

GDF Meeting Report: Webinar for TB Medicine Suppliers

Updates on 2022 WHO Recommendations for Treatment of Drug-Resistant Tuberculosis and Potential Implications on TB Medicine Markets

11 May 2023
2:00pm-3:30pm (CST)

Background

In December 2022, WHO issued **updated and consolidated DR-TB treatment guidelines**, introducing a number of new recommendations, including for BPaLM, a new 6-month regimen of bedaquiline, pretomanid, linezolid, and moxifloxacin for people with multidrug-resistant or rifampicin-resistant TB (MDR/RR-TB) and those with additional resistance to fluoroquinolones (pre-extensively drug-resistant TB (XDR-TB)). **BPaLM is now expected to become the primary treatment regimen for DR-TB in adults.** These changes to the DR-TB medicines landscape, while representing a game-changing opportunity for people with DR-TB, have implications for suppliers.

One key area of GDF's market shaping work is sharing critical information with suppliers so that they can prepare for upcoming changes in client demand and ensure continuous access to quality-assured products appropriate to the specific needs of each person with TB.

GDF Webinar Objectives

As part of GDF's vital market stewardship activities, GDF convened a webinar for TB medicines suppliers on May 11, 2023 to provide a better understanding of the new WHO recommendations and their implications for both suppliers and National TB Programmes (NTPs). The online webinar was attended by 35 suppliers representing 20 different companies, along with donors, technical experts, and GDF personnel.

The objectives of the webinar were to:

- Review the latest WHO recommendations on DR-TB treatment, including eligibility criteria;
- Summarize how NTPs are approaching implementation of these new recommendations, including timelines and extent of adoption;
- Describe GDF's role and value-add in market-shaping and scale-up of these new regimens throughout the product lifecycle;
- Assess how implementation of the new recommendations could affect both procurement volumes and use of different DR-TB medicines.

The information presented in the webinar will support DR-TB medicine suppliers' approach to the development and supply of these new medicines and formulations, as well as safeguard continued access to current DR-TB regimens, particularly medicines required for those who are ineligible for BPaLM. Additionally, information presented will help suppliers to guide planning around medicines for which demand may decrease as a result of the new WHO guidelines.

Summary of Presentations and Discussions

1. Recent Updates to WHO DR-TB Recommendations – Presenter: Fuad Mirzayev (WHO Global TB Program)

Consolidated guidelines for DR-TB along with an operational handbook to support implementation were published in December 2022. WHO now recommends a 6-month regimen of bedaquiline,

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pretomanid, linezolid, and moxifloxacin (BPaLM) for all eligible people with MDR/RR-TB, regardless of HIV status, who are aged ≥ 14 years and without previous exposure to the component drugs of the regimen. **For the first time, treatment duration for MDR/RR-TB is the same as treatment duration for drug-susceptible TB (DS-TB) for most people.**

BPaLM is not recommended for children ≤ 14 years or during pregnancy due to unknown toxicity of pretomanid in both these groups. For those people with MDR/RR-TB **who are ineligible for BPaLM, the consolidated guidelines now include new recommendations for the 9-month, all-oral, bedaquiline-based regimens.** The previous version of the 9-month bedaquiline-based regimen continues to be recommended alongside a new version that replaces 9 months of ethionamide with 2 months of linezolid. A full description of eligibility requirements for these regimens is available in the [consolidated guidelines](#).

Longer (18-month) regimens are reserved as a “last resort” for people who are neither eligible for BPaLM nor 9-month regimens and require individualized treatments. These regimens may include more Group B and C medicines. WHO emphasized that **regimen decisions should be made with consideration of age, drug-susceptibility testing (DST) results, and other eligibility factors**, information for which can be found in both the consolidated guidelines and at WHO’s new [TB Knowledge Sharing Platform](#).

2. New DR-TB Recommendations and Country Implementation – Presenter: Jennifer Furin (Harvard Medical School and the Sentinal Project)

An overview of the country implementation landscape for new and upcoming regimens was presented. Countries are eager to respond to this new guidance. There is particular **interest by NTPs in the BPaLM regimen** and its ability to reduce DR-TB treatment duration. It is estimated that **75 percent of all people with DR-TB will be eligible for BPaLM.**

Meanwhile, **25 percent of people with DR-TB are likely either ineligible for, resistant to, or unable to tolerate components of the BPaLM regimen** and will require the 9-month regimen or longer 18-month regimens. This includes children ≤ 14 years who cannot use pretomanid. Therefore, **the market for 9-and/or 18-month regimens is expected to continue, though at lower volumes.** For example, it is estimated that 25 percent of people on longer all-oral regimens will likely require cycloserine and/or clofazimine, while 5 percent will require P-aminosalicylic acid (PAS) and/or ethionamide, though ethionamide procurement volumes are expected to decrease overall with the substitution of linezolid in 9-month regimens. Intravenous carbapenems serve as rescue regimens for around 5 percent of people with DR-TB; however, these drugs have other indications outside of TB, so a market remains for them.

Many countries are updating national strategic plans and guidelines and aligning procurement with Global Fund grant cycles. A number of **countries already have systems and infrastructure in place to support implementation of BPaLM and other new regimens** due to earlier experience with implementing DR-TB regimens under operational research conditions. **Significant support for implementation** is also available from the global [1/4/6x24 Campaign](#) that seeks to create access to the shortest available regimens for people with TB by the end of 2024, as well as via the recent publication of Global Fund’s [Toolkit for TB Program Essentials](#). There are **no studies comparing different all-oral regimen options to one another**, so countries will be making decisions based on cost, availability of component drugs, and other factors.

Countries continue to balance a **desire for shorter treatment durations** for both DS- and DR-TB with **pill burden considerations**. For example, the new 4-month regimen for DS-TB—2HPMZ/2HPM—is shorter than the current standard of care but does not have a fixed-dose combination (FDC) tablet and country interest has been low. Meanwhile, a number of important clinical trials (e.g., EndTB) are expected to begin publishing results from 2024 onwards, including trials around levofloxacin and delamanid for DR-TB

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preventative treatment and delamanid-based, all-oral, 6-to-9-month regimens. This may affect demand for both drugs. Paediatric DR-TB treatment has benefitted from many of these research projects, and will continue to do so in the future, but work still needs to be done to find and diagnose children with DR-TB.

Sufficient evidence now exists for countries to fully adopt multiple new regimens and recommendations. Resistance to the components of these regimens, including to bedaquiline, is minimal, and the potential for development of resistance should not be a barrier to implementation. However, demand for DR-TB medicines is dependent on case finding and there is **urgent need for improved diagnostics** to ensure people with DR-TB are detected and initiated on treatment.

3. BPaLM: Update on GDF Market-Shaping and Scale-Up Activities – Presenter: Brenda Waning (GDF)

GDF supports end-to-end TB product lifecycle management to optimize access to medicines. Central to this work is the **GDF-hosted TB Medicines Dashboard**. The dashboard is a tool that tracks the status of every DR-TB, DS-TB, and TPT product for adults and children across 13 different data sources.¹ GDF and partners regularly work together via the TB Procurement and Market-Shaping Access Team (TPMAT) to monitor the progress of new products in relation to their status within different guidance documents and identify and address bottlenecks. The Dashboard provides clear signals to suppliers as to medicines and formulations in need of development and those that are no longer needed. Thus, the Dashboard provides a vital service to suppliers and facilitates and expedites countries' access to new products.

GDF and TPMAT partners have coordinated upstream to expedite availability of both bedaquiline and pretomanid, submitting requests to update the GF Expert Review Panel Expression of Interest (EOI) and WHO Prequalification EOI to signal the need for more suppliers of these products and ensure this a quality-assurance pathway available once the products are developed. Over the past five years, prices for the component medicines of DR-TB regimens have decreased dramatically, even though treatment numbers have remained relatively unchanged; however, there is still work to be done. Currently, regimen prices for BPaLM, as well as the bedaquiline-based, all-oral, 9-month regimens, range from \$535 to \$595 when procured via GDF (regimen prices available on GDF website [here](#)). This **exceeds the target regimen price set by TB partners of \$500**, with bedaquiline and pretomanid driving these prices. **The primary patent for bedaquiline will expire** in July 2023, with two generic suppliers already having taken steps to receive Global Fund ERP recommendation and three having dossiers accepted by WHO prequalification. This competition is **expected to lead to significant price reductions for bedaquiline**. GDF's ability to tender for bedaquiline so quickly after the primary patent expiry is due to **GDF's advance planning, monitoring of the research and development pipeline and clear signalling to suppliers on what to develop**. This ensures products are ready for procurement when patents expire, new research results become available, WHO recommendations change, etc.

GDF has been providing technical assistance (TA) to 50 high-burden priority countries since the WHO Rapid Communication was released. Among these, **39 have either started, or are planning to start, BPaLM implementation and scale up, with 28 of 39 starting scale up in 2023 and the remaining countries starting scale up by 2024**. **GDF TA helps countries with planning** on transition from old regimens, ordering and stock management, budgeting, and creation of Global Fund concept notes and funding requests. Already 15 of GDF priority countries have included BPaLM scale-up plans in Global Fund funding window

¹ Including iterations of WHO DS- and DR-TB guidelines, WHO Essential Medicines Lists (EML, EMLc), WHO Prequalification Expressions of Interest (PQ EOI), Global Fund List of Pharmaceutical Products, Global Fund Expert Review Panel Expressions of Interest (ERP EOI), and the GDF Catalog.

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1 of the 2023 funding requests with the remaining 24 planning to include in subsequent funding windows this year.

Demand for pretomanid has seen a 40-fold increase over a 3-month period following the release of WHO guidelines in December 2022, from 600-700 treatments ordered annually in 2020 and 2021 to 27,750 treatments ordered between mid-December 2022 and mid-March 2023 alone, with 67 percent of these new orders **requesting urgent delivery**. Sixty countries are ordering pretomanid from GDF.

While the end of the Global Fund grant cycle has driven some of this demand for BPaLM, **new WHO guidelines have also served as a clear trigger for action**. GDF is managing the BPaLM market, and particularly the rapidly increasing demand for pretomanid, using strategies such as supply forecasting, monthly production planning with the supplier, and the inclusion of pretomanid in the GDF Strategic Rotating Stockpile (SRS). GDF is also **working to ensure product from a second, new supplier is available as quickly as possible, and to attract new suppliers**. GDF is also aiming to prevent stockouts in country programmes and prevent delays to new regimen introduction by prioritizing orders. GDF's approach to prioritization involves gathering information about in-country stock, enrolment plans, orders, and deliveries-in-process and then analyzing this data in relation to a country's risk of stock out, timelines to phase in new regimens, and the possibility of splitting deliveries.

4. Expected Changes in DR-TB Medicine Procurement Volumes – Presenter: Brian Kaiser (GDF)

Presently, **it is estimated that >70 percent of DR-TB regimens are procured through GDF**.² Between 2015-2020, there has been a slow but **steady 3 percent compound annual growth rate of new people being diagnosed with DR-TB and placed on treatment**, increasing from 120,000 people treated in 2015 to 145,000 treated in 2020. Unless there is a change to the diagnostics landscape, it can be assumed that this 3 percent growth rate will continue, reaching an estimated 180,000 people treated for DR-TB in 2027.

Bedaquiline serves as a good example of a new product introduction and scale-up. The first WHO guidance on bedaquiline 100mg was issued in 2016, listing bedaquiline as a Group D2 drug for rescue regimens. Over the next five years, WHO recommended bedaquiline to be used more often and in more people with DR-TB, as a Group A drug for longer (2018) and then shorter (2019) regimens. This expanded use—along with the end of the Global Fund grant cycle (in which countries used remaining grant funds to build up stock) and the end of USAID's donation agreement with Jansen—saw procurement of bedaquiline increase from 1 to 2 million tablets per year to over 25 million.

Approximately 90 percent of people with DR-TB are likely to be eligible for some type of bedaquiline-based treatment with the dosing, duration, and regimen affecting number of tablets procured and overall procurement volumes. Similarly, the 2022 WHO recommendations have contributed to a sharp increase in uptake in pretomanid, with the expectation that countries will scale up over the next 18 months. **Procurement volumes of pretomanid are expected to increase over the coming years with 75 percent of people with DR-TB eligible for BPaLM**. GDF has estimated annual procurement volume of both bedaquiline and pretomanid through 2027; however, these estimates do not necessarily translate into regular scheduled procurements, as **countries' procurement schedules depend on a number of factors** including budget or Global Fund grant availability, implementation timelines, enrolment patterns, and frequency of orders.

Lastly, it is expected that **7 percent of people with DR-TB will require longer, individualized treatment regimens** made up of mostly Group B- and C-based regimens. Ensuring availability of these medicines is

² High-burden DR-TB countries that do not generally procure through GDF include Russian Federation, China, and South Africa.

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essential regardless of low procurement volumes and GDF is committed to working with its supplier partners to ensure these medicines remain available. Moreover, while great strides have been made reducing the costs of DR-TB treatment regimens, GDF and partners continue to work toward **ensuring price reductions in BPALM component medicines** in order to achieve < \$500 per treatment course.

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Q&A

- **Regarding linezolid, is it recommended to reduce the dose to 300 mg in everyone after 16 weeks? Any recommendations about the use of linezolid 150mg for DR-TB?**
In reference to the BPaLM regimen, the use of linezolid at 600mg is encouraged throughout the regimen if possible. The dose can be reduced to 300 mg/daily if necessary to mitigate toxicity. Meanwhile, linezolid 150mg is an important and exciting paediatric product for DR-TB. Prior to this formulation, clinicians were cutting down from 600mg tablets which created waste. The paediatric DR-TB market is very small and the philanthropic approach that suppliers have taken is greatly appreciated. Dose-ranging studies of linezolid are taking place to address toxicity issues.
- **What is the future of DS-TB treatment if rifapentine FDCs for TPT do not seem to have uptake? How will the new 4-month regimen consisting of rifapentine, isoniazid, pyrazinamide, and moxifloxacin for DS-TB change the treatment landscape for DS-TB?**
It is expected that the 4-month regimen of isoniazid, rifapentine, moxifloxacin, and pyrazinamide (HPMZ) will be taken up eventually, but uptake is not happening quickly. Innovations around DS-TB sometimes focus on shorter treatment duration, with less consideration of other factors. Slow uptake of the 4-month regimen is primarily due to its high price and pill burden. There is also concern about the loss of moxifloxacin for DR-TB should resistance develop after its inclusion in a DS-TB regimen. Finally, higher uptake also depends on the expanded access to and use of diagnostics to identify people with TB. There are now additional suppliers on the market producing 300mg rifapentine tablets which should reduce pill burden. Some implementation challenges could be resolved with the development of an FDC. For now, only a handful of countries have started, or are planning to start, small-scale implementation of HPMZ.
- **What are people seeing in terms of bedaquiline resistance?**
Emerging evidence on bedaquiline resistance—in particular, data coming from South Africa—has led to some concern by NTPs about BPaLM implementation. The presenters reminded participants that South Africa is one of the earliest countries to launch bedaquiline and has been implementing the medicine for over ten years across multiple regimens and throughout the entire country. Therefore, some resistance is not alarming in the South African context and should not be a concern to countries that have only just started implementing bedaquiline. Surveillance should be a priority and use of and access to bedaquiline DST should be expanded. However, availability of bedaquiline DST should not be a barrier to the uptake of either bedaquiline or BPaLM, which remains the best regimen available for DR-TB. Utilization of potent regimens like BPaLM, in fact, can help to minimize the development of resistance. Meanwhile, the potential for resistance to bedaquiline and other medicines is an argument for ensuring the continuation of markets for rescue regimens.
- **What is pan-TB? Does it mean that one drug or one pill will treat TB?**
A pan-TB regimen is an ideal regimen, one that might treat all forms of TB. Pan-TB could also refer to a regimen consisting of new drugs with little probability of resistance which might play a role in a setting where DST is not possible, and treatment needs to be rolled out quickly. The idea of “pan-TB” will be discussed in a new WHO document on target regimen profiles, the updated version of which will come out in the second half of 2023. For now, the idea that a single drug to treat all forms of TB will be developed (and as accessible and as inexpensive as current regimens) is unlikely.
- **Prothionamide is not mentioned in any of the presentations. What is the future of this product?**

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Prothionamide and ethionamide are interchangeable. Country programmes can use prothionamide instead of ethionamide wherever ethionamide is recommended in WHO guidance.

- **Are there any promising clinical trials ongoing for new regimens that you foresee being implemented in the near future?**

The TB research pipeline is full of interesting clinical trials. There are research consortia (e.g., UNITE4TB, panTB, SMART4TB) which have attracted significant donor support. There is an endTB extension (endTB-q) for people with additional quinolone resistance. There are also the BEAT-TB and BEAT Tuberculosis studies. WHO will launch the TB Research Tracker website to keep track of clinical trials and provide a consolidated summary of all ongoing TB medicines research (Research Tracker launched after meeting and available here: <https://tbtrialtrack.who.int/#/>).

- **What is the roll out and procurement plan for new the regimens for DS-TB?**

There will hopefully be a better idea on the roll out of new regimens—including the 4-month regimen for DS-TB and BPALM for DR-TB—when the 2023 Global TB Report comes out, as there were specific questions on the implementation of these regimens to be addressed within the report. For now, only a handful of countries have started, or are planning to start, small-scale implementation of HPMZ.

- **Why is pretomanid not a part of TB drug groupings?**

Pretomanid is not part of TB drug groupings because the only evidence that exists on pretomanid is within the BPAL and BPALM regimens. There is no evidence on pretomanid being used in any other way. For this reason, the drug groupings do not include pretomanid.

Conclusion

GDF will follow-up as needed with individual suppliers on questions related to this webinar. GDF will continue to provide updates going forward via its annual suppliers' meeting and additional webinars, as needed. GDF urges its suppliers to reach out at any point if questions remain.

Expected Changes in DR-TB Medicine Procurement Volumes

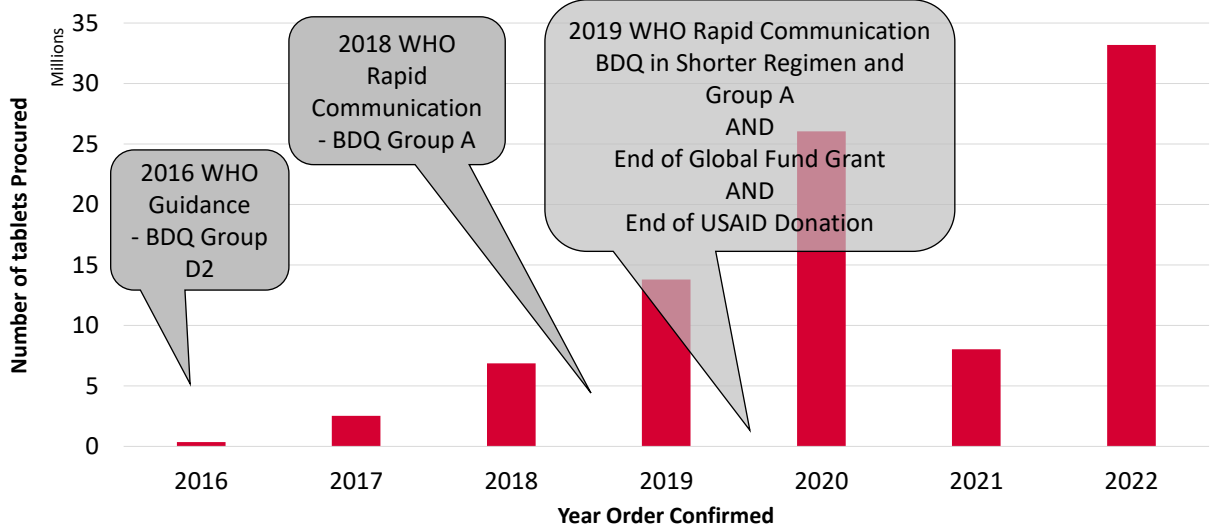
Brian Kaiser

Technical Officer Market Strategies

GDF Supplier Meeting on WHO DRTB Guidance 2022 Update, Virtual, 11 May 2023

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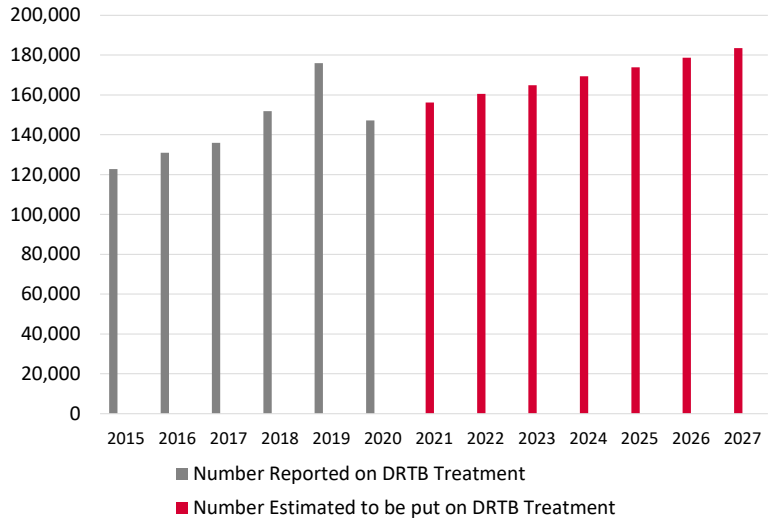
Bedaquiline (BDQ) 100mg tablet Procurement through GDF – Example of introduction, scale-up and funding effects on procurement



2

Actual and Estimated Number of People to be treated for DRTB

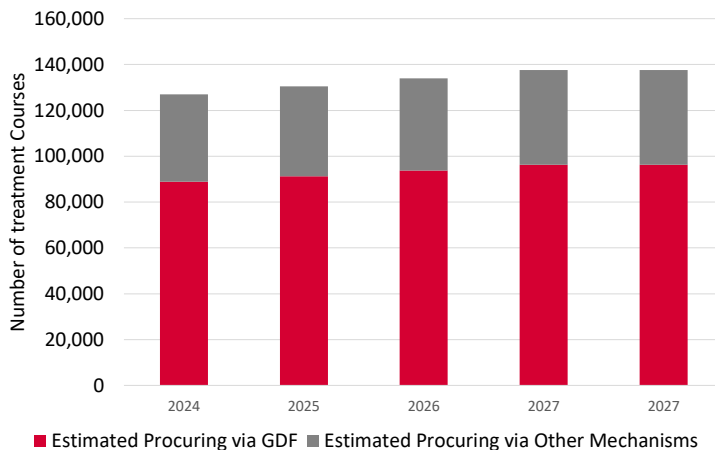
- 2015-2020 reported numbers treated for DRTB (most recent data from WHO GTB Report)
- 3% compound annual growth rate between 2015-2020 – applied prospectively to estimate the number of people treated for DRTB



WHO Global TB Report 2022

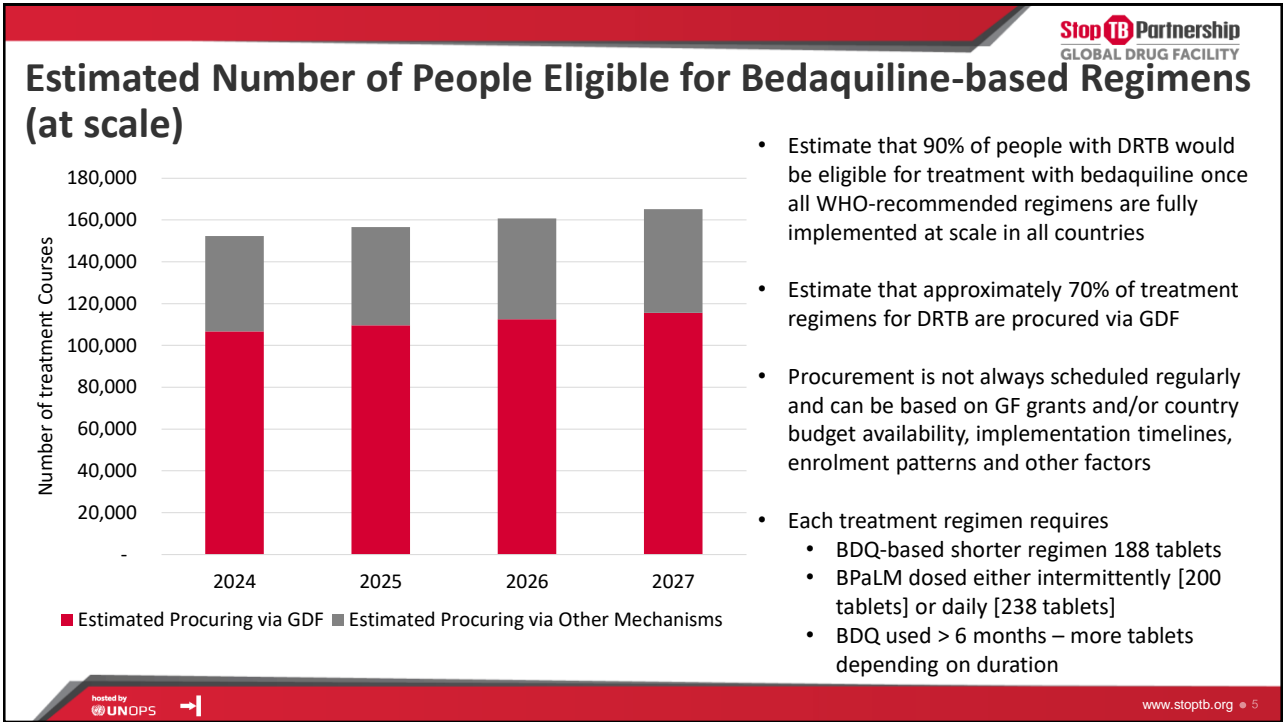
3

Estimated Number of People Eligible for Pretomanid-based Regimens (at scale)

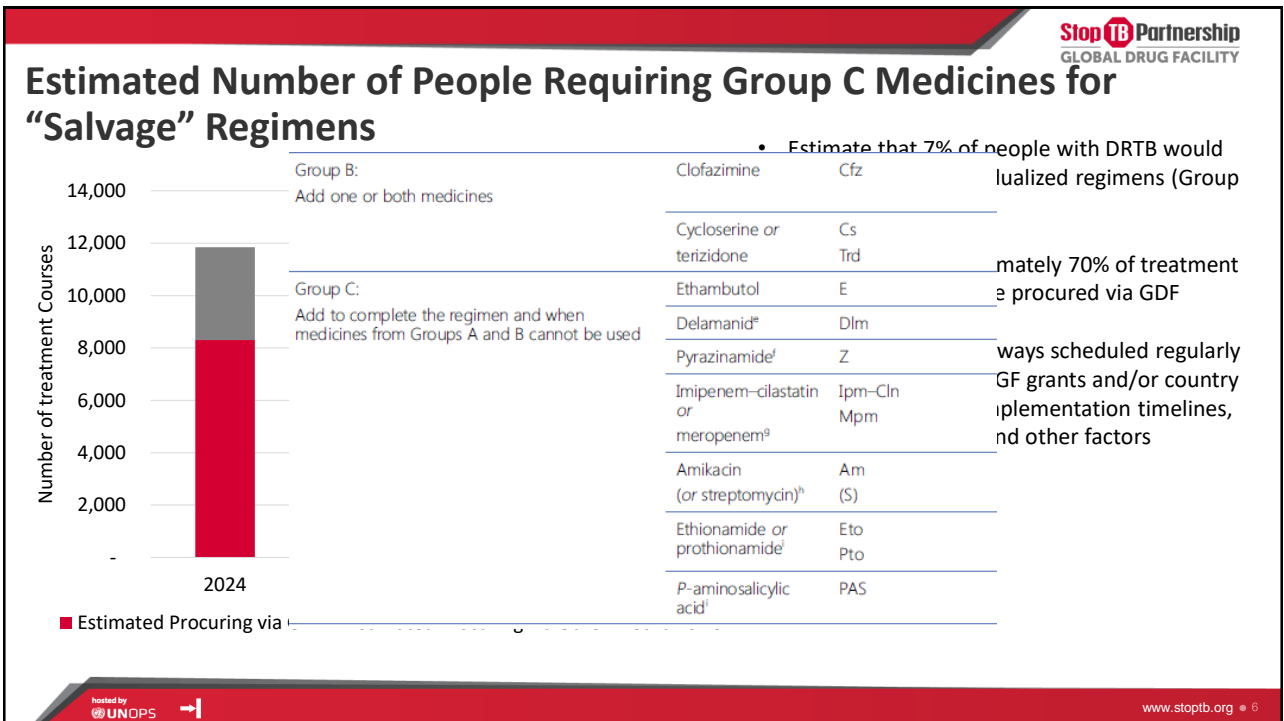


- Estimate that 75% of people with DRTB would be eligible for treatment with BPaLM (or BPaL) once the regimen is fully implemented at scale in all countries
- Estimate that approximately 70% of treatment regimens for DRTB are procured via GDF
- Procurement is not always scheduled regularly and can be based on GF grants and/or country budget availability, implementation timelines, enrolment patterns and other factors
- Each treatment regimen requires 182 tablets of pretomanid

4



5



6

Pricing of DRTB Regimens

BPaLM

| Medicine | Cost (USD) |
|--------------|------------|
| Bedaquiline | 290 |
| Linezolid | 35 |
| Moxifloxacin | 30 |
| Pretomanid | 240 |
| Total | 595 |

A lot of progress has been made in lowering the costs of DRTB treatment regimens

Still not at the target price of <\$500

BPaL

| Medicine | Cost (USD) |
|--------------|------------|
| Bedaquiline | 290 |
| Linezolid | 35 |
| Pretomanid | 240 |
| Total | 565 |

Bedaquiline remains a major cost driver, but GDF expects major decreases in price when the primary patent expires July 2023

Summary and Take Home Points

- There have not been major changes in the number of people treated for DRTB, just slow and steady growth (except for COVID times)
- Bedaquiline will remain a core medicine for DRTB treatment – with 90% of people likely being on a bedaquiline-based regimen
 - The change in patent status should see significant price reductions from generic competition
- Pretomanid is being scaled and likely 75% of people with DRTB will be eligible for these regimens (based on current evidence)
- There remains a subset of people that will require Group B and C-based regimens and GDF wants to ensure these medicines remain available
- Procurement of medicines is not always regular and may be affected by funding availability, Global Fund grant cycles, implementation considerations, enrolment patterns, etc

Thank You

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