Limited Sampling Strategies Using Linear Regression and the Bayesian Approach for Therapeutic Drug Monitoring of Moxifloxacin in Tuberculosis Patients

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ABSTRACT Therapeutic drug monitoring (TDM) of moxifloxacin is recommended to improve the response to tuberculosis treatment and reduce acquired drug resistance. Limited sampling strategies (LSSs) are able to reduce the burden of TDM by using a small number of appropriately timed samples to estimate the parameter of interest, the area under the concentration-time curve. This study aimed to develop LSSs for moxifloxacin alone (MFX) and together with rifampin (MFX+RIF) in tuberculosis (TB) patients. Population pharmacokinetic (popPK) models were developed for MFX ($n = 77$) and MFX+RIF ($n = 24$). In addition, LSSs using Bayesian approach and multiple linear regression were developed. Jackknife analysis was used for internal validation of the popPK models and multiple linear regression LSSs. Clinically feasible LSSs (one to three samples, 6-h timespan postdose, and 1-h interval) were tested. Moxifloxacin exposure was slightly underestimated in the one-compartment models of MFX (mean -5.1% , standard error [SE] 0.8%) and MFX+RIF (mean -10% , SE 2.5%). The Bayesian LSSs for MFX and MFX+RIF (both 0 and 6 h) slightly underestimated drug exposure (MFX mean -4.8% , SE 1.3% ; MFX+RIF mean -5.5% , SE 3.1%). The multiple linear regression LSS for MFX (0 and 4 h) and MFX+RIF (1 and 6 h), showed mean overestimations of 0.2% (SE 1.3%) and 0.9% (SE 2.1%), respectively. LSSs were successfully developed using the Bayesian approach (MFX and MFX+RIF; 0 and 6 h) and multiple linear regression (MFX, 0 and 4 h; MFX+RIF, 1 and 6 h). These LSSs can be implemented in clinical practice to facilitate TDM of moxifloxacin in TB patients.

KEYWORDS drug interactions, population pharmacokinetics, sampling strategy, therapeutic drug monitoring, tuberculosis

Each year, the global tuberculosis (TB) incidence declines with approximately 2%, while by 2020 an annual 4 to 5% decline is strived for by the World Health Organization (WHO) (1). Multidrug-resistant TB (MDR-TB) remains a major problem, with an estimated number of 458,000 cases in 2017 (1). Currently, the worldwide success rate of MDR-TB treatment is 55%, and this is considered low compared to a success rate of 85% for drug-susceptible TB (DS-TB) (1).

Moxifloxacin (MFX), a fluoroquinolone, is one of the most important drugs for the treatment of MDR-TB (2), but it has also been used as an alternative to first-line anti-TB

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drugs if not well tolerated or suggested to include in case of isoniazid resistance (3–5). In general, the toxicity profile of moxifloxacin is rather mild, though it includes concentration-dependent corrected QT interval prolongation and, rarely, tendinopathy (6–9). A clinically relevant drug-drug interaction is the combination of moxifloxacin with rifampin, since these two drugs can be used concomitantly in TB treatment. Rifampin (RIF) lowers the moxifloxacin area under the concentration-time curve of 0 to 24 h (AUC_{0-24}) by approximately 30% by inducing phase II metabolizing enzymes (glucuronosyltransferase and sulfotransferase) (10–12).

The efficacy of fluoroquinolones is related to the ratio of AUC_{0-24} to MIC (AUC_{0-24}/MIC) (13, 14). The fluoroquinolone exposure is effective against Gram-negative bacteria at an AUC_{0-24}/MIC ratio of >100 to 125 and against Gram-positive species at an AUC_{0-24}/MIC ratio of >25 to 30 (13, 15, 16). An *in vitro* moxifloxacin exposure of unbound ($fAUC_{0-24}/MIC$) ratio of >53 was able to substantially decrease the total population of *Mycobacterium tuberculosis* with by >3 $\log_{10}$ CFU/ml, as well as suppress the emergence of drug resistance, while an $fAUC_{0-24}/MIC$ ratio of >102 completely killed the fluoroquinolone-sensitive population of *M. tuberculosis* without the development of drug resistance (17). Approximately 50% of moxifloxacin is assumed to be protein bound, although protein binding is highly variable between individuals and might be concentration dependent (13, 16, 18, 19). Corresponding with an $fAUC_{0-24}/MIC$ ratio of >53 and a fraction unbound of 0.5, the target total (bound and unbound) AUC_{0-24}/MIC ratio of >100 to 125 is regularly used in TB, because individual data of protein binding is often lacking (18, 20, 21). In case of a proven susceptibility for moxifloxacin while lacking a MIC value of the strain, the target AUC_{0-24} is generally set at >50 to 65 $\text{mg} \cdot \text{h}/\text{liter}$ based on a critical concentration of 0.5 mg/liter (22, 23).

Therapeutic drug monitoring (TDM) is recommended by the American Thoracic Society for all second-line drugs, including moxifloxacin (24, 25). It is important to monitor the moxifloxacin exposure in TB patients to determine an individualized dose, because of substantial interindividual pharmacokinetic variability and relevant drug-drug interactions with the risk of treatment failure and developing drug resistance (18, 26–28). However, routine TDM to estimate the AUC_{0-24} requiring frequent blood sampling is time-consuming, a burden for patients and health care professionals, and expensive. Optimizing the sampling schedule by developing a limited sampling strategy (LSS) could overcome these difficulties with TDM in TB treatment (29).

There are two main methods to develop an LSS: the Bayesian approach and multiple linear regression (30). The advantages of the Bayesian approach are the flexible timing of samples as the population pharmacokinetic model can correct for deviations and that it takes a number of parameters into account for example sex, age, and kidney function, leading to a more accurate estimation of AUC_{0-24} . The advantage of multiple linear regression-based LSSs is that these do not require modeling software and AUC_{0-24} can be easily estimated using only an equation and the measurement of drug concentrations. The disadvantage is that samples must be taken exactly according to the predefined schedule and the population of interest should be comparable because patient characteristics are not included in the equations to estimate drug exposure (30).

Pranger et al. described a LSS for moxifloxacin for the first time using $t = 4$ and 14 h postdose samples (21). This sampling strategy can be considered impractical to be used in daily practice. Magis-Escurra et al. described LSSs to simultaneously estimate the AUC_{0-24} of all first-line drugs, together with moxifloxacin ($t = 1, 4$, and 6 h or $t = 2, 4$, and 6 h) but did not differentiate between patients using moxifloxacin alone and moxifloxacin in combination with rifampin (20). Therefore, the influence of the drug-drug interaction between moxifloxacin and rifampin, namely, an increased moxifloxacin clearance, was not taken into account in these LSSs.

Therefore, the aim of this study was to develop and validate two population pharmacokinetic models of moxifloxacin (alone and with rifampin), along with clinically feasible LSSs using the Bayesian approach, as well as multiple linear regression, for the purpose of TDM of moxifloxacin in TB patients.

FIG 1 Moxifloxacin concentrations of the pharmacokinetic curves of MFX ($n = 77$) and MFX+RIF ($n = 24$).

RESULTS

Study population. The group treated with moxifloxacin alone (MFX) included pharmacokinetic profiles of 77 TB patients, and the group with moxifloxacin together with rifampin (MFX+RIF) included profiles of 24 TB patients (Fig. 1). The baseline characteristics sex, age, and height were significantly different ($P < 0.05$) between these two groups (Table 1). In addition, the AUC_{0-24} calculated with the trapezoidal rule ($AUC_{0-24,ref}$) was significantly lower, and the time of peak concentration (T_{max}) was significantly earlier in the MFX+RIF group ($P < 0.05$, Table 2). Several abnormal pharmacokinetic curves (e.g., delayed absorption or single aberrant data point) were observed in both the MFX and the MFX+RIF group.

Population pharmacokinetic model. For both MFX and MFX+RIF, an one-compartment model with lag time resulted in the lowest Akaike Information Criterion (AIC) values and described the data best (Table 3). Two-compartment models were not favorable for either MFX or MFX+RIF. A statistical comparison of the pharmacokinetic parameters of the MFX versus MFX+RIF model is provided in Table 4. The total body clearance (CL) was higher, and the lag time (T_{lag}) was shorter in the MFX+RIF model ($P < 0.05$). Internal validation of the two models resulted in a mean underestimation of AUC_{0-24} of -5.1% (standard error [SE] 0.8%) in the MFX model and a mean underestimation of -10% (SE 2.5%) in the MFX+RIF model (Fig. 2A and Fig. 3A). In the validation of the MFX model, an r^2 of 0.98 , a y -axis intercept of -0.3 (95% confidence interval [CI] = -1.1 to 0.5), and a slope of 0.96 (95% CI = 0.94 to 0.98) were found in

TABLE 1 Patient characteristics of the study population^a

Parameter	Median (IQR)		P^b
	MFX ($n = 77$)	MFX+RIF ($n = 24$)	
Male, no. (%)	47 (61.0)	21 (87.5)	0.023*
Age (yr)	33 (25–41)	48 (36–62)	$<0.001^\dagger$
Ht (m)	1.65 (1.59–1.74)	1.72 (1.64–1.76)	0.047†
Wt (kg)	58.0 (52.5–68.2)	55.5 (52.3–63.9)	0.500†
Dose (mg/kg [body wt])	7.0 (5.9–8.1)	7.3 (6.4–7.7)	0.629†
BMI (kg/m ²)	21.2 (19.3–23.5)	20.1 (17.6–22.7)	0.053†
Serum creatinine level ($\mu\text{mol/liter}$)	71 (59–83)	73 (63–91)	0.752†
No. of samples/curve	7 (6–8)	10 (7–10)	$<0.001^\dagger$
Days on rifampin treatment at time of sampling	NA	35 (13–87)	NA

^aThe data are presented as median (IQR) unless stated otherwise in column 1. BMI, body mass index; NA, not applicable.

^b*, Fisher exact test; †, Mann-Whitney U test.

TABLE 2 Noncompartmental parameters of MFX and MFX+RIF

Parameter	Median (IQR)		<i>P</i> ^a
	MFX (<i>n</i> = 77)	MFX+RIF (<i>n</i> = 24)	
AUC _{0–24,ref} (mg · h/liter)	34.0 (25.2–49.2)	25.5 (20.4–31.6)	0.006
Dose-corrected AUC _{0–24,ref} (mg · h/liter [per 400 mg])	30.8 (24.7–40.3)	25.5 (19.1–31.3)	0.014
<i>C</i> _{max} (mg/liter)	3.00 (2.27–4.64)	2.83 (2.25–3.90)	0.407
<i>T</i> _{max} (h)	2 (1–3)	1.5 (1–2)	0.018

^aMann-Whitney U test.

the Passing Bablok regression (Fig. 2B). For the MFX+RIF model, an *r*² of 0.94, *y*-axis intercept of −1.0 (95% CI = −4.1 to 0.9), and a slope of 0.98 (95% CI = 0.92 to 1.07) were found in the Passing Bablok regression (Fig. 3B).

LSS using the Bayesian approach. The best performing LSSs of MFX and MFX+RIF are shown in Table 5 and Table 6, including the mean prediction error (MPE), the root mean-squared error (RMSE), and *r*² to evaluate the performance of the LSSs. The performance of the LSS using *t* = 2 and 6 h samples was evaluated as well because this strategy is currently used in many health facilities for TDM of anti-TB drugs (31). Not all strategies met the preset acceptance criteria (RMSE < 15%, MPE < 5%).(21) Low *r*² values were observed that were caused by high interindividual variability in performance of the LSSs.

For the MFX model, an LSS using *t* = 0 and 6 h samples was chosen for further evaluation (RSME = 15.17%, MPE = 2.42%, *r*² = 0.874) because it required one sample less than the three-sample strategies, while the RMSE was only slightly above 15%. The internal validation showed a mean underestimation of −4.8% (SE 1.3%). However, low AUC_{0–24} values were more frequently overestimated in contrast to an AUC_{0–24} of >40 mg · h/liter mainly being underestimated by the LSS (Fig. 4A). The Passing Bablok regression showed an *r*² of 0.94, a *y*-axis intercept of 3.4 (95% CI = 1.6 to 4.9), and a slope of 0.85 (95% CI = 0.80 to 0.91) (Fig. 4B).

For the MFX+RIF model, an LSS using *t* = 0 h and 6 h samples was chosen for further evaluation (RSME = 15.81%, MPE = 2.35%, *r*² = 0.885) because of the benefit of requiring only two samples while performance in terms of RSME and MPE remained acceptable. The internal validation showed a mean underestimation of −5.5% (SE 3.1%) in the Bland-Altman plot and an *r*² of 0.90, a *y*-axis intercept of −1.3 (95% CI = −4.4 to 2.8), and a slope of 1.0 (95% CI = 0.88 to 1.10) in the Passing Bablok regression (Fig. 5).

LSS using multiple linear regression. Tables 7 and 8 show the best-performing LSSs for MFX and MFX+RIF. The performance of the frequently used LSS using *t* = 2 and 6 h samples was evaluated as well and included in the tables. None of the MFX LSSs

TABLE 3 Starting parameters of the default one-compartment and two-compartment models of MFX and MFX+RIF, together with the parameters of the final models based on AIC

Parameter	Mean ± SD ^a			
	Default model MFX	Final model MFX	Default model MFX+RIF	Final model MFX+RIF
One compartment				
CL/F (liters/h)	18.500 ± 8.600	14.655 ± 5.683	18.500 ± 8.600	19.898 ± 8.800
V ₁ /F (liters/kg [body wt])	3.000 ± 0.7000	2.7467 ± 1.0077	3.000 ± 0.7000	2.8264 ± 0.6902
<i>K</i> _a (/h)	1.1500 ± 1.1600	6.2904 ± 4.8164	1.1500 ± 1.1600	7.3755 ± 6.8205
<i>T</i> _{lag} (h)	NA	0.8769 ± 0.2357	NA	0.7460 ± 0.1093
AIC	5,564	903	1,361	236
Two compartments				
CL/F (liters/h)	11.800 ± 0.740	13.428 ± 5.494	49.100 ± 2.550	18.108 ± 8.570
CL ₁₂ /F (liters/h)	5.620 ± 1.080	5.620 ± 1.080	3.150 ± 0.800	3.150 ± 0.800
V ₁ /F (liters/kg [body wt])	2.5300 ± 0.0800	2.4898 ± 1.0838	2.8400 ± 0.1500	2.7004 ± 0.7535
V ₂ /F (liters/kg [body wt])	0.6900 ± 0.1300	0.6900 ± 0.1300	0.8900 ± 0.1900	0.8900 ± 0.1900
<i>K</i> _a (/h)	16.7000 ± 2.9200	3.2774 ± 2.9422	2.3200 ± 0.5600	6.2314 ± 9.0508
<i>T</i> _{lag} (h)	0.4600 ± 0.0800	0.7940 ± 0.3720	0.6000 ± 0.0700	0.7312 ± 0.1995
AIC	11,892	940	2,995	249

^aValues are expressed as means ± the SD, except AIC.

TABLE 4 Comparison of pharmacokinetic parameters of the population pharmacokinetic model of MFX versus MFX+RIF

Parameter	Geometric mean $\pm$ SD		<i>P</i> ^a
	MFX (<i>n</i> = 77)	MFX+RIF (<i>n</i> = 24)	
CL/F (liters/h)	14.655 $\pm$ 5.683	19.898 $\pm$ 8.800	0.004
V/F (liters/kg bodyweight)	2.7467 $\pm$ 1.0077	2.8264 $\pm$ 0.6902	0.534
<i>K</i> _a (/h)	6.2904 $\pm$ 4.8164	7.3755 $\pm$ 6.8205	0.231
<i>T</i> _{lag} (h)	0.8769 $\pm$ 0.2357	0.7460 $\pm$ 0.1093	<0.001

^aMann-Whitney U test.

met the acceptance criteria (RMSE < 15%, MPE < 5%) as bias was above 5% for all combinations. For MFX+RIF, the two three-sample strategies and LSS using *t* = 1 and 6 h samples met the acceptance criteria.

The MFX LSS using *t* = 0 and 4 h samples (RSME = 9.25%, MPE = 6.85%, *r*² = 0.957) had a performance comparable to the three-sample strategies while being more clinically feasible and therefore was chosen for further evaluation. In contrast to the Bayesian LSSs for MFX and MFX+RIF, a *t* = 0 and 6 h strategy was not feasible using a multiple linear regression approach since its performance was substantially worse (RMSE = 12.01, MPE = 9.43, *r*² = 0.905) than the LSS using *t* = 0 and 4 h samples. Internal validation of this *t* = 0 and 4 h LSS for MFX showed a mean overestimation of 0.2% (SE 1.3%) in the Bland-Altman plot and an *r*² of 0.95, a *y*-axis intercept of 0.1 (95% CI = −2.1 to 1.6), and a slope of 0.99 (95% CI = 0.95 to 1.06) in the Passing Bablok regression (Fig. 6).

For MFX+RIF, the LSS using *t* = 1 and 6 h samples (RSME = 6.09%, MPE = 4.83%, *r*² = 0.971) was chosen for further evaluation, because of clinical suitability in addition to good performance (RMSE < 15%, MPE < 5%). Internal validation showed a mean overestimation of 0.9% (SE 2.1%) in the Bland-Altman plot and an *r*² of 0.96, a *y*-axis intercept of −0.2 (95% CI = −4.9 to 2.3), and a slope of 1.02 (95% CI = 0.88 to 1.15) in the Passing Bablok regression (Fig. 7).

DISCUSSION

In this study, we successfully developed a population pharmacokinetic model for moxifloxacin alone and in combination with rifampin. Furthermore, we developed and validated sampling strategies using the Bayesian approach (MFX and MFX+RIF *t* = 0 and 6 h) and multiple linear regression (MFX *t* = 0 and 4 h; MFX+RIF *t* = 1 and 6 h) for both groups as well.

It was decided to develop two separate population pharmacokinetic models and

FIG 2 Bland-Altman plot (A) and Passing Bablok regression (B) of internal validation (*n* = 77) of population pharmacokinetic model of MFX (*n* = 77).

FIG 3 Bland-Altman plot (A) and Passing Bablok regression (B) of internal validation ($n = 2$) of population pharmacokinetic model of MFX+RIF ($n = 24$).

therefore also separate LSSs, for moxifloxacin alone and in combination with rifampin, after observing a significant effect of rifampin on the pharmacokinetics of moxifloxacin. The population pharmacokinetic model of MFX+RIF showed an approximately 35% higher total body clearance of moxifloxacin compared to the MFX pharmacokinetic model (Table 4). This was to be expected since rifampin enhances the metabolism of moxifloxacin and increases in total body clearance of 45 to 50% have been reported by others (10, 32). As a result of this drug-drug interaction, the pharmacokinetic profiles of MFX+RIF showed reduced moxifloxacin concentrations and 25% lower median moxifloxacin AUC_{0-24} values after administration of a similar dose (Fig. 1, Table 2). The latter is confirmed by a significant -17% difference in dose-corrected $AUC_{0-24,ref}$ between the MFX and MFX+RIF group (Table 2). The decrease in moxifloxacin exposure by rifampin was estimated at 30% in previous studies (10, 12, 32), although others found nonsignificant or smaller decreases in moxifloxacin AUC_{0-24} (21, 33). In this study, we observed only a slightly smaller effect of rifampin on the total body clearance and exposure than previously reported. This might be explained by the possibility that maximal enzyme induction was not yet achieved at the moment of sampling in a few cases, since it generally takes around 10 to 14 days of rifampin treatment to reach maximal induction (34). Furthermore, we encountered a significant, but small, difference in lag time between the MFX and MFX+RIF models and in the T_{max} of the included pharmacokinetic profiles. Faster absorption of moxifloxacin in combination with rifampin was found in other studies as well; however, some reported the opposite effect. This could suggest that lag time and T_{max} was not influenced by rifampin but more likely by other differences between the MFX and MFX+RIF group, such as concomitantly taken TB drugs or interindividual differences in absorption due to disease state.

In addition to the population pharmacokinetic models, we developed and validated LSSs using the Bayesian approach, as well as multiple linear regression for MFX and

TABLE 5 LSSs of moxifloxacin without rifampin using the Bayesian approach

Sampling time point (h)	MPE (%)	RMSE (%)	r^2
5	2.69	24.64	0.659
6	1.74	22.00	0.726
2, 6	-2.20	20.83	0.742
0, 5	2.84	15.82	0.864
0, 6	2.42	15.17	0.874
0, 4, 6	0.97	13.22	0.883
0, 5, 6	1.03	12.97	0.888

TABLE 6 LSSs of moxifloxacin with RIF using the Bayesian approach

Sampling time point (h)	MPE (%)	RMSE (%)	r^2
5	-1.97	22.35	0.768
6	-0.79	19.22	0.826
2, 6	-2.89	18.38	0.832
0, 5	1.88	16.67	0.877
0, 6	2.35	15.81	0.885
0, 4, 6	1.06	14.10	0.907
0, 5, 6	0.79	13.73	0.912

MFX+RIF. LSSs of moxifloxacin have been described before. Pranger et al. found a Bayesian LSS with a comparable performance (RMSE = 15%, MPE = -1.5%, r^2 = 0.90) compared to our LSSs for MFX and MFX+RIF (21). The LSS of Magis-Escurra et al. performed better (RMSE = 1.45%, MPE = 0.58%, r^2 = 0.9935) than the multiple linear regression LSSs proposed in this study (20). However, a smaller sample size (n = 12) was used to establish the equation, and this was not externally validated. Further, we provided suitable sampling strategies for multiple situations, in patients using moxifloxacin alone or together with rifampin, and for centers that either do or do not have pharmacokinetic modeling software available. Health care professionals may select the LSS that is the most applicable to the circumstances.

The Bayesian LSS for MFX (t = 0 and 6 h) showed a slight downward trend between the bias of the estimated AUC_{0-24} and the mean of the estimated and actual AUC_{0-24} (Fig. 4). Low AUC_{0-24} values were more frequently overestimated in comparison to higher AUC_{0-24} values. A possible cause might be that we could not differentiate between metabolic clearance and renal clearance in both population pharmacokinetic models due to a small range of creatinine clearance in the study population. A relatively high exposure of moxifloxacin in patients with renal insufficiency could be underestimated since renal function may be overestimated and the other way around for patients with normal renal function and relatively low exposures. The pharmacokinetic modeling software will fit a curve, with the greatest likelihood of being the actual pharmacokinetic curve based on drug concentrations at 0 and 6 h, together with patient characteristics and data of the entire population. However, when the influence of creatinine clearance is not available, the software will pick a fit with average parameters, causing overestimation in low AUC_{0-24} and underestimation in high AUC_{0-24} ranges. We decided not to validate one of the better performing three-sample strategies from Table 5, since we focused on developing a clinically feasible LSS with a strong preference for only two samples. Furthermore, we aimed to provide a simple and well-performing alternative LSS for MFX using multiple linear regression (t = 0 and

FIG 4 Bland-Altman plot (A) and Passing Bablok regression (B) of internal validation of Bayesian LSS (t = 0 and 6 h) of MFX (n = 77).

FIG 5 Bland-Altman plot (A) and Passing Bablok regression (B) of internal validation of Bayesian LSS ($t = 0$ and 6 h) of MFX+RIF ($n = 24$).

4 h). We recommend using this LSS instead of the Bayesian LSS for MFX, particularly when low drug exposure is suspected, because overestimation of AUC_{0-24} can lead to sub therapeutic dosing with treatment failure and acquired drug resistance as possible harmful consequence (26, 35, 36).

In this study we decided to validate one LSS for each situation (Bayesian or multiple linear regression; MFX or MFX+RIF), due to the significant influence of rifampin on the pharmacokinetics of moxifloxacin and so there would be a suitable LSS for every patient in each health care center. The LSSs using multiple linear regression performed rather well in our study population but are less flexible in patients with different characteristics. A Bayesian LSS is therefore preferred for patients who are not comparable to our study populations since the population pharmacokinetic model is able to include some patient characteristics. Clinicians are guided to the best option for TDM of moxifloxacin by following the decision tree in Fig. 8. For implementation of moxifloxacin TDM using LSSs in daily practice, it would be convenient to be able to use one sampling strategy for both MFX and MFX+RIF. This study showed that it is possible to use $t = 0$ and 6 h samples in a Bayesian LSS for both MFX and MFX+RIF, and probably even in a multiple linear regression LSS for MFX+RIF, after successful validation. Unfortunately, a multiple linear regression strategy for MFX alone using $t = 0$ and 6 h samples was not feasible because of inferior performance. Considering that TB patients are treated with a combination of multiple anti-TB drugs, one single LSS suitable for all drugs of interest is the ideal situation but, unfortunately, also rather challenging due to the various pharmacokinetic properties of the different drugs. Others did succeed in developing a LSS using multiple linear regression for simultaneously estimating exposure of all first-line drugs and moxifloxacin in a small population of TB patients (20). A 2 and 6 h postdose sampling strategy is frequently used for TDM of anti-TB drugs since it is believed to be able to estimate C_{max} , as well as to detect delayed absorption (31).

TABLE 7 LSSs of MFX without RIF determined using linear regression

Sampling time point (h)	Equation ^a	N ^b	MPE (%)	RMSE (%)	r ²
4	$AUC_{0-24,est} = 3.47 + 12.32 \times C_4$	66	12.68	17.02	0.862
6	$AUC_{0-24,est} = 2.27 + 15.01 \times C_6$	22	14.85	16.89	0.822
2, 6	$AUC_{0-24,est} = -1.44 + 3.55 \times C_2 + 11.24 \times C_6$	22	10.02	12.27	0.901
0, 3	$AUC_{0-24,est} = 3.61 + 28.67 \times C_0 + 5.38 \times C_3$	53	10.08	13.36	0.917
0, 4	$AUC_{0-24,est} = 1.10 + 20.76 \times C_0 + 8.68 \times C_4$	66	6.85	9.42	0.957
0, 2, 4	$AUC_{0-24,est} = 1.10 + 20.37 \times C_0 + 0.92 \times C_2 + 7.71 \times C_4$	65	6.91	9.25	0.958
0, 1, 4	$AUC_{0-24,est} = 1.00 + 21.06 \times C_0 + 0.66 \times C_1 + 8.02 \times C_4$	63	7.07	9.23	0.958

^aC₀, C₁, etc., are moxifloxacin concentrations at $t = 0$ h, $t = 1$ h, etc.

^bN, number of included curves.

TABLE 8 LSSs of MFX+RIF determined using multiple linear regression

Sampling time point (h)	Equation ^a	N ^b	MPE (%)	RMSE (%)	r ²
3	$AUC_{0-24,est} = -2.76 + 13.28 \times C_3$	18	8.27	11.10	0.907
6	$AUC_{0-24,est} = 0.95 + 16.44 \times C_6$	16	6.93	8.87	0.941
2, 6	$AUC_{0-24,est} = 0.08 + 1.21 \times C_2 + 15.02 \times C_6$	13	6.23	7.88	0.945
0, 6	$AUC_{0-24,est} = 1.38 + 7.40 \times C_0 + 14.05 \times C_6$	16	5.85	6.99	0.960
1, 6	$AUC_{0-24,est} = 1.43 + 0.22 \times C_1 + 16.25 \times C_6$	14	4.83	6.09	0.971
0, 3, 6	$AUC_{0-24,est} = 1.20 + 10.66 \times C_0 - 0.39 \times C_3 + 13.52 \times C_6$	15	4.85	5.31	0.977
0, 2, 6	$AUC_{0-24,est} = 0.46 + 9.99 \times C_0 + 0.13 \times C_2 + 13.39 \times C_6$	13	4.20	4.66	0.978

^aC₀, C₁, etc., are moxifloxacin concentrations at *t* = 0 h, *t* = 1 h, etc.^bN, number of included curves.

However, better performances were found for the LSSs proposed in this study, although the 2 and 6 h LSSs performed within acceptable limits as well in the Bayesian approach and the multiple linear regression.

In general, we noticed large interindividual pharmacokinetic variation in terms of moxifloxacin concentrations (Fig. 1), C_{max} , and AUC_{0-24} (Table 2) as described earlier (18), but also in K_d and CL/F (Table 4). Patients received 400, 600, or 800 mg of moxifloxacin; this obviously influenced the drug concentration, C_{max} , and the AUC_{0-24} , but not all variation could be explained by different dosage regimes. For MFX the AUC_{0-24} corrected to a 400-mg standard dose ranged from 10.2 to 79.1 mg · h/liter, and for MFX+RIF the AUC_{0-24} corrected to a 400-mg standard dose ranged from 10.0 to 47.4 mg · h/liter. This substantial interindividual variation is the reason why TDM of moxifloxacin is helpful to ensure optimal drug exposure and thus minimize the risk of treatment failure and developing acquired drug resistance (26, 27). The estimated AUC_{0-24} using one of the LSSs proposed, together with the MIC of the *M. tuberculosis* strain, will provide valuable information on the optimal moxifloxacin dose to be used in an individual patient.

A limitation of the study is the exclusion of the creatinine clearance from the population pharmacokinetic model. As discussed earlier, this could have led to the observed bias in the MFX LSS using 0 and 6 h samples since approximately 20% of moxifloxacin is eliminated unchanged in the urine. On the contrary, a well-performing LSS using multiple linear regression (*t* = 0 and 4 h) is a suitable alternative for MFX. The lack of prospective or external validation of the population pharmacokinetic model and LSSs could be considered another limitation. However, we were able to collect a large data set to develop the model and clinically feasible LSSs using a sufficient number of pharmacokinetic profiles. A strength of our study is that a large part of our dataset consisted of drug concentrations which were collected as part of daily routine TDM.

FIG 6 Bland-Altman plot (A) and Passing Bablok regression (B) of internal validation (*n* = 6) of LSS using multiple linear regression (*t* = 0 and 4 h) of MFX (*n* = 66).

FIG 7 Bland-Altman plot (A) and Passing Bablok regression (B) of internal validation ($n = 1$) of LSS using multiple linear regression ($t = 1$ and 6 h) of MFX+RIF ($n = 14$).

During visual check of the data we noticed several abnormal curves (both MFX and MFX+RIF) that, for instance, showed delayed absorption with $T_{\max}$ values of 4 to 6 h. These curves were not excluded from the study. The models and LSSs appeared to be able to adapt to this delayed absorption. In most cases, the subsequent decision to either increase the dose or not was similar. For these reasons, we expect the results reported here to represent the clinical practice of TDM using these LSSs very closely. The small sample size of the MFX+RIF group can be considered a limitation as well, although comparable to previously published LSS studies (21, 37–40). We consider this sample size to be sufficient for exploratory objectives, since this is the first study that

FIG 8 Clinical guide for choosing the best LSS for TDM of moxifloxacin alone or in combination with rifampin.

developed separate LSSs for moxifloxacin alone and in combination with rifampin. Future research can build on the results described in this study.

In conclusion, we developed and validated two separate pharmacokinetic models for moxifloxacin alone and in combination with rifampin in TB patients. We provided data to show significant differences in drug clearance and drug exposure between these groups. Furthermore, we developed and validated LSS based on the Bayesian approach (MFX and MFX+RIF, 0 and 6 h) and multiple linear regression (MFX, 0 and 4 h; MFX+RIF, 1 and 6 h) that can be used to perform TDM on moxifloxacin in TB patients.

MATERIALS AND METHODS

Study population. This study used three databases. Database 1 consisted of retrospective data of routine TDM in 67 tuberculosis patients treated at Tuberculosis Center Beatrixoord, University Medical Center Groningen, Groningen, The Netherlands, and was collected between January 2006 and May 2017, partly published earlier (18). All patients received moxifloxacin (with or without rifampin) as part of their daily TB treatment and pharmacokinetic curves were obtained as part of routine TDM care. Each patient was only included once. Various sampling schedules were used, but most profiles included $t = 0$, and 1, 2, 3, 4, and 8 h postdose samples. Pharmacokinetic profiles consisting of less than three data points were excluded. The second database included data of 25 TB patients participating in a clinical study in Thessaloniki, Greece (33). After at least 12 days of treatment with moxifloxacin with or without rifampin, blood samples were collected at $t = 0$ and at 1, 1.5, 2, 3, 4, 6, 9, 12, and 24 h after drug intake. The third database consisted of pharmacokinetic data of nine Brazilian TB patients receiving 400 mg of moxifloxacin (no rifampin) daily in an early bactericidal activity study (14). At day 5, blood samples were collected at $t = 0$ and at 1, 2, 4, 8, 12, 18 and 24 h after drug intake.

As steady state is reached within 3 to 5 days of treatment with moxifloxacin, all data were collected during steady-state conditions (11). In general, no informed consent was required, due to the retrospective nature of the study.

The total study population was split in two groups—patients that received moxifloxacin alone (MFX) and patients that received moxifloxacin together with rifampin (MFX+RIF)—because of the pharmacokinetic drug-drug interaction between rifampin and moxifloxacin (10). Since sample collection in the MFX+RIF group was performed after a median number of days on rifampin treatment of 35 (interquartile range [IQR], 13 to 87 days), maximum enzyme induction by rifampin was expected to be reached in most patients (41).

Patient characteristics of both groups were tested for significant differences, median (IQR) using the Mann-Whitney U test, and number (%) using the Fisher exact test in IBM SPSS Statistics (version 23; IBM Corp., Armonk, NY). P values of <0.05 were considered significant.

Population pharmacokinetic model. For each group, MFX and MFX+RIF, a population pharmacokinetic model was developed using the iterative two-stage Bayesian procedure of the KinPop module of MWPharm (version 3.82; Mediware, The Netherlands). Since the pharmacokinetics of moxifloxacin have been described with one compartment (14, 21), as well as two-compartment models (42, 43), both types were evaluated. The population pharmacokinetic parameters of the models were assumed to be log normally distributed, with a residual error and concentration-dependent standard deviation (SD; $SD = 0.1 + 0.1 \times C$, where C is the moxifloxacin concentration in mg/liter). Because the bioavailability (F) of moxifloxacin is almost complete (11) and pharmacokinetic data following intravenous administration were not available, F was fixed at 1 in the analysis and pharmacokinetic parameters are presented relative to F . Moxifloxacin is mainly metabolized in the liver by glucuronosyltransferase and sulfotransferase (ca. 80%) (11). Only total body clearance (CL), the sum of metabolic and renal clearance, was included in the model development because it was not possible to determine renal clearance due to a small range of creatinine clearance values in our data set.

We started the analysis with a single default one-compartment model for both MFX and MFX+RIF developed by Pranger et al. using a very similar methodology (21). This study found comparable pharmacokinetic parameters of MFX and MFX+RIF, although likely due to a small sample size. Two default two-compartment models were used, one for MFX and one for MFX+RIF (42, 44). Modeling was started with all parameters fixed, and the Akaike Information Criterion (AIC) was used to evaluate the model (45). Subsequently, one by one parameters were Bayesian estimated, and each step was evaluated by calculation of the AIC. A reduction in the AIC with at least three points was regarded as a significant improvement of the model (46). One-compartment models included the parameters CL, volume of distribution (V), and absorption rate constant (K_a). Two-compartment models included the parameters K_{12} , CL, the intercompartmental clearance (CL_{12}), the central volume of distribution (V_1), the volume of distribution of the second compartment (V_2), and the lag time for absorption (T_{lag}). Afterward, T_{lag} was added to the best performing one compartment model and evaluated for goodness of fit as well because of oral intake of moxifloxacin. The default two-compartment models already included T_{lag} . The final models of MFX and MFX+RIF were chosen based on AIC values.

The final models were internally validated using 11 different ($n - 7$) submodels for MFX and 12 ($n - 2$) submodels for MFX+RIF, each leaving out randomly chosen pharmacokinetic curves. All pharmacokinetic curves were excluded once (jackknife analysis). The Bayesian fitted AUC_{0-24} of each left out curve ($AUC_{0-24,fit}$) was compared to the AUC_{0-24} calculated with the trapezoidal rule ($AUC_{0-24,ref}$) using a Bland-Altman plot and Passing Bablok regression (Analyze-it 4.81; Analyze-it Software Ltd., Leeds, United Kingdom). In the calculation of $AUC_{0-24,ref}$ moxifloxacin concentrations at $t = 0$ and 24 h after drug

intake were assumed to be equal due to steady-state conditions. The $C_{\max}$ (mg/liter) was defined as the highest observed moxifloxacin concentration and $T_{\max}$ (h) as the time at which $C_{\max}$ occurred. Noncompartmental parameters (i.e., $AUC_{0-24, \text{ref}}$, dose-corrected $AUC_{0-24, \text{ref}}$ to the standard dose of 400 mg, $C_{\max}$, and $T_{\max}$) and population pharmacokinetic model parameters of the MFX and MFX+RIF group were compared and tested for significant differences using the Mann-Whitney U test.

LSS using Bayesian approach. Using the Bayesian approach, we performed two separate analyses to develop LSSs: one for MFX and one for MFX+RIF. Using Monte Carlo simulation in MWPharm, 1,000 virtual pharmacokinetic profiles were created to represent the pharmacokinetic data used in the development of the LSS. The reference patient for the Monte Carlo simulation was selected based on representative pharmacokinetic data and patient characteristics. For MFX, a 36-year-old male with a bodyweight of 57 kg, a height of 1.60 m, a body mass index (BMI) of 22.2 kg/m², a serum creatinine level of 74 $\mu\text{mol/liter}$, and a moxifloxacin dose of 7.0 mg/kg was chosen. For MFX+RIF, a 56-year-old male with a body weight of 56 kg, a height of 1.63 m, a BMI of 21.1 kg/m², a serum creatinine level of 80 $\mu\text{mol/liter}$, and a moxifloxacin dose of 7.1 mg/kg was selected. The LSSs were optimized using the steady-state AUC_{0-24} . Only clinically feasible LSSs using one to three samples between 0 and 6 h postdose and a sample interval of 1 h were tested. The LSSs were evaluated using acceptance criteria for precision and bias (RMSE < 15%, MPE < 5%) (18). For both MFX and MFX+RIF, one LSS was chosen for internal validation based on performance, as well as clinical feasibility. The AUC_{0-24} estimated with the chosen LSS ($AUC_{0-24, \text{est}}$) was compared to the $AUC_{0-24, \text{ref}}$ using a Bland-Altman plot and Passing Bablok regression. In addition, the performance of a LSS using 2 and 6 h postdose samples was evaluated because this is LSS is frequently used for TDM of anti-TB drugs (31).

LSS using multiple linear regression. Two separate analyses (MFX and MFX+RIF) using multiple linear regression were performed.

Only clinically suitable LSSs (one to three samples, 0 to 6 h postdose, and sample interval of 1 h) were included in the analysis. Each analysis excluded the pharmacokinetic curves without data at the selected time points of the LSS, resulting in a variable number of included curves (N). Multiple linear regression in Microsoft Office Excel 2010 was used to evaluate the correlation of moxifloxacin concentrations at the chosen time points of the LSS and $AUC_{0-24, \text{ref}}$. The acceptance criteria (RMSE < 15%, MPE < 5%) were applied to each LSS (18). Internal validation using 11 different ($n = 6$) subanalyses for MFX and 14 ($n = 1$) subanalyses for MFX+RIF was used to evaluate the performance of the LSSs. Each subanalysis excluded randomly chosen profiles, and all profiles were excluded once (jackknife analysis). Agreement of $AUC_{0-24, \text{est}}$ and $AUC_{0-24, \text{ref}}$ was tested using a Bland-Altman plot and Passing Bablok regression.

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REFERENCES

- World Health Organization. 2018. Global tuberculosis report 2018. World Health Organization, Geneva, Switzerland.
- World Health Organization. 2018. Rapid communication: key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB). World Health Organization, Geneva, Switzerland.
- World Health Organization. 2016. WHO treatment guidelines for drug-resistant tuberculosis: 2016 update. World Health Organization, Geneva, Switzerland.
- World Health Organization. 2010. Guidelines for treatment of tuberculosis, 4th ed. World Health Organization, Geneva, Switzerland.
- Fregonese F, Ahuja SD, Akkerman OW, Arakaki-Sanchez D, Ayakaka I, Baghaei P, Bang D, Bastos M, Benedetti A, Bonnet M, Cattamanchi A, Cegielski P, Chien J-Y, Cox H, Dedicoat M, Erkens C, Escalante P, Falzon D, Garcia-Prats AJ, Gegia M, Gillespie SH, Glynn JR, Goldberg S, Griffith D, Jacobson KR, Johnston JC, Jones-Lopez EC, Khan A, Koh W-J, Kritski A, Lan ZY, Lee JH, Li PZ, Maciel EL, Galliez RM, Merle CSC, Munang M, Narendran G, Nguyen VN, Nunn A, Ohkado A, Park JS, Phillips PPJ, Ponnuraja C, Reves R, Romanowski K, Seung K, Schaaf HS, Skrahina A, Soolingen DV, Tabarsi P, Trajman A, Trieu L, Banurekha VV, Viikklepp P, Wang J-Y, Yoshiyama T, Menzies D. 2018. Comparison of different treatments for isoniazid-resistant tuberculosis: an individual patient data meta-analysis. *Lancet Respir Med* 6:265–275. [https://doi.org/10.1016/S2213-2600\(18\)30078-X](https://doi.org/10.1016/S2213-2600(18)30078-X).
- Codecasa LR, Ferrara G, Ferrarese M, Morandi MA, Penati V, Lacchini C, Vaccarino P, Migliori GB. 2006. Long-term moxifloxacin in complicated tuberculosis patients with adverse reactions or resistance to first line drugs. *Respir Med* 100:1566–1572. <https://doi.org/10.1016/j.rmed.2006.01.002>.
- Chen Q, Liu Y, Liu Y, Mendzelevski B, Chanter D, Pu H, Liu G, Weng O, Hu C, Wang W, Yu C, Jia J. 2015. Orally administered moxifloxacin prolongs QTc in healthy Chinese volunteers: a randomized, single-blind, crossover study. *Acta Pharmacol Sin* 36:448–453. <https://doi.org/10.1038/aps.2014.153>.
- Malik M, Hnatkova K, Schmidt A, Smetana P. 2009. Electrocardiographic QTc changes due to moxifloxacin infusion. *J Clin Pharmacol* 49:674–683. <https://doi.org/10.1177/0091270008330984>.
- Owens RCJ, Ambrose PG. 2005. Antimicrobial safety: focus on fluoroquinolones. *Clin Infect Dis* 41 Suppl 2:S144–S157. <https://doi.org/10.1086/428055>.
- Nijland HMJ, Ruslami R, Suroto AJ, Burger DM, Alisjahbana B, van Crevel R, Aarnoutse RE. 2007. Rifampicin reduces plasma concentrations of moxifloxacin in patients with tuberculosis. *Clin Infect Dis* 45:1001–1007. <https://doi.org/10.1086/521894>.
- Naidoo A, Naidoo K, McIlerron H, Essack S, Padayatchi N. 2017. A review of moxifloxacin for the treatment of drug-susceptible tuberculosis. *J Clin Pharmacol* 57:1369–1386. <https://doi.org/10.1002/jcph.968>.
- Weiner M, Burman W, Luo C-C, Peloquin CA, Engle M, Goldberg S, Agarwal V, Vernon A. 2007. Effects of rifampin and multidrug resistance gene polymorphism on concentrations of moxifloxacin. *Antimicrob Agents Chemother* 51:2861–2866. <https://doi.org/10.1128/AAC.01621-06>.
- Shandil RK, Jayaram R, Kaur P, Gaonkar S, Suresh BL, Mahesh BN, Jayashree R, Nandi V, Bharath S, Balasubramanian V. 2007. Moxifloxacin, ofloxacin, sparfloxacin, and ciprofloxacin against *Mycobacterium tuberculosis*: evaluation of *in vitro* and pharmacodynamic indices that best predict *in vivo* efficacy. *Antimicrob Agents Chemother* 51:576–582. <https://doi.org/10.1128/AAC.00414-06>.
- Peloquin CA, Hadad DJ, Molino LPD, Palaci M, Boom WH, Dietze R, Johnson JL. 2008. Population pharmacokinetics of levofloxacin, gatifloxacin, and moxifloxacin in adults with pulmonary tuberculosis. *Anti-*

- microb Agents Chemother 52:852–857. <https://doi.org/10.1128/AAC.01036-07>.
15. Craig WA. 2001. The hidden impact of antibacterial resistance in respiratory tract infection: re-evaluating current antibiotic therapy. *Respir Med* 95(Suppl A):S12–S27. [https://doi.org/10.1016/S0954-6111\(01\)90023-X](https://doi.org/10.1016/S0954-6111(01)90023-X).
 16. Wright DH, Brown GH, Peterson ML, Rotschafer JC. 2000. Application of fluoroquinolone pharmacodynamics. *J Antimicrob Chemother* 46: 669–683. <https://doi.org/10.1093/jac/46.5.669>.
 17. Gumbo T, Louie A, Deziel MR, Parsons LM, Salfinger M, Drusano GL. 2004. Selection of a moxifloxacin dose that suppresses drug resistance in *Mycobacterium tuberculosis*, by use of an *in vitro* pharmacodynamic infection model and mathematical modeling. *J Infect Dis* 190: 1642–1651. <https://doi.org/10.1086/424849>.
 18. Pranger AD, van Altena R, Aarnoutse RE, van Soolingen D, Uges DRA, Kosterink JGW, van der Werf TS, Alffenaar J. 2011. Evaluation of moxifloxacin for the treatment of tuberculosis: 3 years of experience. *Eur Respir J* 38:888–894. <https://doi.org/10.1183/09031936.00176610>.
 19. MacGowan AP. 1999. Moxifloxacin (Bay 12-8039): a new methoxy quinolone antibacterial. *Expert Opin Investig Drugs* 8:181–199. <https://doi.org/10.1517/13543784.8.2.181>.
 20. Magis-Escarra C, Later-Nijland HMJ, Alffenaar JWC, Broeders J, Burger DM, van Crevel R, Boeree MJ, Donders ART, van Altena R, van der Werf TS, Aarnoutse RE. 2014. Population pharmacokinetics and limited sampling strategy for first-line tuberculosis drugs and moxifloxacin. *Int J Antimicrob Agents* 44:229–234. <https://doi.org/10.1016/j.ijantimicag.2014.04.019>.
 21. Pranger AD, Kosterink JGW, van Altena R, Aarnoutse RE, van der Werf TS, Uges DRA, Alffenaar J-W. 2011. Limited-sampling strategies for therapeutic drug monitoring of moxifloxacin in patients with tuberculosis. *Ther Drug Monit* 33:350–354. <https://doi.org/10.1097/FTD.0b013e31821b793c>.
 22. Angeby KA, Jureen P, Giske CG, Chryssanthou E, Sturegard E, Nordvall M, Johansson AG, Werngren J, Kahlmeter G, Hoffner SE, Schon T. 2010. Wild-type MIC distributions of four fluoroquinolones active against *Mycobacterium tuberculosis* in relation to current critical concentrations and available pharmacokinetic and pharmacodynamic data. *J Antimicrob Chemother* 65:946–952. <https://doi.org/10.1093/jac/dkq091>.
 23. World Health Organization. 2018. Technical report on critical concentrations for drug susceptibility testing of medicines used in the treatment of drug-resistant tuberculosis. World Health Organization, Geneva, Switzerland.
 24. Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, Cattamanchi A, Chaisson LH, Chaisson RE, Daley CL, Grzemska M, Higashi JM, Ho CS, Hopewell PC, Keshavjee SA, Lienhardt C, Menzies R, Merrifield C, Narita M, Brien RO, Peloquin CA, Raftery A, Saukkonen J, Schaaf HS. 2016. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines: treatment of drug-susceptible tuberculosis. *Clin Infect Dis* 63:147–195.
 25. Alffenaar J-W, Tiberi S, Verbeeck RK, Heysell SK, Grobusch MP. 2017. Therapeutic drug monitoring in tuberculosis: practical application for physicians. *Clin Infect Dis* 64:104–105. <https://doi.org/10.1093/cid/ciw677>.
 26. Davies Forsman L, Bruchfeld J, Alffenaar J-W. 2017. Therapeutic drug monitoring to prevent acquired drug resistance of fluoroquinolones in the treatment of tuberculosis. *Eur Respir J* 49:1700173. <https://doi.org/10.1183/13993003.00173-2017>.
 27. Srivastava S, Peloquin CA, Sotgiu G, Migliori GB. 2013. Therapeutic drug management: is it the future of multidrug-resistant tuberculosis treatment? *Eur Respir J* 42:1449–1453. <https://doi.org/10.1183/09031936.00073213>.
 28. Alffenaar J-W, Gumbo T, Aarnoutse RE. 2015. Acquired drug resistance: we can do more than we think! *Clin Infect Dis* 60:969–970. <https://doi.org/10.1093/cid/ciu1146>.
 29. Zuur MA, Bolhuis MS, Anthony R, den Hertog A, van der Laan T, Wilffert B, de Lange W, van Soolingen D, Alffenaar J-W. 2016. Current status and opportunities for therapeutic drug monitoring in the treatment of tuberculosis. *Expert Opin Drug Metab Toxicol* 12:509–521. <https://doi.org/10.1517/17425255.2016.1162785>.
 30. van der Meer AF, Marcus MAE, Touw DJ, Proost JH, Neef C. 2011. Optimal sampling strategy development methodology using maximum a posteriori Bayesian estimation. *Ther Drug Monit* 33:133–146. <https://doi.org/10.1097/FTD.0b013e31820f40f8>.
 31. Alsultan A, Peloquin CA. 2014. Therapeutic drug monitoring in the treatment of tuberculosis: an update. *Drugs* 74:839–854. <https://doi.org/10.1007/s40265-014-0222-8>.
 32. Ramachandran G, Hemanth Kumar AK, Srinivasan R, Geetharani A, Sugirda P, Nandhakumar B, Nandini R, Tharani CB. 2012. Effect of rifampicin and isoniazid on the steady-state pharmacokinetics of moxifloxacin. *Indian J Med Res* 136:979–984.
 33. Manika K, Chatzika K, Papaioannou M, Kontou P, Boutou A, Zarogoulidis K, Kioumis I. 2015. Rifampicin-moxifloxacin interaction in tuberculosis treatment: a real-life study. *Int J Tuberc Lung Dis* 19:1383–1387. <https://doi.org/10.5588/ijtld.14.0935>.
 34. Niemi M, Backman JT, Fromm MF, Neuvonen PJ, Kivistö KT. 2003. Pharmacokinetic interactions with rifampicin: clinical relevance. *Clin Pharmacokinet* 42:819–850. <https://doi.org/10.2165/00003088-200342090-00003>.
 35. Pasipanodya JG, McIlleron H, Burger A, Wash PA, Smith P, Gumbo T. 2013. Serum drug concentrations predictive of pulmonary tuberculosis outcomes. *J Infect Dis* 208:1464–1473. <https://doi.org/10.1093/infdis/jit352>.
 36. Modongo C, Pasipanodya JG, Magazi BT, Srivastava S, Zetola NM, Williams SM, Sirugo G, Gumbo T. 2016. Artificial intelligence and amikacin exposures predictive of outcomes in multidrug-resistant tuberculosis patients. *Antimicrob Agents Chemother* 60:5928–5932. <https://doi.org/10.1128/AAC.00962-16>.
 37. Alsultan A, An G, Peloquin CA. 2015. Limited sampling strategy and target attainment analysis for levofloxacin in patients with tuberculosis. *Antimicrob Agents Chemother* 59:3800–3807. <https://doi.org/10.1128/AAC.00341-15>.
 38. Dijkstra JA, van Altena R, Akkerman OW, de Lange WCM, Proost JH, van der Werf TS, Kosterink JGW, Alffenaar J. 2015. Limited sampling strategies for therapeutic drug monitoring of amikacin and kanamycin in patients with multidrug-resistant tuberculosis. *Int J Antimicrob Agents* 46:332–337. <https://doi.org/10.1016/j.ijantimicag.2015.06.008>.
 39. Kamp J, Bolhuis MS, Tiberi S, Akkerman OW, Centis R, de Lange WC, Kosterink JG, van der Werf TS, Migliori GB, Alffenaar J-W. 2017. Simple strategy to assess linezolid exposure in patients with multidrug-resistant and extensively-drug-resistant tuberculosis. *Int J Antimicrob Agents* 49: 688–694. <https://doi.org/10.1016/j.ijantimicag.2017.01.017>.
 40. van den Elsen SHJ, Sturkenboom MGG, Van't Bovenind-Vrubleuskaya N, Skrahina A, van der Werf TS, Heysell SK, Mpagama S, Migliori GB, Peloquin CA, Touw DJ, Alffenaar J-W. 2018. Population pharmacokinetic model and limited sampling strategies for personalized dosing of levofloxacin in tuberculosis patients. *Antimicrob Agents Chemother* 62: e01092-18.
 41. Brillault J, De Castro WV, Harnois T, Kitzis A, Olivier J-C, Couet W. 2009. P-glycoprotein-mediated transport of moxifloxacin in a Calu-3 lung epithelial cell model. *Antimicrob Agents Chemother* 53:1457–1462. <https://doi.org/10.1128/AAC.01253-08>.
 42. Hong T, Han S, Lee J, Jeon S, Park G-J, Park W-S, Lim KS, Chung J-Y, Yu K-S, Yim D-S. 2015. Pharmacokinetic-pharmacodynamic analysis to evaluate the effect of moxifloxacin on QT interval prolongation in healthy Korean male subjects. *Drug Des Dev Ther* 9:1233–1245. <https://doi.org/10.2147/DDDT.S79772>.
 43. Stass H, Dalhoff A, Kubitz D, Schuhly U. 1998. Pharmacokinetics, safety, and tolerability of ascending single doses of moxifloxacin, a new 8-methoxy quinolone, administered to healthy subjects. *Antimicrob Agents Chemother* 42:2060–2065. <https://doi.org/10.1128/AAC.42.8.2060>.
 44. Naidoo A, Chirehwa M, McIlleron H, Naidoo K, Essack S, Yende-Zuma N, Kimba-Phongi E, Adamson J, Govender K, Padayatchi N, Denti P. 2017. Effect of rifampicin and efavirenz on moxifloxacin concentrations when co-administered in patients with drug-susceptible TB. *J Antimicrob Chemother* 72:1441–1449. <https://doi.org/10.1093/jac/dkx004>.
 45. Proost JH, Eleveld DJ. 2006. Performance of an iterative two-stage Bayesian technique for population pharmacokinetic analysis of rich data sets. *Pharm Res* 23:2748–2759. <https://doi.org/10.1007/s11095-006-9116-0>.
 46. Burnham K, Anderson D. 2004. Multimodel inference: understanding AIC and BIC in model selection. *Sociol Methods Res* 33:261–304. <https://doi.org/10.1177/0049124104268644>.