# Being heard on all-oral therapy for resistant tuberculosis


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*Lancet Infect Dis* 2022
Published Online
April 28, 2022
https://doi.org/10.1016/S1473-3099(22)00027-5
See Online/Articles
https://doi.org/10.1016/S1473-3099(21)00811-2

Of all the parts of the Sunday service in his little stone church, Pastor Mafukidze (name changed for privacy) liked listening to the choir best of all. Something about all those voices raised together delighted his heart in a way nothing else could. Which is why the high-pitched buzzing sound that developed in his ears only 6 weeks into his treatment for drug-resistant tuberculosis—an early sign of the hearing loss caused by the injectable medication that was part of his therapeutic regimen—filled him with a sense of dread. More than dying, more than the excruciating pain of the daily injection, he feared living a world of perpetual silence. Pastor Mafukidze's story typifies that of tens of thousands of individuals around the world who continue to receive injectable therapy for treatment of drug-resistant tuberculosis. Seeing the devastation this common side-effect caused in his life led him and his health-care providers to join the global fight to end the routine use of these old and unproven agents in the treatment of drug-resistant tuberculosis.

Injectable therapy—including streptomycin, amikacin, kanamycin, or capreomycin—has long been a cornerstone of treatment for drug-resistant tuberculosis.[1] Despite causing hearing loss in as many as 60% of the people who receive them, these medications have been seen as lynchpins in the fight against resistant tuberculosis strains, both as effective drugs and as a means of ensuring adherence to therapy, since they are administered by health-care professionals on a daily basis. Injectable drugs are also one of the parts of drug-resistant tuberculosis treatment that people living with the disease find the most difficult to bear.[2] Their worldwide dominance continues—even with very limited trial evidence to support injectable efficacy—in part fueled by their use in a shorter, 9–12 month regimen.[3] Until 2020, providers and programmes offering services for people living with drug-resistant tuberculosis had the option of either giving a longer 18–24 month regimen that contained the life-saving and hearing-sparing medication bedaquiline instead of the injectable or the shorter 9–12 month injectable regimen daily. Tuberculosis programmes often opted for the shorter (and cheaper) injectable-containing regimen and rarely considered the preferences or perspectives of the people who were living with the disease.[4] The concept that a shorter regimen is better was accepted in the drug-resistant tuberculosis community, ignoring the long-term impact of hearing loss, because this was not a programmatic outcome captured or monitored in tuberculosis programme registers. In fact, formal audiology testing to assess for hearing loss was not even routinely performed in the trial that provided the evidence base for the shorter, injectable-containing regimen.[5]

A vibrant advocacy community based in South Africa, however, ensured that the voices of those living with the disease were heard on the issue of injectable therapy for drug-resistant tuberculosis. After the "Not Deaf or Dead" advocacy campaign launched by TB Proof,[6] the South African National Department of Health began rolling out an all-oral shorter regimen that contained bedaquiline instead of the injectable drug, a bold choice based on the obvious harms associated with continued injectable use.[7] The long-term results of this decision—based in large measure on hearing the needs of drug-resistant tuberculosis survivors—are presented in the paper by Norbert Ndjeka and colleagues[8] in this issue of *The Lancet Infectious Diseases*. The study reports the outcomes of a national cohort of individuals diagnosed with drug-resistant tuberculosis who were treated with a 9–12 month regimen consisting of seven drugs, including an injectable, compared with those who received a 9–12 month regimen consisting of seven drugs in which bedaquiline was given instead of the injectable.

People who received the bedaquiline-containing regimens fared better across all treatment outcomes. Those treated with bedaquiline had a 14% higher rate of treatment success (95% CI 8–20; 69·5% *vs* 56·7%); a 4% lower rate of loss-to-follow-up (1–8; 6·4% *vs* 12·4%); and an 8% lower mortality risk during treatment (4–11; 17·0% *vs* 22·4%), although this mortality difference did not persist when post-treatment outcomes were assessed. Unfortunately, the authors do not present a safety comparison between the two different regimens, a major limitation of the paper given the high rates of toxicity seen with drug-resistant tuberculosis treatment. The study is also limited by the fact that it was observational—although the authors did two sensitivity analyses to control for potential biases—and the fact that people who started on an injectable-containing regimen

but were later switched to a bedaquiline-containing regimen were excluded. Including such patients, however, would probably have further favoured the bedaquiline-containing regimen.

These long-term efficacy results from South Africa should finally stop the routine use of injectable therapy for drug-resistant tuberculosis. In fact, routine use of these medications for resistant tuberculosis should be immediately halted. This welcome move must be implemented without delay, especially since COVID-19 adds additional risk to injectable use, given the routine interaction with the health-care system due to the daily intramuscular application.[9] More work, however, needs to be done to improve upon this relatively acceptable, all-oral treatment option. The South Africa regimen used in the study by Ndjeka and colleagues[8] still has a high daily pill burden, a high rate of mortality, and a lower rate of treatment success than the agreed-upon global goals (success rates >75%) for the treatment of drug-resistant tuberculosis. And while the dangers associated with the daily use of injectables gave the tuberculosis community a clear mandate to find an alternative as quickly as possible, including outside the bounds of randomised controlled trials, further refining of all-oral shorter regimens must now be done using more exacting methods. Several pivotal trials—including the PRACTECAL (NCT02589782) and endTB (NCT02754765) studies—have been doggedly assessing various all-oral, shorter regimens using rigorous designs and control groups.[10] High-quality studies must drive the future of drug-resistant tuberculosis treatment recommendations. What the South Africa experience shows, however, is that listening to the voices of the affected community in the development and implementation of treatment options for drug-resistant tuberculosis is paramount. People like Pastor Mafukidze, who strive so valiantly to become healthy once again, should not fear their lives will be ruined by the very treatment they seek to save them.

We declare no competing interests.

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1 Furin J, Cox H, Pai M. Tuberculosis. *Lancet* 2019; **393:** 1642–56.
2 Almeida A, Adjuntsov M, Bushura W, et al. Hear us! Accounts of people treated with injectables for drug-resistant tuberculosis. *Public Health Action* 2021; **11:** 146–54.
3 Nunn A, Phillips P, Meredith S, et al. A trial of a shorter regimen for rifampicin-resistant tuberculosis. *N Engl J Med* 2019; **380:** 1201–13.
4 Furin J, Loveday M, Hlangu S, et al. "A very humiliating illness": a qualitative study of patient-centered Care for Rifampicin-Resistant Tuberculosis in South Africa. *BMC Public Health* 2020; **20:** 76.
5 Moodley R, Godec T, STREAM Trial Team. Short-course treatment for multidrug-resistant tuberculosis: the STREAm trials. *Eur Respir Rev* 2016; **25:** 29–35.
6 TB Proof. Not deaf or dead: a third choice. https://tbproof.org/all-oral-drug-resistant-tb-treatmen/ (accessed Dec 24, 2021).
7 Schnippel K, Ndjeka N, Maartens G, et al. Effect of bedaquiline on mortality in South African patients with drug-resistant tuberculosis: a retrospective cohort study. *Lancet Respir Med* 2018; **6:** 699–706.
8 Ndjeka N, Campbell JR, Mentjies G, et al. Treatment outcomes 24 months after initiating short, all-oral bedaquiline-containing or injectable-containing rifampicin-resistant tuberculosis treatment regimens in South Africa: a retrospective cohort study. *Lancet Infect Dis* 2022; published online May 2. https://doi.org/10.1016/S1473-3099(21)00811-2.
9 Zimmer AJ, Klinton JS, Oga-Omenka C, et al. Tuberculosis in times of COVID-19. *J Epidemiol Community Health* 2022; **76:** 310–16.
10 McKenna L. 2Pipeline report 2021: tuberculosis treatment. Treatment Action Group. https://www.treatmentactiongroup.org/wp-content/uploads/2021/11/pipeline_TB_Treatment_2021_final.pdf (accessed Dec 24, 2021).