Meeting report

of the Informal consultation on preferred formulations and packaging of medicines used in BPaL(M/L) regimens for drug-resistant tuberculosis (DR-TB) treatment

Jointly organized by the WHO Global Tuberculosis Program (WHO/GTB),

the Stop TB Partnership and USAID

6 June 2024

Contents

Definitions and abbreviations

Tuberculosis (TB) disease: A disease in humans caused by the *M. tuberculosis* complex, which comprises eight distinct but closely related organisms – *M. bovis, M. caprae, M. africanum, M. microti, M. pinnipedii, M. mungi, M. orygis* and *M. canetti.* The most common and important agent of human disease is *M. tuberculosis*.

TB patient: a person who is in care for TB disease.

Drug-resistant TB (DR-TB): TB disease caused by a strain of *Mycobacterium tuberculosis* complex that is resistant to any TB medicines.

Drug susceptibility testing (DST): in vitro testing using either molecular or genotypic techniques to detect resistance-conferring mutations, or phenotypic methods to determine susceptibility to a medicine.

Extensive (or advanced) pulmonary TB disease: presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography. In children aged below 15 years, advanced disease is usually defined by the presence of cavities or bilateral disease on chest radiography.

Extensively drug-resistant TB (XDR-TB): TB disease caused by a strain of *M. tuberculosis* complex that is resistant to rifampicin (and may also be resistant to isoniazid), and that is also resistant to at least one fluoroquinolone (levofloxacin or moxifloxacin) and to at least one other "Group A" drug (bedaquiline or linezolid).

MDR/RR-TB: refers to either multidrug-resistant TB (MDR-TB) or rifampicin-resistant TB (RR-TB).

Multidrug-resistant TB (MDR-TB): TB disease caused by a strain of *M. tuberculosis* complex that is resistant to rifampicin and isoniazid.

Rifampicin-resistant TB (RR-TB): TB disease caused by a strain of *M. tuberculosis* complex that is resistant to rifampicin. These strains may be susceptible or resistant to isoniazid (i.e. multidrug-resistant TB [MDR-TB]), or resistant to other first-line or second-line TB medicines.

TB **medicines**

B or Bdq	bedaquiline
Eto	ethionamide
FQ	fluoroquinolones
L or Lzd	linezolid
Lfx	levofloxacin
M or Mfx	moxifloxacin
Pa	pretomanid
R	rifampicin

Background and history

Tuberculosis (TB) remains a threat to global public health and is one of the topmost infectious causes of death in the world. In 2022, an estimated 10.6 million people developed TB, and 1.3 million died from the disease. About 410,000 new patients with rifampicin-resistant or multidrug-resistant tuberculosis (MDR/RR-TB) were estimated to emerge in 2022. While all of these patients would have been eligible for a second-line TB treatment regimen, only 175,650 enrolments on treatment were reported by countries in the same year. Significant improvements in the availability of enhanced diagnostics and more effective medicines have occurred in recent years and have led to earlier detection and higher success rates among patients with MDR/RR-TB in a number of national programs.

Treatment of drug-resistant TB requires regimens that use so-called reserve or second-line medicines active against Mycobacteria TB. The regimens for the treatment of DR-TB have changed dramatically in the past ten years. Before 2016, DR-TB regimens were 24 or more months long and included six or more months of daily intramuscular injections with significant adverse events. In 2016, WHO recommended a standardized, shorter regimen for DR-TB treatment. This 9-11 month regimen used the same second-line medicines, including injectable agents.

Bedaquiline was the first new medicine to be added to the group of available second-line TB medicines. In 2013, WHO issued interim guidance for using bedaquiline with other WHO-recommended MDR-TB treatments. This guidance, based on the results of the phase 2b clinical trial, was unprecedented for the WHO. Bedaquiline gradually became a staple drug in the treatment of DR-TB, initially featuring as an add-on agent in the longer regimens for MDR/RR-TB and then becoming a Group A medicine along with Fluoroquinolones and Linezolid. Later, in 2020, bedaquiline was recommended to replace injectables in the 9-11-month and longer regimens, leading to a new era of all-oral regimens for MDR/RR-TB, most of them including bedaquiline.

The pressing need for more effective treatment regimens for patients with extensive drug resistance, including fluoroquinolone resistance and more extensive drug-resistance profiles, has driven several studies and initiatives to test more effective and novel treatment regimens, including newer and repurposed medicines. One such study was the Nix-TB study conducted by TB Alliance. The Nix-TB study was a one-arm, open-label study that assessed the safety, efficacy, tolerability, and pharmacokinetic properties of a 6-month BPaL treatment regimen, the first regimen that could potentially equalize the duration of treatment for almost all drug-resistant or susceptible forms of TB. The narrow evidence base from this study and its very low certainty allowed the WHO to recommend the regimen be studied further under operational research conditions. This new regimen included a new medicine – pretomanid, and the BPaL combination successfully received regulatory approval from the FDA.

Two randomized controlled trials (RCTs) that concluded in 2021 (TB-PRACTECAL and ZeNix) provided new evidence and prompted assessment by WHO to develop new recommendations for wide programmatic use of the BPaLM/BPaL regimen for treatment MDR/RR-TB with or without resistance to fluoroquinolones. The latest evidence-based guidelines for the treatment of drug-resistant TB, including

MDR/RR-TB and pre-XDR-TB,[1] were published by WHO in December 2022 – "WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment"[2].

Fixed Dose Combinations (FDCs) of TB medicines for Drug-Susceptible TB

For many years, fixed-dose combinations (FDCs) have been used for the treatment of TB in national TB programs. Several specifics of *Mycobacteria tuberculosis* and its interaction with a human host require treatment using multiple drug regimens to cure patients and prevent relapse, transmission, and the selection of drug-resistant mutants, which may arise during the course of treatment. The FDCs have been used for the treatment of drug-susceptible TB for many years for several reasons: to simplify treatment regimens and decrease the pill burden, making it easier for patients to adhere to the regimens lasting months, to reduce the risk of acquired drug resistance by ensuring that all medications are taken together and avoiding mono- or inadequate therapies, to simplify the inventory and the supply chain management and also help to cater for the standardized treatment protocols.

While there are some advantages, FDCs limit flexibility for adjusting dosages and treatment combinations when needed; they may cause drug interactions that can affect treatment efficacy. FDCs may be more expensive than individual medications, and supplies may depend on fewer manufacturers and their capacity. Finally, they require navigating additional regulatory processes that can be challenging and time-consuming.

The evidence around the FDCs is unequivocal and is largely limited to the use case for drug-susceptible TB treatment. A systematic review of the evidence from randomized controlled trials[3] and a large Cochrane review[4] point towards the FDCs being non-inferior and as effective as separate drug formulations in terms of treatment failure, death, treatment adherence, and adverse events. A slightly higher rate of disease relapse and acquired drug resistance among patients treated with FDCs compared with the separate drug formulations was not statistically significant, while patient satisfaction was higher among people who were treated with FDCs.

Current situation

WHO-recommended Regimen for DR-TB Treatment

The BPaLM, a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg), and moxifloxacin (BPaLM), is recommended by WHO for all eligible MDR/RR-TB patients (14 years or older)

[1] New XDR-TB definition as result of the WHO consultation (October 2020): Pre-XDR-TB: TB caused by Mycobacterium tuberculosis (M. tuberculosis) strains that fulfil the definition of MDR/RR-TB and which are also resistant to any fluoroquinolone. XDR-TB: TB caused by Mycobacterium tuberculosis (M. tuberculosis) strains that fulfil the definition of MDR/RR-TB and which are also resistant to any fluoroquinolone and at least one additional Group A drug. (https://www.who.int/publications/i/item/meeting-report-of-the-who-expert-consultation-on-the-definition-of-extensively-drug-resistant-tuberculosis, accessed 5 May 2021)

[2] https://www.who.int/publications/i/item/9789240063129

[3] Albanna, A. S., et al. (2013). "Fixed-dose combination antituberculosis therapy: a systematic review and meta-analysis." European Respiratory Journal 42(3): 721-732.

[4] Gallardo CR, Rigau Comas D, Valderrama Rodríguez A, Roqué i Figuls M, Parker LA, Caylà J, Bonfill Cosp X. Fixed-dose combinations of drugs versus single-drug formulations for treating pulmonary tuberculosis. Cochrane Database of Systematic Reviews 2016, Issue 5. Art. No.: CD009913. DOI: 10.1002/14651858.CD009913.pub2. Accessed 29 April 2024.

with or without resistance to fluoroquinolones rather than the 9-month or longer (18-month) regimens. In cases of documented resistance to fluoroquinolones, BPaL without moxifloxacin would be used. BPaLM is the first standardized regimen for the treatment of drug-resistant TB that is as short as the first-line TB regimens and is recommended for programmatic use.

BPaLM Formulations - Availability and Price

Each medicine in the BPaLM regimen – bedaquiline, pretomanid, linezolid, moxifloxacin - has a quality-assured, adult formulation commercially available. All formulations are available in blister packs, while bedaquiline and pretomanid are also available in bottles with loose tablets. There have been significant decreases in prices for these medicines, too. Most recently, on pretomanid and bedaquiline. Currently, the price of the BPaLM regimen can be as low as $430 (through the Stop TB Partnership's Global Drug Facility[5]).

The consultation and perspectives

The advent of the BPaLM regimen two years ago has led to a rapid uptake initiated by 44 countries in 2023[6]. Of the 49 countries with a high burden of TB or DR-TB, 45 countries reported[7] to have a country plan to implement the BPaLM regimen. Enrollment is projected to increase to 62,352 in 2024 and 94,798 in 2025, and it may increase dramatically when two high-burden countries, India and China, update their national policies on drug-resistant TB treatment.

The prices of drugs and components of the BPaLM regimen have dropped recently, and there might still be a tendency for further price change with generic competition entering the market of two of the regimen's newest components—bedaquiline and pretomanid.

The current situation is, therefore, rather dynamic, with many shifting variables. Among them is a new push to introduce a partial FDC (or multiple FDCs), comprising the same two medicines, bedaquiline and pretomanid and/or co-packs of single formulations of all the medicines for the BPaLM/BPaL regimens.

The main topic and purpose of this informal consultation were to discuss several aspects of the BPaLM introduction—clinical, patient, implementation, market, and supply chain—and reach a consensus among partners and stakeholders on the direction, timeliness, and relevance of B-Pa FDCs and/or co-packs for the short term.

[5] https://www.stoptb.org/buyers/plan-order
[6] Global tuberculosis report 2023. Geneva: World Health Organization; 2023. Licence: CC BY-NC-SA 3.0 IGO
[7] End TB Summit, Paris November 2023, https://whoendtbforum.org/topics/40472/media_center/folder/ad7832b6-cfb9-477f-9791-61a548c44b57

Agenda

6 June, Thursday

Moderator – Tamara Kredo, South Africa

Time	Topic	Presenter/discussants
13:00-13:10	**Introduction to the consultation**	WHO/GTB – Tereza Kasaeva Stop TB Partnership – Lucica Ditiu USAID – Cheri Vincent
13:10-13:20	**Clinical perspective**	Fuad Mirzayev, WHO/GTB
13:20-13:30	Discussant- reflection on pros and cons	Mary Rosary Santiago, Philippines
13:30-13:40	**Patient perspective**	Ashna Ashesh, India
13:40-13:50	Discussant- reflection on pros and cons	Naomi Wanjiru, Kenya
13:50-14:00	**Country implementation perspective**	Fatima Razia, Pakistan
14:00-14:10	Discussant- reflection on pros and cons	Fernanda Dokhorn Costa, Brasil Erlina Burhan, Indonesia
14:10-14:20	**Market perspective**	Christophe Perrin, MSF
14:20-14:30	Discussant- reflection on pros and cons	Cherise Scott, Unitaid
14:30-14:40	**Supply chain perspective**	Maya Kavtaradze, GDF
14:40-14:50	Discussant- reflection on pros and cons	Masimba Dube, Zimbabwe
14:50-15:50	**Questions and Answers** **Final discussion**	All
15:50-16:00	**Conclusions**	Tamara Kredo, South Africa

Summary

The consultation consisted of one online meeting held via Zoom (see agenda above). The consultation participants reflected a diverse range of stakeholders and end users from several relevant sectors, including representatives from high TB and MDR-TB burden countries, NTP managers, clinicians, researchers, academics, donors, partner technical organizations, other relevant WHO departments, civil society, and patient advocates. More than 100 participants contributed active ideas and views to the online consultation, which benefited from active contributions and the sharing of ideas and views. The moderator, Dr Tamara Credo, effectively managed the proceeds of the consultation and discussions.

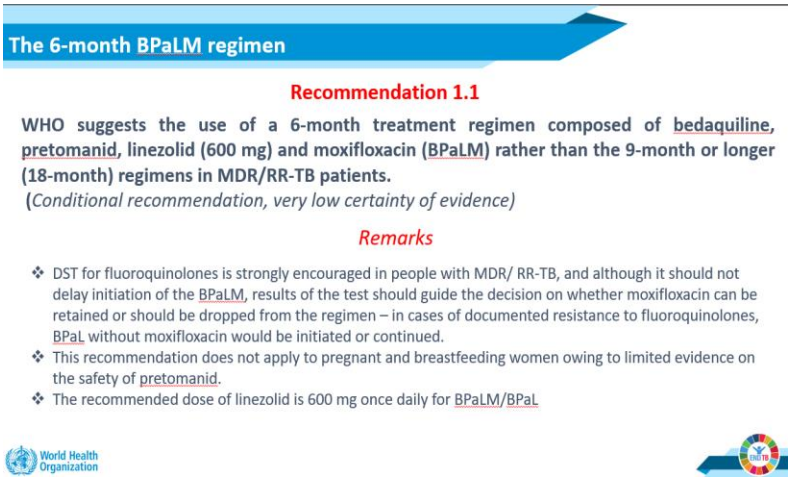
The overall goal of this informal consultation was to bring together representatives from NTPs, implementing partners, patient representatives, funding agencies, and other key stakeholders to discuss the key aspects of the BPaLM introduction in several domains —clinical, patient, implementation, market, and supply chain—and reach a consensus among partners and stakeholders on the direction, timeliness, and relevance of B-Pa FDCs and/or co-packs for the short term perspective (3-5 years).

During the consultation, the discussion traversed five domains in a systematic and structured manner, presenting the main considerations and making this particular aspect important for the eventual conclusions. The pros and cons specific to the presented thematic aspect were examined with additional intervention from a discussant. The consultation around each domain was completed with an open discussion involving all participants. The presenter and discussant for each thematic area were selected based on their expertise and experience in the thematic areas. The background, history, and neutral description of the current situation, as well as the objective of the consultation, were shared with potential participants prior to the consultation.

Tereza Kasaeva, Director of the WHO Global TB Programme, and Lucica Ditiu, Executive Director of the Stop TB Partnership, opened the consultation, welcomed all meeting participants, and thanked them for their eager interest in the consultation theme.

Clinical perspective

WHO plays a pivotal role in globalizing evidence and ensuring its local application. The WHO Global TB programme regularly synthesizes and reviews research findings and formats them into global policy to guide clinical practice and policy decisions in countries. It is important to remember that it's not just about introducing new medicines; it's about integrating them effectively into existing and developing healthcare systems.



In the last decade, WHO guidance on the treatment of drug-resistant TB has evolved using new trial data of repurposed and novel anti-TB drugs and regimens. The availability of the new evidence has enabled WHO to update treatment guidelines to support the global deployment of the regimens shown to be effective after licensure by stringent regulatory authorities. The regimen that brings probably the most important change in the map of possible treatment options for DR-TB is the BPaLM regimen recommended by WHO in 2022[8].

This regimen becomes a regimen of choice and can be used for a wide majority of patients, including those with HIV coinfection, with the exception of children and adolescents below 14 years of age and pregnant and lactating women. The exception is primarily driven by the lack of evidence on the use of the novel agent in the regimen, pretomanid, in these population groups, and it may take some time to generate relevant evidence to enable the expansion of the current policy.

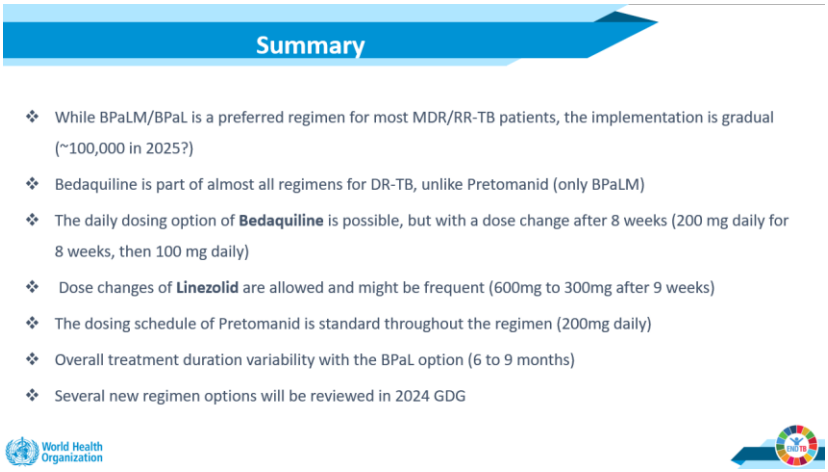
BPaLM is a combination of bedaquiline, pretomanid, linezolid and moxifloxacin. Depending on susceptibility to fluoroquinolones, the BPaLM regimen can be modified from a four- to a three-drug regimen (BPaL). The regimen may use two different approaches for the dosing of bedaquiline, daily and three times per week, as well as different loading and maintenance doses of bedaquiline.

After the initial nine weeks of treatment, due to the complex safety profile of linezolid, the regimen may have a lower 300 mg dose of this medicine with a provision of omitting the drug in less frequent but

[8] WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO

possible cases of serious adverse effects. The duration of the regimen can also vary between 26 and 39 weeks. For the BPaLM regimen, the duration is standardized to 26 weeks, but the BPaL combination can be extended with an additional three months to a total of 39 weeks, depending on the response to the therapy.

Following the WHO recommendation released in December 2022, the use of the BPaLM/BPaL regimen is rapidly increasing. The vigorous uptake by many countries with a sizeable burden of drug-resistant TB will be reflected in the next Global TB report, but the scale of uptake is already evident from the planning reported by the 49 countries to reach close to 100'000 patients in 2025.



While the BPaLM regimen is an important improvement in the array of treatment options that can be used for people suffering from DR-TB, this is only one regimen in the range of tools that are becoming available in addition to the 9-month or longer regimens currently recommended. The evidence on several new regimens, 6- or 9-month long, is expected to be reviewed in the WHO-convened guidelines development group meeting in June 2024.

Patient perspective

The patient perspective, which is the cornerstone of the WHO's principle of person-centered care, was critical in this consultation to help understand patients' treatment preferences, values, and the concerns of affected communities.

The need for shorter and safer oral regimens is undeniable from a patient's perspective. However, it is worth bearing in mind that by focusing on quantity alone, whether it is reduced pill burden, or a reduced duration, to the exclusion of considerations of quality of life and care, we run the risk of not considering the potential tradeoffs or downsides before recommending a regimen, or a combination.

Key considerations to factor in from a patient perspective include:

- Quality over quantity: focus on the overall impact on quality rather than just reducing the pill burden.
- Informed consent: patients should be aware of the pros, cons, and trade-offs.
- Bias: independent, community-led studies are necessary to avoid vested interests.
- Diversity: recognize the varied perspectives and preferences of patients.

- Safety and efficacy: more evidence is needed to confirm the best approach for second-line treatments.
- Flexibility: avoid one-size-fits-all solutions, as treatments often need customization.

Patients need to be given all the relevant information on their treatment options and tradeoffs and asked about their treatment preferences and values. Further, we need to understand that the patient perspective is not a monolith. Different communities and individuals will have varied needs and preferences. A one-size-fits-all approach would not align with person-centered approach to TB care.

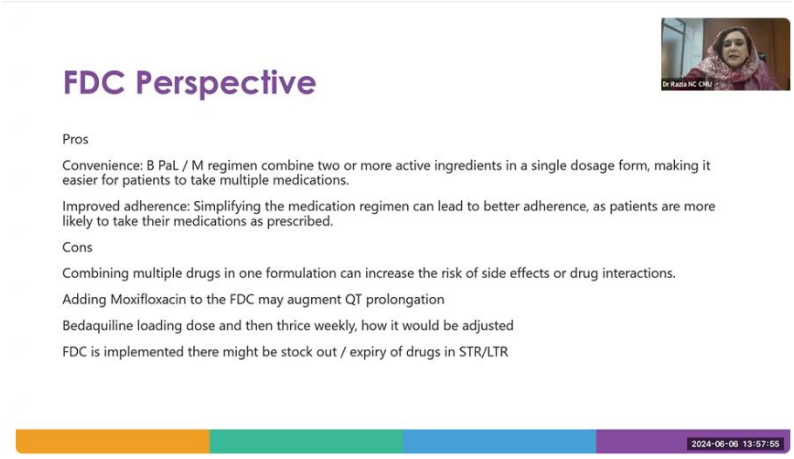
Patient perspectives are crucial in implementing new treatment-related interventions, as they can significantly influence treatment acceptance and success. By incorporating patient insights, healthcare providers can tailor regimens to be more tolerable and easier to follow, improving quality of life, adherence, and outcomes.

At present, from a patient perspective, we do not have enough clinical evidence to justify a shift to FDCs or co-packs in drug-resistant TB treatment, given there are multiple regimens recommended for different patient groups. Further, we do not have evidence of patients' treatment preferences in the case of FDCs or co-packs. To understand what patients want and guard against vested interests influencing their decisions, we need rigorous, independent studies co-led by researchers and affected communities. Additionally, we need safety, efficacy, and quality of life studies for any such intervention before we consider offering it to patients to gauge their preferences. Operational research bearing in mind accessibility implications in programmatic settings is also critical.

In the absence of the above, introducing FDCs and co-packs at this stage in second-line treatment could potentially hamper accessibility and confine patients to their treatment options. It may also limit options for managing adverse events. The introduction of FDCs and co-packs must be considered only when it can be backed by evidence from a clinical and patient perspective.

Country implementation perspective

Different countries have unique approaches and challenges when it comes to the implementation of new medicines. Understanding these diverse perspectives helps in identifying best practices and areas for improvement in the global effort to ensure equitable access to new medicines.



Patient-friendly formulations are always beneficial as they can enhance patient compliance and adherence to the regimen. They also enable healthcare providers to manage the regimen more efficiently. However, there are several pros and cons to consider from an implementation perspective.

The use of well-formulated FDC may lead to shorter acquisition times with product simplification. At the same time, combining multiple drugs in one formulation can increase the risk of adverse effects or drug interactions and make it more difficult to adjust the regimen to avoid those

adverse effects. In theory, combining medicines in a single medicinal form can make it easier and more convenient for patients to take multiple medications, and simplification of the regimen using FDC can lead to better adherence.

The use of the FDC could enhance the potential for decentralizing treatment to smaller, regional units. However, it may complicate adherence to the bedaquiline loading dose and thrice-weekly dosing schedule. While it might reduce acquisition costs and free up resources for other needs, the B-Pa FDC could also lead to stockouts of drugs required for other shorter or longer regimens.

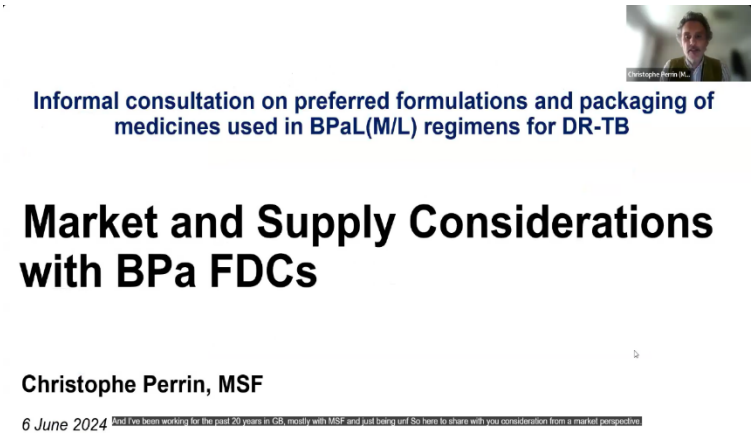
In many countries, people face vulnerabilities such as food insecurity and limited access to education, making it challenging to adhere to medical treatments. When implementing new technologies or treatments, it's crucial to consider their safety, effectiveness, cost, and budget impact. Fixed-dose combinations (FDCs) can simplify daily treatments, improve adherence, and make follow-up easier for patients and their families. From a program perspective, managing FDCs requires fewer resources, potentially making the drugs cheaper and easier to transport. This could free up resources to purchase other medicines for the tuberculosis program. It's important to evaluate the best presentation of medications; for instance, large bottles are difficult to manage for patients needing long-term treatment, whereas smaller FDCs can improve treatment logistics.

While FDCs may benefit the majority of patients, individual drugs will still be needed for specific cases. Fixed combinations are common in treating diseases like HIV, high blood pressure, and diabetes, as they improve the quality of life. We should embrace new medicines and technologies, understanding that they will evolve over time.

Overall, the use of FDCs can offer benefits in terms of convenience and adherence, but it is important to consider the potential drawbacks and have a detailed risk-benefit analysis to determine if the FDC is the best option for the national DR-TB management programmes.

Market perspective

Many LMICs face significant challenges in accessing quality-assured medicines. Issues such as substandard and falsified medicines are prevalent, costing these countries billions annually. Strengthening regulatory systems, improving registration efficiency, and enhancing post-marketing surveillance are critical strategies being employed to address these challenges.



Given that only two Indian generic manufacturers licensed by TB Alliance for the production and supply of pretomanid in LMICs also produce bedaquiline, there is a significant risk of a mono/duopoly for the supply of B-Pa FDCs. This could lead to high FDC prices due to limited competition. With the high global demand for BPaLM/BPaL regimens, there is also a considerable risk of supply disruptions with such a limited number of suppliers.

Since 75% of people affected by DR-TB are eligible for BPaLM/BPaL regimens, further segmenting the bedaquiline market with B-Pa FDCs could shrink the market for single bedaquiline tablets. This could negatively impact the availability and price of bedaquiline for lower-volume regimens (other than BPaLM/BPaL) where it is still needed, as suppliers of quality-assured bedaquiline would face very limited demand. Some countries also expect regulatory challenges for the local registration of B-Pa FDC (e.g., local clinical data are required).

Supply chain perspective

Managing TB medicine supply chains is extremely complex, and involves numerous decisions around medicines' sourcing, procurement, storage, and distribution to ensure that they reach their intended populations. Supply chain management can be simplified for procurers and national TB programmes by reducing the number of stock-keeping units. FDCs and co-packs are potentially two important means to reduce the number of stock-keeping units, especially when the vast majority of people are treated with one standardized regimen. In this context, FDCs and co-packs may help streamline sourcing and stock management by reducing or eliminating the need for single formulations.

For example, the 2RHZE/4RH regimen has been the standard treatment for DS-TB for both adults and children for over 30 years. Initially, 2RHZE/4RH treatment involved multiple tablets daily of up to four separate medicines. The introduction of FDCs simplified this to one FDC for the first two months and one FDC for the next four months. Though it took nearly 20 years for these FDCs to be widely adopted, they effectively replaced the single formulations as nearly every person with DS-TB qualified for this regimen. In this case, the FDCs simplified stock management.

DR-TB treatment regimens are not standardized like DS-TB regimens. People affected by DR-TB will receive different regimens based on several factors (e.g., resistance pattern, age, co-morbidities, etc.). While BPaLM is the initial recommended regimen for people with DR-TB, it is likely that 20-30% of people with DR-TB would not be eligible for BPaLM. Programmes would need to maintain all of the current single formulations needed for DR-TB treatment plus add additional FDCs for BPaLM. An FDC that supported BPaLM would increase the number of products to manage and increase stock management complexity for programmes.

Co-packs have their own challenges. DS-TB kits are co-packs intended to provide all the medicines for the treatment of one person with DS-TB, however they have been adopted by less than 20% of countries. There are a number of reason for this. Co-packs may not meet individual needs and end up being unpacked or repacked, often leading to waste. There are limited suppliers that can make co-packs and managing differing expiration dates within a co-pack complicates inventory management. And, co-packs tend to take up more storage space.

Country programmes need to adjust systems to accommodate additional formulations. Logistics management and TB information systems need to be adjusted. Quantification and forecasting need to be revised to ensure accurate procurement of potential B-Pa FDCs and single formulations. Inaccurate information in any of these systems could contribute to potential shortages of products (single formulations, FDCs or both) either nationally and/or at specific sites (e.g., a site has insufficient single bedaquiline because they started more people on individualized regimens and a B-Pa FDC cannot be used).

Many of the global market challenges would also apply at the country level, particularly in countries that procure using domestic funds and national processes. These include potential monopolies leading to decreased competition and higher prices. Or decreased access to single formulations due to lower volumes of procurement. There may also be national regulatory barriers to FDCs.

In contexts in which adjustments to medicine dose and duration are unlikely, then, FDCs and co-packs do offer advantages in procurement and supply chain operations. However, because of the many dosing and duration issues of the multiple BPaLM components—and because of the large number of people with DR-TB who will continue to require single formulations—B-Pa FDCs or co-packs may potentially increase the number of products managed by pooled procurers and TB programs, disrupt supply chains for critical DR-TB regimen component medicines, and create serious challenges for global TB medicines supply chain stewardship.

Conclusions

Bedaquiline and pretomanid are essential components of the BPaLM regimen. While many individuals with DR-TB will be eligible for this regimen, it won't be suitable for everyone. The BPaLM regimen represents a significant advancement in the treatment options for DR-TB, but it is just one of several emerging tools. In addition to the currently recommended 9-month or longer regimens, new 6- or 9-month regimens are also being considered. The evidence for these new regimens will be reviewed at the WHO guidelines development group meeting in June 2024.

The relatively standard composition of the BPaLM regimen could pave the way for developing fixed-dose combinations (FDCs) of bedaquiline and pretomanid. However, regimen composition and duration can differ, and there are complex dosing requirements (such as daily versus thrice-weekly bedaquiline) along with the need for additional safety data for certain populations. There are several potential issues with FDCs, such as pill size and burden, limited treatment options, accessibility concerns, and possible negative impacts on quality of life. While FDCs may simplify product acquisition, increase decentralization potential, and reduce acquisition costs, their introduction could remove single formulations of pretomanid from the market. This would create new challenges for accessing single formulations of bedaquiline, which are still needed for those not eligible for BPaLM regimens. Additionally, there is a risk of supply monopoly, higher prices, regulatory challenges, and potential supply disruptions for both new FDCs and the single formulation of bedaquiline.

From a supply chain perspective, FDCs simplify stock management only when most people are treated with the same standard regimen, as seen with FDCs for DS-TB treatment. Since DR-TB currently lacks a single standard regimen, introducing FDCs for DR-TB would add more products to manage, alongside the single formulations needed for those who do not qualify for the FDC. This added complexity in stock management increases the risk of wastage and stockouts, making it harder to ensure that people with DR-TB have access to appropriate treatment.

Overall, the emerged consensus from the consultation can be summarized as follows:

- Combining bedaquiline and pretomanid into an FDC could be beneficial in the long term for people affected by DR-TB who qualify for a B-Pa-based regimen. However, this FDC would not support people on other DR-TB regimens.
- The development and introduction of B-Pa FDC should be carefully timed to avoid disrupting the initial uptake phase of new DR-TB treatment regimens.
- Ensuring wide availability, reasonable prices for new medicines, and a vibrant, competitive market with multiple providers are essential prerequisites for developing a suitable FDC.
- Rigorous, independent studies co-led by researchers and affected communities are needed to better understand and document patients' preferences regarding the FDCs and co-packing of medicines for the treatment of drug-resistant TB.

Annex. Pros and Cons analysis.

Perspectives	Pros	Cons
Clinical perspective	Bedaquiline and pretomanid are part of the regimen of choice for the majority of DR-TB patients 14 years of age and above - BPaLM	While bedaquiline is a component in the majority of regimens recommended for the treatment of drug-resistant TB, pretomanid is currently only included in the BPaLM
	BPaLM regimen has a fairly standard composition (with possible variations) that can facilitate the development of a potential partial FDC	Variability in the BPaLM regimen composition, dosing approaches, and duration
	Bedaquiline can be given daily in BPaLM (as all other medicines)	For the BPaLM regimen, there are two possible approaches to the dosing of bedaquiline: daily and thrice weekly. The thrice-weekly approach makes FDC design more complex since all other medicines are dosed daily.
		For both dosing approaches, bedaquiline requires 2 or 4 weeks of loading using a higher dose of the drug and subsequent maintenance with a lower dose.
		There are several current and possible additional regimen alternatives for DR-TB treatment that would not combine bedaquiline and pretomanid.
Patient perspective	Reduced pill burden	Pill burden is not the only parameter, pill size is also important, and FDC may lead to a bigger pill that is difficult to swallow, even for adults.
		B-Pa FDC pill burden reduction must be understood in the context of other tradeoffs and of improving quality of life.
		FDC may limit treatment options for patients
		Potential accessibility implications
		The use of the FDC can potentially negatively impact quality of life by limiting ways to manage AEs.

		This push for FDC in second-line treatments is not evidence-based yet. It cannot be implemented in the absence of evidence and patients' informed choice.
Country implementation perspective	Possible shorter time for acquisitions with product simplification	Combining multiple drugs in one formulation can increase the risk of adverse effects or drug interactions and make it more difficult to adjust the regimen to avoid those adverse effects
	Greater potential for decentralization of treatment to smaller units	The B-Pa FDC may make it difficult to follow the bedaquiline loading dose and thrice weekly dosing approach
	Possibility of reducing acquisition costs and making resources available for other needs	The B-Pa FDC may cause stockouts for drugs needed for the other shorter or longer regimens.
	Simplification of the regimen using FDC can lead to better adherence	
	In theory, combining medicines in a single medicinal form can make it easier and more convenient for patients to take multiple medications.	
Market Perspective		Globally, risk of mono/duopoly for the supply of B-Pa FDCs due to the limited number of suppliers that can make quality-assured versions of the individual medicines. This could limit competition and create higher prices with FDCs. This could also create potential supply security challenges with the limited number of suppliers – more prone to supply disruption.
		The risk that access to single bedaquiline tablets for lower volume regimens (other than BPaLM/BPaL) may be challenged in volume and price if B-Pa FDCs are marketed now
		Regulatory challenges to expect in some countries for local registration of FDCs (e.g., local clinical data required)

		Potential challenges for countries procuring using domestic funding or procurement processes with limited suppliers globally and potentially only a single supplier registered in a country.
Supply chain perspective	The potential reduction of the volume of bedaquiline and pretomanid managed may have a positive impact on the costs of (i.e., freight and in-country storage and distribution), although, this is dependent on the presentations and packaging of the proposed FDCs.	For supply security, more than one B-Pa FDC would be needed and—while a B-Pa FDC might lead to the discontinuation of single pretomanid formulations—all other single medicines required for DR-TB treatment would still need to be maintained for the many people with DR-TB ineligible for BPaL/M/L regimen, including single bedaquiline.
	Co-packs, if designed for the full patient regimen and complete duration, reduce the risk of incomplete regimens being supplied at the service delivery level.	Co-packs for the full regimen will nearly always result in wastage as the dose of linezolid will need to be reduced or held (or both). BPaL/M/L regimens may be used for 6-to-9 months, further complicating a co-pack for a full regimen.
		Introducing BPa FDCs and/or co-packs will lead to an increase in the number of products managed by pooled procurers and TB programs.
		A lack of clarity in country rollout plans and varying levels of country readiness to introduce B-Pa FDCs and/or co-packs may lead to inaccurate quantification data, impact forecasts, and potentially lead to shortages of both bedaquiline and pretomanid at country and global levels.
		Limited competition among suppliers could keep prices higher than they would be with more robust competition, impacting budgets.
		A monopoly on B-Pa FDCs may create challenges in executing national and pooled procurements.
		Managing inventory levels and planning accurate distribution becomes more complex as multiple products of the same molecule are added to existing stock-keeping units.

		The addition of new products to the existing single formulations requires TB programs to adjust their PSM practices.
		Global supply issues may result from B-Pa FDCs and/or co-packs that affect procurers to utilize tools to ration and prioritize medicines to prevent stockouts and ensure countries receive medicines based on immediate need.