

Frequently asked questions about the use of bedaquiline according to the WHO guidelines and evidence from its early use in selected countries

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Since 2013, the World Health Organization (WHO) has recommended the use of bedaquiline for the treatment of multidrug-resistant tuberculosis (MDR-TB) subject to the following conditions^a:

1. Proper patient inclusion;
2. Patient informed consent;
3. Adherence to principles to design a WHO-recommended *longer* regimen;
4. Treatment administered under closely monitored conditions; *and*
5. Active pharmacovigilance^b and proper management of adverse events.

From June to September 2016, WHO convened a guideline development group^c to review available evidence on the global use of bedaquiline since this policy was issued. The evidence assessment was based on the GRADE process used by WHO for guideline development since 2008.^d This assessment included data from 537 MDR-TB patients treated in South Africa, France, Armenia and Georgia, as well as data from a multi-site study conducted by the drug manufacturer, *Janssen Pharmaceuticals*, in 11 countries. The outcome of the GRADE process upheld the existing WHO recommendations for the use of bedaquiline with no significant changes to its conditionality.^e

It should also be noted that the conditions for bedaquiline use as approved by the United States Food and Drug Administration (U.S. FDA) and the European Medicine Agency (EMA) are still in place, and that guidance by WHO will remain interim until complete phase III data are available.

This FAQ addresses the main implications of the findings of the 2016 evidence assessment for the implementation of current WHO policies on the use of bedaquiline in the context of the 2016 WHO recommendations for the management of drug-resistant TB.^{f,g}

1. What is bedaquiline and how does it work?

Bedaquiline is a bactericidal drug which belongs to a new class of antibiotics (diarylquinolines). Although the drug is active against many different bacteria, it has been registered specifically for the treatment of MDR-TB. The drug is unique among the anti-tuberculosis drugs currently used in that it interferes with the function of an enzyme required by the tuberculosis bacterium to produce energy and to replicate. After the drug was tested in a phase IIb trial, bedaquiline was approved under the U.S. FDA's accelerated-approval regulations in December 2012, and subsequently, it was recommended by

^a The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: interim policy guidance [WHO/HTM/TB/2013.6]. Available from: http://apps.who.int/iris/bitstream/10665/84879/1/9789241505482_eng.pdf. World Health Organization: 2013.

^b In recent documents, *active pharmacovigilance* has been replaced with “active TB drug safety monitoring and management”.

^c [Public notice] Guideline Development Group (GDG) Meetings: Revision of the interim policy on bedaquiline for MDR-TB treatment and special session on delamanid use in children. Link: http://who.int/tb/areas-of-work/treatment/gdg_bedaquiline_delamanid/en/. World Health Organization: 2016.

^d WHO handbook for guideline development. Available from: http://apps.who.int/iris/bitstream/10665/75146/1/9789241548441_eng.pdf?ua=1. World Health Organization: 2014.

^e Report of the Guideline Development Group Meeting on the use of bedaquiline in the treatment of multidrug-resistant tuberculosis: A review of available evidence (2016). 28 - 29 June 2016. [WHO/HTM/TB/2017.01]. Published on 13 March 2017. Available from: <http://apps.who.int/iris/bitstream/10665/254712/1/WHO-HTM-TB-2017.01-eng.pdf>. World Health Organization: 2017.

^f WHO treatment guidelines for drug-resistant tuberculosis 2016 update. [WHO/HTM/TB/2016.04]. Available from: <http://apps.who.int/iris/bitstream/10665/250125/1/9789241549639-eng.pdf?ua=1>. World Health Organization: 2016.

^g Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. [WHO/HTM/TB/2014.11]. Available from: http://apps.who.int/iris/bitstream/10665/130918/1/9789241548809_eng.pdf. World Health Organization: 2014.

the WHO for the treatment of MDR-TB in addition to WHO-recommended *longer* treatment regimen in June 2013, under specific conditions.

2. *What were the main findings of the systematic review conducted by WHO on the use of bedaquiline since 2013?*

- A total of 537 patients, receiving treatment with bedaquiline added to a WHO-recommended longer regimen, were included in the analysis.
- More than three-quarters out of 391^h patients receiving bedaquiline in the reported cohorts culture-converted at the end of the six-months-treatment with bedaquiline (79.7%; 95% CI: 75.2 - 83.5).^{e,i}
- Treatment outcome data indicated that about two-thirds out of 351^j patients receiving bedaquiline added to a WHO-recommended regimen were reported as cured at the end of treatment (63.8%; 95% CI 57.8 - 69.4).^{e,i}
- Although the causality of adverse events was not established in this review, 20% of patients reported severe adverse events, and 7% developed serious adverse events.^{e,i}
- Among patients with electrocardiogram data ($n = 511$ patients), prolonged QTcF intervals (> 450 ms) were observed in up to 30% of patients ($n = 155$ patients), including 4.7% patients experiencing a QTc prolongation >500 ms.^{e,i}
- Though the risk of *undesirable effects* could not be entirely explained by current observational data, the guideline development group noted that mortality was not increased in patients receiving bedaquiline, conversely to what was shown in the data assessed in 2013. On that account, the group decided to downgrade the *undesirable effects* from large to moderate.^{e,i}

3. *What are the limitations of the data reviewed and their implications for the interim WHO recommendation on the use of bedaquiline?*

Although the findings in this review attest to the effectiveness of bedaquiline when used in the treatment of MDR-TB, the guideline development group concluded that significant uncertainty remained on various factors as described below:

- The review was based *only* on observational data and not on *randomized controlled trial* data (phase III studies). Though the guideline development group recognised the value of observational studies to inform about “real-life” conditions, there were concerns that observational studies could overestimate the effects of treatment, underestimate safety and introduce bias in the assessment of outcome.
- Treatment outcome comparisons between patients receiving bedaquiline (*added to a WHO-recommended longer regimen*) and patients who did not receive bedaquiline was not possible given that *only* data from single-cohort studies were available. In addition, there was substantial heterogeneity in the way the observational cohort studies were conducted in the various settings. Therefore, the certainty in the estimates of effect was considered by the guideline development group as remaining “*very low*”.
- Mortality data were collected from a retrospective cohort study of routinely reported data from one setting only (South Africa).^{e,i} Contrary to what was observed in the 2013 data assessment, the cohort data evaluated in 2016 indicated a lower number of deaths in the group

^h The denominator used to calculate *effectiveness* (sputum culture-conversion at 6 months) only included records of patients who had a culture done at 6 months.

ⁱ Review of available evidence on the use of bedaquiline for the treatment of multidrug-resistant tuberculosis: Data analysis report. Analysis commissioned to the Department of Health Research Methods, Evidence and Impact at McMaster University. Published on 13 March 2017. Available from: http://www.who.int/tb/publications/2017/Appendix_GDGRReport_Bedaquiline.pdf

^j The denominator used to calculate *treatment outcomes* (sputum culture conversion at 6 months) only included records of patients who had completed follow up (18 months and more) and had available outcome data.

of patients receiving bedaquiline. However, data on potential confounders were not available and other sources of bias could not be adequately addressed in the evidence analysis. The guideline development group concluded that the data and the methods used for patient selection and follow-up were subject to a number of limitations (e.g. selection and ascertainment bias) that could bias the results of the analysis and limit their generalizability. Therefore, the initial concerns about unexplained mortality in patients receiving bedaquiline – as expressed by the U.S. FDA in 2012 and the 2013 WHO evidence assessment – although much lessened by the data, could not be allayed fully.

- Nonetheless, the guideline development group judged that *the observed effect of bedaquiline on culture conversion after six months of treatment, and more largely, on treatment success, outweighed the harms for most patients.*

Based on the above, the guideline development group agreed that the recommendation, as outlined in 2013, should remain valid as a conditional recommendation and that this was to be prolonged as “interim” until more evidence (including data from the on-going phase III trial)^k are available.

4. *Is there any change in the criteria to be used for selecting patients to be treated with a regimen that includes bedaquiline?*

In the context of the new WHO recommendations for the use of a shorter regimen to treat MDR-TB (issued by the WHO in May 2016),^{f,g} **bedaquiline is indicated for MDR-TB patients who are NOT eligible for the shorter regimen**, i.e. in case that a minimum of five effective TB drugs regimen cannot be composed with agents from groups A, B, C and the addition of pyrazinamide.

In practical terms, bedaquiline continues to be indicated for the treatment of adult MDR-TB patients with:

- i) *confirmed additional resistance* to fluoroquinolones (MDR-TB_{+FQ}), or second-line injectable drugs (MDR-TB_{+SLI});^{l,m}
- ii) patients with extensively drug-resistant TB (XDR-TB);
- iii) patients with known adverse drug reaction, poor tolerance, or contraindication to any component of the WHO-recommended *longer* regimen; *or*
- iv) in case of unavailability or lack of guaranteed supply of a medicine being part of the WHO-recommended *longer* regimen.

The principle of never using less than five effective second-line drugs is maintained.^{f,g} Bedaquiline should not be added alone to a regimen which is clearly failing to achieve a response in a patient. In such a case, the regimen would need to be completely redesigned in order to ensure that any changes would make it strong enough to overcome any confirmed or suspected resistance to its components.

As per the 2016 treatment guidelines, WHO-recommended *longer* MDR-TB regimens are constructed using at least five medicines during the intensive phase, including pyrazinamide and four second-line agents (one from Group A; one from Group B; and at least two from Group C). Bedaquiline may be added to such a regimen (Table 1).

^k ISRCTN - ISRCTN18148631: STREAM 2 - The evaluation of a standard treatment regimen of anti-tuberculosis drugs for patients with multi-drug-resistant tuberculosis. Available from: <http://www.isrctn.com/ISRCTN18148631?q=&filters=conditionCategory:Respiratory&sort=&offset=2&totalResults=637&page=1&pageSize=50&searchType=basic-search> and <https://clinicaltrials.gov/ct2/show/NCT02409290?term=stream+bedaquiline&rank=1>

^l Either molecular or culture-based phenotypic drug susceptibility testing (DST) could be considered to identify additional resistance to second-line drugs for patients with confirmed rifampicin-resistant or MDR-TB. WHO recommends the use of second-line LPA for the detection of resistance to fluoroquinolones and second-line injectable agents as the initial test, instead of phenotypic culture-based DST.

^m 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]. Available from: <http://www.who.int/tb/WHOPolicyStatementSLLPA.pdf> World Health Organization: 2016.

Table 1: General steps in designing the composition of a WHO-recommended *longer* MDR-TB regimen¹

STEPS	MEDICINES Groupings & options	Abbreviations
1. INCLUDE ONE LATER GENERATION FLUOROQUINOLONE	A ² Levofloxacin Moxifloxacin Gatifloxacin	Lfx Mfx Gfx
2. ADD ONE SECOND-LINE INJECTABLE AGENT	B ³ Amikacin Capreomycin Kanamycin (Streptomycin)	Am Cm Km (S)
3. ADD TWO OR MORE SECOND-LINE AGENTS	C ² Ethionamide / Prothionamide Cycloserine / Terizidone Linezolid Clofazimine	Eto / Pto Cs / Trd Lzd Cfz
4. ADD PYRAZINAMIDE AND OTHER FIRST-LINE AGENT if they can help strengthen the regimen	D1 Pyrazinamide Ethambutol High-dose isoniazid	Z E H ^h
5. ADD BEDAQUILINE OR DELAMANID ⁴	D2 Bedaquiline Delamanid	Bdq Dlm
6. ADD ANY OF THESE AGENTS if the regimen cannot be composed otherwise	D3 <i>p</i> -aminosalicylic acid Imipenem-cilastatin ⁵ Meropenem ⁵ Amoxicillin-clavulanate ⁵ (Thioacetazone) ⁶	PAS Ipm-Cln Mpm Amx-Clv (T)

Notes

¹ This stepwise approach guides the design of WHO-recommended *longer* (individualised) regimens for patients who are not eligible for the WHO-recommended shorter regimen (the composition of the shorter MDR-TB regimen is standardised).^{f,n} The aim is to combine at least **5 effective agents** in the intensive phase; more medicines can be included if they can safely increase the chances of cure. The choice of a medicine is based on the likelihood of its effectiveness, on reliable information of drug-resistance, and on the balance of expected benefits to risk. For instance, in case of nephrotoxicity or hearing loss, an injectable agent may be omitted and an agent from Group C or D2 added.

² Medicines in Groups A and C are shown by the decreasing order in the usual preference of use (subject to other considerations).

³ Streptomycin may substitute other injectable agents when the other three cannot be used.

⁴ Bedaquiline or delamanid may be added to a WHO-recommended *longer* regimen to replace another second-line agent or to strengthen it.^{a,o,p}

⁵ Carbapenems and clavulanate are used together; clavulanate is only available in formulations combined with amoxicillin.

⁶ HIV-status must be tested and confirmed to be negative before thioacetazone is started.

5. Can bedaquiline be used beyond WHO and regulatory authority recommendations?

- There is limited evidence to support off-label use of bedaquiline, especially its use in patient populations other than those recommended by the U.S. FDA, EMA, as well as the WHO, and on composition of alternative regimens.

ⁿ WHO | Frequently asked questions (FAQ) about the shorter MDR-TB regimen. Available from: http://www.who.int/entity/tb/areas-of-work/drug-resistant-tb/treatment/FAQshorter_MDR_regimen.pdf

^o The use of delamanid in the treatment of multidrug-resistant tuberculosis. Interim policy guidance (WHO/HTM/TB/2014.23) [Internet]. Geneva, World Health Organization. 2014. Available from: http://apps.who.int/iris/bitstream/10665/137334/1/WHO_HTM_TB_2014.23_eng.pdf

^p The use of delamanid in the treatment of multidrug-resistant tuberculosis in children and adolescents: interim policy guidance (WHO/HTM/TB/2016.14) [Internet]. Geneva, World Health Organization. 2016. Available from: <http://apps.who.int/iris/bitstream/10665/250614/1/9789241549899-eng.pdf>

- It is conceivable that selected patients may require changes to their MDR-TB regimen based on a limited number of effective medicines remaining. In such cases, the decision to use bedaquiline is entirely at the discretion of the clinical practitioner treating the patient and should include patient informed consent in writing and active TB drug safety monitoring (aDSM) and proper management of adverse events as per conditions for bedaquiline use.
- Use of the drug in pregnant women and children is not advised due to a lack of evidence on safety and efficacy in these populations. The guideline development group reviewed data on 39 patients aged 12 – 17 years who had been started on treatment with bedaquiline; however, since outcome data were incomplete, no further conclusions could be drawn.
- Although longer bedaquiline use (> 6 months) has been reported in some cohorts,^q safety data on prolonged use of this drug are limited. Hence the current indications for bedaquiline dose and duration of administration remain the same as in the 2013 interim WHO guidance. Any use beyond the recommended period is entirely at the discretion of the treating clinician.
- As there is currently no evidence on the simultaneous use of bedaquiline and delamanid, no recommendation is yet possible for the concurrent administration of these two medicines.

6. *What are the practical implications of the new safety data on bedaquiline reviewed in 2016?*

Data on adverse events included in the updated analysis were incomplete; however, the safety profile of bedaquiline remains similar to that initially described in 2013, particularly with regard to cardiotoxicity (prolongation of the QT space on the electrocardiogram). In line with the WHO guidance for management of MDR-TB, the implementation aDSM^f continues to be required in order to monitor and ensure proper action if an adverse event develops. This would also contribute to a future larger knowledge base about the safety profile of bedaquiline^s.

Bedaquiline should continue to be used with caution in persons living with HIV infection treated with ARVs that exhibit drug-drug interactions with bedaquiline (efavirenz) or prolong the QT interval (lopinavir/ritonavir).

A duly informed consent process should be followed for all patients undergoing treatment for MDR-TB with bedaquiline as per current WHO recommendation for the use of this drug. Bedaquiline is to be presented as an option and include information about the effects.

7. *What happens if a patient presents with serious adverse events^t while receiving a WHO-recommended longer regimen which contains bedaquiline?*

Countries introducing bedaquiline must apply the aDSM^f framework to rapidly identify, report, assess, manage and report any serious adverse event. On the basis of this assessment the discontinuation of bedaquiline and/or other regimen components may be considered on an individual patient basis. Prior to bedaquiline introduction, programmes should prepare their response plan to ensure that measures to investigate, manage and communicate information regarding adverse events can be done in a timely manner. For further information on the management of adverse events, please consult the *Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis*.^g

^q Guglielmetti L, Le Dû D, Jachym M, Henry B, Martin D, Caumes E et al. Compassionate use of bedaquiline for the treatment of multidrug-resistant and extensively drug-resistant tuberculosis: interim analysis of a French cohort. *Clinical Infectious Diseases*. 2015;60(2):188-194.

^f Active tuberculosis drug-safety monitoring and management (aDSM): Framework for implementation. [WHO/HTM/TB/2015.28] Available from:

http://apps.who.int/iris/bitstream/10665/204465/1/WHO_HTM_TB_2015.28_eng.pdf?ua=1. World Health Organization: 2015.

^s TDR | WHO global database for TB active drug safety monitoring home page. WHO. Available from: http://www.who.int/tdr/research/tb_hiv/adsm/en/

^t **Serious adverse event** refers to an adverse event which either leads to death or a life-threatening experience; to hospitalization or prolongation of hospitalization; to persistent or significant disability; or to a congenital anomaly. Serious events which do not result immediately in one of these outcomes but which might require an intervention to prevent it from happening are included. SAEs may require a drastic intervention such as termination of the drug suspected of having caused the event.

8. *Can bedaquiline be added to the shorter MDR-TB regimen?*

Data on bedaquiline use come from studies evaluating the use of this drug on top of a WHO-recommended *longer* regimen. Although current research efforts strive to determine the efficacy and safety of bedaquiline when added to or included in the shorter MDR-TB regimen,^k the results are not expected before 2020. Until more evidence becomes available, bedaquiline use is limited to its addition to a WHO-recommended *longer* regimen.

9. *Is assessment of drug susceptibility to bedaquiline required for patients receiving this treatment?*

Drug susceptibility testing protocols and the use of critical concentrations for bedaquiline with different media are currently being validated, *and*, these protocols should become available during the second half of 2017. In the interim, culture should always be performed as part of the treatment monitoring for all patients receiving bedaquiline. Additionally, any positive culture should be stored frozen to allow for further laboratory investigations to be performed for strains that may have developed resistance to bedaquiline during treatment.

10. *Do the results of this review affect the conditions and implementation of the bedaquiline donation programme supported by USAID-Janssen Pharmaceutical?*

No. Countries adopting the interim WHO recommendations for the use of bedaquiline are encouraged to continue placing their orders for bedaquiline through the Stop TB Partnership's Global Drug Facility^u. WHO will continue to work with partners to assist countries in the development of plans for the rational introduction and use of bedaquiline.

^u How to access the bedaquiline donation program: Step by step. Announcements 2015. Available from: http://www.stoptb.org/news/announcements/2015/a15_013.asp. Stop TB Partnership's Global Drug Facility: 2015.