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REVIEW

Therapeutic drug monitoring in patients with tuberculosis and concurrent medical problems

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ABSTRACT

Introduction: Therapeutic drug monitoring (TDM) has been recommended for treatment optimization in tuberculosis (TB) but is only is used in certain countries e.g. USA, Germany, the Netherlands, Sweden and Tanzania. Recently, new drugs have emerged and PK studies in TB are continuing, which contributes further evidence for TDM in TB. The aim of this review is to provide an update on drugs used in TB, treatment strategies for these drugs, and TDM to support broader implementation.

Areas covered: This review describes the different drug classes used for TB, multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB), along with their pharmacokinetics, dosing strategies, TDM and sampling strategies. Moreover, the review discusses TDM for patient TB and renal or liver impairment, patients co-infected with HIV or hepatitis, and special patient populations – children and pregnant women.

Expert opinion: TB treatment has a long history of using 'one size fits all.' This has contributed to treatment failures, treatment relapses, and the selection of drug-resistant isolates. While challenging in resource-limited circumstances, TDM offers the clinician the opportunity to individualize and optimize treatment early in treatment. This approach may help to refine treatment and thereby reduce adverse effects and poor treatment outcomes. Funding, training, and randomized controlled trials are needed to advance the use of TDM for patients with TB.

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Therapeutic drug monitoring; tuberculosis; mdr-TB; pharmacokinetics; pharmacodynamics

1. Introduction

The use of therapeutic drug monitoring (TDM) [1–5] has become an accepted strategy to optimize the management of tuberculosis (TB) and is recommended in the most recent World health Organization (WHO) and The American Thoracic Society, U.S. Centers for Disease Control and Prevention, European Respiratory Society, Infectious Diseases Society of America (ATS/CDC/ERS/IDSA) Drug-Resistant TB treatment guidelines [6,7]. There are clear benefits to TDM in TB: avoiding toxicity, guiding therapy in special patient populations, assessing concordance to therapy, assessing potential drug interactions, but also prevention of antimicrobial resistance [2,8]. TDM is more used in certain countries, for example, USA, Germany, the Netherlands and Sweden. A recent review on mass spectrometry for TDM of anti-tuberculosis drugs listed the number of published drug assays by country and the most published assays were in India, USA and China [9].

Before starting TDM it is important to identify which drugs are the best candidates for performing TDM. Criteria for TDM include pharmacokinetic (PK) variability and stability, pharmacodynamic (PD) relationships like concentration-related toxicity and a narrow therapeutic window [10]. Furthermore, it is important to know whether and how specific PK/PD targets are defined for each drug. Traditionally PK/PD targets were based on animal models; however, this has moved on to using hollow fiber infection models, mimicking human pharmacokinetics [11]. With the hollow fiber infection model, it is possible to explore the impact of both PK and PD over a specified time period.

For TDM in TB either specific concentrations C_1, C_2, C_6 (concentration at 1 h, 2 h and 6 h after administration, respectively), C_{min} (trough concentration), C_{max} (maximum concentration), or measures of drug exposure like AUC (area under the concentration–time curve, drug exposure over time) and *f*AUC (the area under the undbound drug concentration–time curve) are used. Limited Sampling Strategies (LSS) have been developed using population pharmacokinetic models, and Monte Carlo simulations based on clinical data in order to provide 2 or 3 time-points, which can be used for accurate determination of the AUC [12,13]. For the estimation of unbound drug (the amount of drug that reaches the tissues) it is important to have information on drug-protein binding as only the unbound drug reaches the target cite of infection [14]. More advanced TDM includes drug susceptibility in addition to using solely drug concentrations. The main PK/PD indexes used for optimization of TB therapy are AUC or *(f)* AUC/MIC (minimal inhibitory concentration), *(f)*C_{max}/MIC and

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Article highlights

- TDM could have an important role in prevention of acquired drug resistance associated with low exposure.
- Pharmacokinetic/pharmacodynamic considerations could help clinicians select the right dose for optimization of therapy.
- Implementing optimal sampling strategies strategies for TDM will be a game changer in implementation of precision dosing.
- Special consideration needs to be given to vulnerable subpopulations – e.g. children, HIV positive/diabetic patients and during renal and hepatic impairment.
- TDM will only be beneficial if sufficient access and short turn around time can be guaranteed at community, regional and central level.

This box summarizes key points contained in the article.

*(f)*T (time)/MIC. These are then derived from previously described hollow fiber infection models, animal studies as well as from clinical studies. It has been well presented in a review by Dheda *et al* that low exposure to TB drugs, as a result of low drug penetration and, pharmacokinetic variability is one of the main risk factors for development of drug resistance, for example, for fluoroquinonlones [15,16]. The TB treatment guidelines include suggestions whether to commence TDM for specific drugs (e.g. fluoroquinolones, linezolid and aminoglycosides and specific situations like HIV, diabetes, toxicity, failure of sputum culture conversion in case of proven drug susceptibility, and drug–drug interactions) [6,7,17].

TDM, however, is rarely performed in TB endemic settings due to its perceived costs/technical constraints [18]. Recent developments in the field of alternative and sampling strategies is changing the landscape of traditional TDM [18,19]. Some methods may be more user friendly for low resource settings, such as finger prick blood spots (dried blood spot method) or saliva. These could be suitable alternative matrixes to predict drug concentrations in serum/plasma [19–21]. Similarly, limited sampling strategies that utilizes two- to three-sampling time points for estimation of pharmacokinetic parameters, reduces sampling burden on both patients and clinicians [13,22]. Using multiple linear regression equations, concentrations measured at optimal sampling time points can accurately estimate $AUC_{0\text{-}24}$ with an acceptable bias and imprecision of less than 15% (e.g. fluoroquinolones) [13,22].

The evidence linking low drug plasma concentrations and worse treatment outcomes is scarce in TB [4,5,23]. A recent systematic review and meta-analysis on first-line TB drugs concluded that low pyrazinamide and rifampicin concentrations might contribute to poor outcomes [5]. For ethambutol and isoniazid, the authors suggested that the relationship with poor treatment outcomes could not be defined, due to the wide therapeutic ranges applied to the TDM of these drugs [5]. Furthermore, the studies looking into TDM in TB are heterogeneous, including different study designs, drugs and regimens [4,5]. Still, there are clear benefits in utilizing an easy tool like TDM in TB patients. Currently, there are new drugs emerging, and PK studies in TB are continuing, which contributes further evidence for TDM in TB.

The aim of this review is to provide an update on newer drugs, novel dosing strategies and treatment regimens for TB. In addition, we provide an overview of TDM during concomitant therapy for hepatitis, HIV and during liver and kidney impairment. Finally, we present an overview of TDM in special patient populations – children and pregnant women.

2. Specific drugs

The drugs listed in this review are presented based on the WHO consolidated guidelines grouping of MDR-TB drugs and drugs for drug-susceptible TB (Table 1) [7]. The specific pharmacokinetic parameters and sampling strategies are presented in Table 2.

2.1. Drugs for drug-susceptible TB

2.1.1. Isoniazid

Isoniazid is a powerful first-line anti-TB drug with excellent early bactericidal activity [26]. Following administration, isoniazid is readily absorbed from gastrointestinal tract and penetrates all body fluid cavities, where concentrations are similar to serum. The C_{max} arrives approximately 0.75–2 h after administration and is expected to be 3–6 mg/L, the protein binding is described to be around 14% [2,27]. Based on hollow fiber model of TB, isoniazid efficacy is predicted by attainment of free $AUC_{0\text{-}24}$/MIC> 567 in the lung [28]. On the other hand, clinical study derived target $AUC_{0\text{-}24}$ in blood is 52 mg*h/L [28,29]. This target can be utilized for TDM. A new susceptibility breakpoint for isoniazid was identified at MICs of 0.0312 and 0.0334 mg/L [15,28,30,31] (Table 2).

Pharmacokinetic studies also reveal that the currently used dose of isoniazid is sub-optimal and needs to be increased. In a shorter MDR-TB regimen, isoniazid dose of 900 mg/day is used. This is because not all resistance-conferring mutations lead to similar MIC increases. For instance, *katG* S315T confers 30-fold increase in MIC to isoniazid, in contrast, *inhA* c-15 t

Table 1. Drugs used in TB and MDR-TB.

Group	Medicine
Drug-susceptible TB	Isoniazid
	Rifampicin
	Rifabutin*
	Rifapentine*
	Ethambutol
	Pyrazinamide
Group A	Levolofloxacin
	Moxifloxacin
	Bedaquiline
	Linezolid
Group B	Clofazimine
	Cycloserine/Terizidone
Group C	Delamanid and Pretomanid*
	Amikacin
	Streptomycin
	Ethionamide
	Prothionamide
	p-aminosalicylic acid
	Imipenem-cilastatin
	Meropenem

*added to the review, however not in the WHO classification

Table 2. Pharmacokinetic parameters of anti-TB drugs.

Drug	Normal adult dose	C_{max} (mg/L)	T_{max} (h)	AUC_{0-24h} (mg*h/L)	PK/PD index (serum/plasma)	$T_{1/2}$ (h)	Protein binding	Sampling strategy	Pregnancy Category
Isoniazid	5 mg/kg daily	3–6	0.75–2	52	AUC_{0-24}/MIC > 567 (lung) [26]	fast acetylators 1.5 h; slow acetylators 4h	14% (range 0–34%) [25]	2, 4, 8 h [31] 1, 2.5, 6 h [32]	A
Rifampicin [25]	10–20 mg/kg daily	8–24	3–6		AUC/MIC ≥ 271 C_{max}/MIC ≥ 175 [35–37]	3–5	88%	1, 3, 8 h& [43]	C
Rifabutin [2,45–47]	300 mg daily	0.45–0.9	3–4	4.5 [48]		35–36	71%		B
Rifapentine [2,45–47]	600 mg daily	8–30	5	324 [49]		14–15	98%		C
Ethambutol	25 mg/kg daily	2–6	2–3		C_{max}/MIC > 0.46 [27]	Biphasic: 2–4, then 12–14	12% (range 4–24%) [25]	0, 2.5, 6 h [32]	A
Pyrazinamide	25–35 mg/kg daily	20–60 (recommend >35)	1–2	363 [27]	AUC_{0-24}/MIC >11.3 [27]	9	1% (range 0–7%) [25]	2, 4, 8 h [31] 0, 2, 6 h [32]	B
Levofloxacin [22,64]	750–1000 mg daily	8–13	1–2	150, if MIC is 1 mg/L or unknown	AUC/MIC > 146[1] AUC/MIC > 360[2] [70]	6–8	24–38%	0, 4h* 0, 5 h#	C
Moxifloxacin [13]	400 mg daily	3–5	1–2	55, if MIC is 0.5 mg/L or unknown	*f*AUC/MIC > 130 [72]	7	30–50%	0, 4h* 0, 6 h# 0, 1.5, 6 h [32]	
Bedaquiline [78,79]	400 mg daily for 2 weeks then 200 mg three times per week	2.8–3.3 (week 2) 1.7 (week 8) 1.3 (week 24)	4–6			5.5 months	>99.9%		B
Linezolid [90,91]	600 mg daily	12–26	1–2	100 [96]			31%		C
Clofazimine [2,105,106]	100 mg daily	0.5–2.0	2.3			25 days			C
Cycloserine [110,111]	250–750 mg daily, sometimes divided as two doses	20–35	2		T> MIC = 30% [114–116]	15.79–25.1			
Terizidone [111]	250–750 mg daily					20.93–33.1			
Terizodone dosing, Cycloserine exposure [116,193]	250–500 mg	38.1 (IQR 32.6–47.2)	4	0–10 hours 319 mg/L*h		14.7 (IQR 9.5–14.8)		4h& 2, 7 h& 3, 8 h&	
Delamanid [194]	100 mg twice daily	1.35 initial 4.14 steady state	4			30–38	>99%		
Pretomanid [122]	200 mg once daily	1.4–2.6 initial 2.3–4.3 steady state	5			16	87%		
Streptomycin	15 mg/kg daily 25 mg TIW	35–45 65-80	0.5–1.5			5–6	35%	1, 4h	D
Amikacin [127]	15 mg/kg daily 25 mg TIW	35–45 65-80	0.5–1.5		C_{max}/MIC > 75 AUC_{0-24}/MIC>103 [126]	3	0–11%	1, 4h	D
Prothionamide [137]	250–500 mg once or twice daily	1–5	3.0						C
Ethionamide [3,139]	250–500 mg once or twice daily	1–5			*f*AUC/MIC > 10 [63,141]		30%		C
PAS [3,110]	4000 mg two-three times daily	20–60					50–60%		C

* = Multiple linear regression equations, # = Bayesian methods, & = using population pharmacokinetic model, TIW – three times per week
Further citations used for Table 1 [2,6,7,26]:
1. For maximum *M. tuberculosis* kill 2. For the prevention of acquired drug resistance

leads to only modest MIC increase at 0.2–1 mg/L [30]. For this reason, treating patients with low-level resistance to isoniazid with higher doses (15–20 mg/kg) have been associated with favorable clinical outcomes [15,30]. Furthermore, isoniazid metabolism occurs by acetylation. Based on acetylation status patients can be categorized into two or three groups: fast acetylators and slow acetylators, and when the data support it, heterogeneous fast [15,29,30]. Fast acetylators are at a risk of not attaining therapeutic concentrations of isoniazid due to short half-life (~1.5 h), whereas, prolonged half-life in slow acetylators (~4 h) may make them prone to drug-related toxicities, most notably peripheral neuropathy [15]. On the other hand, acetylation status is seldomly known. Based on multiple drug concentrations it is possible to classify a patient, who might be fast or slow acetylators. Most likely the acetylation status is unknown, thus multiple measurements after administration to calculate clearance might be the appropriate approach. Hepatotoxicity by far is the major side-effect of isoniazid. The concentration-relatedness of hepatotoxicity, however, is far from a settled matter. Pharmacogenomic-based dose individualization in NAT 2 slow- and fast- acetylators could be a promising strategy, especially in order to avoid under-dosing of fast-actylators [2,32]. Optimal sampling strategies of 2, 4, 8 h [33] and 1, 2.5, 6 h [34] have been proposed.

2.1.2. Rifampicin (rifampin)

Rifampicin is used in the treatment of drug-susceptible TB [35]. Rifampicin C_{max} is reached in approximately 1–3 hours and $t_{1/2}$ is estimated 3.5 hours with single doses, declining to 1–2 hours at steady state [36]. For many years the C_{max}, in the range 8–24 mg/L, was considered the PK parameter to be used in TDM [36,37]. After reaching steady state in TB patients, it is not uncommon to find C_{max} values around 6 mg/L [37]. To achieve PK/PD targets, higher dosing should be used, and a higher C_{max} range can be proposed. The main PK/PD indexes used to guide therapy with rifampicin are AUC/MIC ≥ 271 and C_{max}/MIC ≥ 175 [23,37–39]. Routine TDM of rifampicin is suggested as low 24-hour AUCs have proven to estimate poor long-term outcomes and both low AUC and C_{max} can cause acquired drug resistance [23,40]. However, PK parameters of rifampicin has been shown to have wide inter-and intra-patient variability and it has been suggested that therapy with rifampicin should use higher doses [37,40,41]. Moreover, rifampicin is known to iduce its own metabolism (auto-induction) through increasing its clearance; however, this has shown to be similar in doses 450 mg and 600 mg daily [42,43]. Recent studies have shown that higher rifampicin doses lead to substantially higher efficacy than the standard doses. A rifampicin dose-ranging trial in DS-TB patients by Boeree and colleagues reported that doses (up to 35 mg/kg) were safe, well tolerated and further improved the extended early bactericidal activity in TB patients [41].

Commonly, sampling times for rifampicin are 2 and 6 hours after dose, to capture the peak concentration and potential delayed absorption [3,44]. An optimal sampling strategy of 1, 3 and 8 hours after dose has been suggested using a pharmacokinetic model to estimate an accurate $AUC_{0\text{-}24}$ [45]. This sampling strategy will provide more accurate results as the T_{max} can vary resulting in varied C_{max}. In order to capture rifampicin concentrations after auto-induction takes place, TDM should take place at least 7 days into therapy (Table 2).

2.1.3. Rifabutin and rifapentine

Rifabutin and rifapentine are used for drug-susceptible TB as alternative for rifampicin. Protein binding is described for rifabutin approximately 71% and for rifapentine 98% [46,47]. The C_{max} for rifabutin is around 0.46 mg/L, the usual range is considered to be 0.45–0.9 mg/L and the T_{max} is expected at 3–4 h [2,48]. For rifapentine the C_{max} range to target that has been recommended is 8–30 mg/L and T_{max} is expected at 5 h [2]. The long half-life of 25–36 h (also reported to be 45 h) of rifabutin and 14–15 h of rifapentine need to be considered when performing TDM [2,47–49]. Rifabutin $AUC_{0\text{-}24h}$ of 4.5 mg*h/L has been proposed in order to prevent (acquired) resistance [50]. For 600 mg daily dosing rifapentine $AUC_{0\text{-}24h}$ of 324 (SD 143) mg *h/L has been reported [51]. For TDM of rifabutin it is suggested to use 3 h and 7 h and for rifapentine 6 h sampling [2].

As with rifampicin drug interactions by rifabutin are caused by induction of the CYP3A4 enzyme, however has documented to be of lower extent than rifampicin [48]. Furthermore, rifabutin exposure can also be reduced by other drugs, most significantly by antiretroviral efavirenz (reduction of 37% of AUC) and increased doses have been used [52]. The opposite effect, induction, has been described when co-administered with azoles and clarithromycin.

2.1.4. Ethambutol

Ethambutol is considered as a companion drug, valued for its protection against the development of resistance when combined with other first-line agents (isoniazid, rifampicin and pyrazinamide). Currently, ethambutol is prescribed at 25 mg/kg once daily dosing (max 1200 mg), although clinicians often prescribe smaller doses, around 15 mg/kg to avoid toxicity [7]. The T_{max} for ethambutol is expected around 2–3 hours and the half-life is biphasic first 2–4 h and then 12–14 h, C_{max} is expected to be 2–6 mg/: and protein binding is 12% [27,53,54]. Ethambutol exhibits dose-dependent efficacy which is predicted by both C_{max}/MIC and $AUC_{0\text{-}24}$/MIC. In the hollow fiber model of TB, C_{max}/MIC of 0.51 and $AUC_{0\text{-}24}$/MIC of 119 is identified as a target ratio in the lung whereas, in clinical studies C_{max}/MIC ratio of 0.46 in blood was associated with the likelihood of treatment success [29,55]. The susceptibility breakpoint for ethambutol is 4 mg/L. Ethambutol use can be associated with deteriorating visual acuity or red-green color discrimination (two manifestations of ocular toxicity). This is most likely to occur in patients with renal dysfunction, who are unable to clear the drug efficiently. Patients should be closely monitored for potential optic neuritis [26]. In particular, TDM usually is performed in patients with compromised renal function to prevent dose-dependent toxicity [26,56]. Pharmacokinetic parameters with optimal sampling strategies are presented in Table 2.

2.1.5. Pyrazinamide

Pyrazinamide is a key component of anti-TB regimens [26]. It is a prodrug that undergoes in vivo conversion to pyrazinoic acid. Resistance is associated with mutations in mycobacterial *pnc* A gene that codes for the enzymes responsible for conversion of pyrazinamide to pyrazinoic acid [57,58]. Currently, pyrazinamide is prescribed at 25–35 mg/kg daily dose (max 1600 mg/day) [7]. The C_{max} of pyrazinamide is expected to be 20–60 mg/L, the T_{max} around 1–2 h, the $T_{1/2}$ 9 h and the $AUC_{0\text{-}24h}$ 363 mg*h/L [2,26,54]. Following oral administration, pyrazinamide is rapidly and almost completely absorbed. Intake with food reduces C_{max} by 17% and T_{max} by 80% [59]. In patients, this mg/kg dose has resulted in sub-therapeutic concentrations associated with the risk of treatment failure (C_{max} below 35 mg/L) and delayed sputum culture conversion (C_{max} below 58 mg/L) [23, 24, 60]. Higher doses might contribute to a more efficacious regimen for the treatment of both DS-TB and MDR-TB [61,62]. However, caution should be exercised, as higher doses might heighten the occurrence of hepatotoxicity and uric acid-related adverse effects.

Pyrazinamide efficacy is predicted by a free target $AUC_{0\text{-}24}$ /MIC>209 in the lung (hollow fiber model of tuberculosis) whereas, clinically derived target $AUC_{0\text{-}24}$ > 363 mg*h/L and $AUC_{0\text{-}24}$/MIC>11.3 was reported in the blood (Table 2) [29]. Moreover, two optimal sampling strategies with three time-points are presented in Table 2. The clinical susceptibility breakpoint of pyrazinamide is 50 mg/L, although this target comes with a number of caveats due to the difficulty of performing phenotypic susceptibility testing with pyrazinamide [63].

2.2. Drugs for MDR-TB and XDR-TB

2.2.1. Fluoroquinolones (Levofloxacin and Moxifloxacin)

Levofloxacin and moxifloxacin are recommended fluoroquinolones in the WHO list of second-line drugs for programmatic management of drug-resistant tuberculosis, and are used interchangeably [7]. Following oral administration, bioavailability of levofloxacin and moxifloxacin is 99% and 90%, respectively. Levofloxacin ingestion with food causes a moderate delay in its time to achieve maximum serum concentrations. T_{max} increases by 1 h and C_{max} reduces by 14 to 25% whereas, moxifloxacin absorption is not affected by food intake.

Both drugs exhibit high inter-individual variability. Moxifloxacin PK variability was found to be nine-fold in plasma on 400 mg/day [64]. Similarly, a striking four-fold difference was observed between the highest and lowest levofloxacin $AUC_{0\text{-}24}$ in Nepalese patients on 750–1000 mg/day [19,65]. These findings corroborate results from other available studies [34,65–70]. Acquired fluoroquinolone resistance during standard treatment has become a serious concern, and was associated with poor outcomes in a prospective observational cohort study [71].

In the absence of data on TB bacteria, $AUC_{0\text{-}24}$/MIC >100-125 was generalized for understanding dose-concentration-response relationship in TB patients [66,71]. Recently, the hollow fiber model on tuberculosis has established a levofloxacin total drug $AUC_{0\text{-}24}$/MIC target of 146 for maximum bacterial kill (EC_{80}) and 360 for the prevention of acquired drug resistance [72]. Earlier, a study by Gumbo and colleagues identified moxifloxacin $fAUC_{0\text{-}24}$/MIC > 53 associated with complete suppression of drug resistance mutant sub-population ($AUC_{0\text{-}24}$/MIC>106, 30–50% protein bound) [73]. In another hollow fiber model study, Heinrichs and colleagues reported higher *f*AUC/MIC>130 for moxifloxacin under conditions of acidic pH [74]. However, target derived from both pre-clinical *in vitro* and *in vivo* models have limitations. For instance, $C_{max}/AUC_{0\text{-}24}$ achieved in animal models can be different from those seen in humans due to differences in metabolism and clearance, as a result, efficacy might vary. On the other hand, hollow fiber model misses the host-immune component and in humans it might be necessary to have a different concentration to penetrate cavity wall.

An ongoing randomized, blinded, phase II dose-finding trial (OptiQ trial, NCT 01918397) is evaluating $AUC_{0\text{-}24}$/MIC that provides shortest time to sputum culture conversion in TB patients [75,76]. This will be a first clinically validated levofloxacin target in TB patients. Nonetheless, it is important to note that debates regarding the precise PK/PD target does not imply a lack of confidence in TDM. Available data from clinical studies show that at least 25% of the patients on standard daily doses do not achieve the desired $AUC_{0\text{-}24}$, C_{max} and $AUC_{0\text{-}24}$/MIC for both levofloxacin and moxifloxacin [34,65–69]. Therefore, TDM has a crucial role in addressing the effect of inter-individual pharmacokinetic variabilities in patients by ensuring adequate drug exposure. In clinics, in the absense of actual MICs, one could aim to attain C_{max} and/or $AUC_{0\text{-}24}$ targets mentioned in Table 2. However, practically, TDM without utilizing the actual MICs could be problematic because depending on the actual MICs (0.25, 0.5 or 1 mg/L for levofloxacin); desired AUC or C_{max} could to be twice as high especially for patients infected with strains exhibiting higher MICs in order to attain the same AUC/MIC target. This could, however, be addressed by utilizing susceptibility breakpoint MICs for both levofloxacin and moxifloxacin (assuming worst-case scenario); but the risk of higher dosing cannot be ignored. For this, molecular tests with second-line drugs must be performed to provide information on susceptibility. Based on the distribution of MICs for particular mutations, specific dose could be selected. Caution should be applied, as the use of FQs have been associated with side-effects involving muscles, joints, tendons, nerves and the central nervous system. Moxifloxacin is known to prolong the QTc interval, but a direct link to moxifloxacin-induced fatal dysrhythmias is lacking [77]. Furthermore, it is imperative to identify patients on levofloxacin with diminished renal function, who may accumulate the drug, and to identify the concomitant use of corticosteroids, which may predispose to tendon rupture. Using optimal sampling strategies in order to estimate $AUC_{0\text{-}24h}$ might be appropriate (Table 2) [13,22].

2.2.2. Bedaquiline

Bedaquiline (BDQ) was FDA approved for MDR-TB in 2012. In 2019, BDQ gained FDA approval as part of BPaL regimen for treatment of highly drug-resistant TB.

The typical trough and peak serum or plasma concentration of BDQ is approximately 0.9 (SD 0.5) mg/L, 2.4 (SD 0.8) mg/L at week 2 (loading phase), 0.6 (SD 0.3) mg/L, 1.5 (SD 0.6) mg/L at week 24 (maintenance phase) respectively, [78]. Bedaquiline has an exceptionally long half-life (5–6 months) and thus dosage adjustments should be made carefully. The exposure–response relationship in bedaquiline has been described with PK/PD modeling, where it was shown that half maximal effective concentration of bedaquiline is 1.42 mg/L and it was shown that besides dynamic exposure metrics, PK parameters like C_{min} and $AUC_{0\text{-}24h}$ had significant effect on the response [79]. Variability about these typical values should be expected. Peak concentrations occur approximately 4 to 6 hours after an oral dose. Administering BDQ with food is recommended and increases the drug bioavailability, in healthy volunteers 2–2.4 fold increase of the AUC has been reported when administered with food [80,81].

The typical bedaquiline trough concentration is 0.73 to 0.96 mg/L at week 2 (24-hour sample), approximately 0.62 mg/L at week 8 (48-hour sample), and approximately 0.36 mg/L at week 24 (48-hour sample) [80,81] (Table 2). Bedaquiline penetration in cerebrospinal fluid was undetectably low [82]. Based on the average plasma concentration of 0.60 mg/L in humans and MIC distribution a clinical breakpoint of 0.25 mg/L was selected [83]. Although TDM has not been evaluated for bedaquiline, several situations where TDM could be of help were suggested, as acquired resistance has already been documented [83,84]. Moreover, optimal sampling strategies for BDQ have not been identified.

BDQ is metabolized by CYP3A4 to its less active M2 metabolite [81]. The most serious BDQ toxicities including prolonged QT inverval and elevated liver enzymes are thought to be related to accumulation of M2. Due to potent CYP induction by rifamycins, co-administration of these drugs is not currently recommended [85,86]. In contrast, clofazimine does not appear to have significant effect on BDQ exposure [87].

2.2.3. Linezolid

Linezolid, an oxazolidinone antimicrobial, is an important candidate for TDM due to its narrow therapeutic window and toxicity that poses an issue, especially during TB therapy [88–91]. Linezolid has oral bioavailability of 100%, and it is metabolized through oxidation into inactive derivatives [92]. The expected C_{max} is 12–26 mg/L and T_{max} 1–2 hours, protein binding has described to be 31% [92,93]. Drug interactions with linezolid can be due to its effects as a nonselective monoamine oxidase inhibitor. Linezolid also interacts with rifampicin and clarithromycin, the former decreases linezolid concentrations, and the latter increases linezolid concentrations [94–96]. A study of MDR-TB patients showed that co-administration of linezolid and clarithromycin results in an 44% increase of linezolid $AUC_{0\text{-}12h}$ [95].

Most frequently, linezolid is given once daily for mycobacterial infections to avoid toxicity during the prolonged treatment which exceed the licensed use of 28 days. Mitochondrial toxicity appears to be correlated with the trough concentration [97]. AUC emerges as a significant predictor of efficacy when linezolid is combined with other drugs [98]. In a hollow fiber model $AUC_{0\text{-}24h}$ of 600 mg dose has shown to be around 100 (107.5 ± 30.16) mg * h/L using a Monte Carlo simulation [98]. The optimal time of sampling to calculate AUC has been suggested to be C_{trough} (before administration) and 2 hours after administration (C_{peak} is estimated to be at 1–2 hours) [93,99] (Table 2). The reported C_{peak} and C_{trough} and ranges for 600 mg orally twice daily are 21.2 (SD 5.78) mg/L and 6.15 (SD 2.94) mg/L, respectively, [93].

For TB, doses as high as 1200 mg once daily have been studied, and these produced considerable toxicity [100]. A dose of 600 to 900 mg once daily probably is equally efficacious but with lower toxicity [101]. Even lower dosing of 300 mg twice daily has been suggested to be able to be efficacious [102]. Twenty-four-hour trough values less than 2 mg/L appear to minimize toxicity. The benefits of lower dosage regimens still need to be confirmed in larger trials [103,104]. In the absence of well-designed studies daily dose of 600 mg seems appropriate to balance between efficacy and toxicity [105]. TDM for linezolid is however mainly for toxicity as mentioned in order to reduce the dose, which becomes especially important in the long therapy duration for TB.

2.2.4. Clofazimine

Clofazimine is being used more frequently for highly resistant TB, and it has been used as part of shorter treatment regimens (less than 1 year) [7,106]. The normal range for clofazimine serum or plasma concentrations is 0.5 to 2.0 mg/L approximately 2–3 hours after an oral dose, although the T_{max} can vary widely [2,107,108] (Table 2). Clofazimine PK have been also described using simulations from a population model [109]. It was described that the $AUC_{0\text{-}24h}$, maximum and average concentrations of clofazimine were higher after 2 months of therapy compared to 2 weeks of therapy, which suggests accumulation. Moreover, the time to steady state was described to be higher in men than women – 105 days for men and 230 days for women [109]. Although there is not sufficient data on clofazimine TDM, for practical reasons, 2 h and 6 h post dose samples are used to distinguish between malabsorption and delayed absorption.

Clofazimine concentrates in tissues such as the skin and displays complex pharmacokinetics and a prolonged terminal elimination half-life (weeks long) [108]. A precise relationship between clofazimine concentrations and effect has not been established. However, one study observed delayed concentration-dependent antimicrobial activity in vitro [106]. Cardiotoxicity has been described as a rare side-effect during clofazimine therapy; however, it should be monitored [110,111]. Until more studies are completed, clofazimine plasma or serum concentrations primarily are useful for confirming that absorption is taking place. No optimal strategies for guiding therapy have been reported.

2.2.5. Cycloserine and terizidone

Cycloserine and terizidione (contains two cycloserine molecules) therapy has been complicated by frequent adverse effects on the central nervous system, ranging from mild

confusion or lethargy, all the way up to seizures [6]. The half-lives of cycloserine are both around 20–30 h and for cycloserine a T_{max} of 2 h and C_{max} of 20–35 mg/L has been described [112,113]. Due to its relatively long half-life, it has been suggested to wait 3–4 days for natural accumulation to occur. Peak concentrations of cycloserine are expected to be within 20–35 mg/L and the sample should be drawn at 2 and 6 hours, as delayed absorption can occur [3,114,115]. For terizidone, specific targets have not been set; however, C_{max} concentrations have been reported in multiple studies (Table 2). T> MIC = 30% has been used as a PK/PD index for cycloserine, which has been used in population pharmacokinetic modeling and confirmed in a hollow fiber model [116–118]. In order to achieve this target twice daily dosing is necessary especially at the beginning of therapy [116].

Adverse events are especially seen with elevated serum concentrations (over 35 mcg/ml); however, toxicity has also been described with lower concentrations [3,6,119]. Moreover, it has been proposed in a hollow fiber infection model that current dosing regimens might not be effective for MDR-TB and dosages should be increased to 500 mg twice daily. Higher doses also may be a good option for tuberculous meningitis, as cycloserine penetrates the CSF [116]. However, cycloserine also may complicate the assessment of mental status in a patient with meningitis.

Although the use of TDM for cycloserine predates that for most TB drugs, the origins of the range are not well documented. Very few clinical trial data are available for cycloserine from the time of its development. A typical range of 20–35 mg/L has been used with reasonable safety for decades, but its ability to predict either efficacy or safety is hard to prove (Table 2). Rather, it has a strong element of tradition. A study conducted in Northern Taiwan showed that 22% patients had delayed absorption, and a majority of them had lower than expected cycloserine concentrations, suggesting the need for TDM [114].

2.2.6. Delamanid

Delamanid is a nitroimidazole approved by the European Medicines Authority (EMA) for the treatment of MDR TB. The drug may enhance culture conversion in this population, especially with >6 months or more of therapy. However, this benefit has not been observed in XDR TB patients [120]. It may be useful as salvage therapy in combination with BDQ, but this combination poses a risk for QT prolongation since both drugs have been associated with this adverse effect [121,122]. Delamanid mean C_{max} 100 mg twice daily dosing is around 0.4 mg/L and C_{min} around 0.3 mg/L [123] (Table 2). Specific PK/PD index for delamanid is lacking as well as clinical PK data, further studies are needed before TDM before can be decided or if TDM is indicated.

2.2.7. Pretomanid

Pretomanid (PMD) gained FDA approval in late 2019 in combination with BDQ and linezolid (BPaL) for the treatment of highly resistant tuberculosis [100,124]. The typical peak serum or plasma concentration of pretomanid is around 2.0 mg/L, occurring about 5 hours after a 200 mg dose. Peak after a single dose ranges from 1.4–2.6 mg/L, and at steady state, about 2.3–4.3 mg/L. Trough concentrations are about 1.0–2.4 mg/L (Table 2). Administering pretomanid with food is recommended and increases the drug bioavailability, both C_{max} and AUC have shown to be close to doubled during fed conditions in healthy adults [125]. In a Phase I clinical study it has been described that efavirenz reduces the AUC of pretomanid by 35% and rifampin reduces the AUC by 66% and lopinavir/ritonavir by 17% [126]. Another study assessing pretomanid effect on midazolam concluded that pretamonid does not induce or inhibit CYP3A4 in order to have a clinically meaningful effect [127]. TDM during concomitant administration with these drugs may be beneficial. As there is limited data available on this new drug, TDM could also be useful during malabsorption.

The most common adverse events observed during pretomanid therapy included peripheral neuropathy, anemia, GI upset, and elevated liver enzymes. Hepatic adverse effects were more common in HIV-positive patients compared to HIV-negative patients. Peripheral neuropathy and anemia are commonly associated in combination with linezolid therapy. Additional clinical trials are in progress [124].

2.2.8. Aminoglycosides (amikacin and streptomycin)

Amikacin has been in use for more than 40 years; still there are limited data available on its pharmacokinetics in relation to TB disease [128]. Besides, right dose and dosing strategies (daily 15 mg/kg *vs* intermittent 25 mg/kg three times weekly) are often debated [128]. Blood samples collected at 1 h and 4 h post dose reliably predicted $AUC_{0\text{-}24}$ (Table 2) [129].

Notorious for its serious adverse reactions that include ototoxicity (hearing loss), vestibular toxicity and nephrotoxicity, this drug is a good candidate for TDM. When nephrotoxicity occurs amikacin can accumulate causing higher concentrations, which can lead to even further kidney damage, thus TDM during fluctuating kidney function and during kidney failure is especially warranted [130,131]. However, in younger patients who are diagnosed early kidney function can be easily monitored and does not pose as high risk as hearing loss [132]. In older patients with preexisting kidney failure therapy with aminoglycosides poses a higher risk for toxicity. The C_{max}/MIC ratio of 10.1 (at the site of infection) seems to be the primary efficacy parameter closely followed by $AUC_{0\text{-}24}$/MIC ratio [128,133,134]. Due to its poor penetration in lung tissue, a target C_{max}/MIC ratio of 75 and $AUC_{0\text{-}24}$/MIC>103 is desired in serum [128]. Van Altena *et al*. utilized a low C_{max}/MIC target of 20 and concluded that hearing loss was associated with a -cumulative mg/kg doses of amikacin [132]. In this study, amikacin was used at lower mg/kg dose. Clearly, toxicity does not seem to be linked with the size and frequency of dosages but rather to increased age, cumulative days of therapy, and cumulative AUC [135,136]. Therefore, TDM should be performed to control toxicity resulting from long-term amikacin treatment, while at the same time optimizing therapy [128].

Streptomycin is used as a substitute for amikacin only when amikacin is not available or there is confirmed resistance to it. Recommended dose of streptomycin is 12–18 mg/kg [7]. The recommendations also cap the dosing at 1000 mg, which may lead to the under-dosing of large patients, particularly if they are not overweight. Pharmacokinetic parameters along with sampling time-points are shown in Table 2. Kanamycin and capreomycin are no longer recommended for use by the WHO based on observational data [137].

2.2.9. Ethionamide and prothionamide

Ethionamide and prothionamide, isonicotinic acid derivatives, frequently cause gastrointestinal toxicity (nausea, sometimes vomiting). They are reserved for MDR-TB when limited options exist, due to and their limited efficacy and poor patient tolerance. Further, more effective newer drugs are currently available [6,110,138].

Ethionamide and prothionamide have very similar pharmacokinetics, and the C_{max} occurs around 2 hours for ethionamide and 3–4 hours for prothionamide [139,140]. Delayed and variable absorption can occur with ethionamide, especially if it is administered with food or other medications. Dosing with food may improve tolerability [3,140,141]. For ethionamide, the PK parameters may be more variable in TB patients compared to healthy volunteers; these are presented in Table 2 [141]. The usual concentration range for ethionamide and prothionamide C_{max} is 1–5 mg/L [3,141,142]. In order to observe delayed absorption, and to assess elimination, sampling at 2 and 6 hours post dose is suggested [3,141]. A *f*AUC/MIC target of 10 has been proposed for 1.0-log kill, which has shown to be attained with daily dose of 750 mg and higher [65,143]. TDM of ethionamide could be useful in order to strive toward PK/PD targets, although patient tolerability often limits doses [143].

2.3. 2.2.10 p-Aminosalicylic acid

As with ethionamide and prothionamide, p-Aminosalicylic acid (PAS) is considered as a reserve agent, due to its limited potency and its side effects [6,144]. C_{max} of PAS is expected at 1–2 hours for immediate release dosage forms, and up to 6 hours post dose for different extended release dosage forms [145]. For doses up to 5,000 mg the C_{max} can range up to 50–100 mg/L, especially with immediate release tablets. However, for 4,000 mg (administerd 2–3 times daily) extended release granules, a Cmax of 20–60 mg/L occurs about 6 hours post dose (Table 2) [4,84,86,87]. PAS TDM allows for an assessment of absorption; some patients require single doses of 6,000 mg [146].

Gastrointestinal side effects are common with the older formulations of PAS; however, the granules have shown to cause less gastrointestinal toxicity [147,148]. Other side effects include hypothyroidism, hepatoxicity and hypersensitivity reactions [110]. It has been shown that PAS clearance is more than 50% higher in patients with HIV infection treated with efavirenz [149]. Furthermore, the probability of target attainment from this study showed that 4000 mg twice daily dosing for PAS is sufficient for exceeding the MIC for the dosing interval [149].

2.3.1. Beta-lactam antibiotics/beta-lactamase inhibitors

Ceftazidime/avibactam has been utilized in the treatment of rapid growing mycobacterial infections (RGM) such as *M. abscessus*, rather than slow-growing mycobacteria (e.g. MAC) [150]. However, given the increase in MDR/XDR TB cases, poor clinical outcomes, and the slow development of novel agents, more attention has been given to potentially repurposing beta-lactams, for example amoxicillin/clavuanate, for highly resistant TB [151]. Most beta-lactams have C_{max} values of about 70–80 mg/L per gram of dose, and short elimination half-lives of about 1 hour. The PK/PD target used for beta-lactam antibiotics is T > MIC, thus in a hospital setting prolonged infusions are recommended [152]. Drugs in this class are often unstable in human plasma, therefore accurately measuring drug concentrations can present logistical challenges. Most rely on renal elimination, and should be used with caution in patients with decreased renal function. Major limitations of many beta-lactams is that they must be given intravenously, and in combinations with a beta-lactamase inhibitor as *M. tuberculosis* has a highly active beta-lactamase [153]. As clavulanic acid is not available as a product it must be given as a combination of amoxicillin-clavulanic acid, even though the latter contributes little to the regimen but does cause gastrointestinal adverse effects [154].

Avibactam is a potent beta-lactamase inhibitor and was recently approved in combination with ceftazidime (CAV) for the treatment of gram-negative infections. Due to its good lung penetration [155], CAV was investigated for activity against *M. tuberculosis* in a hollow fiber model [156]. Neither ceftazidime nor avibactam alone effectively killed *M. tuberculosis*, however the combination demonstrated a sterilizing effect [156]. Up to 12 g daily in adults and 100 mg/kg three times daily in children was proposed as optimal regimens. The CAV exposure that achieved the same kill rates as those of the most active of the first-line drugs was a $\%T_{MIC}$ of ≥47%. The calculated the CAV exposure associated with maximal kill, which was a $\%T_{MIC}$ of ≥63%. Therefore, CAV has to be dosed at exposures exceeding a $\%T_{MIC}$ of 63% (that is, 63 to 100%) for optimal efficacy [156].

Clinical studies examining ertapenem for the treatment of MDR and XDR TB are limited, but a small (18 pts) retrospective study in the Netherlands examined the safety and pharmacokinetics of ertapenem [157]. Subsequently, a hollow fiber infection study was performed showing that 2000 mg as a once daily dose could be considered a more suitable dose for further clinical testing [158]. A prospective PK study evaluating a single 2000 mg ertapenem dose given as a 30 minute infusion showed that the PK/PD target of $\%T_{MIC}$ > 40% was achieved in most patients [159].

Additional carbapenems have been investigated as potential components of drug regimens for MDR and XDR TB, but clinical studies remain limited [160,161]. Imipenem and meropenem have been included in the guidelines based on historical data and use. A comparison study found that

meropenem/clavulanate resulted in a shorter time to culture conversion and higher treatment success relative to imipenem/clavulanate [162].

3. TB in special patient populations

3.1. TDM in patients with hepatitis

Patients co-infected with hepatitis B or C and tuberculosis are more likely to experience drug-induced hepatotoxicity and hepatic dysfunction relative to patients without viral hepatitis [163]. A recent study suggests that prophylactically treating hepatitis B infection may reduce the incidence of liver failure in patients co-infected with TB [164].

Fortunately, several direct-acting antivirals (e.g. ledipasvir/sofosbuvir) that are superior to the conventional ribavirin and pegylated interferon regimens have been developed for the treatment of hepatitis C in the past decade. However due to the potential for drug interactions between these novel therapies and rifamycin-based anti-tuberculosis regimens, simultaneous treatment of these infections has largely been contraindicated. Few studies have directly examined simultaneous treatment of TB and hepatitis C [165,166]. While TDM is not routine performed for hepatitis drugs, it could be a valuable tool in order to navigate drug-drug interactions for coinfected and co treated patients in the future [166].

3.2. TDM in patients with hepatic dysfunction

Managing anti-tuberculosis therapy in patients with liver disease presents several challenges. Multiple first-line medications can cause liver injury and occurs more frequently in patients with underlying liver disease [167]. Although the measurement of liver enzymes in serum can indicate that damage has been done to the liver, it cannot measure residual hepatic clearance potential for drugs.

Unfortunately, there is little information on serum concentrations of anti-tuberculosis drugs and hepatotoxicity. Furthermore, a small study found an association between elevated rifampin exposure and drug-induced hepatotoxicity [168]. Because of conflicting results, it is difficult to determine the utility of TDM to monitor for hepatotoxicity but can be considered in the management of therapy for patients with liver disease. In patients with hepatic dysfunction, it is prudent to measure serum concentrations of the TB drugs to make sure that adequate, but not excessive, drug concentrations are being obtained.

3.3. TDM in HIV-infected TB patients

TDM plays an important role in HIV-infected TB patients. There are multiple reasons for introducing TDM in this patient cohort. Firstly, in addition to TB drugs, these patients are receiving multiple antiretroviral drugs. Therefore, the potential for drug–drug interactions is high. The most recent MDR-TB guidelines include recommendations for the use bedaquiline and/or delamanid. Interactions between these drugs and the HIV medications should always be considered [6,84]. Bedaquiline drug exposure has shown to be altered by strong CYP3A4 inducers [169,170].

Secondly, patients who are co-infected with HIV have been shown to have lower exposures of the first-line TB drugs. Reasons for this include underlying disease, diarrhea, and drug interactions [6,60,171,172]. Rifampicin, a potent CYP 450 enzyme inducer, causes drug interactions with many antiretroviral drugs, including atazanavir/ritonavir, emtricitabine/tenofovir/alafenamide, darunavir/cobicistat [173]. Hepatically cleared HIV drugs likely will be affected by co-administration with rifamycins. An overview of overlapping toxicities between non-rifamycin based regimens and antiretroviral drugs have been well described in a recent clinical guideline focusing on MDR-TB [6].

It often is recommended to avoid co-administration of selected antiretrovirals with rifamycin-based TB drug regimens, however, that is not always possible. Rifabutin can be used instead of rifampicin in some situations, thus reducing but not eliminating the effects of hepatic enzyme induction. Also, there is a risk for overlapping toxicities between TB and HIV drugs. When multiple classes of drugs are started within a short period of time, often it is hard to tell which drug is causing the adverse effect (nausea, vomiting, rash, peripheral neuropathy, etc.) [6]. Further, the immune reconstitution inflammatory syndrome (IRIS) can be problematic in this circumstance. When the clinical situation allows for it, starting TB therapy, and then introducing the HIV therapy 2–8 weeks later, can mitigate these problems. However, in patients with very low CD4 counts, delays in starting HIV therapy may not be possible.

Drug interaction and pharmacokinetic/pharmacodynamic studies are still ongoing, especially with newer TB drugs and antiretrovirals. Since limited data are available, TDM can be used to monitor drug exposure in individual patients. A systematic review describing the interaction between HIV infection and first-line TB drugs suggested that HIV is one of factor leading to low drug exposures [174]. In addition, HIV patients can have delayed absorption, and this can be identified using TDM.

3.4. TDM in patients with renal impairment

Essential drug therapy cannot be avoided in patients with renal impairment. When dosage reductions are necessary, TDM is a great tool to ensure effectiveness while avoiding overdosing patients [175]. During TB therapy, special consideration should be given to the aminoglycosides, ethambutol, cycloserine, and levofloxacin, as these drugs can be accumulated with poor renal function [6,176,177]. It should be noted that serum creatinine is lagging indicator for kidney function, reflecting what already has transpired [178]. Applying TDM for patients on dialysis is useful, as dialysis is known to play a role in elimination of drugs [179]. It should be noted that most data are for hemodialysis, and patients undergoing peritoneal dialysis can respond differently. For patients receiving dialysis, a sample drawn before and after dialysis (allowing some time

for rebound) can be used to estimate how much was drug eliminated during dialysis. Ethambutol has been shown to be removed by hemodialysis, but may not be removed by peritoneal dialysis. Given the risk for ocular toxicity, consideration may be given to substituting moxifloxacin for ethambutol in patients with renal dysfunction. TDM has been suggested for guiding therapy in patients receiving dialysis [180,181].

3.5. TDM in children

Children are known to be under-represented in studies, and for TB this is not different. Pediatric dosing guidelines often are derived from adult guidelines. Depending on the age of the child, the absorption, distribution, metabolism and elimination vary and must always be taken into account [182]. For neonates, there are significant early changes in kidney function, drug protein binding and drug metabolism [182].

In order to decrease the blood volume used for TDM with children, dried blood spots (DBS) might be a good alternative where available [183]. It has been suggested that children tolerate TB therapy better than adults, but it can be difficult to monitor for adverse events [6]. However, a prospective study was conducted to assess drug-induced liver injury in children with TB and liver function tests were performed every 2 weeks, which could be feasible in routine clinical care [184]. The authors concluded that children with hypoalbuminemia and hepatotoxic comedications can be at higher risk in developing liver toxicity [184]. Thus here, TDM can be a good tool to assess drug exposure both for efficacy and for potential toxicities. Another reason to perform TDM in children is the wide pharmacokinetic variability that has been observed in children with TB [185].

3.6. TDM in pregnancy

Optimal tuberculosis treatment regimens during pregnancy still need to be established. A multitude of physiologic changes occur during pregnancy that can affect the pharmacokinetics of the treatment regimen and thus make optimal dosing challenging. These changes include increased cardiac output, increased clearance (hepatic and renal), and increased gastrointestinal transit time. This can further be complicated if the patient is also living with HIV and on an antiviral regimen with the potential for drug interactions. TDM is a vital tool to effectively monitor anti-tuberculosis therapy in these patients [186].

Two different studies examined the population pharmacokinetics of the first-line TB medications and did not find clinically relevant changes in exposure [187,188]. Authors found that rifampin clearance was moderately (14%) decreased during pregnancy in the third trimester, but dose adjustment was not required [188].

Data on second-line medications are sparse. Moxifloxacin and linezolid exposure has been reported to decrease during pregnancy compared to postpartum serum concentrations [189]. More studies examining the pharmacokinetics of anti-tuberculosis drugs are needed. An international expert panel proposed that studies of MDR-TB, LTBI regimens in women with HIV and pharmacokinetics by stage of pregnancy to be of high priority. They also encouraged earlier inclusion of pregnant women in phase 3 trials where phase 2 safety and pharmacokinetic data from non-pregnant women is available [190]. The known FDA pregnancy categories are presented in Table 2 alongside other PK parameters.

4. Expert opinion

TB treatment has a long history of using 'one size fits all.' Although convenient, this has contributed to treatment failures, treatment relapses, and the selection of drug-resistant isolates.

An abundance of data has been published since the publication Alsultan and Peloquin in 2014 [2], which was a comprehensive review on TDM in TB. The current review focuses on covering also special populations children and pregnant women, but also provides an update for the previous publications. During the past decade many dosing regimens and strategies have changed and new research has provided further insight into which PK/PD indexes to be used in order to guide therapy.

While challenging in resource-limited circumstances, TDM offers the clinician the opportunity to individualize and optimize drug exposure early in treatment. It is true that not every location will have an LC MS-MS [9]. But excellent work can be done with relatively inexpensive HPLC UV systems that are not as demanding on the purity of reagents and the training of the chemists [191]. Ideally cheap and fast point-of-care test should be available to truly implement TDM in every setting to benefit all patients. Semi-quantitative test could be a solution to preselect patients that actually would require TDM [192]. There is a good example based on DBS how to introduce TDM into practice. Ghimire *et al.* have proposed a strategy how to implement TDM in the form of DBS into the three tiers of World Health Organization (WHO) tuberculosis diagnostics. The sampling could be done on a peripheral and intermediate level, when the measuring can be done at the central level laboratories [18]. It is more probable than on a central level the results would be more credible as high volume of samples require robust and reproducible methodology. Moreover, this leads to the approach suggested by Alffenaar *et al* that specific key drugs (rifampicin, pyrazinamide, isoniazid, levofloxacin, moxifloxacin and linezolid) should be screened on community level (peripheral) and phenotypic drug susceptibility and drug exposure should be determined on a regional level [29]. The need for guidance on implementing TDM for TB is definitely warranted, especially guidance is needed from WHO [193].

PK/PD provides the necessary insight into drug action in order to extract the full benefit of the drugs. Current short course regimens are 6 or more months long. The longer treatment continues, the greater the opportunity to acquire drug resistance. Individualization of treatment takes into account the TB isolate (degree of drug susceptibility), the extent of disease (including cavities, abscesses, penetration into bone or the

central nervous system), liver and kidney function. Rather than 'one size fits all,' the regimen is tailored to the patient so that it fits the patient. Once the initial regimen is started, its suitability is confirmed using TDM, as well as the more typical clinical and microbiological assessments. This approach provides the patient with the best chance to avoid negative treatment outcomes. Clearly, the evaluation of such approach in a randomized trial would advance the implementation of TDM. Currently, the biggest hurdles for the implementation of TDM for TB are funding and training of local staff.

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