

Therapeutic Drug Monitoring: The Need for Practical Guidance

TO THE EDITOR—Sekaggya-Wiltshire et al demonstrated in an important observational study in patients coinfecting with tuberculosis and human immunodeficiency virus (N = 268) that time to sputum culture conversion was longer in patients with low drug concentrations [1]. In a similar high-tuberculosis-burden setting in East Africa, we have also found such pharmacokinetic variability to be common and peak concentrations for key drugs to be well below the expected range [2].

In the accompanying editorial, Pasipanodya and Gumbo highlighted the central role of pharmacokinetic variability in determining treatment response, justifying that therapeutic drug monitoring (TDM) is necessary in tuberculosis-endemic settings, and recommended implementation of TDM to detect patients at risk for suboptimal drug exposure [3].

While the first opus of TDM for management of tuberculosis was penned by Peloquin in 2002 [4], few settings routinely employ it in 2018. Clearly, more needs to be done to deliver TDM to patients in most need. We suggest 3 practical steps.

First, it is a logistic and financial challenge to be able to process multiple blood samples to determine serum exposure within a dosing interval using current assays [1] in a programmatic setting. Rapid turnaround time of TDM results conveyed to the bedside is required to make a difference in treatment. Such barriers to care can be overcome with multianalyte assays combining the analysis of drugs in a single test using modern mass spectrometry while developing protocols to streamline specimen collection and delivery to regional laboratories such as the use of dried blood spots [5]. Additionally, some essential drugs [6] are heat stable;

for example, levofloxacin was stable in serum at 50°C for >10 days (data on file, JWC Alffenaar), which would facilitate TDM. We acknowledge that such a patient-centered expansion of services in tuberculosis-endemic settings will require a significant infusion of funding. A “Global TDM Implementation Fund,” we argue, would be in line with the World Health Organization’s (WHO) current End TB Strategy.

Second, just as not all people with tuberculosis are alike, programs will need to prioritize aspects of TDM most fitting to their setting and their patients’ needs (Figure 1). For instance, we believe that development of robust semiquantitative point-of-care tests to distinguish between patients with low or normal/high drug exposure may reduce the need to perform high-performance liquid

chromatography with ultraviolet detection or mass spectrometry. Promising platforms include colorimetric testing of urine and saliva [7, 8].

Third, technical and clinical guidance is urgently needed [5]. Although indications for TDM are clearly mentioned in some guidelines [9], practice has varied where, for instance, at least one state program in the United States routinely performs TDM for all people with tuberculosis and diabetes, human immunodeficiency virus, or those prescribed second-line drugs [10]. The WHO established a task force in 2017 to optimize dosing of antituberculosis drugs based on pharmacokinetic/pharmacodynamic (PK/PD) science [11], and ongoing clinical trials (eg, NCT01918397) will further validate in vitro models, refine existing PK/PD science, and determine optimal drug concentration targets. Yet

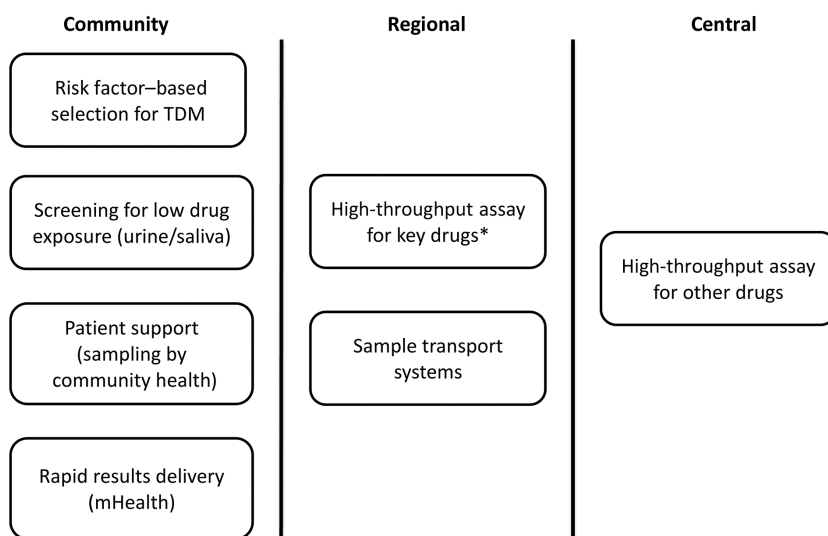


Figure 1. Levels of programmatic therapeutic drug monitoring (TDM). Screening for low drug exposure using semiquantitative assays can be done at the bedside of the patient in the local healthcare facility. Patients with low drug exposure will qualify for a dose increase and TDM of the key drugs by measuring the concentrations in plasma/serum/dried blood spot. These more advanced analytical assays should be made available at a regional level. In addition, some patients may qualify immediately for TDM based on risk factors [9]. For patients with specific needs, TDM for other drugs should be made available at a central level. To reduce sample shipment costs, dried blood spot is the preferred sample material unless the drug has proven to be stable at high temperatures for a prolonged time.

*Key drugs include: isoniazid, rifampicin for drug susceptible tuberculosis and levofloxacin/moxifloxacin, linezolid for multidrug resistant tuberculosis.

in the interim, we urge the WHO to issue guidance on the use of TDM to facilitate uptake and implementation study in tuberculosis-endemic settings.

Note

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Strengthen Village Malaria Reporting to Better Target Reservoirs of Persistent Infections in Southeast Asia

TO THE EDITOR—The recent World Health Organization malaria surveillance, monitoring, and evaluation manual highlights the importance that strengthened community health worker (CHW) programs and their ability to report accurate and timely data hold for the elimination of malaria [1]. Mass Drug Administration (MDA) is proposed as a means of interrupting *Plasmodium falciparum* transmission in areas of emergent, multidrug-resistant parasites [2, 3]. The 2017 World Health Organization recommendations on MDA inform control programs how to implement this strategy, but there is no specific advice on how to target suitable populations in Southeast Asia [4, 5].

Since 2013, we have conducted population-based surveys to define the micro-epidemiology of asymptomatic malaria infections and have piloted MDA in Southeast Asia [6]. Asymptomatic *P. falciparum* infections persist, on average, for several months, with varying parasite densities that are periodically capable of transmission [7]. Our experience is that prevalence surveys are an expensive and time-consuming means of identifying foci of transmission in pre-elimination (low-transmission) settings, particularly where highly-sensitive molecular techniques are used to detect asymptomatic infections. Currently, CHWs are active in

many more villages than could be practicably included in a baseline prevalence survey, but are well positioned—with strengthening of the reporting system where needed—to routinely collect travel and residency data to determine whether individual locations are sources where transmission occurs or sinks where cases are reported but not acquired.

If of sufficient quality, CHW data could be used to identify locations for targeted MDA, such as village clusters where the *P. falciparum* incidence is above a locally-defined threshold. High-quality incidence data has been shown to be predictive of asymptomatic carriage rates in low-transmission settings, thus potentially obviating the need to screen populations using more expensive molecular methods to define targets for MDA [8]. Incidence data determined from reliable case reporting could also be the preferred metric to evaluate the impact of MDA. For example, a recent elimination program in Myanmar demonstrated a rapid decline in the incidence of malaria following the implementation of a strong village malaria worker network, demonstrating the effectiveness of conducting an MDA in a transmission hotspot [9].

In Southeast Asia, asymptomatic *Plasmodium vivax* infections are even more under-detected and undertreated than *P. falciparum* [10]. In our studies, a history of clinical malaria was a consistently strong risk factor for persistent asymptomatic infection. In a prior survey, we matched participants to treatment records and found that approximately a third of people with a history of clinical *P. vivax* were parasitaemic [11]. Therefore, local health services already have recorded the names and locations of thousands of people harboring *P. vivax* infections that contribute to ongoing transmission. These people could be screened for G6PD deficiencies and offered safe treatment with primaquine for radical cures of liver-stage parasites. Targeting persistent *P. vivax* from treatment records alone would neither catch all carriers nor interrupt transmission,