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Understanding pharmacokinetics to improve tuberculosis treatment outcome

Jonathan Reynolds¹ [Research associate] and Scott K Heysell, MD MPH^{†,2} [Assistant Professor]

¹University of Virginia, School of Medicine, PO Box 801340, Charlottesville, VA 22908-1340, USA

²University of Virginia, Infectious Diseases and International Health, PO Box 801340, Charlottesville, VA 22908-1340, USA

Abstract

Introduction—Tuberculosis (TB) remains the leading cause of death from a curable infectious disease; drug-resistant TB threatens to dismantle all prior gains in global control. Suboptimal circulating anti-TB drug concentrations can lead to lack of cure and acquired drug resistance.

Areas covered—This review will introduce pharmacokinetic parameters for key anti-TB drugs, as well as the indications and limitations of measuring these parameters in clinical practice. Current and novel methodologies for delivering anti-TB pharmacokinetic-pharmacodynamic data are highlighted and gaps in operational research described.

Expert opinion—Individual pharmacokinetic variability is commonplace, underappreciated and difficult to predict without therapeutic drug monitoring (TDM). Pharmacokinetic thresholds associated with poor TB treatment outcome in drug-susceptible TB have recently been described and may now guide the application of TDM, but require validation in a variety of settings and comorbidities. Dried blood spots for TDM and prepackaged multidrug plates for minimum inhibitory concentration testing will overcome barriers of accessibility and represent areas for innovation. Operationalizing pharmacokinetics has the potential to improve TB outcomes in the most difficult-to-treat forms of the disease such as multidrug resistance. Clinical studies in these areas are eagerly anticipated and we expect will better define the rational introduction of novel therapeutics.

Keywords

dried blood spot; minimum inhibitory concentration; multidrug-resistant tuberculosis; pharmacokinetics; therapeutic drug monitoring; tuberculosis

Declaration of interest

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1. Introduction

In the past two decades, major progress has been made globally in reducing cases of tuberculosis (TB) and TB-related deaths, yet considerable work remains. TB is the leading cause of death from a curable infectious disease, and is second only to HIV/AIDS as a cause of death from any infectious disease. In 2011, there were an estimated 8.7 million new cases of TB and 1.4 million deaths from TB [1]. While cure rates can be high for drug-susceptible TB with appropriate multidrug therapy and when given in supervised treatment settings, success rates can drop as low as 65% in less-resourced areas [1,2].

Among the multitude of systemic contributors, treatment failure can result from drug resistance prior to initiation of therapy (primary drug resistance) and drug resistance developing while on therapy (acquired drug resistance). Novel and rapid drug-susceptibility testing has targeted primary drug resistance, but acquired resistance was thought almost exclusively to be the result of patient nonadherence or programmatic barriers to receipt of guideline-endorsed multidrug regimens. While implementation of directly observed therapy in certain TB endemic settings improved adherence with TB treatment, relapse and acquired drug resistance were not entirely eliminated [3,4]. Recently, however, suboptimal drug concentrations, due to individual pharmacokinetic variability and independent of nonadherence, have been associated with acquired drug resistance in *in vitro* models [5,6]. Even more definitively, they have been associated with poor outcome in prospective patient cohorts [5,7,8]. This concept cannot be overstated as the majority of all TB cases in endemic settings are treated with empiric weight-based regimens, often in fixed-dose combination and without the benefit of pharmacokinetic monitoring.

The consequences of treatment failure and amplified drug resistance can be devastating for both patient and public health. Quite simply, drug-resistant TB threatens to eliminate all gains made in global TB control [9]. Multidrug-resistant (MDR)-TB is now estimated in 3.7% of new cases and 20% of previously treated cases worldwide, and by definition, is resistant to the two most potent anti-TB medications, isoniazid and rifampin [1]. Furthermore, approximately 9% of all MDR-TB cases are categorized as extensively drug-resistant (XDR)-TB with additional resistance to a fluoroquinolone and an injectable agent (kanamycin, amikacin or capreomycin). The so-called 'second-line' drugs used in the treatment of drug-resistant TB are of greater cost, less potency and increased toxicity [10]. While treatment duration is typically 6 months for drug-susceptible TB, already a burdensome duration for many patients and TB programs, treatment of MDR-TB can last more than 20 months. As such, global success rates for treatment of MDR-TB and XDR-TB are estimated at 48 and 33%, respectively [1].

Such dismal outcomes represent the end result of a considerable personal and financial toll on patient, community and the governmental TB program. Where such estimates are calculable in the European Union in 2011, for instance, the economic loss for care of drug-resistant TB in disability-adjusted life years was 10 times greater than the treatment cost itself [11]. Consequently, optimization of existing drug regimens for TB would carry tremendous downstream benefit if even modestly associated with improved treatment outcome or shortened treatment duration. Therefore, the following review will provide an

introduction to standard pharmacokinetic parameters for critical anti-TB drugs, the clinical application and limitations of therapeutic drug concentration monitoring for TB, and discussion of specific settings, patient populations and anatomic disease sites that may influence this application. Opportunities of operational research and technological innovation are highlighted.

2. Pharmacokinetic and pharmacodynamic principles in TB treatment

Incidentally, the first anti-TB drug, streptomycin, played a key role in the foundational pharmacokinetic–pharmacodynamic experiments of Dr. Harry Eagle, and was demonstrated to kill in a concentration-dependent manner compared to penicillin, which was time dependent in activity [12,13]. Today, the most common pharmacokinetic–pharmacodynamic measures used to describe antibacterial agents, including those with anti-TB activity, are the duration of time a drug concentration remains above the minimum inhibitory concentration ($T > MIC$), the ratio of the peak drug concentration relative to the MIC (C_{max}/MIC) and the ratio of the area under the concentration–time curve at the end of the dosing interval relative to the MIC (AUC_{0-24}/MIC) [14].

Unconventionally, however, TB drug-susceptibility testing in clinical laboratories differs from that of nearly any other infectious disease where MICs are determined by dilution schemes [15]. In contrast, most TB susceptibility testing is performed with a version of the proportion method where equal amounts of organism are inoculated on plates or in liquid media with and without a single ‘critical’ concentration of drug. Prior studies to determine the single critical concentration have used a midpoint concentration between the lowest MICs of known resistant strains and the highest MIC of known wild-type strains, where the clinical outcome is well described [16-18]. Yet this method does not allow for accurate individual pharmacokinetic–pharmacodynamic assessment. Commercially available MIC plates for *Mycobacterium tuberculosis* are now available and may ultimately facilitate pharmacokinetic–pharmacodynamic testing for TB patients outside the research setting (Figure 1) [19-21]. Nevertheless, MIC remains a static parameter and like all phenotypic susceptibility testing for TB measures only the dominant subpopulation of infecting *M. tuberculosis* cultured from the specimen.

Given that the clinical response to anti-TB treatment can take weeks to months to become apparent and adequate assessment of relapse-free cure may span years, early bactericidal studies in humans (measuring the decrement of bacteria growing in serially collected sputum from patients with pulmonary TB) as well as *in vitro* and animal models have played a growing role in determining anti-TB drug dosing and new drug development. Population-based statistical application, such as Monte Carlo simulation, has further allowed the integration of human pharmacokinetic data into models of large patient cohorts that otherwise could not be easily studied [22]. Additionally, novel multiple arm and multiple dosing strategies for TB clinical trials have been advocated for new drug assessment [23,24].

3. Anti-TB parameters

The bulk of pharmacokinetic–pharmacodynamic studies have focused on the first-line medications to treat drug-susceptible TB (Table 1) [7,24]. The majority of the best-studied

agents, including rifampin, isoniazid, ethambutol and pyrazinamide, as well as the fluoroquinolones, have been shown to be concentration dependent in activity [25-29]. This effect was first seen in a guinea pig model for isoniazid in 1968, and was later confirmed in the modern pharmacokinetic–pharmacodynamic era in a murine model in 2004 and using the *in vitro* hollow fiber system (HFS) in 2007 [30-32]. The data for rifampin follow a similar trend, with guinea pig and murine models showing its concentration-dependent activity as early as 1969, and modern murine and HFS models confirming the link between its activity and the AUC/MIC ratio [33-36]. This is true for both bacterial killing [34] as well as prevention of resistance, which was calculated to occur at $C_{\max}/MIC > 175$ [35]. For rifampin in particular, the C_{\max} correlates well with AUC and may serve as a functional proxy [36]. Importantly, however, the standard rifampin dose for TB treatment, 10 mg/kg, was chosen in 1971 without a dose escalation study. Yet, a recent trial has found doses as high as 35 mg/kg as tolerable and bactericidal activity remains linear with dose escalation, and thus rifampin may be uniquely suitable for dose optimization to shorten total treatment duration [37]. Preclinical models of novel drug development seeking combination with rifampin must therefore view these more aggressive dosing strategies as presaging the norm.

One recent study marks the first prospective effort to date that rigorously defines the pharmacokinetic thresholds associated with treatment failure in the first-line treatment of drug-susceptible TB [7]. A landmark investigation to disentangle the multiplicity of contributors to TB treatment failure, the study of 142 adults with TB from the Western Cape in South Africa found the top three independent predictors of poor long-term outcome to be AUC of pyrazinamide, rifampin and isoniazid in decreasing order of predictive magnitude. Secondary analysis allowed threshold values to be set whereby patients with an AUC of at least one drug below the threshold were over-whelmingly more likely to have a poor outcome (odds rate 14.14; 95% confidence interval 4.08 – 49.08) compared to patients with an AUC for each drug above the threshold (Table 1). Furthermore, the study clearly demonstrated that an individual’s pharmacokinetic variability was not able to be predicted by easily measurable factors, asserting the clinical relevance of individual drug concentration monitoring. It remains to be studied whether these findings are replicable in other settings or among patients with other comorbidities, and if similar pharmacokinetic thresholds can be established for key second-line drugs within the MDR-TB regimen.

Of the second-line TB agents, the fluoroquinolones have been subjected to rigorous testing, and like their first-line counterparts show concentration-dependent killing exemplified by AUC/MIC in murine models, HFS and human studies [38-42]. Though less so than rifampin, C_{\max} and AUC track reasonably well for the fluoroquinolones, covary over fixed doses and intervals, and C_{\max} alone has been used for clinical action regarding dose adjustment [38]. Notably, the fluoroquinolones have also exhibited considerable pharmacokinetic variability when tested in TB-infected human cohorts [43]. For instance, in a study of ofloxacin pharmacokinetics from South Africa, only 45% of patients reached target AUC/MIC, and for all those with an isolate harboring an increased MIC of 2.0 $\mu\text{g/ml}$, but still considered within the conventional susceptible range, 0% reached the target [44]. Given these observations and that fluoroquinolone anti-TB activity is not consistent across the class, the fluoroquinolones may be particularly applicable for pharmacokinetic

monitoring and dose optimization in the treatment of MDR-TB [44,45]. Less is known about the pharmacokinetic–pharmacodynamic parameters of other second-line drugs in TB-specific treatment settings, and has instead been extrapolated from non-TB models [46]. Linezolid, and the recently FDA-approved diarylquinoline, bedaquiline, are exceptions, given their comparatively recent introduction [47,48]. In an early bactericidal study in human TB, linezolid activity was linear at AUC/MIC values up to 120, but the correlation was diminished once $T > MIC$ reached 100% [49]. Both animal and human data on bedaquiline support time-dependent bactericidal activity with a rather delayed onset of action [50].

4. Therapeutic drug concentration monitoring in practice and emerging methods to optimize treatment

The clinical application of drug concentration monitoring and adjustment of drug dosages in individual patients, termed therapeutic drug monitoring (TDM), has been employed regularly by specialized TB treatment centers [51]. The C_{max} is practically targeted for TDM for many of the key first-line drugs, and can be closely approximated by a 2- and 6-h post-dose blood draw. Many of the first-line drugs reach peak concentrations within 1 – 3 h of administration, yet the 6-h blood draw can help distinguish between delayed absorption and malabsorption among those patients with abnormal 2-h concentrations. Blood is centrifuged after it is drawn, and the serum is immediately frozen. Methods differ for each drug but commonly utilize high-performance liquid chromatography, gas chromatography or, more recently, tandem mass spectrometry for determining serum concentrations. Consequently, drug concentration analysis is usually performed by experienced laboratories, in relatively few settings worldwide. Even in settings with access to specialized laboratories, overall cost including serum transport and logistical coordination has limited more widespread uptake. Furthermore, concentrations below the expected range for key drugs in the anti-TB regimen have been found in patients responding well to treatment [10,52], and even more refined means of interpreting TDM results may evolve, such as measuring plasma protein binding of the drugs in question [53]. Thus, some large governmental programs have sought guidance for the strategic selection of patients that would benefit most from TDM.

The application of dried blood spot (DBS) analysis instead of serum analysis may ultimately overcome the obstacle of specimen storage and transport [54]. For DBS analysis, blood is obtained by single-use lancing devices and dropped directly on DBS paper, generally cellulose- or a cotton-based filter. The paper is left to dry at room temperature and then stored in a plastic bag with desiccant packages. The samples can be sent to outside laboratories using normal postal systems without the need for special mailing cartons or preservation of the cold chain. Once received by the laboratory, a disc of uniform size is punched from the paper and subjected to solvent extraction with subsequent drug quantification through standard means [55]. The lower blood volume required for DBS reduces its biohazardous risk compared to conventional serum sampling and makes it more applicable to pediatric populations. A recent study using second-line drugs for MDR-TB found little variation with ranges of hematocrit between 20 and 50% and acceptable

correlation between whole blood and plasma values by calculable conversion factors from the geometric mean DBS/plasma concentration ratios [56]. The stability in DBS does vary from drug to drug, depending on temperature ranges [54]; hence, further study is needed to refine drug-specific protocols.

Other TB bioassays provide functional pharmacodynamic information without the use of chromatography or mass spectrometry and have utilized TB culture accessible in many mycobacteriology laboratories worldwide. Wallis *et al.* developed a method of performing culture of *M. tuberculosis* with a subject's whole blood while on TB therapy to quantify the predominately intracellular bactericidal activity of a drug individually, or in a combination regimen [57]. Given the bactericidal activity observed for common drugs in whole blood culture closely approximated that observed in clinic practice, and total bactericidal activity correlated with two-month sputum culture conversion in subjects on a drug-susceptible TB regimen, whole blood culture has been proposed as a functional biomarker and continues to be used in new drug development [58-60]. Others have constrained similar analysis to plasma and employed the patient's own *M. tuberculosis* isolate, finding significant correlation with drug concentrations for isoniazid and rifampin in a drug-susceptible TB regimen [61]. The plasma drug activity assay has also been applied to subjects with MDR-TB in Tanzania, and it was found that subjects with the worst plasma drug activity against their *M. tuberculosis* isolate had significantly lower kanamycin C_{max}/MIC [43]. While lacking the precision of individual drug concentration and MIC information, plasma drug activity is being considered for use in stratifying MDR-TB patients for early hospital discharge and decentralized management. In addition to ensuring adequate drug exposure, methods are being designed to limit toxicity. Approaches include CY450 enzyme activity and hERG gene channel pathway assessment used in the evaluation of new anti-TB compounds [62].

5. Pharmacokinetics of TB drugs in special populations

5.1 HIV

Of the 8.8 million incident cases of TB in 2010, 1.1 million were infected with HIV and at risk for shortened survival and higher rates of TB recurrence compared to TB patients without HIV [63-65]. In a cohort of TB patients from Botswana, the majority HIV infected, those with low pyrazinamide peak concentrations were 3 times more likely to have poor TB treatment outcome even when adjusting for HIV infection [8]. Furthermore, low rifampin concentrations were so common, found in 84%, that differences in outcome may have been difficult to appreciate in dichotomous analysis. Additionally, the increased number of medications required for both diseases early in the course of TB therapy [66-69] may lead to drug toxicity or poor adherence that further limits treatment success. Independent of drug interactions, TB drugs may be improperly absorbed in HIV patients with various forms of enteropathy [70-72]. This may be particularly problematic for rifampin in which absorption is dependent upon both gut permeability and solubility, the latter affected by both pH and gut transit time [73]. Indeed, HIV patients with $CD4 < 100$ on intermittent (twice or thrice weekly regimens) in the clinical trial setting have shown increased rates of acquired resistance to the rifamycins, explained by poor exposure (as marked by AUC_{0-24}) to the

study drug of rifabutin, but also isoniazid, and for these reasons daily dosing is recommended [74,75].

HIV-related TB also presents the paradoxical problem that rifampin is a potent CYP450 inducer, limiting the role of key antiretrovirals such as protease inhibitors and some non-nucleoside reverse transcriptase inhibitors (NNRTIs) that are heavily metabolized through this system [76]. Unfortunately, HIV patients treated with rifamycin sparing anti-TB regimens have been shown to have worse outcomes [77]. Of the NNRTI class, efavirenz, at standard doses, has been shown to be effective in patients treated with rifampin without compromise of HIV virological suppression [78,79]. Yet while rifampin induces CYP2B6, isoniazid also inhibits a secondary pathway of CYP2A6-related metabolism and may actually increase efavirenz concentrations during TB treatment in those patients with a slow CYP2B6 metabolizer genotype, thereby risking efavirenz-related toxicity [80,81]. Rifabutin, a much less potent inducer, may be used in replacement of rifampin, but when employed in combination with protease inhibitor-based antiretroviral regimens plasma concentrations of rifabutin are increased due to protease inhibitor inhibition of CYP3A4 necessitating considerable dose reduction [82-84]. Thus, for these complex interactions and to balance efficacy and toxicity, HIV-infected TB patients represent an ideal population for operational research in TDM-directed management.

5.2 Diabetes mellitus

Diabetes is a risk factor for TB infection and progression to active disease with the largest meta-analysis to date concluding that diabetics were 3.1 times more likely than non-diabetics to develop active TB [85-88]. Furthermore, diabetic patients have been shown to have higher rates of treatment failure and death [89-91]. Concentrations of isoniazid and rifampin below the expected range are commonly found in TB patients with diabetes, and in some studies diabetes has been independently associated with decreased serum concentrations of rifampin [92,93]. In settings where TDM is routinely practiced, some TB programs have elected to check drug concentrations early in the course of therapy in all diabetics [94]. In one such initiative, 76% of all diabetics had peak concentrations of isoniazid, rifampin or both medications below the expected range that were then corrected with a single dose increase [94]. Other means of regimen intensification or extended duration of anti-TB treatment have yet to be prospectively studied in diabetic patients, and no consensus recommendations for treatment modification currently exist. Therefore, as the incidence of diabetic-related TB is anticipated to rise, we expect considerable new study in this subpopulation [95].

5.3 Pediatrics

Pediatric TB is estimated at 500,000 cases annually contributing to 64,000 deaths among children in 2011 [1]. Pediatric patients metabolize drugs differently than adults, most notably evidenced by the more rapid metabolism of isoniazid and the subsequently higher mg/kg dose requirement [96]. Host genetic predisposition for the rate of isoniazid metabolism can be predicted by polymorphisms in the *N*-acetyltransferase 2 gene responsible for acetylation, but can more functionally be measured by the serum isoniazid and acetyl-isoniazid fraction [96]. Additionally, lower anti-TB drug concentrations have

been found in malnourished children compared to those without malnourishment. As in adults, children with TB and HIV are also at risk for suboptimal drug exposure [97,98]. We expect an expansion of pharmacokinetic data in pediatric TB patients given requests for this study from WHO and other international advocacy groups and that evaluation of novel anti-TB drugs in pediatric patients is now a prerequisite for approval in the US and Europe [99-101]. Innovation in this setting is not only expected to center on novel compounds but also on pediatric friendly preparations and optimal dose combinations.

5.4 Extrapulmonary TB

Despite mainly infecting the lung, TB can affect any organ of the body, and does so with increased frequency in pediatric and HIV-infected populations [102]. While treatment of most forms of extrapulmonary TB (EPTB) does not differ from pulmonary TB, meningitis and bone/joint disease may require a longer duration, and TB meningitis in particular carries considerable morbidity and mortality [103]. Given anatomic barriers to drug penetration, these forms of EPTB may be apt for study of dose optimization.

For instance, studies of cerebrospinal fluid concentrations of anti-TB drugs show good penetration of isoniazid, but relatively poor penetration of rifampin, which is larger, more protein bound, and susceptible to alteration in membrane drug transporters. Consequently, rifampin rarely exceeds the MIC at standard doses [104]. Despite this, higher-dose rifampin for TB meningitis has not been formally recommended. Yet a recent study of adults with TB meningitis in Indonesia found lower cerebrospinal fluid than plasma concentrations of rifampin and those treated with higher-dose intravenous rifampin during the first 2 weeks of therapy had significantly lower 6-month mortality (35 vs 65%) than patients treated with standard-dose rifampin [105]. No increase in adverse effects was seen with increased dosages of rifampin. Given the high early mortality of TB meningitis in resource-limited settings, these patients may represent a subpopulation for an empiric higher dose of rifampin, followed by the application of DBS for dose adjustment. Similar to the ongoing trials of higher-dose rifampin to shorten the treatment duration for pulmonary TB, we anticipate a growing body of studies to inform the optimal dosing of rifampin and the later-generation fluoroquinolones in the treatment of TB meningitis.

6. Conclusion

Individual pharmacokinetic variability is far more common than previously understood and contributes to poor TB outcomes independent of adherence. Yet such pharmacokinetic variability has proven difficult to predict without TDM. Application of pharmacokinetic data has thus far been limited to experienced treatment centers, but may become increasingly accessible by means of DBS. Incorporation of TDM with the MIC from an individual patient's *M. tuberculosis* isolate may be particularly beneficial for second-line drugs used in the treatment of drug-resistant TB. These applications require operational research in patients at high risk of poor treatment outcome. Doing so will better inform new drug development because unlike many other infectious diseases, TB is treated not with a single drug, but rather a complex multidrug regimen.

7. Expert opinion

Initially, we anticipate considerable operational research to validate the pharmacokinetic thresholds associated with poor TB treatment outcome in drug-susceptible TB, and determination if similar thresholds can be established for key second-line drugs in the MDR-TB regimen. In TB endemic settings, the vast majority of TB treatment is delivered by governmental or non-governmental organizations with poorly funded mandates from local health ministries informed by international or national guidelines. Resource constraint in these settings does not favor individualized management. Yet if validation studies continue to demonstrate that pharmacokinetic variability contributes as significantly to TB outcome as has been found in the work of Pasipanodya *et al.* in South Africa [7], then resource-constrained organizations and guiding bodies will be compelled to redefine empiric dosing or critical concentrations for drug resistance, or rather adopt a degree of individualized management in the form of applied pharmacokinetics (Figure 2). Each approach carries consequence for innovation and novel drug development.

For instance, we may predict given the encouraging clinical trial results in higher-dose rifampin that empiric dose increase will eventually become standard practice for drug-susceptible pulmonary TB and TB meningitis, and may therefore lessen the need for individual TDM in that setting. TB programs may ultimately opt for individualized management in only specialized scenarios, limiting the market for innovative improvement in TDM delivery. Yet we agree with others that MDR-TB may represent an emerging niche [106,107]. Certainly TDM of plasma may not reflect drug concentrations at the site of infection, yet recent reports of correlative plasma concentrations of MDR-TB drugs with concentrations from pathologic specimens of affected lung are encouraging [106]. Furthermore, molecular diagnostics for *M. tuberculosis* drugresistance mutations will be more extensively informed by deeper sequencing methods and individual mutations may become increasingly precise in predicting quantitative change in MIC. In this scenario, we could anticipate TDM results for key MDR-TB drugs to be used in concert with rapid quantitative susceptibility in order to guide therapeutic decisions at the bedside. Regardless, rigorously performed studies of currently available second-line drug pharmacokinetics will better define the rational introduction of novel therapeutics.

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highlights

- Tuberculosis (TB) is responsible for approximately 1.4 million deaths per year, the leading cause of death from a curable infectious disease worldwide.
- Individual pharmacokinetic variability is underappreciated and can lead to poor long-term treatment outcome including relapse and acquired drug resistance.
- Threshold pharmacokinetic parameters associated with poor treatment outcome will guide further validation across diverse patient populations and comorbidities, and will be sought for second-line drugs used in the treatment of multidrug-resistant (MDR)-TB.
- Therapeutic drug monitoring (TDM) is the most accurate means of assessing individual pharmacokinetic variability but is inaccessible in most TB endemic settings.
- Optimizing treatment regimens based on individual pharmacokinetics in TB endemic settings may become more realizable with dried blood spot TDM and commercialized MIC plates – areas of innovative opportunity – but uptake will be tempered by programmatic unfamiliarity with individualized management.
- A relative explosion of pharmacokinetic research is anticipated in special populations including MDR-TB and those at higher risk of poor treatment outcome and should inform new drug development and application.

This box summarizes key points contained in the article.

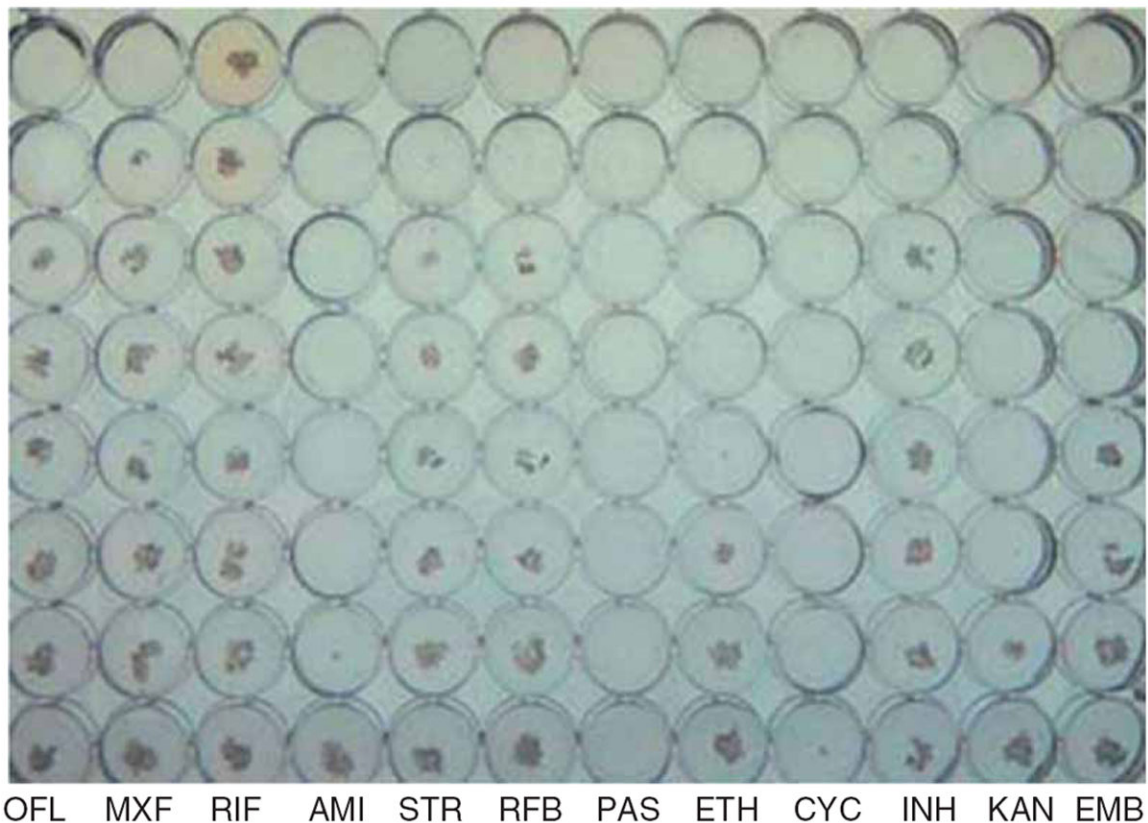


Figure 1. TREK MYCOTB Sensititre plate of a multidrug-resistant isolate

Each column contains prefilled wells of lyophilized drugs of increasing (from bottom to top) concentration. Shelf-life is 2 years at room temperature. Standardized inoculum of a patient's *Mycobacterium tuberculosis* in liquid media is added to each well and can be read manually at set growth intervals thereby allowing MIC interpretation. Photo courtesy of Prof. Eric Houpt, University of Virginia.

AMI: Amikacin; CYC: Cycloserine; EMB: Ethambutol; ETH: Ethionamide; INH: Isoniazid; KAN: Kanamycin; MXF: Moxifloxacin; OFL: Ofloxacin; PAS: Para-aminosalicylic acid; RFB: Rifabutin; RIF: Rifampin; STR: Streptomycin.

Scenarios for operational research in optimizing anti-TB pharmacokinetics in resource-limited settings

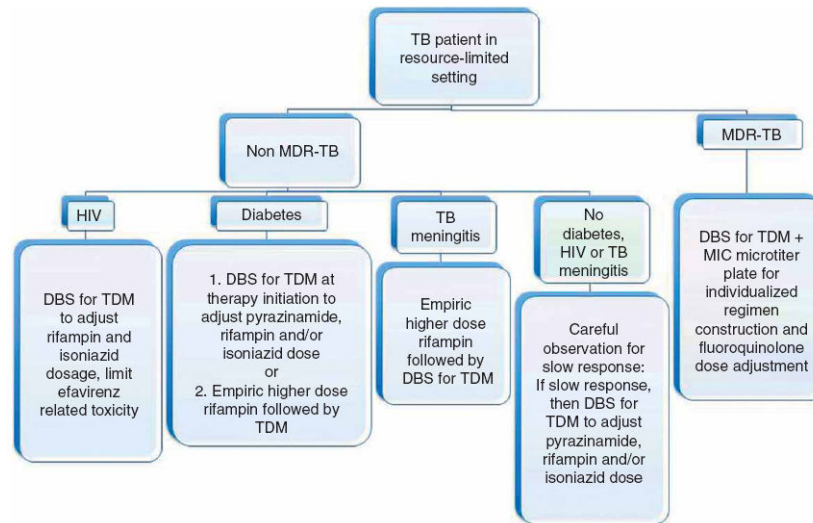


Figure 2. Depicted are scenarios for operational research that can be studied to optimize anti-TB regimens in resource-limited and TB endemic settings

In these scenarios the term resource-limited setting assumes that therapeutic drug monitoring and minimum inhibitory concentration (MIC) may be available at a national or supranational reference laboratory and multidrug-resistant (MDR)-TB is diagnosed by rapid molecular test. Each subpopulation of MDR or non-MDR-TB patient may represent a separate interventional opportunity thereby necessitating their own control group.

DBS: Dried blood spot, a distinct delivery system with innovative opportunity; TB: Tuberculosis.

Table 1

Predictive pharmacokinetic parameters of currently recommended anti-tuberculosis drugs.

Category	Route	Drug	Parameter best predictive of activity*	Predominant methods of evaluation	Threshold associated with poor outcome [‡]
First line	Oral	Isoniazid	AUC/MIC > C _{max} /MIC	Animal TB, HFS	AUC 52 mg·h/l
		Rifamycins (rifampin, rifabutin)	AUC/MIC ~ C _{max} /MIC	Animal TB, HFS	AUC 13 mg·h/l
		Ethambutol	AUC/MIC	Animal TB, HFS, Human TB	N/A
		Pyrazinamide	AUC/MIC	HFS, Human TB	AUC 363 mg·h/l
Second-line	Oral	Fluoroquinolones (ofloxacin, levofloxacin, moxifloxacin)	AUC/MIC > C _{max} /MIC	Animal TB, HFS, human TB	N/A
		Thioamides (ethionamide, prothionamide)	Unknown		N/A
		Serine analogs (cycloserine, terizidone, thicetazone)	Unknown		N/A
		Para-aminosalicylic acid	Unknown		N/A
		Bedaquiline	T/MIC	Animal TB, human TB	N/A
		Aminoglycosides (streptomycin, amikacin, kanamycin)	AUC/MIC	Non-TB	N/A
Third-line	Oral	Capreomycin	Unknown		N/A
		Linezolid	T/MIC	Non-TB, human TB	N/A
		Amoxicillin-clavulanate	T/MIC	Non-TB	N/A
		Clarithromycin	T/MIC	Non-TB	N/A
		Clofazimine	Unknown		N/A
		Carbapenems (Imipenem, meropenem)	T/MIC	Non-TB	N/A

* See refs [30-50].

[‡]Ref. [6]; poor long-term outcome included microbiological failure, death or relapse.

HFS: Hollow fiber system, an *in vitro* pharmacodynamics model; TB: Tuberculosis.