# TDM of Anti-Tuberculosis Medications

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**Scope of the lecture:**
The lecture will discuss the strengths and weaknesses of the current "one size fits all" approach to TB drug dosing. It will review recent pharmacological findings from clinical trials, and how these support the use of individualized dosing of TB drugs.

**Learning objectives:**
1. Actual success rates with the current approach to dosing.
2. Findings from high-dose rifampin and rifapentine studies
3. Practical application of these findings to clinical practice.

**Extended abstract:**
Citation: Peloquin C. 2017. The role of therapeutic drug monitoring in mycobacterial infections. Microbiol Spectrum 5(1):TNMI7-0029- 2016.

Tuberculosis (TB) is a leading cause of infectious death. Nontuberculous mycobacteria (NTM) cause a wide variety of difficult-to-treat infections in various human hosts. Therapeutic drug monitoring (TDM) remains a standard clinical technique that uses plasma drug concentrations to determine dose. The reason to do this is simple: drug exposure (that is, the free drug area under the plasma concentration-time curve) relative to the MIC and not the dose per se largely determines the outcome of the infections. TDM provides objective information that clinician can use to make informed dosing decisions. The normal plasma concentration ranges provide reasonable guidance for initial target concentrations. Clinicians then combine concentration data with knowledge about the patients, in order to decide how aggressive to be with dosing. With sicker patients, who are closer to a poor outcome, one may be willing to accept an increased risk of potential toxicity in order to secure patient survival. In the clinic, time and resources are limited, so typically only two samples are collected postdose. The 2-h postdose concentrations approach the peak for most TB and NTM drugs. A 6-h sample allows the clinician to distinguish between delayed absorption and malabsorption, because patients with the latter need higher doses in order to gain the benefit associated with standard doses. Plasma concentrations do not account for all of the variability in patient responses to TB or NTM treatment, and concentrations cannot guarantee patient outcomes. However, combined with clinical and bacteriological data, TDM can be a decisive tool, allowing clinicians to look inside of their patients and adjust doses based on objective data. Knowing the dose, rather than guessing at the dose, is the path to shorter and more successful treatment regimens.

Citation: Daily Rifapentine for Treatment of Pulmonary Tuberculosis: A Randomized, Dose-Ranging Trial. Susan E. Dorman, Radojka M. Savic, Stefan Goldberg, Jason E. Stout, Neil Schluger, Grace Muzanyi, John L. Johnson, Payam Nahid, Emily J. Hecker, Charles M. Heilig, Lorna Bozeman, Pei-Jean I. Feng, Ruth N. Moro, William MacKenzie, Kelly E. Dooley, Eric L. Nuermberger, Andrew Vernon, Marc Weiner, and the Tuberculosis Trials Consortium. Am J Respir Crit Care Med. 2015; 191: 333–343.

Methods: Adults with sputum smear-positive pulmonary tuberculosis were assigned rifapentine 10, 15, or 20 mg/kg or rifampin 10 mg/kg daily for 8 weeks (intensive phase), with isoniazid, pyrazinamide, and ethambutol. The primary tolerability end point was treatment discontinuation. The primary efficacy end point was negative sputum cultures at completion of intensive phase.

Measurements and Main Results: A total of 334 participants were enrolled. At completion of intensive phase, cultures on solid media were negative in 81.3% of participants in the rifampin group versus 92.5% (P = 0.097), 89.4% (P = 0.29), and 94.7% (P = 0.049) in the rifapentine 10, 15, and 20 mg/kg groups. Liquid cultures were negative in 56.3% (rifampin group) versus 74.6% (P = 0.042), 69.7% (P = 0.16), and 82.5% (P = 0.004), respectively. Compared with the rifampin group, the proportion negative at the end of intensive phase was higher among rifapentine recipients who had high rifapentine areas under the concentration–time curve. Percentages of participants discontinuing assigned treatment for reasons other than microbiologic ineligibility were similar across groups (rifampin, 8.2%; rifapentine 10, 15, or 20 mg/kg, 3.4, 2.5, and 7.4%, respectively).

Conclusions: Daily rifapentine was well-tolerated and safe. High rifapentine exposures were associated with high levels of sputum sterilization at completion of intensive phase. Further studies are warranted to determine if regimens that deliver high rifapentine exposures can shorten treatment duration to less than 6 months. Clinical trial registered with www.clinicaltrials.gov (NCT 00694629).