fluoroquinolones and injectable agents helps programmes to decide within a few days which patients would be eligible for shorter MDR-TB regimens – or what modifications to longer MDR-TB regimens would be necessary based on the resistance associated mutations detected. Studies demonstrated that initial resistance to SLI and fluoroquinolones led to poor treatment outcomes for patients enrolled on standard standardized shorter regimen. Therefore, it is strongly recommended to test for these medications either before or during the first two weeks of treatment. Criteria other than DST, however, may be applied to rule out likely resistance to fluoroquinolones and injectables in selected populations in which, in the absence of laboratory capacity, representative drug resistance surveys are available and previous use of the standardized shorter regimen have shown high cure rates (see pages 39-40).

1.29 - Is WHO recommending to routinely stop bedaquiline or delamanid after six months? What is the evidence for the length of therapy with bedaquiline or delamanid? Is this consistent with the evaluation methods applied to other medications?

The WHO recommendations on the use of bedaquiline and delamanid are based on the studies conducted by the drug developers and on data from observational studies and programmes which have used these two products for up to six months. The GDG found that the evidence from small cohorts suggesting that these products are safe and effective beyond six months was insufficient to routinely recommend their use beyond six months, though clinicians may find it to be appropriate for selected patient groups, particularly patients with XDR-TB who lack other treatment options. The [Consolidated Guidelines](#) indicate though, that “Use beyond this duration needs to be decided by the programme on a case-by-case basis and currently represents “off-label” use”. The [Best-practice statement on the off-label use of bedaquiline and delamanid for the treatment of multidrug-resistant tuberculosis](#) released by WHO in 2017, enables clinicians, patients and TB programmes to make an informed choice for using bedaquiline beyond six months, and prevents that patients are being deprived of the potential benefits of such a practice, while the recommendation is will be updated once sufficient evidence becomes available. Off-label use of other medications recommended for the treatment of MDR-TB is supported by acceptable evidence on safety and effectiveness.

1.30 - Why does WHO not have a recommendation on the combined use of bedaquiline and delamanid while DELIBERATE trial results have been reported?

The [DELIBERATE trial results](#) presented at the 2019 Conference on Retroviruses and Opportunistic Infections, March 6; Seattle, USA, showed that patients who received these two medicines together did not experience additive QT-interval prolongation beyond what is usually considered as unsafe. The trial did not measure the added value on cure when the two agents are given together. WHO has no recommendation against the concomitant use of bedaquiline and delamanid and in some patients this may be necessary when building a regimen with agents from Groups A to C. In such cases the same attention should be given to cardiotoxicity as when giving other QT-interval prolonging medicines together. In the forthcoming update of the 2018 WHO recommendations for DR-TB treatment any evidence available to assess the safety and added value of concomitant use of bedaquiline and delamanid will be invited in order for the GDG to assess whether additional recommendations are needed in this respect.

1.31 - What is the advice on the combined use of bedaquiline and delamanid in a treatment regimen?

The combined use of bedaquiline and delamanid was envisaged in the PICO question 2 (see page 82, footnote 44) of the 2018 update of the DR-TB guidelines. The GDG found that data available at the time of the meeting was insufficient to make any GRADE assessment which could inform a recommendation on the value and safety of adding delamanid to a bedaquiline-based regimen (see footnote 3 of page 24). Until data is available for WHO review the statement presented in the [Best-practice statement on the off-label use of bedaquiline and delamanid for the treatment of multidrug-resistant tuberculosis](#) released by WHO in 2017 prevails, that is, concomitant use of bedaquiline and delamanid is not regarded as ‘off-label use’ and should be reserved for regimens in patients with limited treatment options such as extensive patterns of drug resistance, drug intolerance or serious adverse effects. Such regimens should be used under prevailing ethical standards.

1.32 - Can bedaquiline be used for the treatment of MDR-TB in pregnancy?

The GDG, which included clinicians with experience in treatment of MDR-TB in pregnancy, did not advise against the use of bedaquiline in pregnancy, but for an individualized approach to include components with a safety profile that is sufficiently established. Whenever this is not possible then resort to agents such as bedaquiline may well be the best

course of action if the patient accepts the potential risk, which at present is not known. This position reflects the uncertainties surrounding the limited experience with any new drug particularly for situations where vulnerability is more likely.

1.33 - How often should culture be used to monitor response to treatment among people on the standardized shorter regimen?

The Consolidated Guidelines proposes that programmes implementing the standardized shorter regimen aim for more frequent culture testing, especially after the intensive phase, to confirm bacteriological cure in patients who complete treatment without signs of failure (see page 44). The data analysis from longer MDR-TB regimens showed the added value of culture over smear microscopy alone in the early detection of treatment failure, and the increased yield of culture when it was used more frequently. The GDG extrapolated its recommendation for use of culture, preferably at monthly intervals, to standardized shorter regimens too. Annex 6 of the [Companion Handbook to the WHO Guidelines for the programmatic management of drug-resistant tuberculosis](#) proposes a timeline for laboratory monitoring for treatment response.

1.34 - Does WHO support the evaluation of shorter, all-oral treatment regimens under operational research conditions?

WHO promotes and supports the development of evidence to inform policy updates, including randomized clinical trials and operational research on MDR-TB treatment regimens. The [Consolidated Guidelines](#) state the need for operational research on fully oral standardized shorter regimens (see page 34 and 40); and is listed as a research priority (see page 59). For more detailed guidance on the implementation of this type of research see Annex 10 of the [Companion Handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis](#) and the [Evaluation of Effectiveness and Safety of Novel Shorter Treatment Regimens for Multidrug-Resistant Tuberculosis](#). Countries or technical partners planning to conduct operational research on MDR-TB regimens may want to seek advice from TB technical partners and WHO.

PROGRAMMATIC & TRAINING-RELATED QUESTIONS

2.01 - What are national TB programmes expected to do in response to the changes?

While understanding that it will not be immediately possible to achieve the new standards of care in every patient, strategic planning, focused on longer-term issues such as drug forecasting and procurement should start immediately to enable rapid transition to the upcoming new WHO guidelines. The national TB programme (NTP) will need to establish its own transition plan in agreement with relevant partners, stakeholders and donors. A realistic timeline should apply (e.g. aiming to start using the new classification within 12 months). The release of new national policies, decision making aids or training material based on MDR-TB treatment should best await the release of the detailed WHO policy guidelines. In the interim WHO has convened a multi-stakeholder Task Force composed of major donors and technical agencies to support countries as they prepare to introduce the necessary changes.

2.02 - Should NTPs start preparing country-specific policies and protocols based on the Rapid Communication?

NTPs can begin to draft a transition plan with timelines and costings, taking into account the main changes to MDR/RR-TB treatment signalled by the Rapid Communication. The draft can be finalized once the new MDR-TB guideline is released at the end of 2018. This will enable NTPs to transit to new WHO guidelines in the shortest possible time. The WHO Task Force, with the support of in-country implementing partners, can help the NTP on different components: in assessing the national context, budget planning and development (all possible sources of funding to be noted in the budget plan), in human resource development planning, training plan of various cadre of staff, sensitization/training of stakeholders in public and private sectors, minimum upgrading of laboratory capacity, calculation of drug needs, changes in the recording and reporting system and monitoring and evaluation framework and developing process and outcome indicators for programme performance.

2.03 - What are some key milestones and timelines that NTPs should account for when planning for phase-in of the new changes?

Generally, NTPs will need to determine how to implement the guidelines in their specific settings, including choice of regimens, DST capacity and background drug resistance patterns. Once these programmatic decisions are determined, countries should plan for any of the following activities that may be required:

- Inclusion of any products not previously used in the national essential medicines list;
- Ensuring that new products can be procured and imported (e.g., registration, import waivers, etc.);
- Identify any funding gaps between the old and new guidelines and secure the necessary additional funds by working with all potential partners;
- Planning procurement of products with adequate lead times for procurement processes and for the products to be produced, delivered and available at the point of use (e.g., a 4 to 6-month lead time after order finalization and payment);
- Planning for the disposal of drugs no longer required;
- Strengthening laboratory capacity to undertake DST for the essential drugs as well as aDSM;
- Updating national treatment policies/ guidelines;
- Healthcare working trainings.

A number of these activities can only be started and completed once the full guidelines will become available at the end of 2018.

2.04 - Should countries start prioritizing individualized longer regimens rather than standardized regimens?

Some degree of standardization of regimen composition and duration may be possible at country level to help simplify treatment delivery and drug procurement. However, regimens designed using the revised grouping of medicines for the longer MDR-TB regimen need to be adjusted to the specific needs of the individual patient (e.g. additional drug resistance). The degree to which this can be done depends on the availability of DST or different drugs from Groups A & B and the flexibility needed to cater for patients in whom one or more of these drugs is contraindicated or unlikely to be effective.

2.05 - How do I register patients and which definitions do I use to assign treatment outcomes now?

The MDR/RR-TB outcome definitions and registration parameters released by WHO in 2013 continue to apply (http://apps.who.int/iris/bitstream/10665/79199/1/9789241505345_eng.pdf).

2.06 - Will WHO change the definition of XDR-TB? What is the significance of “pre-XDR”?

XDR-TB – currently defined as MDR-TB with additional resistance to a fluoroquinolone and an injectable agent (amikacin, kanamycin or capreomycin but not streptomycin) - will still be of relevance for regimens including second-line agents from these two classes, such as the shorter MDR-TB regimen. Strains with MDR-TB and additional resistance to fluoroquinolones only - a form of so-called “pre-XDR” - will remain important for the shorter regimen and for most longer regimens. MDR-TB strains with additional resistance to aminoglycosides only preclude the use of the shorter MDR-TB regimen but are expected to become less relevant for longer regimens in future, as many more patients will benefit from regimens without injectable agents. The current definition of XDR-TB is therefore likely to require changes to reflect a pattern of resistance that is more relevant to future regimens and taking also into account advances in diagnostic methods for anti-TB agents that until now could not be routinely tested for. Changes to these parameters will be the subject of future expert consultation and will be included in the revised surveillance and reporting guides.

2.07 - How can drug resistance to the medicines in the MDR-TB regimens be diagnosed?

The updated WHO policy guidelines will continue to underline the importance of DST for the agents for which rapid molecular tests are now available and results can thus be envisaged before treatment starts. These include rifampicin, isoniazid, fluoroquinolones (levofloxacin and moxifloxacin) and injectable agents (amikacin).

National programmes need to work towards the establishment of DST for all anti-TB medicines for which there are now agreed, accurate and reproducible phenotypic methods, including also bedaquiline, linezolid, clofazimine, delamanid, and pyrazinamide. The WHO Supranational TB Reference Laboratories (SRL) Network is developing capacity to support National TB Reference Laboratories in performing quality-assured DST for these medicines. A [WHO technical consultation in 2017](#) established critical concentrations to test for susceptibility to bedaquiline, delamanid, clofazimine and linezolid, and also revised the ones for fluoroquinolones and aminoglycosides. Even if available to some laboratories, phenotypic DST for cycloserine/terizidone, ethambutol, imipenem-cilastatin/meropenem, ethionamide/prothionamide, and *p*-aminosalicylic acid is not recommended for clinical decision-making.

The absence of rapid DST techniques for several of the regimen components hampers the prospect for having a comprehensive drug susceptibility profile for all regimen components at the time of treatment start. As in any potentially life-saving situation, treatment for drug-resistant TB should not be withheld from a patient due to a lack of full DST capacity. Molecular DST methods such as sequencing are increasingly becoming available at national TB reference laboratory level and sequencing results can inform much more targeted regimen design. Susceptibility to some of the medicines may in part be inferred from the results of molecular testing using commercially available line

probe assay (LPA). The technical details are beyond the scope of these FAQ and WHO and GLI will be publishing a detailed guide for clinicians on the interpretation of LPA results later in 2018.

2.08 - Are there any changes to the current recommendations for DST at start and during treatment?

Rapid molecular tests such as Xpert MTB/RIF and LPA should be performed at the time of treatment initiation. In the absence of a rapid test then phenotypic DST should be performed for all TB medicines for which there is an accurate and reproducible DST method (see above), either at diagnosis or on the first strain isolated from patients during treatment monitoring.

Regular microscopy and culture of sputum or other specimens remains important to ensure that treatment failure is detected early. Isolates grown from patients during treatment, particularly when culture conversion is delayed, should be tested for potential acquisition of additional resistance. If DST to certain agents is not available the strains should be stored for further investigations at the SRL. If risk of resistance is high (e.g. after treatment failure, in TB cases who are contacts of a drug-resistant TB case), sequencing methods may provide valuable information.

2.09 - Should a country only retain or introduce phenotypic DST to amikacin and streptomycin and stop performing testing for kanamycin and capreomycin?

LPA allows the detection of most resistant mutations for amikacin (as well as kanamycin and capreomycin), but not to streptomycin. If countries are prioritizing phenotypic DST they should work towards developing the capacity to test for amikacin and streptomycin. The need to test for kanamycin and capreomycin should eventually disappear as these two injectable agents are replaced by better options in the local regimens.

2.10 - Should a country test for drug resistance to bedaquiline, delamanid and linezolid before using these medicines?

The availability of DST to these agents is currently limited in many settings and the resistance levels to them is likely to be very low at this point. Performing DST to bedaquiline, delamanid and linezolid is therefore not essential before using these medicines at this stage. However, if resistance is suspected during treatment and DST is not available the strains should be conserved and referred for SRLs for further testing.

2.11 - What changes have been done to the monitoring of adverse events?

The new guidance will stress the importance of developing capacity for aDSM for all patients on MDR-TB treatment. Therefore, in addition to bacteriological investigations, several tests including audiometry, clinical assessments for peripheral neuropathy and psychiatric disturbances, liver and kidney function and blood indices are necessary, based on clinical manifestations and medications in use. Medicines with known risks for QT-interval prolongation require electrocardiography and monitoring of electrolytes, both at baseline and regularly during treatment. Details on monitoring and managing the toxicity of individual drugs are described in the Companion Handbook and will be updated in the 2018 edition.

2.12 - Is in-person direct observation of treatment (DOT) required for patients on MDR-TB regimens?

Close monitoring and treatment support of patients is needed to maximize treatment adherence and enable early detection of patients who are not responding to treatment, in a patient-centred approach. Community- or home-based DOT is conditionally recommended over health facility-based DOT or unsupervised treatment. DOT administered by trained lay providers or health-care workers is conditionally recommended over DOT administered by family members

or unsupervised treatment. Moreover, video (virtual) observed treatment (VOT) can replace DOT when the technology is available and can be appropriately organized and operated by health-care providers and patients.

Apart from DOT, several other interventions are considered important to promote treatment adherence and a patient-centred approach. NTPs need to improve patient access to a package of treatment adherence interventions in conjunction with the selection of a suitable treatment administration option: being defined as material support (e.g. food, financial incentives, and reimbursement of transport fees); psychological support; home visits; use of information technology; medication monitors; and staff education. Moreover, counselling and patient education on the disease and on treatment adherence are strongly recommended.

2.13 - Will WHO issue new training modules based on the new guidelines?

WHO will update the Companion Handbook by the end of 2018 and definitions and reporting framework and develop implementation aids to complement the guidance. Countries are encouraged to develop their own training modules based on the local context (e.g. implementation model, access to computers for eLearning tools). NTPs may seek support from technical agencies and donors to undertake this work.

2.14 - What dosage schedule is recommended for the medicines used in the new regimens?

WHO will be issuing revised dosage schedules for children and adults at the time the new guidelines will be released at the end of 2018.

PROCUREMENT-RELATED QUESTIONS

TB programmes will need to revise national procurement and supply plans immediately based on the changes, reviewing orders for drugs that are no longer recommended (Km/Cm). New orders would otherwise need to be based on usual parameters: patients on treatment and expected cases (sub-divided into different expected regimens based on resistance patterns), the latest data on consumption and stock of medicines etc. before placing new orders with national agents or Stop TB / GDF. As many countries do not yet have experience with new regimens, the forecasting and quantification will be based on the best-knowledge assumptions and may thus not be precise, NTPs are advised to place smaller orders at increased frequency with their suppliers with a right to amend them, rather than full annual or biannual orders. GDF will engage in frequent communication with suppliers to keep track of the market situation and global availability of medicines. Functional early warning systems (such as e.g. based on QuanTB tool) are useful to monitor access to medicines and to inform rapid decision making to avoid stock-outs and treatment interruptions.

3.01 - How can the Global Fund support countries during the phase-in and phase-out period including improving capacity for DST and aDSM, procurement of drugs, dealing with potential stock outs and destruction with replacement of obsolete drugs?

The Global Fund secretariat is working closely with WHO, STP/GDF and other partners to support countries during transition to new and better treatment regimens. Global Fund is part of the WHO Task force and will continue engaging in resource mobilization activities to address gaps. The Global Fund teams are working closely with GDF and NTPs on the current stocks, preliminary quantifications and assessment of cost implications of transition to new regimens country-by-country.

3.02 - The Global Fund advised country teams not to process new orders for kanamycin and capreomycin. If the conditions in the country do not allow programmes to place new orders, what are the alternatives?

In line with the WHO Rapid Communication, in principle countries should not place new orders of kanamycin and capreomycin. However, this should be done in a way so as not to interrupt patient treatment and cause a stock-out. If a country faces this situation, you should contact your country Fund Portfolio Manager (FPM) and GDF to review available options.

3.03 - Should we stop all orders of kanamycin and capreomycin?

NTPs need to transition swiftly to replace kanamycin and capreomycin with amikacin for patients receiving the shorter MDR-TB regimen. Transition towards the new longer MDR-TB regimens should also take place rapidly in parallel. This transition needs to be implemented in coordination with the procurement specialists and clinicians to ensure no patient receives suboptimal regimen that may lead to amplified drug resistance or exposure to other unnecessary risks. Once sufficient stocks of amikacin are ensured, stocks of kanamycin and capreomycin should be destroyed.

3.04 - A programme has placed an order with GDF based on previous recommendations – can that order be cancelled or modified?

This will depend on how far the order has been processed, on other medicines included in the same order and on country programmatic needs (e.g., risk of stock outs). For confirmed orders where NTPs wish to cancel, please contact GDF, who will do its best to find a solution on a case-by case basis. Orders for which purchasers have given the green light for packing typically cannot be modified or cancelled; it is therefore important for the purchaser to be sure that the products will be used before giving the green light for packing.

3.05 - We have excessive stock of capreomycin and ethionamide. What shall we do with it?

A very first step for the national TB programmes is to ensure availability of all necessary medicines to treat MDR-TB patients using new regimens. For the management of medicines no longer required ordered via GDF or the Global Fund please contact these agencies.

3.06 - How many MDR-TB cases should I plan treatment for? Is it realistic to use old estimates for future enrolments with new regimens?

The NTP will need to make changes to the previous plans. They should aim for continued expansion of treatment coverage to achieve their enrolment targets. Changes to the planning will need to be made according to the local context and epidemiology, based on considerations such as the capacity for countries to get new drugs into the country, increased demand for laboratory work and resource mobilization amongst others.

3.07 - Should I design 2-3 regimens to be used in most MDR-TB and XDR-TB patients and plan all procurement around them?

The individualization of longer regimens implies that planning should be done by medicine rather than by standardized regimen (see also FAQ 2.04). However, some degree of standardization of regimen composition and duration may be possible at country level to simplify treatment delivery and drug procurement. When planning the composition of such regimens NTPs need to consider patient history, DST profiles of the patient, local setting (the prevalence of different resistance patterns) and the benefits/harms of different possible components of the regimens. For the quantification and forecast of appropriate volumes of consumables please see below.

3.08 - How many patients will require bedaquiline, linezolid, delamanid and carbapenems?

The NTP and other stakeholders need to discuss the expected demand for new medicines and other second-line TB agents that are now higher on the priority list of agents for longer MDR-TB regimens. The expansion plan to roll out the new regimens needs to take into account the pace at which the new agents can be introduced, the logistics and the patient profile (e.g. how many patients will be expected to need to be transferred from the shorter regimen to longer one given revisions to the policy). These considerations are context specific and no global recommendation is possible. GDF will be gathering country-specific information to work towards global forecasts for these medicines.

3.09 - How many patients should I expect to be treated with the shorter MDR-TB regimen?

While no precise global estimate for the proportion of cases to be placed on the shorter MDR-TB regimen is possible, this is an important consideration to make at the national level in order to be able to anticipate the expected volumes of consumables necessary. The numbers will vary between settings and may also differ from previous estimates that a country may have done given that the eligibility criteria for the shorter MDR-TB regimen and its role within the triage algorithm will change with the revised WHO guidelines. Moreover, the preferences for its use in eligible patients may vary depending on the country and patient decision. Any estimates need to be reviewed regularly and adjusted on the basis of actual adoption of the different regimens recommended.

3.10 - What are the lead times for ordering new medicines?

The lead time for most products from GDF are between 4 to 6 months. This is calculated once the order is finalized and payment has been made. This lead time does not include the time taken to finalize an order and to receive all

programme, country and donor approvals, which may add 1-2 months or more depending on factors such as delays to cleared Customs and complete administrative procedures.

3.11 - Can the Global Drug Facility (GDF) provide all the medications, laboratory equipment and consumables needed to expand treatment services as per the new guidelines?

Yes! All of the medications, laboratory equipment and consumables to implement the new guidelines are available from the GDF. Please see the [GDF Product Catalogue](#) for more details. Eligible programmes procuring laboratory equipment and consumables for LPA and culture from GDF may benefit from preferential concessional prices. Programmes should plan for a 4-6 month lead time on new orders for these products once the order is finalized and payment has been received.

3.12 - Are there any anticipated supply limitations for GDF around drugs in groups A or B (e.g., linezolid, clofazimine, bedaquiline, cycloserine or terizidone), or for amikacin to replace kanamycin and capreomycin? Is there a risk that any of my new orders for these drugs will be delayed or cannot be fulfilled?

For linezolid: There are an additional three suppliers with formulations quality-assured by a stringent regulatory authority on the Global Fund's list of products eligible for procurement.

For clofazimine: There is one supplier with formulations that are quality-assured by a stringent regulatory authority. Two additional suppliers have developed clofazimine formulations and submitted them for quality-assurance by WHO Prequalification. GDF has and continues to work closely with both Global Fund and WHO Prequalification to prioritize the review of these products so they can be procured by programmes.

For bedaquiline: The manufacturer of bedaquiline has confirmed that they are ready for increased demand. GDF will follow up with them to monitor the situation.

For cycloserine and terizidone: GDF has a sufficient number of suppliers to cover for increased demand.

For amikacin: GDF has three EU-based suppliers with quality-assured formulations approved by stringent regulatory authorities.

For delamanid: GDF has one supplier and will follow up with them should demand increase.

3.13 - Is there any mechanism to signal the likely demand to suppliers based on preliminary estimates so that the suppliers can start preparing for the anticipated higher volumes of orders in order to minimize the lead time once final orders are placed?

GDF will be updating its demand forecast for its regular international tender before end of 2018, which will account for demand changes as observed in revised quantifications from its client countries. This updated forecast will then be communicated to manufacturers to understand and prepare for changes in demand for all impacted TB products. GDF will provide updated forecasts on a regular basis to inform production planning.

3.14 - With the anticipated increase in demand for new prioritized medicines (linezolid, clofazimine bedaquiline) and the likely submission of orders by countries after release of guidelines, can the standard lead time of 4-6 months after order finalization & payment still be applicable?

Yes. GDF does not anticipate any change in the standard delivery lead-time of 4-6 months from the time of order confirmation and receipt of payment from clients to time of in-country delivery.

3.15 - Do the new DST guidelines require a review of the list of DST reagents with the possibility of cancelling some orders or initiating fresh orders?

Orders for which purchasers have given the green light for packing typically cannot be modified or cancelled. If the NTP orders through GDF and has a confirmed order that it wished to cancel, it is best to contact GDF, who will do its best to address each case on an individual basis.

3.16 - Will GDF continue to provide pure drug substances for drug susceptibility testing for medicines no longer recommended?

Yes. GDF will continue to provide pure drug substances for DST of medicines that are no longer recommended in the new WHO rapid guidance on MDR-TB treatment. Moreover, GDF has started the process of adding linezolid and clofazimine to the GDF catalogue, which is anticipated to be ready to order in one to two months' time – by November 2018.

GDF is also in contact with bedaquiline and delamanid manufacturers to also add these two products in the GDF catalogue, with timelines for ordering through GDF still being determined.

3.17 - Is technical assistance available for planning, preliminary quantification, drug registration and implementation of phase-in and phase-out for new medicines and regimens at country level?

Yes! The WHO Task Force is mapping needs in technical assistance to available resources and funding for technical assistance to countries to estimate gaps. The WHO Task Force includes key TB partners supporting countries including WHO, USAID, GDF, KNCV, the Union and Global Fund. GDF provides support to many national TB programmes on the procurement and supply chain aspects of phase-in and phase-out plans of products or regimens. Please contact GDF at <mailto:gdf@stoptb.org> to request support.

3.18 - What are the estimated costs of the new regimens?

An approximate estimate of the costs of the new regimens based on the Rapid Communication document is available here: [GDF News Alert on WHO Rapid Communication](#). This information is intended at this stage for planning purpose and can change once the final guidelines are released. Programmes are also able to estimate costs based on the specific regimens chosen and the product prices available on [GDF's website](#). GDF can assist on quantifying cost implications when developing phase-in and phase-out plans.

3.19 - How do I contact the GDF if I have a question on drug procurement?

Please contact GDF focal point at this email address: <mailto:gdf@stoptb.org>.

FUNDING-RELATED QUESTIONS

4.01 - With costs of new longer regimens estimated to be 2-3 times more than previous regimens, and assuming total available budgets will remain unchanged (from domestic finances, Global Fund grants and other sources), how will programmes be able to achieve thei

The implications of transitioning to the new regimens, including the costs and targets, should be assessed for each country. Any increased overall cost in MDR-TB regimens should not be offset by enrolling less patients. New regimens are expected to be more effective and any increased cost that they incur on the NTP or donor may translate in health benefit. There should be discussions at all levels to identify additional resources (including through savings from Global Fund grants, domestic, and support by technical partners) to address potential gaps in the budget. As the MDR-TB treatment coverages are already low, countries are encouraged to maintain the targets agreed in the National Strategic Plans and Global Fund Performance Frameworks.

4.02 - Can I apply for a Global Fund grant to expand services?

The NTP will need to use the existing Global Fund grants. This will require discussions with Fund Portfolio Manager and relevant teams.

4.03 - How can the NTP expand its capacity to diagnose MDR/RR-TB and additional resistance?

The national TB programme will need to use the existing Global Fund money and other grants and sources. This will require discussions with relevant teams, the Fund Portfolio Manager and other donors.

4.04 - In addition to the lower price of bedaquiline announced recently, should programmes expect decreases in prices for other recommended medicines?

The biggest drivers of medicine prices are demand and generic competition. Should these newly prioritized medicines increase in demand, GDF would expect prices to decrease in future tenders.

4.05 - How do I budget ahead of introducing a new MDR-TB treatment component in my national TB programme?

NTPs should first decide on the treatment algorithm they will use to determine the allocation of MDR TB regimens. That algorithm could take into account several factors, such as the prevalence of resistance to fluoroquinolones and injectables agents. Based on that information the NTP would forecast the quantity of medicines that it will need and determine the level of efforts and other resources that will be required to support the implementation of regimens. The NTP will have to identify funds that it already has as well as funds that it can mobilize from national budget and from other donors. NTPs are encouraged to initiate discussions with stakeholders on best scenarios for the introduction of the new treatment including timing, additional budget needed and potential sources of additional budget. The plan could be finalized after the release of the new WHO guideline.

4.06 - Will the Global Fund support the introduction of bedaquiline in shorter regimens as operational research?

In the past, the Global Fund has supported several countries to pilot the introduction of shorter MDR-TB regimens, ahead of the WHO recommendation of 2016. If a country is considering introducing bedaquiline in a shorter treatment regimen as part of operational research, please contact your Fund Portfolio Manager. Eligible countries can request funds for operational research on variants of the shorter regimen “[initiative 5%](#)” (close of applications on 26 October 2018).

ADVOCACY & COMMUNICATION-RELATED QUESTIONS

5.01 - What should patients be aware of regarding the new MDR-TB treatments?

The new treatment guidelines will emphasize the need for improved communication with persons who are starting MDR-TB treatment about the potential benefits of the new regimens (i.e. improved outcomes with Group A drugs) and the potential risks. Cautions about key adverse reactions, such as QT-interval prolongation with drugs like moxifloxacin and bedaquiline, neuropathy for linezolid, hearing loss and kidney damage for amikacin and skin discolouration for clofazimine (see more complete list in Chapter 11 of the [Companion handbook](#)). Patients should also be informed about who to report adverse events to should they emerge. The patient and medical team need to find the most acceptable form of communication to ensure continued treatment follow up.

Patients also need to be aware that the benefits of the medications depend upon completing them as prescribed. Adherence support is important. The basic principle that applies to any TB regimen - to take all the medicines prescribed for the recommended duration – remains critical. If treatment interruptions occur the clinical team needs to address them rapidly to ensure resumption of care.

5.02 - Is informed consent mandatory?

Informed consent and participatory decision-making are key elements of patient-centred care. All patients receiving TB care should be informed of the procedures and treatments they are being offered or are receiving in a manner by which they appreciate the uncertainties, potential risks and benefits, alternative treatment options, as well as the commitments needed. Ahead of enrolment on any MDR-TB treatment, with or without new TB drugs, all patients should be counselled for them to understand the main issues involved with their treatment. This process needs to comply with the local requirements, including written or verbal consent as necessary. Any patient information material previously developed for this purpose needs to be updated to reflect the new changes, so that patients are appropriately informed about their treatment options. Sample information material to use when explaining the options to patients are available in the WHO Companion handbook (e.g. page 391 in current version).

FURTHER READING

WHO TB treatment guidelines and implementation aids for drug-resistant TB

- Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. (WHO/HTM/TB/2014.11). Geneva, World Health Organization, 2015.
http://apps.who.int/iris/bitstream/10665/130918/1/9789241548809_eng.pdf
- Guidelines for the treatment of drug-susceptible tuberculosis and patient care, 2017 update. (WHO/HTM/TB/2017.5). Geneva, World Health Organization, 2017.
<http://apps.who.int/iris/bitstream/10665/255052/1/9789241550000-eng.pdf>
- Latent TB Infection : Updated and consolidated guidelines for programmatic management (WHO/CDS/TB/2018.4). Geneva, World Health Organization. 2018.
<http://apps.who.int/iris/bitstream/handle/10665/260233/9789241550239-eng.pdf>
- Compendium of WHO guidelines and associated standards: ensuring optimum delivery of the cascade of care for patients with tuberculosis (WHO/HTM/TB/2017.13). Geneva, World Health Organization, 2017.
<http://apps.who.int/iris/bitstream/10665/259180/1/9789241512572-eng.pdf>
- WHO Information Note on developing policy guidance for drug-resistant tuberculosis (WHO/CDS/TB/2018.14). Geneva, World Health Organization, 2018.
<http://apps.who.int/iris/bitstream/handle/10665/2175010/WHO-CDS-TB-2018.14-eng.pdf?ua=1>

WHO & GLI TB diagnostic guidelines and implementation aids

- GLI model TB diagnostic algorithms. Geneva, Stop TB Partnership, 2017.
http://www.stoptb.org/wg/gli/assets/documents/GLI_algorithms.pdf
- Implementing tuberculosis diagnostics: a policy framework (WHO/HTM/TB/2015.11). Geneva, World Health Organization, 2015. http://apps.who.int/iris/bitstream/10665/162712/1/9789241508612_eng.pdf
- The use of molecular Line Probe Assays for the detection of resistance to second-line anti-tuberculosis drugs. Policy guidance. (WHO/HTM/TB/2016.07). Geneva, World Health Organization, 2016.
<http://www.who.int/tb/publications/lpa-mdr-diagnostics/en/>
- Technical report on the critical concentrations for drug susceptibility testing of medicines used in the treatment of drug-resistant tuberculosis (WHO/CDS/TB/2018.5). Geneva, World Health Organization, 2017.
<http://apps.who.int/iris/bitstream/10665/260470/1/WHO-CDS-TB-2018.5-eng.pdf>
- The use of next-generation sequencing technologies for the detection of mutations associated with drug resistance in Mycobacterium tuberculosis complex: technical guide (WHO/CDS/TB/2018.19). Geneva, WHO/FIND; 2018. <http://apps.who.int/iris/bitstream/handle/10665/274443/WHO-CDS-TB-2018.19-eng.pdf>

Other resources (estimates, surveillance, procurement)

- Rapid communication: key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB) (WHO/CDS/TB/2018.18). Geneva, World Health Organization, 2018.
http://www.who.int/tb/publications/2018/WHO_RapidCommunicationMDRTB.pdf
- Global tuberculosis report 2018 (WHO/HTM/TB/2018.20). Geneva, World Health Organization; 2018. Available from: <http://apps.who.int/iris/bitstream/handle/10665/274453/9789241565646-eng.pdf>

- Definitions and reporting framework for tuberculosis – 2013 revision (WHO/HTM/TB/2013.2). Geneva, World Health Organization, 2013. http://apps.who.int/iris/bitstream/10665/79199/1/9789241505345_eng.pdf
- Stop TB Partnership | Global Drug Facility (GDF) - GDF Products List. http://www.stoptb.org/gdf/drugsupply/drugs_available.asp
- Global Drug-resistant TB Initiative (GDI). The evaluation of effectiveness and safety of novel shorter treatment regimens for multidrug-resistant tuberculosis. Operational research protocol template. Geneva, Stop TB Partnership, 2018. <http://www.stoptb.org/wg/mdrtb/assets/documents/GDI%20OR%20generic%20protocol%20final.pdf>
- Initiative 5% Call (APPEL A PROPOSITIONS «Amélioration du dépistage, du traitement et de la prévention de la tuberculose» Référence : AP-5PC–2018–03-RO) https://www.initiative5pour100.fr/wp-content/uploads/2018/08/TDR_AP_5PC_2018-03_RO_VF.pdf
<https://www.initiative5pour100.fr/en/partnerships-and-expertise/calls-for-proposals/>