

Frequently Asked Questions

on the

WHO Rapid Communication 2019: Key changes to the treatment of drug-resistant TB

Version: 1.1

The Frequently Asked Questions and the answers proposed in this document have been prepared by the Global TB Programme of the World Health Organization (WHO), the Global Fund to Fight AIDS, Tuberculosis and Malaria, the United States Agency for International Development and the Global Drug Facility of the Stop TB Partnership.

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ABBREVIATIONS

aDSM	active TB drug safety monitoring and management
AIDS	acquired immunodeficiency syndrome
DST	drug susceptibility testing
FPM	Fund Portfolio Manager
GDF	Global Drug Facility
GDG	Guideline Development Group
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
PK/PD	pharmacokinetics/pharmacodynamics
RR-TB	rifampicin-resistant TB
SRL	supranational TB reference laboratory
STBP	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:

- *A shorter all-oral bedaquiline containing MDR TB regimen refers to a regimen lasting 9-12 months consisting of 4-6 Bdq*-Lfx/Mfx-Eto-E-Z-Hh-Cfz / 5 Lfx/Mfx-Cfz-Z-E (*Bdq is given for 6 months);*
- *An MDR-TB all oral longer regimen refers to a regimen with a total duration of 18-20 months designed using the priority grouping of medicines recommended by WHO;¹*
- The BPaL regimen is defined as a novel treatment regimen lasting 6-9 months and composed of bedaquiline, pretomanid and linezolid as used in the Nix-TB study by the TB Alliance.

¹ WHO Consolidated guidelines on drug-resistant tuberculosis treatment 2019, Table 2.1.

1. POLICY-RELATED QUESTIONS

1.1 Why are there changes to the World Health Organization Consolidated Guidelines on DR-TB treatment issued in 2018?

New evidence on the effectiveness and safety of all-oral shorter regimens for MDR/RR-TB treatment was made available to WHO during 2019, specifically from the Nix-TB study and from observational studies and programmatic data. These data addressed some of the evidence gaps identified in 2018 and were felt to have direct public health benefit. It is expected that ongoing studies on treatment of MDR/RR-TB will be completed in the coming few years and data will be regularly reviewed by WHO as part of our mandate for global policy development to improve therapeutic options for patients.

1.2 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 for MDR/RR-TB treatment based on the latest evidence; to facilitate policy uptake and planning at country level; and to facilitate budget and procurement planning by countries and their stakeholders, especially in light of countries application to the Global Fund by mid-2020.

1.3 What are the main changes signaled by the Rapid Communication?

The most important changes signaled by the Rapid Communication are the following:

- Injectable medicines should be phased out as a matter of priority in all treatment regimens and replaced by bedaquiline. A shorter all-oral bedaquiline-containing treatment regimen of 9-12 months duration is the preferred option for eligible MDR/RR-TB patients (see regimen presented on page 2);
- Individualized all-oral longer regimens, designed using the WHO priority grouping of medicines (Table 2.1), may be still used for MDR/RR-TB patients who do not meet the eligibility criteria for an all-oral shorter bedaquiline-containing regimen;
- The BPaL treatment regimen may be used under operational research conditions in eligible XDR-TB patients;
- More emphasis is placed on the need for drug susceptibility testing, active TB drug safety monitoring and management (aDSM), support to patients and close monitoring of treatment response, and rigorous data collection;

1.4 What are the dosages of the medicines in the shorter all-oral bedaquiline-containing MDR/RR-TB regimen recommended by WHO?

In the evidence provided by South Africa that supported the decision by the GDG, treatment regimen contained bedaquiline for 6 months, plus levofloxacin, ethionamide, ethambutol, isoniazid (high-dose), pyrazinamide, and clofazimine for 4 months (with the possibility to extend to 6 months if the patient remains sputum smear-positive at the end of four months); followed by 5 months of treatment with levofloxacin, clofazimine, ethambutol, and pyrazinamide. Smaller proportion of patients received moxifloxacin instead of levofloxacin.

The recommended dosages for levofloxacin, ethionamide, ethambutol, pyrazinamide, isoniazid (high-dose) and clofazimine by weight were published in the WHO Consolidated Guidelines on Drug-Resistant Tuberculosis Treatment in 2019 and remain valid. The use of bedaquiline for the evidence assessed was limited to 6 months with the dosage recommended by the manufacturer (400mg daily for the first 2 weeks followed by 200 mg three times weekly for 22 weeks).

Medicines are taken once a day, all days of the week (except where otherwise specified).

1.5 Which MDR/RR-TB patients are eligible to be treated with the shorter all-oral bedaquiline containing regimen?

All MDR/RR-TB patients in whom resistance to fluoroquinolones was ruled out and without:

- Confirmed resistance to or suspected ineffectiveness of a medicine in the shorter MDR-TB regimen (except isoniazid resistance)
- Exposure to one or more second-line medicines in the shorter MDR-TB regimen for >1 month (unless susceptibility to these second-line medicines is confirmed)
- Intolerance to medicines in the shorter MDR-TB regimen or risk of toxicity (e.g. drug-drug interactions)
- Pregnancy
- Disseminated, meningeal or TB of the central nervous system.

1.6 Can a shorter all-oral bedaquiline containing MDR-TB regimen be used in HIV-co-infected patients?

Yes. The data from South Africa used for the analysis included a high proportion of HIV co-infected patients (71%).

1.7 Can changes be made to the duration and composition of the shorter all-oral bedaquiline containing regimen?

No. The shorter all-oral bedaquiline containing regimen was implemented as a standardized package under programmatic conditions in South Africa. The current WHO recommendation is based on these data. Therefore, it is not advised to further shorten the duration of the regimen. Likewise, changes to the regimen composition may have an unpredictable impact on its effectiveness and are therefore not currently recommended to be implemented programmatically. Medicines in the same class could, nevertheless be switched as follows:

- Prothionamide used instead of ethionamide;
- Moxifloxacin used instead of levofloxacin; and
- The initial phase extended until 6 months if required; the duration of the continuation phase is fixed at 5 months.

National TB programmes that intend to make any further modifications to the shorter all-oral bedaquiline-containing regimen are advised to do so under operational research conditions.

1.8 Can the shorter all-oral bedaquiline containing regimen be used in children? What dosages should be used?

Yes, in children older than six years, as no evidence is available for the use of bedaquiline in children under 6 years of age. Pediatric dosing of second-line medicines as outlined in the 2019 WHO Consolidated Guidelines remain valid. Quality-assured pediatric formulations of levofloxacin, moxifloxacin, clofazimine, cycloserine, ethionamide, ethambutol, and pyrazinamide are available through the Stop TB Partnership's (STBP) Global Drug Facility (GDF) while a pediatric formulation of linezolid is under development.

1.9 Can bedaquiline be used in pregnant women?

Yes. The use of bedaquiline as a part of an all-oral longer MDR-TB regimen was shown to be generally safe in pregnant women in a study in South Africa. In this study exposure to bedaquiline (most frequently used together with clofazimine and levofloxacin), was associated with an increased risk of low birth weight (<2500g), although normal growth was achieved in these babies.

1.10 Can all MDR-TB patients be treated with the BPaL regimen?

No. The BPaL regimen is relevant in patients with confirmed XDR-TB who have not had previous exposure to bedaquiline and linezolid for more than two weeks. This regimen is not appropriate for programmatic use worldwide until additional evidence on efficacy and safety has been generated. Nevertheless, in individual XDR-TB patients for whom the design of an effective regimen based on existing WHO recommendations is not possible, the BPaL regimen may be considered as a last resort under prevailing ethical standards.

1.11 Can pretomanid be added to other TB treatment regimens?

No. In August 2019, pretomanid (Pa) was approved by the US Food and Drug Administration as part of the BPaL regimen, that is in combination with bedaquiline and linezolid. The data from Nix-TB study provided for the review by the GDG in November 2019 also included the data on BPaL regimen and use of pretomanid in combination with two other medicines. There is no currently available evidence on the use of Pa outside the BPaL regimen and it is therefore not included in the priority grouping of TB medicines recommended by WHO. Although it is a nitroimidazole (i.e. in a similar class as delamanid) it is a new chemical compound and cannot be used as a replacement for delamanid or added on its own to first- and second-line treatment regimens.

2. PROGRAMMATIC & TRAINING-RELATED QUESTIONS

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

While understanding that it may not be immediately possible to achieve the new standards of care rapidly in every patient, strategic planning, focused on issues such as drug forecasting and procurement should start immediately to enable rapid transition to the upcoming new WHO recommendations. Phasing out injectables and replacing them with bedaquiline is an urgent priority. National TB programmes will need to establish transition plans in agreement with relevant partners, stakeholders and donors. Updated national policies, decision-making aids and/ or training materials on the new MDR-TB treatment regimens should be done as soon as the detailed WHO guidelines are released (expected in April, 2020).

2.2 What are the key steps that national TB programmes should take when planning transition to updated recommendations?

In general, national TB programmes and their stakeholders need to determine how to implement the new recommendations in their specific settings, including the choice of regimens based on current laboratory capacity for drug susceptibility testing and background drug resistance patterns. Countries should also plan for the following:

- 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);
- Identifying any funding gaps between the old and new guidelines and securing the necessary additional funds;
- 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. 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 for aDSM;
- Updating national treatment policies/ guidelines;
- Healthcare worker training.

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

The MDR/RR-TB patient registration and treatment outcome definitions published by WHO in 2013 continue to apply (http://apps.who.int/iris/bitstream/10665/79199/1/9789241505345_eng.pdf). The definitions are planned to be reviewed and updated by WHO in 2020.

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

The current definition of XDR-TB - MDR-TB with additional resistance to a fluoroquinolone and an injectable agent (amikacin, kanamycin or capreomycin) - is likely to require changes given the phasing out of injectables, anticipating patterns of resistance that are more relevant to current and future regimens, and taking into account advances in diagnostic methods

and drug susceptibility testing. Changes to the definition of XDR-TB will be the subject of future expert consultation and will be included in revised WHO surveillance and reporting guides.

Choosing appropriate regimens for patients with strains showing MDR-TB plus additional resistance to fluoroquinolones (so-called “pre-XDR”) are increasingly becoming more important and feasible thanks to rapid advances in molecular drug-susceptibility testing (see 2.5).

2.5 How can resistance to the medicines in MDR-TB regimens be determined?

The updated WHO guidelines will stress the importance of drug susceptibility testing (DST) prior to treatment, especially for the medicines for which WHO-recommended rapid molecular tests are available. These include rifampicin, isoniazid and quinolones. In addition, NTPs need to scale-up laboratory capacity for medicines for which there are accurate and reproducible phenotypic methods, including bedaquiline, linezolid, clofazimine and delamanid.

The WHO Supranational TB Reference Laboratories (SRL) Network is available to support national TB reference laboratories in performing quality-assured DST. A [WHO technical consultation in 2017](#) established critical concentrations for susceptibility testing for the fluoroquinolones, bedaquiline, delamanid, clofazimine and linezolid. Methods for testing pretomanid susceptibility are currently under development.

As in any potentially life-saving situation, treatment for drug-resistant TB should not be withheld from a patient due to a lack of complete DST results. Even if available in some laboratories, phenotypic DST for cycloserine/terizidone, ethambutol, imipenem-cilastatin/meropenem, ethionamide/prothionamide, and *p*-aminosalicylic acid is not recommended for clinical decision making. Molecular DST methods such as sequencing are increasingly becoming available at the national TB reference laboratory level and sequencing results can inform the development of individualized regimens. Susceptibility to some of the medicines may in part be inferred from the results of molecular testing using commercially available line probe assays (LPA).

2.6 Should DST be done before bedaquiline and linezolid are used?

The availability of DST for these medicines is currently limited in many settings and the resistance levels are likely to be very low at this point. Performing DST to bedaquiline and linezolid is therefore not essential before using these medicines at this stage; however, national TB programmes are strongly advised to start building capacity for drug resistance surveillance of these medicines. If resistance is suspected during treatment and DST is not available, the strains should be conserved and referred to SRLs for further testing.

2.7 What changes are expected to the monitoring of drug adverse events?

The updated WHO guidelines will stress the importance of appropriate capacity for aDSM for all patients on MDR-TB treatment. In addition to bacteriological investigations, several monitoring tests including electrocardiography (ECG), clinical assessments for peripheral neuropathy and psychiatric disturbances, laboratory assessment of liver and kidney function and blood profiles are necessary, based on the medications in use. Medicines with known risks for QT-interval prolongation require ECG and monitoring of electrolytes, both at baseline and regularly during treatment. Details on monitoring and managing the safety of individual drugs are described in the WHO Companion Handbook available at https://www.who.int/tb/publications/pmdt_companionhandbook/en/ which will be available in a 2020 edition.

2.8 How should patient support be provided when taking MDR TB medication?

Close monitoring, supervision and treatment support of patients as part of a person-centered approach are needed to maximize treatment adherence and enable early detection of patients who are not responding to treatment. Evidence-informed recommendations about patient support are provided in the 2019 Consolidated Guidelines and will be included in the 2020 update also.

Health education and counselling on the disease and treatment adherence is strongly recommended to patients on TB treatment. 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 essential to promote treatment adherence and a patient-centered approach. NTPs need to improve patient access to a package of treatment adherence interventions in conjunction with the selection of a suitable treatment regimen. This includes material support (e.g. food, financial incentives, and reimbursement of transport fees); psychological support; home visits; use of modern information technology; medication monitors; and staff education. Moreover, counselling and patient education on the disease and on treatment adherence are strongly recommended.

3. 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 (kanamycin, capreomycin, and amikacin in the shorter regimen). NTPs are advised to place smaller orders at increased frequency with their suppliers, rather than full annual or biennial 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 those based on the QuantTB tool) are useful to monitor access to medicines and to inform rapid decision making to avoid stock-outs and treatment interruptions.

3.1 How can the Global Fund support countries during transition to all-oral regimens including BPaL and phase-out of injectable agents including improving capacity for DST and aDSM, procurement of drugs, dealing with potential stock outs, excess stocks and destruction of injectable agents?

The Global Fund encourages countries to accelerate implementation and scale up the new regimens for MDR/RR and XDR-TB. The Global Fund secretariat will continue working closely with WHO, STBP/GDF and other partners to support countries during transition to new and better treatment regimens. Global Fund will continue engaging in resource mobilization activities to address gaps. The Global Fund teams are working closely with STBP/GDF and NTPs on the current stocks, preliminary quantifications and assessment of the cost implications of transitioning to new regimens including destruction of agents that are no more recommended. Contact your Global Fund country team for more information when considering destruction of agents that are no more recommended.

3.2 What support is available to countries without Global Fund funding during the phase-in and phase-out period?

WHO, StopTB/GDF and other partners are available to support countries during the transition to new and better treatment regimens. STBP/GDF can provide support to develop phase-in and phase-out plans for programmes, assist in quantifying and forecasting for new regimens and help programmes to determine the number and cost of injectable agents that would need to be destroyed or re-allocated to other parts of the healthcare system (for example Amikacin can be used for treatment of several bacterial infections). When programmes decide to destroy a product, it should be done in alignment with current recommendations and national guidelines.

3.3 We have excessive stock of amikacin. What shall we do with it?

Countries are encouraged to phase out injectable containing regimens and replace injectables with bedaquiline. Amikacin could be used for the treatment of several bacterial infections and therefore can be allocated to the other parts of the healthcare system.

3.4 The Global Fund country teams were advised not to process new orders for kanamycin, capreomycin in 2018. This advice will be extended to exclude amikacin from new orders for use in shorter regimen for DR-TB as per the 2019 Rapid Communication. If the conditions in the country do not allow programmes to transition to bedaquiline-based shorter regimens immediately, what are the alternatives?

In line with the WHO Rapid Communication 2019, in principle, countries should not place new orders of amikacin for use in the shorter regimen. However, this should be done in a way so as not to interrupt patient treatment or cause a stock-out. If a country faces this situation, you should contact your country Global Fund country team and STBP/GDF to review available options.

3.5 Should we stop all orders of kanamycin, capreomycin and amikacin (for use in the shorter regimen)?

NTPs need to transition swiftly to replace kanamycin, capreomycin and amikacin with bedaquiline for patients receiving the shorter MDR-TB regimen. 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.

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

Each order will need to be reviewed individually and in the context of the order status, the country programmatic needs (e.g., risk of stock outs and treatment interruptions) and other medicines included in the order. In general, for orders that have been confirmed (i.e., price quote approved by the programme and payment transferred) but are not ready for shipment, programmes should contact STBP/GDF who will work to find a solution on a case-by-case basis. Orders that have been confirmed and the programme has authorized packing generally cannot be modified or cancelled.

3.7 How many MDR-TB, XDR-TB cases should I plan to treat? Is it realistic to use old estimates for future enrolments with new regimens?

Programmes should aim to align their national strategic plans to expand case detection and treatment targets in line with the updated Global Plan to Stop TB and the targets set out in the United Nations High-Level Meeting on Tuberculosis. Changes to the programme planning will need to be made according to the specific programme context and epidemiology, and based on considerations such as programme procurement capacity, demand for laboratory analyses, resource availability and mobilization .

3.8 How should programmes begin to take this Rapid Communication into account when quantifying and forecasting their procurement needs?

Programmes need to collect the usual information required to quantify and forecast procurement needs, including the number of people currently on treatment, the latest data on consumption of medicines and current available stocks of medicines. Programmes will need to know the number of people that are expected to be enrolled and make assumptions on which treatment regimens will be used and the allocation between the different regimens. These assumptions should:

- Estimate the number of people that would qualify for a bedaquiline-based shorter regimen, the preferred initial regimen for MDR/RR-TB. These estimates need to account for the current eligibility criteria for use of the shorter regimen.
- The remaining number of people that would not qualify for the bedaquiline-based shorter-regimen and should receive an individualized longer regimen based on the criteria set out in the most recent WHO Guidance on DR-TB.
- If a programme is planning to introduce the BPAL regimen for the treatment of XDR under operational research conditions, this should be estimated as well.

Planning should be done by medicine for those receiving individualized regimens (and those that may move to an

individualized regimen after starting the bedaquiline-based shorter regimen). 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.

Any estimates need to be reviewed regularly and adjusted based on actual adoption of the different regimens recommended.

3.9 What are the lead times for ordering new medicines?

The lead time for most products from STBP/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 clear Customs and complete administrative procedures. For more information on planning for an order with STBP/GDF, please see the "[Category and Product-Level Procurement and Delivery Planning Guide](#)" available here:

<http://stoptb.org/gdf/planOrder.asp>

3.10 Can STBP/GDF procure 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 STBP/GDF. Please see the [GDF Product Catalogue](#) for more details. Eligible programmes procuring laboratory equipment and consumables for LPA and liquid culture from STBP/GDF may benefit from preferential concessional prices.

STBP/GDF is ready to provide pure substances of all of the medicines for which DST is currently recommended, including linezolid and clofazimine. Pure drug substances for bedaquiline and delamanid are available from manufacturers under the following mechanisms:

- Bedaquiline: Bedaquiline pure drug substance is provided for free through the NIH AIDS Reagent Program (<https://www.aidsreagent.org>). Delivery is also free when one indicates "JNJ" as the "Shipping Co. Account No." during registration. Note that ordering bedaquiline is a two-step process: First one needs to register to become eligible to receive reagents from the NIH catalog, and then second, one needs to place an order for bedaquiline in particular.
- Delamanid: Delamanid pure drug substance is provided for free through the ATCC BEI Program: <https://www.beiresources.org/About/BEIResources.aspx>. Delamanid is item number NR-51636.

STBP/GDF has initiated discussions with the manufacturer of pretomanid to include this pure drug substance in its catalogue once it becomes available.

3.11 Are there any anticipated supply limitations through STBP/GDF? Is there a risk that any of my new orders for these drugs will be delayed or cannot be fulfilled?

No! STBP/GDF is working closely with the all suppliers and they have confirmed they are ready for increased demand. GDF will monitor the supply situation closely.

3.12 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?

STBP/GDF will be updating its demand forecast and will communicate it as part of its next regular international tender, which will account for demand changes as observed in revised quantifications from its client countries. This updated forecast and information on products that require additional qualified suppliers will be communicated to manufacturers during STBP/GDF regular TB medicines manufacturers meeting.

3.13 With the anticipated increase in demand for 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.

3.14 Will GDF continue to provide pure drug substances for DST for medicines no longer recommended?

Yes. GDF will continue to provide pure drug substances for DST of medicines that are no longer recommended until GDF client countries no longer require them or until they are no longer commercially available.

3.15 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! 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.

3.16 What are the estimated costs of the new regimens?

STBP/GDF estimates the cost of the bedaquiline-based shorter regimen is approximately \$400 USD per treatment course. This estimate uses a weighted average price according to the volumes allocated to suppliers in STBP/GDF's 2019 tender. These estimates are valid through the end of the tender period (March 2020).

Programmes can estimate costs based on the specific regimens chosen. STBP/GDF has a "Budgeting Prices for TB Medicines" document to assist programmes when planning. It is available on STBP/GDF's website here: <http://www.stoptb.org/gdf/planOrder.asp>. The prices are for budgeting purposes only and may be different from the price ranges (and thus actual prices that will be found in the final price quote) found in the GDF Product Catalogue. GDF can assist on quantifying cost implications when developing phase-in and phase-out plans.

3.17 How do I access pretomanid, to be used as part of the BPaL regimen under operational research conditions?

Pretomanid is available from STBP/GDF for use with bedaquiline and linezolid under operational research conditions for the treatment of XDR-TB as a part of BPaL regimen. Programmes will be requested to complete an annex to the procurement request form with their first order of pretomanid from STBP/GDF. This annex will confirm the programme will use pretomanid in alignment with WHO recommendations, including those made in the Rapid Communication. For more information on the procurement of pretomanid from GDF, please see the following STBP/GDF document: <http://stoptb.org/assets/documents/gdf/FAQs%20for%20pretomanid.pdf>

3.18 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>.

4. FUNDING-RELATED QUESTIONS

4.1 As the estimated costs of the new regimens (all-oral STR and BPaL) are different from the previous regimens, and assuming total budget available will remain unchanged (from domestic, Global Fund and other sources), how will national programmes be able to achieve and increase their targets?"

The implications of transitioning to the new regimens, including the costs and targets, should be assessed for each country. Any savings from overall costs of MDR/RR-TB and XDR-TB regimens should be used to enroll more patients. New regimens are expected to be more effective, less toxic and shorter and more convenient for patients and the health system and this would contribute to improvement in treatment outcome. There should be discussions at all levels to identify savings (including in the Global Fund grants, domestic, and support by technical partners) and reinvest these to increase targets, strengthen aDSM, laboratory capacity and improve quality of care. As the MDR/RR-TB and XDR-TB

treatment coverages are already low, countries are encouraged to revise and increase the targets agreed in the National Strategic Plans and Global Fund Performance Frameworks.

4.2 Can I apply for a Global Fund grant to expand services including laboratory for diagnosis/DST, aDSM and patient support?

The NTP could use the existing Global Fund grants to support expansion of services including aDSM and lab capacity to accelerate transition to new regimens. Use of savings (from reduced costs of new regimens) and/or additional costs needed for expansion require discussions with the Global Fund country teams. All countries which received Global Fund allocations for TB are encouraged to include implementation and scale up of the new all-oral regimens (including BPaL) and other related interventions in their upcoming funding requests during the 2020-2022 cycle.

4.3 Given the anticipated increase in uptake of the agents included in bedaquiline-based all-oral regimens, should programmes expect further decreases in prices for recommended medicines?

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

4.4 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 other drugs. 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 in April 2020.

4.5 Will the Global Fund support the introduction of bedaquiline-based modified shorter regimens and/or BPaL under 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 and all-oral shorter regimen based on the 2019 guideline under operational research. If a country is considering introducing bedaquiline-based modified shorter treatment regimen including BPaL as part of operational research, please contact the Global Fund country teams. Eligible countries can request funds for operational research on variants of the shorter regimen as far as these are in line with the WHO recommendations. In addition, USAID has funding allocated for DR-TB and operational research related to shorter regimen for 23 priority countries.

5. ADVOCACY & COMMUNICATION-RELATED QUESTIONS

5.1 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 and the potential risks. Cautions about key adverse reactions, such as QT-interval prolongation with drugs like moxifloxacin and bedaquiline, neuropathy for linezolid, and skin discoloration for clofazimine (see more complete list in Chapter 11 of the [Companion handbook](#)). Patients should also be informed that with the use of pretomanid containing regimen (BPaL), reproductive toxicities have been observed in animal studies and that the potential effects on human male fertility have not been adequately evaluated at this point in time.

The patient and treatment provider 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.

5.2 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/RR-TB and XDR-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).

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FURTHER READING

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

- WHO consolidated guideline on drug-resistant tuberculosis treatment. (WHO/CDS/TB/2019.4). Geneva, World Health Organization, 2019
<https://apps.who.int/iris/bitstream/handle/10665/311389/9789241550529-eng.pdf>
- Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. (WHO/HTM/TB/2014.11). Geneva, World Health Organization, 2015.
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- 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.
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- 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/>