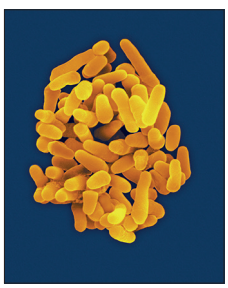
# Equitable, personalised medicine for tuberculosis: treating patients, not diseases

Tuberculosis, an ongoing pandemic, highlights and exacerbates global disparities. With the prevailing model of standardised treatment in vertical health programmes, it is unsurprising that personalised medicine is viewed with caution in tuberculosis control strategies.

Principles of stratified medicine already inform tuberculosis management. Following the British Medical Research Council's clinical trials in the mid-20th century, we have learnt the hard way that effectively curing tuberculosis requires treatment regimens that are adapted to the drug susceptibility pattern of each *Mycobacterium tuberculosis* strain. Nowadays, it is unacceptable to treat rifampicin-susceptible and rifampicin-resistant tuberculosis with a uniform standardised approach. It is also widely agreed that severe extrapulmonary tuberculosis forms, such as meningitis, require tailored treatment. However, beyond these exceptions, tuberculosis treatment generally follows a one size fits all paradigm, which often leaves practitioners with the uneasy feeling of having prescribed the wrong treatment for most patients.

In the last two decades, pioneering clinical research efforts have attempted to address this gap by developing trials that avoid overtreating patients with limited extent of tuberculosis lung disease, with mixed results. A first study of 4-month compared with 6-month treatment in adult patients without lung cavities at baseline and with negative sputum cultures at 2 months was stopped early due to high relapse rates.[1] A second study, aiming to shorten the first-line treatment to 4 months for patients at low risk defined with repeated PET-CT scans, sputum bacterial load, and on-treatment adherence, was unsuccessful.[2] In 2022, however, a similar approach succeeded in establishing the non-inferior efficacy of a 4-month regimen for children with non-severe tuberculosis.[3] During the same time, results of phase 3 trials of treatment shortening for patients with drug-susceptible tuberculosis without stratification became available. These data shed more light on the factors driving relapse, such as extent of tuberculosis lung disease and high sputum bacterial load measured with smear microscopy or cycle threshold GeneXpert values.[4,5] Recently, the endTB-Q trial successfully implemented a novel stratified design, which adapted treatment duration for patients with pre-extensively drug-resistant tuberculosis, defined by resistance to rifampicin and fluoroquinolones, according to disease extent.[6] In this phase 3, randomised, controlled clinical trial, patients with baseline limited extent of tuberculosis lung disease (defined by negative smear, or scanty or 1+ smear without any cavity) and sputum culture conversion at 2 months would receive 6 months of treatment, while others would receive 9 months of treatment. Ongoing trials are looking at similar, stratified approaches to optimise the treatment duration of current standard-of-care regimens for drug-susceptible (SPECTRA-TB) and rifampicin-resistant tuberculosis (NCT06441006) and testing intensified treatment regimens for tuberculosis patients living with advanced HIV (NCT04738812 and NCT04951986).

Personalised medicine, however, goes beyond defining the most appropriate regimen and duration for each patient subgroup: it requires the involvement of people with tuberculosis as active decision makers in their treatment. Multiple treatment options are currently available to both clinicians and patients (table). For drug-susceptible tuberculosis, in addition to the long-standing standard 6-month regimen, a 4-month regimen is recommended.[7] There are even more options for rifampicin-resistant tuberculosis, with four new shorter regimens recently added to the three that were previously recommended.[8] These alternatives are precious as they allow selection of treatment to avert drug–drug interactions, adverse events, intolerances, contraindications, and gaps in drug supply. More importantly, they represent a key opportunity to move towards shared decision making between clinicians and tuberculosis patients.[9] Some people with tuberculosis, for instance, might prefer a longer but better-tolerated treatment regimen—particularly if this regimen allows for reduction of the risk of permanent and debilitating sequelae—or a longer treatment with a reduced pill burden among regimens with similar efficacy.[10] The ultimate, informed choice should lie with the affected individuals.



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| | Composition | Advantages | Opportunities for improvements through personalised medicine | Threats to equity |
|---|---|---|---|---|
| **Drug-susceptible tuberculosis** | | | | |
| Standard regimen | 2 months isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by 4 months isoniazid and rifampicin | Fixed dose combinations available | Intensified treatment for severe HIV-tuberculosis and tuberculosis meningitis | High price of rapid molecular tests |
| 4-month regimen | 2 months isoniazid, rifapentine, pyrazinamide, and moxifloxacin, followed by 2 months isoniazid, rifapentine, and moxifloxacin | Shorter regimen (4 months) | Optimised duration according to tuberculosis severity | High price of rapid molecular tests; limited availability of rifapentine |
| **Rifampicin-resistant tuberculosis** | | | | |
| BPaLM regimen | 6 months bedaquiline, pretomanid, linezolid, and moxifloxacin | Shortest regimen (6 months); low pill burden | Optimised duration according to tuberculosis severity | High price of rapid molecular tests; limited availability of targeted next-generation sequencing or whole genome sequencing and pretomanid |
| BEAT–tuberculosis regimen | 6 months bedaquiline, delamanid, linezolid, and levofloxacin or clofazimine, or both | Possible use in children and pregnant women; shortest regimen (6 months); treatment can be prolonged to 9 months if no response | Treatment duration according to tuberculosis severity in pre-extensively drug-resistant tuberculosis | High price of rapid molecular tests and delamanid; limited availability of targeted next-generation sequencing or whole genome sequencing |
| endTB regimens | Bedaquiline, linezolid, moxifloxacin, and pyrazinamide, or bedaquiline, clofazimine, linezolid, levofloxacin, and pyrazinamide, or bedaquiline, delamanid, linezolid, levofloxacin, and pyrazinamide | Possible use in children and pregnant women; shorter regimen (9 months) | Best approach for pyrazinamide-resistant strains to be defined | High price of rapid molecular tests and delamanid (for bedaquiline, delamanid, linezolid, levofloxacin, and pyrazinamide); limited availability of targeted next-generation sequencing or whole genome sequencing |
| 9-month regimen | 4–6 months bedaquiline, levofloxacin (or moxifloxacin), ethionamide, ethambutol, pyrazinamide, high-dose isoniazid, and clofazimine, followed by 5 months levofloxacin (or moxifloxacin)–clofazimine, pyrazinamide, and ethambutol | Can be used in children and pregnant women*; shorter regimen (9 months); treatment can be prolonged to 11 months if no response | Linezolid can be used to replace ethionamide | High price of rapid molecular tests; limited availability of targeted next-generation sequencing or whole genome sequencing |
| Individualised regimen | At least four effective drugs according to drug susceptibility testing | Only option for severe extrapulmonary and extensive resistance (including extensively drug-resistant tuberculosis); allows for maximum personalisation of treatment | Not applicable | High price of rapid molecular tests; limited availability of targeted next-generation sequencing or whole genome sequencing |

*Use of the 9-month regimen in pregnant women may be considered with the replacement of ethionamide.

***Table:*** **Composition, advantages, future improvements, and equity challenges of available treatment options for tuberculosis**

Finally, personalised medicine requires careful attention to enhance equity. Implementing new tools for decision making and stratified treatment options could deepen inequalities in global health, particularly for socially vulnerable groups. For instance, the 4-month treatment for children is rarely implemented because of the need for chest x-ray to establish non-severe disease. Similarly, inadequate access to rapid molecular tests can potentially increase disparities in access to the best treatment.[11] The price of GeneXpert cartridges, especially those that can determine effectiveness of the historical powerhouse in drug-resistant tuberculosis treatment, fluoroquinolone, is still unacceptably high.[12] Access to advanced diagnostics with the potential to accelerate the detection of resistance to new drugs, such as targeted sequencing, remains limited due to the price and technical challenges. In another example, the 4-month treatment for drug-susceptible tuberculosis is not available in many countries due to the continued high price of rifapentine and the limited scope of marketing authorisation.[13] Use of shorter treatment regimens for rifampicin-resistant tuberculosis is severely restricted by the high price of drugs, in particular delamanid.[14] Personalised approaches will benefit all people with tuberculosis only if access to optimal diagnostics and therapeutics is guaranteed.[15]

Times are changing in the slow-moving world of tuberculosis. As Willliam Osler said, if "the good physician treats the disease, the great physician treats the patient who has the disease".[16] So far, as a tuberculosis community, we have been much better at killing bacteria than at curing individuals affected by this disease. Personalised medicine, shared clinical decision making, and equitable access to innovation will promote successful treatment and fulfilment of the human right to science.

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1 Johnson JL, Hadad DJ, Dietze R, et al. Shortening treatment in adults with noncavitary tuberculosis and 2-month culture conversion. *Am J Respir Crit Care Med* 2009; **180:** 558–63.
2 Malherbe ST, Chen RY, Yu X, et al. PET/CT guided tuberculosis treatment shortening: a randomized trial. *medRxiv* 2024; published online Oct 4. https://doi.org/10.1101/2024.10.03.24314723 (preprint).
3 Turkova A, Wills GH, Wobudeya E, et al. Shorter treatment for nonsevere tuberculosis in African and Indian children. *N Engl J Med* 2022; **386:** 911–22.
4 Imperial MZ, Nahid P, Phillips PPJ, et al. A patient-level pooled analysis of treatment-shortening regimens for drug-susceptible pulmonary tuberculosis. *Nat Med* 2018; **24:** 1708–15.
5 Chang VK, Imperial MZ, Phillips PPJ, et al. Risk-stratified treatment for drug-susceptible pulmonary tuberculosis. *Nat Commun* 2024; **15:** 9400.
6 Patil SB, Tamirat M, Khazhidinov K, et al. Evaluating newly approved drugs in combination regimens for multidrug-resistant tuberculosis with fluoroquinolone resistance (endTB-Q): study protocol for a multi-country randomized controlled trial. *Trials* 2023; **24:** 773.
7 WHO. WHO consolidated guidelines on tuberculosis. Module 4: treatment: drug-susceptible tuberculosis treatment. 2022. https://www.who.int/publications/i/item/9789240048126 (accessed Jan 27, 2025).
8 WHO. Key updates to the treatment of drug-resistant tuberculosis: rapid communication. 2024. https://www.who.int/publications/i/item/B09123 (accessed Jan 27, 2025).
9 Makone A, Angami K, Bhattacharya D, et al. One size does not fit all: community views on choices for TB treatment and prevention. *Public Health Action* 2023; **13:** 67–69.
10 Rucsineanu O, Agbassi P, Herrera R, et al. Shorter TB treatment regimens should be safer as well. *Public Health Action* 2023; **13:** 104–6.
11 Engel N, Ochodo EA, Karanja PW, et al. Rapid molecular tests for tuberculosis and tuberculosis drug resistance: a qualitative evidence synthesis of recipient and provider views. *Cochrane Database Syst Rev* 2022; **4:** CD014877.
12 Access Campaign MSF. Hidden costs: GeneXpert tests and Danaher's delayed audit. https://msfaccess.org/hidden-costs-genexpert-tests-and-danahers-delayed-audit (accessed Jan 9, 2025).
13 Treatment Action Group. An activist's guide to Rifapentine. 2024. https://www.treatmentactiongroup.org/wp-content/uploads/2024/05/rifapentine_guide_2024_final.pdf (accessed Feb 4, 2025).
14 Treatment Action Group. 1/4/6×24 campaign concerned prices hinder uptake of important updated World Health Organization drug-resistant TB treatment recommendations. 2024. https://www.treatmentactiongroup.org/statement/1-4-6x24-campaign-welcomes-updated-world-health-organization-drug-resistant-tb-treatment-recommendations-but-access-concerns-remain. (accessed Jan 9, 2025).
15 Engel N, Apolosi I, Bhargava A, et al. Building social equity and person-centred innovation into the end TB response. *Int J Tuberc Lung Dis* 2024; **28:** 517–20.
16 Barondess JA. Tobias Venner: a 17th century Oslerian prototype. *Pharos Alpha Omega Alpha Honor Med Soc* 2019; **82:** 8–12.