

The Global TB Community Advisory Board's (TB CAB) proposed development pathway for regimens to treat extensively drug-resistant tuberculosis

One of the most critical scientific questions in tuberculosis (TB) today is the optimal combination of new and repurposed drugs for the treatment of extensively drug-resistant, pre- extensively drug-resistant, and hard-to-treat multidrug-resistant TB (XDR-TB, pre-XDR-TB, MDR-TB).

Preliminary results from a small, single-arm trial, and the potential to swap in possibly safer and more efficacious medicines from the same class of drugs as those included in that trial, have captured the attention of researchers and donors. As members of the Global TB Community Advisory Board (TB CAB), a group of science-literate, treatment research activists, we have developed the following position regarding the evaluation of regimens for the treatment of XDR-TB in order to influence the direction of discussions ongoing among stakeholders in the TB field.

At present, the most promising regimen for treating XDR-TB is composed of bedaquiline, pretomanid, and linezolid (commonly referred to as the Nix-TB or BPaL regimen) and given for six months, with an extra three months added if participants' sputum is culture-positive at four months.

The Nix-TB regimen is currently undergoing evaluation in a small, single-arm, open-label trial– an acceptable trial design given the length, toxicity, lack of clinical trial evidence, and poor performance of the standard of care for the treatment of pre-XDR and XDR-TB. At the Conference on Retroviruses and Opportunistic Infections (CROI) in February 2017, the TB Alliance reported that of 31 participants who finished six months of follow-up (excluding the four who died in the first eight weeks of treatment), all had culture-converted by four months and only two had relapsed or been re-infected. In addition to the four deaths, 71 percent of patients had at least one linezolid dose interruption.¹ These interim findings demonstrate great promise for the Nix-TB regimen compared to the historical performance of the existing standard of care, which has five-year mortality rates as high as 73 percent.² But they also point to the potential for further improvement, particularly in reducing linezolid toxicity. The TB Alliance is already planning a study to evaluate how to optimize linezolid dosing and duration in the context of the Nix- TB regimen to reduce toxicity without sacrificing efficacy (ZeNix or NC-007).³

Two of the three drugs that make up the Nix-TB regimen have alternative compounds in the same class that have either been approved for the treatment of or shown early signs of efficacy against drug-resistant TB (DR-TB). Pretomanid and delamanid are both nitroimidazoles, and linezolid is in the oxazolidinone class along with sutezolid (a new chemical entity) and tedizolid (approved for acute bacterial skin and skin structure infections). The possibility that replacing pretomanid and/or linezolid with other compounds from their respective classes could produce a regimen that is superior in efficacy or safety (or both) to the Nix-TB regimen begets the need for additional research. Further randomized controlled trials (RCTs) to determine the optimal regimen for the treatment of XDR, pre-XDR and hard-to-treat MDR TB are necessary, as are earlier stage studies to determine which oxazolidinones should advance within these RCTs and at what dose. But there has been a lack of consensus regarding the need for this additional research and the form such trials should take.

Given the preliminary findings from the Nix-TB study and the TB Alliance's plans to register pretomanid for XDR-TB in the context of this regimen, a feasible control arm for future studies in this population exists, and it would no longer be ethical to forego a randomized, controlled trial. An essential requirement of any future study to evaluate novel regimens for the treatment of XDR-TB is the inclusion of a control arm in which patients are treated according to BPaL.

From here, there are several options as to potential experimental arms, whether the trial should be powered for superiority or non-inferiority, whether an adaptive design should be used, and what the primary end-point(s) should be (for example whether the focus should be on cure or safety or both).

Some of the trial design options we have considered as the TB CAB are as follows:

Option 1: A phase III non-inferiority trial comparing:

- bedaquiline, delamanid, sutezolid/tedizolid against
- bedaquiline, pretomanid, linezolid (Nix-TB)

Option 2: A phase III non-inferiority trial comparing:

- bedaquiline, delamanid, sutezolid/tedizolid
- bedaquiline, pretomanid, sutezolid/tedizolid
- bedaquiline, delamanid, linezolid
- bedaquiline, pretomanid, linezolid (Nix-TB)

Option 3: A phase III superiority trial comparing:

- bedaquiline, delamanid, sutezolid/tedizolid
- bedaquiline, pretomanid, sutezolid/tedizolid
- bedaquiline, delamanid, linezolid
- bedaquiline, pretomanid, linezolid (Nix-TB)

Option 4*: A phase IIb/c superiority study comparing:

- bedaquiline, delamanid, sutezolid/tedizolid
- bedaquiline, pretomanid, sutezolid/tedizolid
- bedaquiline, delamanid, linezolid
- bedaquiline, pretomanid, linezolid (Nix-TB)

Our recommendation is for option 3, a single, large phase III trial that will definitively settle the question as to which regimen is preferable both in terms of safety and efficacy. In our view, having one large trial that provides sound and scientifically clear answers is preferable, logical, and more cost-effective to multiple trials that provide less definitive answers. We prefer the more rigorous and definitive superiority design that provides a clearer answer to the most important question for patients and for programs – which regimen is the safest and most effective.

*Option 4 may however have to be followed up by, or expanded into, a phase III trial of the best performing arms. Regimens selected for further evaluation in phase III should demonstrate superiority against the control given that phase IIb/c designs provide investigational regimens for the full course of treatment and use relapse-free cure at 12 months as a primary endpoint. If more than one regimen proves superior to the control in phase IIb/c, they should be compared head to head in phase III.

We stress that superiority should not solely be defined in terms of efficacy – for example in the form of relapse-free cure at 12 months. For patients with XDR-TB, a superior regimen could be one that is safer and more tolerable while preserving similar efficacy. To this end, we would propose a novel primary endpoint. Rather than just relapse-free cure at 12 months post treatment, we propose a composite endpoint based on the number of relapses and severe adverse events (SAEs) reported at 12 months post treatment to ensure that superiority is assigned to the regimen with both the fewest relapses and the fewest SAEs.

The proposed novel primary endpoint is intended to capture and allow for consideration of differences in safety as part of the primary endpoint of interest. If sutezolid or tedizolid is indeed much safer than linezolid, a smaller sample size may still enable the detection of differences between the investigational regimens, even if they perform similarly in terms of efficacy.

In our view, the challenges that come with a larger sample size are outweighed by the massive benefit of, in the process, providing many more people who would alternatively only have poor treatment options, access to new regimens, and gathering more evidence to inform the optimal treatment strategies. It is likely to be some years before many of the drug candidates in question are registered and available in most high burden countries. Given that in the absence of these regimens, mortality rates will remain extremely high, access through the proposed trial is a pre-approval access mechanism through which many patients can access these drugs and the potential for better treatment outcomes. Further, the potential costs of not conducting head-to-head comparisons, such as those we have proposed, must also be considered.

Without a RCT, developing unequivocal normative guidance about treatment in this population will be challenging, if not impossible. Without data to say which regimen is superior, country TB programs, already hesitant to implement new drugs and regimens,⁴ will be empowered to attribute their inertia to a lack of data to inform their decision about which, if any, regimen to roll-out. Additionally, the implementation of multiple regimens, without clear indication for when use of one might be advantageous over another, will further fragment the fragile TB medicines market, likely decreasing country purchasing power, and increasing drug prices and delivery lead times.

One important caveat is that any of the above-proposed trials can only progress with the collection and dissemination of additional longer-term data on sutezolid and tedizolid. At present, too little is known about the efficacy of these drugs for TB, their optimal dose, and the safety of using them for several months to allow use in a larger trial such as the one proposed. At a minimum, two-month dosing and toxicity information on these drugs would be required before the proposed trial could start recruitment.

Any public funding invested in the development of a new or repurposed chemical entity for TB should be conditional upon sponsor commitment that if proven, the drug will be made widely available and accessible, including through rapid registration in all high TB burden countries.

¹ Low, Marcus. The Tuberculosis Treatment Pipeline: A Breakthrough Year for the Treatment of XDR-TB. In: Pipeline Report 2017. Treatment Action Group: New York, July 2017. Available from: <http://www.pipelinereport.org/2017/tbtx>.

² Pietersen E, Ignatius E, Streicher EM, et al. Long-term outcomes of patients with extensively drug-resistant tuberculosis in South Africa: a cohort study. *Lancet*. 2014 April 5; 383 (9924): 1230–1239.

³ Low, Marcus. The Tuberculosis Treatment Pipeline: A Breakthrough Year for the Treatment of XDR-TB. In: Pipeline Report 2017. Treatment Action Group: New York, July 2017. Available from: <http://www.pipelinereport.org/2017/tbtx>.

⁴ Drug-Resistant Tuberculosis Scale-up Treatment Action Team. Country Updates [Internet]. DR-TB STAT, April 2017. Available from: <http://drtb-stat.org/country-updates/>.