Pre-Approval Access to Novel Compounds is an Urgent Priority to Treat People with Strains of Tuberculosis that are Resistant to Bedaquiline, Linezolid, Clofazimine, and/or the Nitroimidazoles

A Statement from The BETTER Project
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Background

Treatment regimens containing bedaquiline, linezolid, clofazimine, and the nitroimidazoles (delamanid or pretomanid) have revolutionized the care of people with rifampicin-resistant forms of tuberculosis (RR-TB), making cure possible for the majority in as short as six months. Strains of TB that have resistance to these newer medications are an emerging problem globally, leaving individuals sick with these forms of TB fighting for their lives with limited treatment options.

At the same time, there are more new TB drugs than ever before in stage 2b or later phases of clinical testing, with much of the development of these products subsidized by public agency and donor investments. These novel compounds need to be made available urgently to save the lives of people with TB that has expanded resistance to bedaquiline, clofazimine, linezolid, and/or the nitroimidazoles (delamanid and pretomanid) and to stop the spread of these resistant strains in the community.

A Way Forward

A group of front-line clinical providers and civil society organizations—including impacted community members—came together to form the "BETTER" Project to share best practices around the management of people with forms of TB that have expanded resistance. Collaborating members of the BETTER Project call for novel TB compounds to be made available urgently and in accordance with the components articulated in the following pages, of equitable and ethical pre-approval access/compassionate use programs required to respond to the rising resistance rates that threaten the lives of people around the world.

What is Expanded Resistance?

Expanded resistance refers to strains of rifampicin-resistant TB with resistance to bedaquiline, linezolid, clofazimine, or the nitroimidazoles.

What does BETTER stand for?

Building Expertise Treating TB with Expanded Resistance

Components of Equitable and Ethical Pre-Approval Access/Compassionate Use Programs:

1. **Free, equitable access to novel TB compounds** through **transparent mechanisms** prior to their regulatory approval but **as soon as early efficacy and safety data** have been demonstrated in the treatment of *M. tuberculosis* in phase 2b or later studies;

2. Access for people with strains of TB that have expanded resistance to these novel compounds **both as single agents and as part of regimens that combine multiple new drugs.** Single drugs cannot be used on their own in failing regimens, and some people with certain strains of expanded resistance may require access to more than one new drug to form an adequate regimen. Other people, however, may only need one new drug to construct an adequate treatment regimen if other approved TB drugs can be given in combination with the single novel medication. Drug sponsors, being private, public or product development partnerships, must collaborate with one another and with front-line providers and people needing treatment to ensure this range of options is available. When more than one novel compound is required to form an adequate regimen, the real risk of poor treatment outcome and/or death must outweigh potential risks stemming from absence of evidence to support concomitant use.

3. Access to these novel compounds must encompass **all drug-resistant forms of TB**, with the drug provided for the duration of therapy recommended by the treating clinicians. Although some new drugs are currently being assessed only for fully drug-susceptible TB as part of shorter regimens (i.e. lasting for 4 months or less), this does not preclude their use in people with drug-resistant TB for longer durations. The new drugs may be of greater benefit to people with drug-resistant forms of TB (compared with susceptible strains) since those individuals have limited treatment options. Unless there is a compelling reason to believe there will be unacceptable toxicity with a higher cumulative exposure, **the new drug should be given for as long as it is deemed necessary** by the front-line provider in consultation with global experts and the person undergoing treatment. Expanded access/compassionate use programs may have the added value that safety and efficacy data can be systematically collected on new drug use beyond the short courses drug developers and trialists are studying. Pre-approval access for people with limited treatment options—alongside to post-marketing surveillance or individual off-label use which may take place after drug registration—is an additional setting in which to better monitor longer durations of the necessary drug. Once a drug has been shown to be effective against *M. tuberculosis*, the maximum duration of therapy for people with TB who have limited treatment options should be determined by attending clinical care providers in discussion with a clinical expert/review committee (see point #5 below) and people receiving treatment through a shared decision-making process that includes **regular monitoring for adverse events**.

4 **All populations must be able to access new drugs, and there are no groups or individuals who should be systematically excluded** from expanded access/ compassionate use programs. This includes (but is not limited to) children/adolescents; pregnant women/people; people who are incarcerated; and people who have substance use disorders. These vulnerable populations are often "protected" from enrolling in research studies since they may be subject to additional risks. When they have forms of TB with expanded resistance, however, the risk-benefit ratio of receiving a new drug once data from phase 2b trials are available must be considered on a person-by-person basis since limited treatment options are available. Prior delays seen with new drugs access for these populations are unacceptable in the current TB landscape. In addition to these groups, people who have had adherence challenges in the past should not be excluded from expanded access/compassionate use programs. Unless there is a clinical indication for hospitalization, **flexible models of service delivery** should also be provided, including community-based care.

5 The decision regarding whether a person qualifies to receive a drug via an expanded access/ compassionate use program should not be made by a drug developer or those working for drug developers. Rather, **an independent body** of clinical providers, civil society organizations, impacted community members, and other relevant specialists should review the clinical files of people needing access to novel compounds via expanded access/compassionate use and make a recommendation on the optimal treatment regimens. **The BETTER Project stands ready to contribute to such clinical review processes** through its medical committee composed of recognized clinical experts in the TB field.

6 People needing access to novel compounds and the TB clinicians and programs requesting them should not have to pay for any part of the expanded access/ compassionate use programs. Rather, **the costs of the drugs as well as the shipping and importation expenses should be covered by the drug developers**. These costs are likely to be minimal in the context of overall drug development and should be planned for in budgeting and grant requests.

7 Systematic and standardized safety, effectiveness, and other **data on the use of new drugs through expanded access/compassionate use programs should be collected, anonymized, and shared** with relevant stakeholders (including product developers and regulatory authorities). Standardized data should also be collected on **resistance to new drugs**, including at baseline and throughout treatment to ensure the drugs are being used in an optimized way that does not drive selection of resistance. This will require access to the drug compounds and sharing of methods for resistance testing. As with bedaquiline, such implementation research will prepare scale-up once the new drug is more widely recommended. Methods for compiling and sharing data and lessons learned should also be explored as part of pre-approval access programs.

8 **Ongoing informed consent** that emphasizes true understanding and **shared decision making** should supersede complicated "one-off" consent forms that were designed to minimize liability for drug developers. Consent must be robust and meaningful and protect vulnerable people living with TB that has expanded resistance. Consent language must clearly explain potential risks but should do so using terminology and a style that is appropriate for people receiving care.

9 Counseling, mental health screening, psychosocial support, nutritional support, and other forms of **socioeconomic support** needed to minimize suffering for people undergoing treatment with new drugs as part of expanded access/compassionate use programs must be provided as an integral part of pre-approval access programs. These services would preferably be funded by the global community and provided by local groups who are trained and paid to provide this essential work.

10 **Pharmacovigilance requirements** for new drugs should build upon the structures and processes that were put into place in TB programs over the past decade (including past experiences gained through previous expanded access/compassionate use programs) rather than creating new systems that are unique to the different drug developers.

Call to Action

Public funds and philanthropic investments in TB drug development have supported the advancement of promising new TB compounds to phase 2b or 2c trials. These drugs must be made available urgently to people with forms of TB that have expanded drug resistance. This is essential not only to save the lives of individuals who are sick with these forms of TB but also to halt the spread of these types of TB in the community. Access to these drugs is imperative and helps fulfill the right of every human being to benefit from scientific progress. The BETTER Project calls for the rapid implementation of the ten components of ethical expanded access/compassionate use programs described above and stands ready to support the global community in supporting access to these new drugs in the pre-approval period.

Selected References

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