The importance of getting the dose right in the treatment of tuberculosis

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Getting the dose right in the treatment of tuberculosis (TB) is a key tool for safe and effective administration of existing anti-TB drugs and for acceleration of the development of new agents or regimens https://bit.ly/3V4ATyj

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Abstract

Prescribing the optimal combination of anti-tuberculosis drugs at the right dose is a fundamental step to achieve successful treatment outcomes. To aid the decision, clinicians should consider multiple factors, such as body weight, age, results of drug susceptibility testing, risk of intolerance and potential drug–drug interactions. In this viewpoint, we outline different aspects of dose selection in the treatment of tuberculosis (TB) such as traditional pharmacokinetics/pharmacodynamics, population pharmacokinetics models, the importance of real-world evidence and clinical trial design in the development of shorter treatment regimens and the new TB drug pipeline. Therapeutic drug monitoring for rifampicin, linezolid and amikacin may significantly improve their risk–benefit profile promoting their responsible administration. Precision dosing of novel, repurposed or conventional TB drugs should ensure optimal efficacy, while minimising toxicity and the development of resistance.

Introduction

Tuberculosis (TB) claims over a million lives annually, returning this year to being the top infectious cause of death worldwide due to lengthy treatment, poor adherence and the inappropriate use of anti-TB medicines [1]. Since the administration of the first anti-TB agent, streptomycin, in 1944 [2], clinicians have faced many challenges in selecting the correct dose, due to treatment-related adverse events (AEs) and the emergence of resistance. Despite the standard TB regimen achieving an 88% treatment success rate in drug-susceptible (DS)-TB, treatment success is only registered in 68% of patients treated for rifampicin-resistant (RR)-TB [1].

Why dose matters

A classic dose concept was introduced to medicine by Paracelsus: "The dosage alone makes it so a thing is not a poison". As a result, the early stages of antibiotic development mainly focus on a drug candidate's safety, pharmacokinetics (PK) and optimal dose range in healthy volunteers [3].

The traditional approach to dosing anti-TB drugs is weight-based, using the milligram per kilogram across all ages. This approach assumes a linear, rather than allometric, relationship between drug clearance and

body weight, leading to under-dosing in children [4, 5]. Conversely, it may result in over-dosing, such as with isoniazid (H) use in slow *N*-acetyltransferase (NAT2) acetylators. Standard TB treatment involves a 2-month intensive phase with H, rifampicin (R) pyrazinamide (Z) and ethambutol (E), followed by 4 months of HR continuation therapy [6]. However, this treatment strategy neglects the extent of the disease as indicated by the number of acid-fast bacilli observed on sputum microscopy and the radiological pulmonary lesions, and remains a disputed topic among clinicians.

The current TB drug development pipeline contains a variety of new and repurposed drugs aiming to achieve shorter, all-oral regimens for both DS-TB [7] and drug-resistant (DR)-TB [8]. Strategies to reduce treatment length include finding more effective anti-TB drug combinations or boosting the bactericidal activity of regimen components through dose optimisation. For example, using high-dose rifapentine (1200 mg daily) instead of R and replacing E with moxifloxacin (Mfx) for a 4-month treatment of DS-TB was found to be non-inferior to the standard 6-month regimen (2HRZE/4HR) [9]. A similar approach was applied to the 9-month, all-oral regimen for RR-TB where a double-dosage of Mfx (800 mg daily if low-level resistance was documented) and H (600 mg a day) in combination with other drugs halved the length of treatment in eligible patients [10].

The prioritisation of certain anti-TB drugs over others in dose selection should take into account clinical context, including factors contributing to variability in drug efficacy or toxicity such as co-administered antiretroviral therapy (ART), malnutrition, obesity or age [11]. In resource-restricted areas, dose adjustments should be, foremost, accessible for critically ill TB patients (*e.g.* those with TB meningitis).

Pharmacokinetics/pharmacodynamics

PK aims to understand a drug's behaviour in the human body, including its absorption, distribution, metabolism and elimination, while pharmacodynamics (PD) refers to a drug's pharmacological effect on the body [11]. Despite the lungs being well-perfused organs, penetration into fibrotic cavities above the minimal inhibitory concentration is drug-specific. A modelling study examining drugs entering different types of pulmonary lesions in TB patients who underwent lung resection surgery found Mfx and clofazimine achieved higher concentrations in pulmonary tissue compared with plasma. Several other drugs investigated in this study, such as R, Z and linezolid (Lzd), had moderate lesion-focused penetration, while H demonstrated a suboptimal probability of reaching target breakpoints of efficacy [12].

The population pharmacokinetics approach

Population pharmacokinetics (popPK) models use non-linear, mixed-effect methods to describe the PK behaviour and variability of a drug within a population. They evaluate primary PK parameters such as absorption rate, volume of distribution and clearance, adjusting for covariates such as body size, age, sex, nutrition, disease and genetic polymorphisms, while considering inter- and intra-individual variability. The development of popPK models is based on widely accepted standards, applying software packages such as NONMEM or Monolix [13].

Modelling and simulations using popPK models can have a considerable impact. For example, it enabled the development of a joint age- and weight-based approach in the paediatric dosing of bedaquiline (Bdq) and delamanid, accounting for body size and immature cytochrome P450 (CYP450) enzyme functions, which was adopted in World Health Organization (WHO) guidelines before the drug developers provided any dosing advice for younger children [8]. Similarly, a model-based meta-analysis of several trials demonstrated that higher R doses in adults with TB meningitis corresponded to reduced mortality [14]. Advanced PK/PD modelling allows the simultaneous analysis of time–kill curves and protein unbound exposure, as well as the prediction of drug–drug interactions (DDIs) [13].

The role of PK/PD in drug development

Pharmacometrics opens a new era in the investigation of drug candidates using advanced PK/PD model simulations to understand the relationship between dose-exposure-safety and dose-exposure-efficacy [15]. In the Nix-TB trial, 1200 mg of Lzd in combination with pretomanid (Pa) and Bdq for the treatment of DR-TB achieved 90% favourable treatment outcomes, but led to high rates of AEs such as myelosuppression (48%) and peripheral neuropathy (81%) [16]. The ZeNix study, the arm which halved the Lzd dose (600 mg) achieved much lower rates of AEs (2% and 24% with myelosuppression and peripheral neuropathy, respectively) and almost the same favourable treatment outcomes as the arm with a Lzd dose of 1200 mg [17]. Recently, a novel 6-month regimen containing Bdq-Pa-Lzd (600 mg) and/or Mfx (BPaL/M) for programmatic use in the treatment of DR-TB demonstrated comparable treatment efficacy and duration as with treatment of DS-TB [18]. Moreover, the WHO has announced alternative 6- and 9-month, all-oral regimens for DR-TB that are expected to be implemented in early 2025 [19].

Integration of data from various sources drives decision-making at all stages of TB drug development. In phase 1 dose escalation studies, PK/PD inform whether the suggested therapeutic dose is well-tolerated. In phase 2 studies, they provide a basis for establishing exposure–response relationships and dose optimisation. Finally, during phase 3 studies, PK/PD support the evaluation of DDIs in combination therapies [20].

DDIs are common in TB due to the simultaneous management of underlying diseases and comorbidities. Rifampicin interacts with CYP450 enzymes and transporters, and may significantly reduce plasma levels of methadone, impacting adherence in people under opioid substitution treatment or resulting in overdose if abruptly discontinued [21]. The co-administration of Bdq with certain antiretrovirals inhibiting CYP3A4 results in an increased risk of hepatotoxicity and QTc prolongation [22]. Notably, standard ART (bictegravir/emtricitabine/tenofovir alafenamide) and hepatitis C therapy (glecaprevir/pibrentasvir) are well tolerated with the BPaL regimen [23].

The general PD interaction (GPDI) approach may predict outcomes of combination therapy pending clinical outcome readouts. This has allowed dose selection of novel candidates, such as the oxazolidinone TBI-233, a potentially safer alternative to Lzd, along with Bdq and Pa, allowing accelerated development into combination phase 2 trials [24].

Model-informed precision dosing

The conventional "one-size-fits-all" TB treatment strategy involves an identical treatment scheme for patients with the same drug susceptibility test result, irrespective of disease phenotype. Model-based risk stratification studies favour individualised treatment regimens, considering baseline sputum mycobacterial load, extent of lung abnormalities, sex, HIV infection, treatment adherence and clinical improvement [25]. To move away from standardised combinations of anti-TB drugs and programme-centred TB treatment duration, we must encourage clinical trials that consider model-informed precision dosing, pharmacogenomics and the validation of the time to culture conversion or chest radiography as markers of treatment success [26]. Individual drug concentration measurement can be a key part of this process elaborating the balance between tolerability and efficacy of TB treatment.

Therapeutic drug monitoring

Patients with lower than expected clinical treatment responses should be re-evaluated to rule out the acquisition of drug resistance, possible non-adherence or gastrointestinal malabsorption. Furthermore, regular therapeutic drug monitoring (TDM) could help achieve the optimal concentration of anti-TB drugs with a narrow therapeutic index (*i.e.* a slight difference between their effective and toxic doses, for example, cycloserine, Lzd and amikacin) [27]. Point-of-care assays based on mobile ultraviolet spectrophotometry of saliva or urine have been validated for TDM of several anti-TB agents [28]. A practical approach to defining optimal dose ranges would involve considering the area under the 24-h time–concentration curve values (AUC_{24}) as a surrogate marker of reduced bactericidal activity, *e.g.* 25 $mg \cdot h \cdot L^{-1}$ for 600 mg R [29]. The genetic algorithms previously used in cancer chemotherapy can predict the dynamic change between susceptible and resistant bacterial populations [30]. The algorithms generate optimal dosage schedules similar to the current Bdq dose schedule, where the initial high-loading dose of 400 mg once a day for 2 weeks is followed by a tapering dose of 200 mg thrice weekly.

If standard dosage should not apply to all patients, the same principle should be followed with higher dosage. A gap remains to be clarified regarding whether the same approach to dose adjustment can be used in regimens where evidence was collected only for high dosage combinations, such as 1200 mg of rifapentine. Integrating TDM within multi-arm/multi-stage clinical trial designs may be a right step towards individualised TB treatment regimens based on disease severity and patient response.

Conclusion

PK/PD modelling is a crucial mechanism for optimising the dose of available agents and accelerating novel TB drug development. Personalised dose adjustment promotes the responsible use of anti-TB medicines, maximising their safety and efficacy.

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References

1 World Health Organization. Global tuberculosis report 2024. Geneva, World Health Organization, 2024. https://iris.who.int/bitstream/handle/10665/379339/9789240101531-eng.pdf
2 Schatz A, Bugie E, Waksman SA. Streptomycin, a substance exhibiting antibiotic activity against gram-positive and gram-negative bacteria. 1944. *Clin Orthop Relat Res* 2005; 437: 3–6.
3 US Food and Drug Administration. Step 3: Clinical Research. Date last updated: 4 January 2018. www.fda.gov/patients/drug-development-process/step-3-clinical-research
4 Muliaditan M, Della Pasqua O. How long will treatment guidelines for TB continue to overlook variability in drug exposure? *J Antimicrob Chemother* 2019; 74: 3274–3280.
5 Svensson EM, Yngman G, Denti P, *et al.* Evidence-based design of fixed-dose combinations: principles and application to pediatric anti-tuberculosis therapy. *Clin Pharmacokinet* 2018; 57: 591–599.
6 American Thoracic Society. Medical Section of the American Lung Association: Treatment of tuberculosis and tuberculosis infection in adults and children. *Am Rev Respir Dis* 1986; 134: 355–363.
7 World Health Organization. WHO operational handbook on tuberculosis. Module 4: treatment – drug-susceptible tuberculosis treatment. Geneva, World Health Organization, 2022. www.who.int/publications/i/item/9789240050761
8 World Health Organization. WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment, 2022 update. Geneva, World Health Organization, 2022. www.who.int/publications/i/item/9789240063129
9 Dorman SE, Nahid P, Kurbatova EV, *et al.* Four-month rifapentine regimens with or without moxifloxacin for tuberculosis. *N Engl J Med* 2021; 384: 1705–1718.
10 Ndjeka N, Campbell JR, Meintjes 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; 22: 1042–1051.
11 Alffenaar JWC, Stocker SL, Forsman LD, *et al.* Clinical standards for the dosing and management of TB drugs. *Int J Tuberc Lung Dis* 2022; 26: 483–499.
12 Strydom N, Gupta SV, Fox WS, *et al.* Tuberculosis drugs' distribution and emergence of resistance in patient's lung lesions: a mechanistic model and tool for regimen and dose optimization. *PLoS Med* 2019; 16: e1002773.
13 Sturkenboom MGG, Märtson A-G, Svensson EM, *et al.* Population pharmacokinetics and Bayesian dose adjustment to advance TDM of anti-TB drugs. *Clin Pharmacokinet* 2021; 60: 685–710.
14 Svensson EM, Dian S, Te Brake L, *et al.* Model-based meta-analysis of rifampicin exposure and mortality in Indonesian tuberculous meningitis trials. *Clin Infect Dis* 2020; 71: 1817–1823.
15 Usman M, Khadka S, Saleem M, *et al.* Pharmacometrics: a new era of pharmacotherapy and drug development in low- and middle-income countries. *Adv Pharmacol Pharm Sci* 2023; 2023: 3081422.
16 Conradie F, Diacon AH, Ngubane N, *et al.* Treatment of highly drug-resistant pulmonary tuberculosis. *N Engl J Med* 2020; 382: 893–902.
17 Conradie F, Bagdasaryan TR, Borisov S, *et al.* Bedaquiline–pretomanid–linezolid regimens for drug-resistant tuberculosis. *N Engl J Med* 2022; 387: 810–823.
18 Nyang'wa B-T, Berry C, Kazounis E, *et al.* Short oral regimens for pulmonary rifampicin-resistant tuberculosis (TB-PRACTECAL): an open-label, randomised, controlled, phase 2B-3, multi-arm, multicentre, non-inferiority trial. *Lancet Respir Med* 2024; 12: 117–128.
19 World Health Organization. Key updates to the treatment of drug-resistant tuberculosis: rapid communication, June 2024. Geneva, World Health Organization, 2024. https://doi.org/10.2471/B09123
20 Davies G, Boeree M, Hermann D, *et al.* Accelerating the transition of new tuberculosis drug combinations from phase II to phase III trials: new technologies and innovative designs. *PLoS Med* 2019; 16: e1002851.

21 Riccardi N, Canetti D, Rodari P, *et al.* Tuberculosis and pharmacological interactions: a narrative review. *Curr Res Pharmacol Drug Discov* 2020; 2: 100007.

22 Office of AIDS Research, National Institutes of Health. Considerations for antiretroviral use in people with coinfections. Date last updated: 12 September 2024. Date last accessed: 14 October 2024. https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/tuberculosishiv-coinfection

23 Trauth J, Kantelhardt V, Usenko B, *et al.* Bedaquiline, pretomanid and linezolid in multidrug-resistant and pre-extensively drug-resistant tuberculosis in refugees from Ukraine and Somalia in Germany. *Eur Respir J* 2024; 63: 2400303.

24 Strydom N, Ernest JP, Imperial M, *et al.* Dose optimization of TBI-223 for enhanced therapeutic benefit compared to linezolid in antituberculosis regimen. *Nat Commun* 2024; 15: 7311.

25 Imperial MZ, Nahid P, Phillips PPJ. A patient-level pooled analysis of treatment-shortening regimens for drug-susceptible pulmonary tuberculosis. *Nat Med* 2018; 24: 1708–1715.

26 Center for Tuberculosis, University of California San Francisco. Therapeutics trials and pharmacokinetics. Date last accessed: 8 April 2024. https://tb.ucsf.edu/therapeutics-trials-pharmacokinetics

27 World Health Organization. Technical report on the pharmacokinetics and pharmacodynamics (PK/PD) of medicines used in the treatment of drug-resistant tuberculosis. Geneva, World Health Organization, 2018. https://iris.who.int/bitstream/handle/10665/260440/WHO-CDS-TB-2018.6-eng.pdf

28 Kim HY, Ruiter E, Jongedijk EM, *et al.* Saliva-based linezolid monitoring on a mobile UV spectrophotometer. *J Antimicrob Chemother* 2021; 76: 1786–1792.

29 Akkerman OW, Kerstjens HAM, Kingma M, *et al.* Reply to 'Therapeutic drug monitoring for isoniazid and rifampicin exposure'. *Int J Tuberc Lung Dis* 2024; 28: 169–170.

30 Paterson IK, Hoyle A, Ochoa G, *et al.* Optimising antibiotic usage to treat bacterial infections. *Sci Rep* 2016; 6: 37853.