

Population Pharmacokinetics of Levofloxacin and Moxifloxacin, and the Probability of Target Attainment in Ethiopian Patients with Multidrug-Resistant Tuberculosis

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Objective: This study aimed to explore the population pharmacokinetic modeling (PopPK) of levofloxacin (LFX) and moxifloxacin (MXF), as well as the percent probability of target attainment (PTA) as defined by the ratio of the area under the plasma concentration-time curve over 24 h and the in vitro minimum inhibitory concentration (AUC₀₋₂₄/MIC) in Ethiopian multidrug resistant tuberculosis (MDR-TB) patients.

Methods: Steady state-plasma concentration of the drugs in MDR-TB patients were determined using optimized liquid chromatography-tandem mass spectrometry. PopPK and simulations were run at various doses, and pharmacokinetic parameters were estimated. The effect of covariates on the PK parameters and PTA for maximum mycobacterial kill and resistance prevention was also investigated.

Results: LFX and MXF both fit in a one-compartment model with adjustments. Serum-creatinine (Cr) influenced ($p = 0.01$) the clearance of LFX, whereas body mass index (BMI) influenced ($p = 0.01$) the apparent volume of distribution (V) of MXF. The PTA for LFX maximal mycobacterial kill at the critical MIC of 0.5 mg/L with the simulated 750 mg, 1000 mg, and 1500 mg doses were 29%, 62%, and 95%, respectively, whereas the PTA for resistance prevention at 1500 mg was only 4.8%, with none of the lower doses achieving this target. At the critical MIC of 0.25 mg/L, there was no change in the PTA for maximum bacterial kill when the MXF dose was increased (600 mg, 800 mg, and 1000 mg), but the PTA for resistance prevention was improved.

Conclusion: The standard doses of LFX and MXF may not provide adequate drug exposure. PopPK of LFX is more predictable for maximum mycobacterial kill, whereas MXF's resistance prevention target increases with dose. Cr and BMI are likely important covariates for dose optimization in Ethiopian patients.

Keywords: population pharmacokinetics, probability of target attainment, moxifloxacin, levofloxacin, MDR-TB patients, Ethiopia

Introduction

Fluoroquinolones (FQs) are used off-label for the treatment of multidrug-resistant tuberculosis (MDR-TB), and for evaluation in shortening the duration of drug susceptible TB in recently prioritized regimens.¹ Within the class, levofloxacin (LFX) and moxifloxacin (MXF) play a substantial role in ensuring success in treatment outcomes and are important components of the World Health Organization (WHO) Group A regimen.²⁻⁵ However, pharmacokinetic (PK) variability within and between individuals is very common and may lead to suboptimal plasma levels and undesired treatment outcomes.⁶⁻⁸ The observed FQs PK variability may be due to comorbidities (diabetes mellitus or HIV) that contribute to malabsorption, concomitant medications, dietary intake, medication adherence, or host pharmacogenetics,

and can impact other PK drivers such as drug metabolism.^{9–11} Dosage optimization based on an understanding of plasma exposure profile of FQs in patients (PK factor) and in vitro drug susceptibility patterns (PD factor) of *Mycobacterium tuberculosis* (Mtb) may improve treatment outcomes.^{12,13}

The ratio of the 24 h area under the concentration-time curve (AUC) and in vitro minimum inhibitory concentration (MIC) (AUC0-24/MIC) has been accepted as the strongest predictor of FQs exposure and favorable clinical outcome.^{14–16} A hollow fiber bioreactor system (HFS) experiment has established that an unbound AUC0-24/MIC ratio of 53 for MXF substantially decreases the total population of Mtb by more than 3 log₁₀ CFU/mL and suppresses the emergence of drug resistance. Moreover, an AUC0-24/MIC ratio of ≥ 100 for MXF completely kills FQ-sensitive population of Mtb without development of drug resistance.^{17,18} Another HFS experiment with LFX recently showed that the AUC0-24/MIC associated with maximal Mtb killing was 146, while the ratio associated with resistance suppression was 360. The experiment suggested that up to 1500 mg LFX doses are needed for best microbial killing if adverse effects are not an issue.¹⁹

Even though Ethiopia has recently transitioned out of the MDR-TB/Rifampicin resistant (RR)-TB world countries list, it remains on the list of 30 high TB/HIV burden countries.²⁰ People of diverse ethnic background live in Ethiopia, although one-size-fits-all scenario is practiced in TB therapeutics.^{21,22} Evidence of interindividual variability (IIV), drug exposure profiles in MDR-TB patients and its impact on treatment outcomes are lacking. To the best of our knowledge, the PK of LFX and MXF among Ethiopian patients treated for MDR-TB is not yet studied. Furthermore, whether adequate in vivo serum exposure is attained with the current standard dose to achieve maximal bacterial kill and prevent resistance is not yet explored. The aim of this study was therefore to determine the population pharmacokinetic modeling (PopPK) of LFX and MXF and the probability of target attainment (PTA) for maximal mycobacterial kill and prevention of resistance in a group of people treated for MDR-TB in Ethiopia.

Materials and Methods

Study Setting and Design

This is a follow-up of our previous prospective cohort study,²³ enrolling MDR-TB/RR-TB patients in four hospitals of Southern Ethiopia, namely, Butajira, Yirgalem, Arbaminch, and Nigist Eleni Mohammed Memorial teaching hospitals. These hospitals were among the first four hospitals identified by the Ministry of Health of Ethiopia as treatment initiative centers for MDR-TB treatment in Southern Ethiopia.

Participant Eligibility

As recommended by the recently integrated WHO Treatment Guidelines,²⁴ eligible study participants were outpatients who visited the center monthly for drug refills and treatment response monitoring. MDR-TB patients aged 18 years and older with or without co-infection with HIV, receiving LFX (750 or 1000 mg/day) – or MXF (600 mg/day)-based regimens for at least 8 days (see Ref 23 for details of regimens) and provided written informed consent were included. Those severely ill and anemic defined by a hematocrit less than 25% (most recent value, measured within 30 days of the PK study) were excluded. All patients included in this study received standard TB treatment according to the National Guidelines for Tuberculosis and Leprosy, which is adopted from the WHO Guidelines.^{25,26}

Variables, Sample Collection and Bioanalysis

Demographic, clinical and laboratory data were collected using a data abstraction form by trained public health specialists in each hospital. Upon giving informed consent, the patients were asked to stay for 48 h at the centres for blood sampling during one of their monthly visits. About 4 mL blood was drawn using a vacutainer (Becton–Dickinson Biosciences, San Jose, CA, USA) in EDTA tubes at 0 (pre-dose sampling), 2, 4, 6, 9, 12, and 24 h following drug intake. After mixing the blood with the anticoagulant, plasma was immediately separated, and the test tubes were appropriately labeled. The samples were transported to Wolaita Sodo University Hospital, stored at -80°C and then shipped to Inje University College of Medicine, South Korea for bioanalysis. Plasma concentrations of LFX and MXF were determined using a high-performance liquid chromatography-electrospray ionization–tandem mass spectrometry previously developed and validated by the Inje University research group.²⁷

Determination of Minimum Inhibitory Concentration

MICs of the second-line antitubercular drugs were determined from patients for whom pre-treatment clinical isolates of *Mtb* were available. MIC was determined using the broth microdilution method in Middlebrook 7H9 broth supplemented with 10% Oleic Albumin Dextrose Catalase (OADC) and 0.05% tyloxapol.²⁸ *M. tuberculosis* H37Rv (ATCC 27294) was used as the reference strain and its targeted MIC values were in the range of 0.0625–8.0 mg/L for LFX and 0.0625–16.0 mg/L for MXF.

Pharmacokinetic Model Development

Structural Model

Individual PK profiles for both LFX and MXF were estimated using a non-compartmental approach in Phoenix WinNonlin version 8.0 (Certara, Princeton, NJ, USA) and maximum plasma concentration (C_{max}) and AUC_{0–24} were calculated and reported as mean ± S.E and median (IQR). The PopPK was developed using nonlinear mixed effect modelling (Phoenix NLME) and analysis of covariates was performed. First-order conditional estimation algorithms were used for model development. Various structural models were tested, including one or two compartment distributions with first-order absorption and elimination (with or without absorption lag time). Additive, proportional, and combined residual error models were also tested. Model selection was based on model fit and visual inspection of diagnostic plots, the precision of parameter estimation, minus two log likelihood (–2LL) value, and Akaike information criterion (AIC) and Bayesian information criterion (BIC). The reliability of the final model was assessed by the 95% confidence intervals (CIs) of the 2.5th and 97.5th percentiles of the simulated concentration-time profile. The PK parameters of a typical population along with their IIV were estimated using an exponential function. The PopPK estimated PK parameters were reported in terms of geometric mean (GM) and percent relative standard error (%RSE) while IIV was reported in terms of percent coefficient of variability (%CV).

Covariates

Based on previous similar studies and scientific interest, we included the following covariates in the current PopPK: nutritional status, gender, serum creatinine (Cr), adverse drug effects, comorbidities, alanine aminotransferase (AAT), aspartate aminotransferase (AST), bilirubin, and body mass index (BMI). The covariate selection was performed by forward addition ($p = 0.05$) and backward subtraction ($p = 0.01$). Visual predictive checks (VPCs) based on 1000 Monte Carlo simulations were performed to assess robustness of the final model. For continuous covariates, a power function was used using Equation 1:

$$\text{TVPi} = \theta_1 \times (\text{COVi} / \text{COV}_{\text{mean}})^{\theta_2} \quad (1)$$

Where TVPi is the typical value of a PK parameter (P) for an individual i with a COVi value of the covariate, while θ_1 is the typical value for an individual with a mean covariate value of COV_{mean} and θ_2 is the power coefficient describing covariate parameter relationship.

For binary covariates, the fractional change in the typical parameter values was determined according to Equation 2:

$$\text{TVPi} = \theta_1 \times \theta_2^N \quad (2)$$

where TVPi is as defined in Equation 1 above, θ_1 is the typical value for an individual in whom the covariate takes the value 0 ($N = 0$), and θ_2 is the fractional change in the typical value when the covariate takes the value 1 ($N = 1$).

Interindividual Variability

Distributions of IIV were assumed to be log-normal and described by the following exponential error model (Equation 3):

$$\text{Pi} = \text{TVP} \times \exp(\eta \text{Pi}) \quad (3)$$

Where Pi is the parameter value for an individual i , TVP is the typical population value of the parameter, and ηPi (ETAs) are individual-specific IIV for an individual i and the parameter P. ETAs were assumed to be normally distributed with a mean of 0 and variances of ω^2 : $\eta \sim N(0, \omega^2)$. For all PK parameters, IIV was estimated and described as percent coefficient of variability (%CV).

Residual Error

The residual error model was described by both combined additive and proportional error models for individual and population predicted plasma concentrations as depicted in Equations 4 and 5, respectively:

$$DV_{ij} = IPRED_{ij} + IPRED_{ij} \times \epsilon_{1ij} + \epsilon_{2ij} \quad (4)$$

$$DV_{ij} = PRED_{ij} + PRED_{ij} \times \epsilon_{1ij} + \epsilon_{2ij} \quad (5)$$

Where DV_{ij} is the observed plasma concentration of the individual i at time j , $IPRED$ is the corresponding model predicted concentration, and $PRED$ is the population predicted plasma concentration, ϵ_{1ij} and ϵ_{2ij} are proportional and additive components, respectively, of the residual random error. The residual error components were assumed to be normally distributed with a mean of 0 and variances of σ^2 : $\epsilon \sim N(0, \sigma^2)$

Drug Exposure and the Percent Probability of Target Attainment

The final model was used to construct simulated PK profiles for individual patients at various doses (using individual PK parameters and covariates, assuming dose-independent PK) and to calculate % PTA. The simulated doses of LFX were 750 mg, 1000 mg and 1500 mg, while those of MXF were 600 mg, 800 mg, and 1000 mg. C_{max} and AUC0-24 were calculated using the individual simulated profiles. Box plots were used to show simulated concentrations and patient exposure (C_{max} and AUC0-24) for each drug.

Using the assumed MIC based on those values determined for some patients involved in this study, and excluding those values well above the typical cut-off for resistance, the %PTA as defined by AUC0-24/MIC ratio for each MIC value for the original and simulated doses of LFX and MXF was analyzed descriptively. The number of patients achieving a specific target AUC0-24/MIC was described in % PTA against the total observations. The targets selected for the maximal mycobacterial kill and resistance suppression in the mutant strains for LFX were 146 and 360, respectively.¹⁹ Similarly, the two targets selected for MXF were 53 and 100, respectively.^{17,18} The formula we used for the PTA calculation was:

$$PTA(\%) = \frac{\text{number of patients attained the required AUC0-24/MIC}}{\text{Total number of patients}} \times 100\% \quad (6)$$

Ethical Considerations

This study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from both the Institutional Review Board of College of Health Sciences, Addis Ababa University (Protocol number 078/17/Pharma) and the National Ethical Review Committee of the Ministry of Science and Higher Education (Reference number MoSHE//RD/141/2318/19). Written informed consent was obtained after participants were informed about the purpose, benefits, and risks of the study. Confidentiality and anonymity were ensured by restricting access and removing identifiers.

Results

Patient Characteristics

There were 62 MDR/RR-TB patients for a potential PK sampling, out of which 7 were excluded due to critical illness. Plasma samples were therefore obtained from 55 patients. Of these, a total of 39 patients (21 for LFX and 18 for MXF) had adequate sample collection and plasma concentration with acceptable concentration-time profiles. Samples with lower than 5 time-point concentrations over 24 h and those with erratic concentration profiles were excluded from the analysis. Demographic, laboratory, and clinical characteristics of the patients are summarized in Table 1. There were no statistically significant differences in baseline characteristics between the LFX and MXF groups. Of the 39 patients included in the analysis, 19 patients (9 from LFX-and 10 from MXF-based regimen treatment group) had encountered at least one ADRs during the follow-up.

Table 1 Demographic and Clinical Characteristics of Ethiopian MDR-TB Patients Receiving the Standardized LFX- (n=21) and MXF- (n=18) Based Regimen

Characteristics	Total N=39	LFX-Regimen (n= 21)	MXF-Regimen (n=18)
Age	26 (20–32)	26 (20–30)	26 (20–37)
Male	20 (51.3)	12 (57.1)	8 (44.4)
Weight (Kg)	49 (43.0–52.4)	45 (42.5–52.3)	51 (46.6–65.0)
Height (cm)	165.5 (160–172)	168 (160–174)	165 (161.5–171.5)
BMI (kg/m ²)	17.1 (15.6–18.9)	16.7 (15.6–18)	17.3 (16.2–19.2)
Co-existing illness	13 (33.3)	8 (38.1)	5 (27.8)
Prior TB treatment	30 (77)	15 (71.4)	15 (83.3)
Smoking	5 (12.8)	3 (14)	2 (11.1)
Malnourished*	19 (48.7)	9 (42.9)	10 (55.6)
Cavitary disease	18 (46.2)	9 (42.9)	9 (50)
Cr. (mg/dL)	0.9 (0.8–1.3)	1 (0.8–1.3)	1 (0.8–1.4)
AST (IU/L)	29 (20–38)	25 (18.0–34.6)	31 (21.0–40)
ALT (IU/L)	23 (15–45)	19.2 (14.0–35)	28 (17.8–50.2)
Hgb (g/dl)	13.8 (12.3–15.1)	12.8 (12.1–14.3)	13.4 (12.2–14.3)

Notes: Data presented as n (%) or median (IQR); *Patients with BMI less than 16 kg/m² were considered as malnourished.

Abbreviations: AST, alanine aminotransferase; ALT, alanine transaminase; ALB, albumin; BMI, body mass index; cm, centimeter; g/dl, grams per deciliter; Hgb, hemoglobin; IU/L, international units (IU) per liter.

The Population PK Model

Whilst the LFX dataset fits into a one-compartment model that includes both additive and multiplicative error models with lag time, the MXF dataset fits into a one-compartment model with additive error models without lag time. Residual variation was taken into account for all parameters. Table 2 shows the PopPK estimates in GM and %RSE, and IIV as %

Table 2 Overall and Final One-Compartment Model for LFX (n=21) and MXF (n=18), and Covariates Included in the Model in Ethiopian MDR-TB Patients

Drug	PK Parameter	Final Model	
		GM (%RSE)	%CV (Shrinkage, %)
LFX	Ka (1/h)	0.2 (4.0)	14 (60)
	V (Liter)	122 (21.5)	26 (30)
	Cl (L/h)	10.4 (7.7)	66 (60)
	Tlag (h)	0.2 (6.1)	3.4 (60)
	Cr (mg/dL)	1.1 (10)	14.7 (NA)
	–2LL	449.2	
	AIC	473.2	
	BIC	507.2	(9)
MXF	Ka (1/h)	0.5 (18.8)	59 (50)
	V (Liter)	102.2 (10.0)	10 (40)
	Cl (Liters/h)	20 (3.5)	2.7 (70)
	BMI (Kg.m2)	17.8 (1.1)	4.5 (NA)
	–2LL	184.2	
	AIC	202.2	
	BIC	225.7	(3)

Note: Lag time (Tlag) is the time taken for the drugs to appear in circulation following the drug dosing.

Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion; Cl, clearance; Percent coefficient of variation (% CV= 100 × IIV/parameter estimate); Ka, absorption constant; GM, geometric mean; IIV, interindividual variability; –2LL, minus two log likelihood; LFX, levofloxacin; MXF, moxifloxacin; NA, not applicable; PK, pharmacokinetics; %RSE, percentage of relative standard error (%RSE = 100 × standard error/parameter estimate); Cr, serum creatinine; Tlag, lag time for absorption; V, apparent volume of distribution.

CV of the PK parameters for both groups. The Goodness-of-fit of the final model for LFX and MXF is summarized in Figure 1. VPCs for both models showed that most of the data are within the 90% prediction interval and around median values (Figure 2). Upon performing a stepwise search for covariates, the $-2LL$ value was significantly reduced in scenarios, where Cr was used as a covariate for clearance (CL) of LFX data set. Therefore, this was selected as the final model for LFX. In a similar covariate screen, BMI as the apparent volume distribution (V) covariate, the $-2LL$ score was significantly reduced and this was selected as the final model for MXF.

Total Drug Exposure

The individual participants' mean \pm standard error and median (Interquartile range) values of C_{max} and AUC₀₋₂₄ from the non-compartmental analysis of the original and simulated drug doses are summarized in Table 3. Figure 3 depicts box plots of C_{max} and AUC₀₋₂₄ for LFX and MXF.

MIC Distribution of the Clinical Isolates

The MIC of LFX and MXF were successfully determined from the clinical isolates of 28 patients. However, the MICs for the remaining clinical isolates could not be determined as they did not grow from subculture after transportation to the referral laboratory. The individual MIC values (percent) for LFX were 0.25 mg/L (46.4%), 0.50 mg/L (42.8%), 2.0 mg/L (3.6%), 4 mg/L (3.6%), and 8 mg/L (3.6%); whereas they were 0.0625 mg/L (25%), 0.125 mg/L (53.6%), 0.25 mg/L (10.7%), 2.0 mg/L (7.1%), and 8.0 mg/L (3.6%) for MXF. Given that the WHO recommended critical susceptibility value for Mtb is 0.5 mg/L for LFX and 0.25 mg/L for MXF, 7.2% of the clinical isolates were resistant to LFX and 10.7% were resistant to MXF.

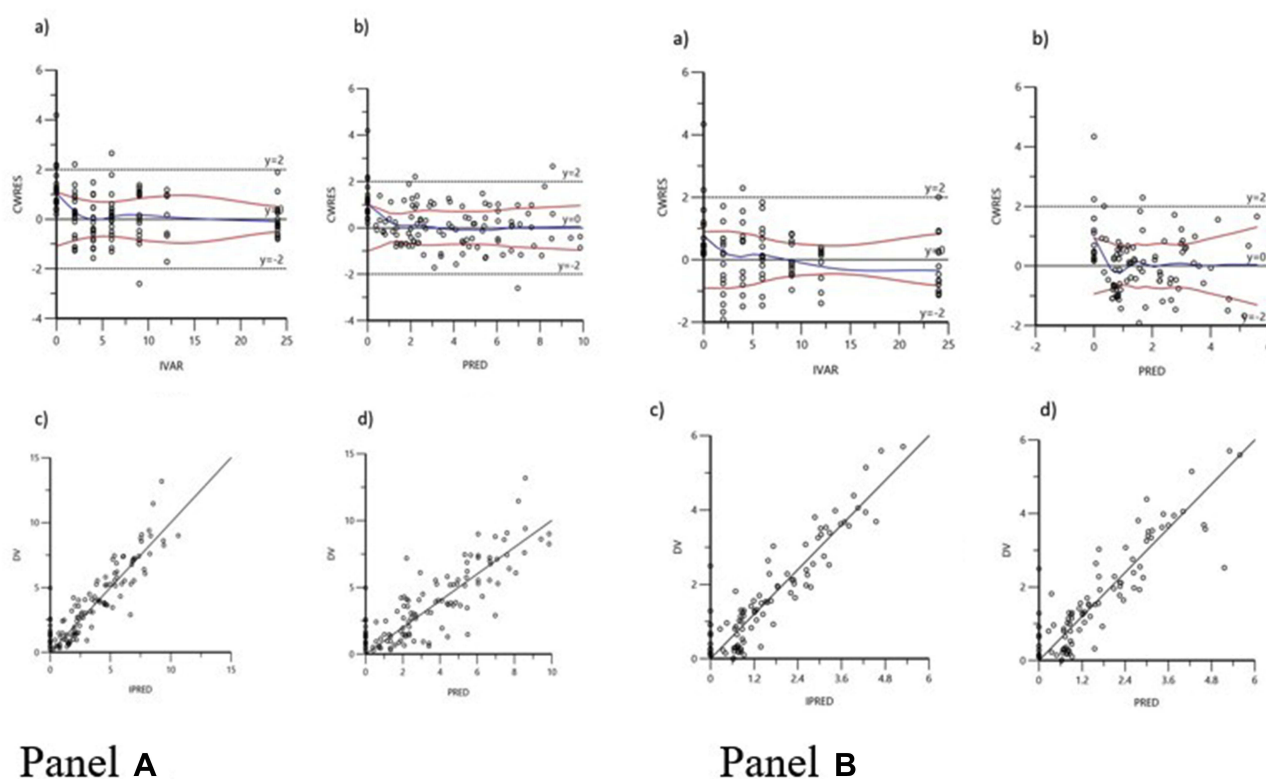


Figure 1 Goodness-of-fit plots for the final population pharmacokinetics of LFX (**A**) and MXF (**B**): conditional weighted residuals versus time (CWRES versus IVAR) (a); conditional weighted residuals versus population predicted concentrations (CWRES versus PRED) (b); observed versus individual predicted concentrations (DV versus IPRED) (c); observed versus population predicted concentrations (DV versus PRED) (d). The red lines in the panels represent smoothed regression lines.

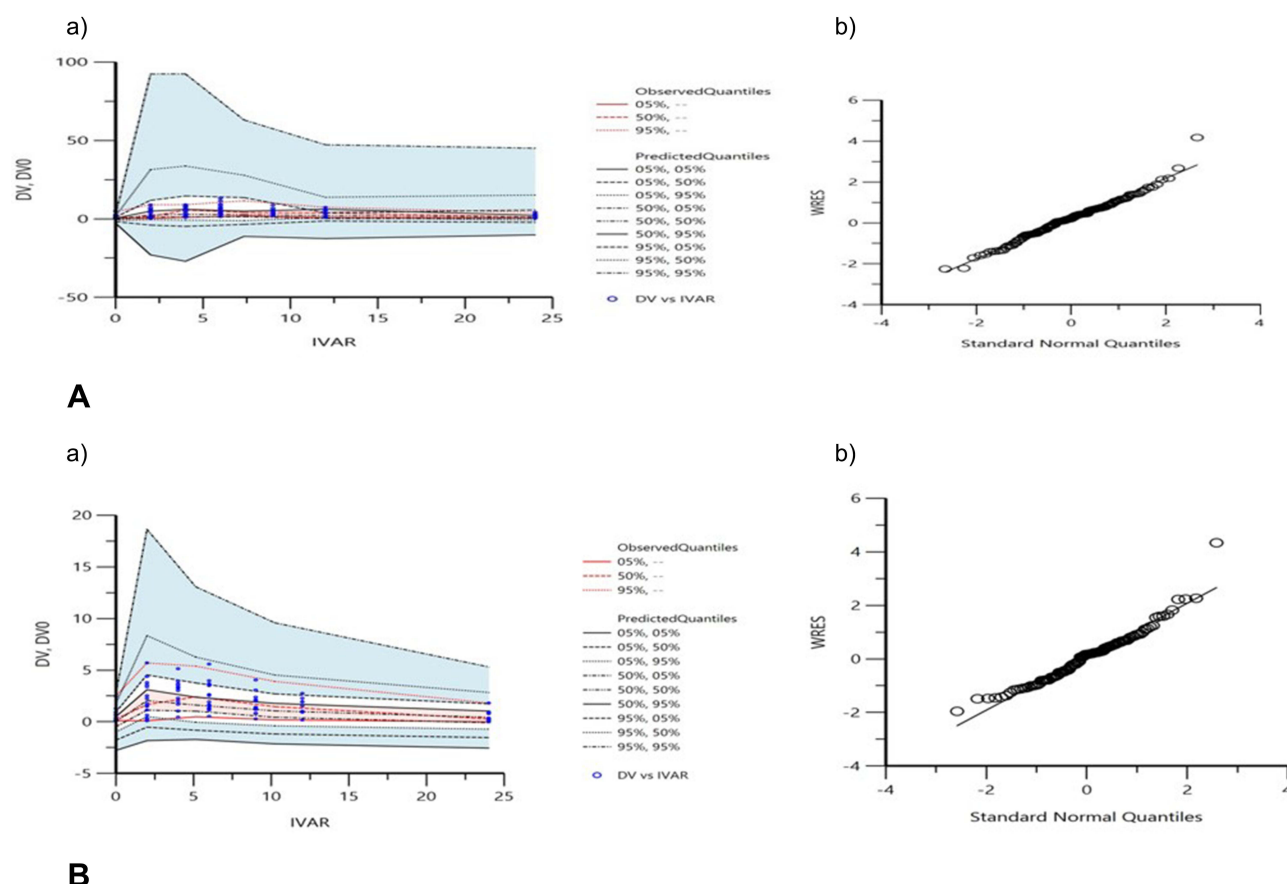


Figure 2 Visual predictive checks (a) and WRES versus Standard Normal Quantiles (b) for the final model of LFX (**A**) and MXF (**B**): red lines represent the 5th, 50th, and 95th percentiles of the observed concentrations; the shaded areas represent the 90% confidence intervals of the 5th, 50th, and 95th percentiles of the simulated concentrations, respectively; the dots represent the observed data; DV represents observed concentration; DV0, observed concentration at zero time; IVAR, time; WRES, weighted residuals.

The Probability of Target Attainment

The % PTA for the simulated doses of 750 mg, 1000 mg, and 1500 mg of LFX for the two targets ($AUC_{0-24}/MIC \geq 146$, for the mycobacterial kill and $AUC_{0-24}/MIC \geq 360$, for resistance suppression) is depicted in Figure 4. At the WHO recommended critical MIC of 0.5 mg/L, the PTAs for the maximal bacterial kill were 29%, 62%, and 95% for the simulated doses of LFX, respectively. As regards to resistance suppression, whilst the 750 mg and 1000 mg LFX did not achieve the PTA needed for resistance suppression, only 4.8% attained the PTA needed with the 1500 mg LFX. Only the 1500 mg LFX achieved 24% PTA for the maximal bacterial kill when the MIC was changed to 1 mg/L. Interestingly, none of the doses were able to attain the PTA for resistance suppression at MIC values ≥ 1 mg/L.

In a similar fashion, the PTA for the simulated doses of 600 mg, 800 mg, and 1000 mg of MXF at the two targets ($AUC_{0-24}/MIC \geq 53$, for the mycobacterial kill and $AUC_{0-24}/MIC \geq 100$, for resistance suppression) is depicted in Figure 5. At the WHO recommended critical MIC of 0.25 mg/L for MXF, the PTA needed for the maximal mycobacterial kill was the same (94.4%) for all doses. However, the PTA needed for resistance suppression varied with doses, 50%, 77.8%, and 94.4%, respectively. The PTAs calculated for the mycobacterial kill decreased with increasing the MIC value to 1 mg/mL and were 11.1%, 27.8%, and 38.9%, respectively. However, none of the doses achieved the PTA needed for resistance suppression at the MIC value of 1 mg/L and above.

Table 3 Descriptive Summary of the Non-Compartmental Analysis of the Estimated Individual PK Parameters for the Original and Simulated Doses of LFX (n=21) and MXF (n=18) in Ethiopian MDR-TB Patients

Drug	Dose (mg)	C _{max} ±SE (mg/L)	C _{max} (IQR) (mg/L)	AUC ₀₋₂₄ ±SE (h. mg/L)	AUC ₀₋₂₄ (IQR) (h. mg/L)
LFX*	750	7.8 ± 0.6	7.5 (5.5–9.7)	63.8 ± 6.4	60.9 (40.0–81.8)
	1000	10.3 ± 0.8	10.0 (7.3–12.8)	85.3 ± 8.6	81.5 (51.9–109.2)
	1500	15.4 ± 1.2	15.1 (10.8–19.2)	128 ± 13.0	122.7 (77.8–164.1)
LFX†	750	5.8 ± 0.5	5.3 (4.6–6.7)	66.5 ± 9.5	58.1 (45.0–80.5)
	1000	8.2 ± 0.7	7.4 (6.1–9.4)	97.9 ± 9.3	103.4 (71.5–108.6)
MXF*	600	2.7 ± 0.4	2.6 (1.5–3.9)	31.5 ± 4.1	25.1 (19.0–47.0)
	800	3.5 ± 0.4	3.5 (2.0–5.0)	40.6 ± 4.8	33.4 (25.2–62.7)
	1000	4.40 ± 0.6	4.4 (2.5–6.3)	50.8 ± 6.0	41.8 (31.6–78.4)
MXF†	600	2.9 ± 0.4	3.2 (1.4–3.9)	33.4 ± 4.2	28.2 (19.3–50.8)

Notes: *Simulated doses and †Observed doses.

Abbreviations: AUC₀₋₂₄, area under the concentration-time curve over twenty-four hours; C_{max}, maximum serum concentration; IQR, interquartile range; mg/L, milligram per liter; SE, standard error.

Discussion

In this first PopPK of LFX and MXF in Ethiopian patients treated for MDR-TB, we importantly demonstrated that current doses of both medications led to poor probability of attaining PK targets that have previously been associated with microbial kill and prevention of acquired resistance. While multiple factors may have influenced this underexposure, the observed IIV in PK/PD parameters may result in poor treatment outcomes.²⁹ We also demonstrated that the LXF

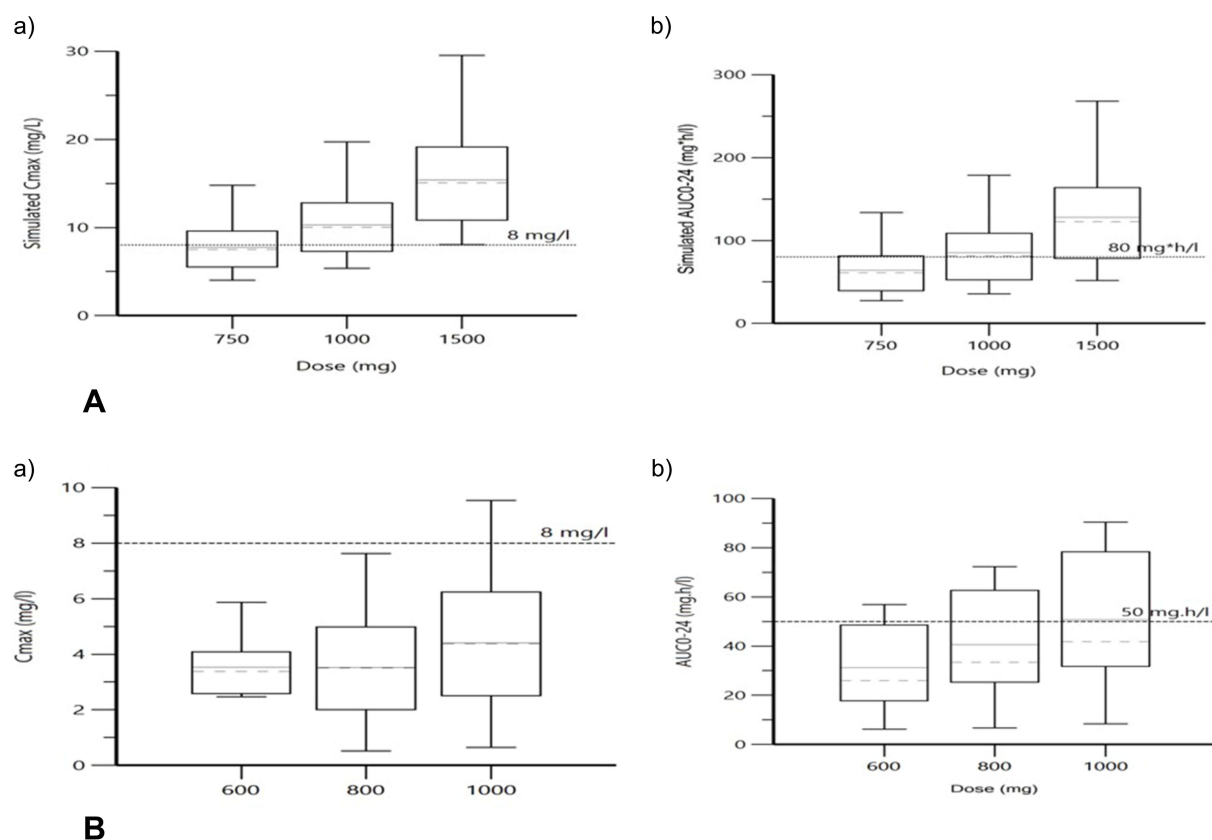


Figure 3 Box plot for simulated C_{max} (a) and AUC₀₋₂₄ (b) of LFX (A) and MXF (B): the dashed line indicates the minimum threshold for C_{max} and AUC₀₋₂₄.

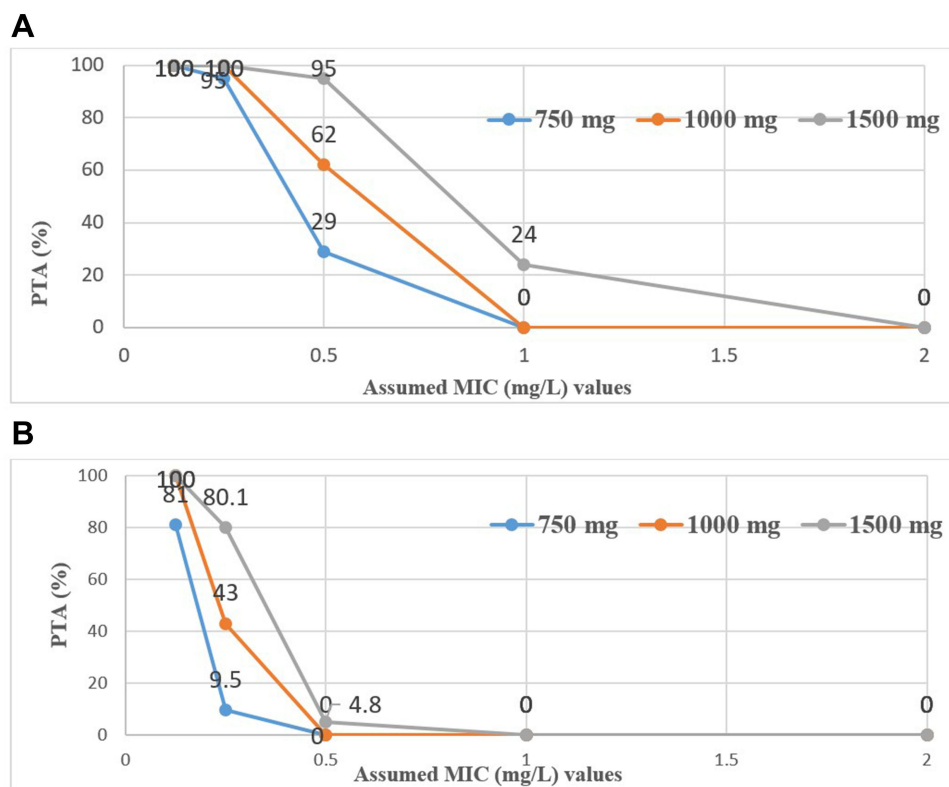


Figure 4 Percent probability of target attainment, PTA (%) for the maximal mycobacterial kill ($AUC_{0-24}/MIC \geq 146$) (A) and resistance suppression ($AUC_{0-24}/MIC \geq 360$) (B) of the simulated doses of LFX (750 mg, 1000 mg, and 1500 mg) against the assumed MIC values in Ethiopian MDR-TB patients (n=21).

Note: The formula used for the calculation of the percent probability of target attainment (PTA) was: $PTA (\%) = \frac{\# \text{ of patients attained the required } AUC_{0-24}/MIC}{\text{Total \# of patients}} \times 100\%$.

concentration dataset was described best by a one-compartment model with both additive and multiplicative combination error model with lag time, whereas that of MXF was described best by a one-compartment additive error model with no lag time. MXF and LFX data for MDR-TB patients have been described by a one-compartment model in some previous studies^{30,31} and by a two-compartment model in others.^{32,33} The reason for this variation is unclear. The differences in the total sample size and number of plasma samples collected during the elimination phases in the studies could be a reason for the observed variations. For example, MXF PopPK was described by a two-compartment model in 241 MDR-TB patients from South Africa.³³ Plasma samples on 10 different occasions were collected over 50 h while in the present study 5 to 7 plasma samples were collected over 24 h. We found that the relative IIV (%CV) of the population estimated K_a was higher in the MXF group than in the LFX group, and the IIV of V and CL was higher in the LFX group than in the MXF group. High shrinkage was observed for some model estimated PK parameters in this study. This might be associated with fewer number observations per subjects as it is consistent with other previous studies.³⁴

Overall, higher doses were predicted to result in improved maximal bacterial kill target for LFX but not for MXF, although MXF achieved resistance prevention targets better than LFX. The AUC_{0-24} for MXF corrected to a 400 mg standard dose ranged from 10.2 to 79.1 mg.h/L in a study by Van den Elsen et al,³⁵ which compared MXF with and without rifampin. The corresponding AUC_{0-24} values for the 600 mg in our study ranged from 3.5 to 72.2 mg.h/L. Given that no rifampin was used in our cohort, we expected even higher MXF exposure. At the in vitro critical concentration of 0.25 mg/L, which is currently recommended by WHO to determine susceptibility,³⁵ there was no difference in the PTA (94.4%) needed for the maximal bacterial kill between the lower and higher MXF simulated doses. However, significant improvements in PTA were reached for the target of resistance prevention with the highest simulated MXF dose (1000 mg). Nevertheless, when utilizing an MIC value just a dilution higher at the borderline of susceptible (0.5 mg/liter) and the target AUC_{0-24} of 50–65 mg.h/liter,^{36,37} the PTA needed for the resistance suppression with the 600 mg dose of MXF in Ethiopian patients would be only 22.2%. Yet, at higher simulated doses of 800 mg and

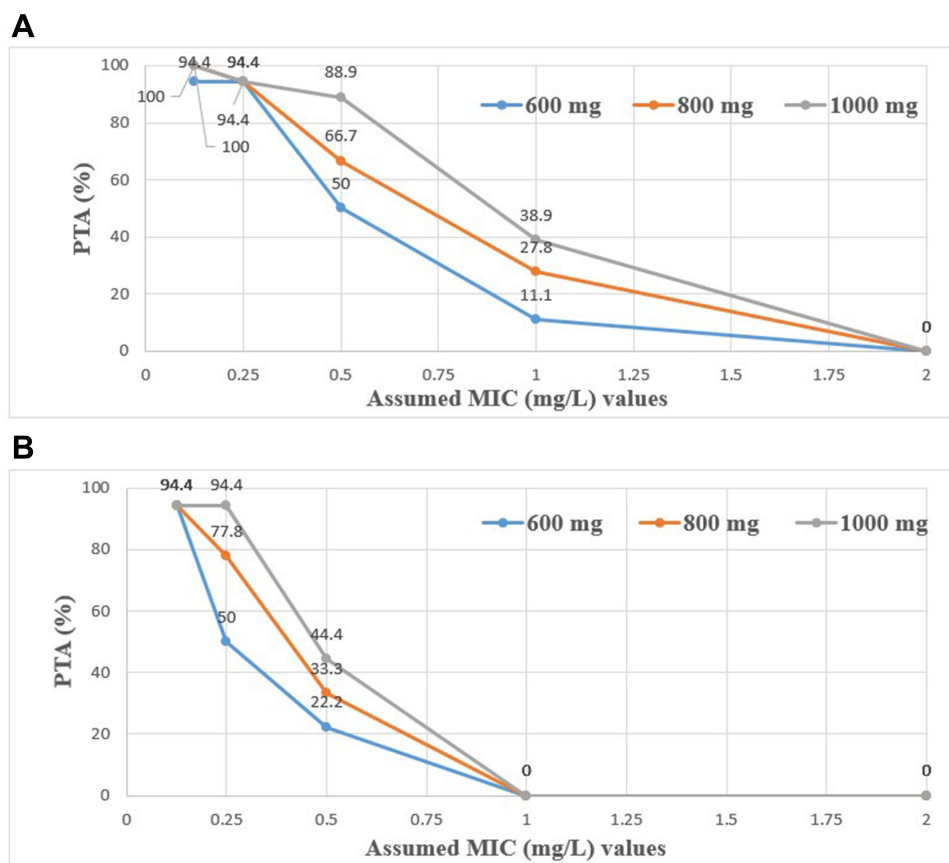


Figure 5 Percent probability of target attainment, PTA (%) for the maximal mycobacterial kill ($AUC_{0-24}/MIC \geq 53$) (**A**) and resistance suppression ($AUC_{0-24}/MIC \geq 100$) (**B**) of the simulated doses of MXF (600 mg, 800 mg, 1000 mg) against the assumed MIC values in Ethiopian MDR-TB patients ($n=18$).

Note: The formula used for the calculation of the percent probability of target attainment (%PTA) was: $PTA (\%) = \frac{\# \text{ of patients attained the required } AUC_{0-24}/MIC}{\text{Total \# of patients}} \times 100\%$.

1000 mg, this was improved only to 33.3% and 44.4%, respectively. Ethiopian MDR-TB patients are rarely given a dose of 800 mg MXF based on body weight. Therefore, the current WHO recommendation of a critical concentration of 0.25 mg/L is likely to be accurate for this population, and well-powered interventional studies would be needed to determine if higher doses of MXF improve PTA.

Despite the appeal of a higher starting dose of MXF for optimizing outcomes, our findings may explain a study in Indian MDR-TB patients in a tertiary care center in Mumbai, which found that an increased MXF dosing did not improve treatment outcomes in the presence of low-level resistance to MXF.³⁸ More interestingly, another recent study by Yun et al³² suggested a twice 400 mg instead of a single 800 mg MXF is an optimal dosing regimen for MDR-TB patients because it provides superior efficacy and safety. BMI was shown to have a statistically significant influence on V for MXF. The fact that BMI affected V may justify weight-based dosing of MXF in Ethiopian patients. It is important to note that the median CL and V values of MXF in the Ethiopian MDR-TB patients are greater than previously reported values from European patients.⁸ This higher CL and V of MXF may explain the lower AUC_{0-24} of MXF in this study compared to previous studies.³⁵

Genetic diversities in drug transporters in African populations has been reported to have implications for conventional therapies, notably in TB and HIV.³⁹ The study reported the prevalence of genetic variation in UGT1A and ABCB1 genes in black South African TB patients and assessed the effect of these on MXF PK. The study revealed that genetic variation in UGT1A rs8175347 reduced MXF clearance by 20.6%, whereas rs3755319 increased by 11.6%, and the ABCB1 rs2032582 SNP reduced the bioavailability by 40%. Therefore, our findings fit with other recommendations that more rigorous PK and pharmacogenetic studies may be of further benefit in settings such as Ethiopia.^{40,41}

The overall drug exposure of the standard LFX doses (750–1000 mg) in Ethiopian patients was also inadequate. Specifically, the conventional 750 mg LFX dose neither achieved an adequate maximal bacterial kill nor a resistance prevention targets. Moreover, the PTA for the resistance prevention with the highest simulated dose (1500 mg) was only 4.8%, whereas none of the lower doses achieved this target. However, the PTA needed for the maximal mycobacterial kill with the simulated LFX doses (750 mg, 1000 mg, and 1500 mg) was increased more proportionately and predictably with a dose increase compared to that of MXF. For instance, the PTA required for a maximal bacterial kill at a critical MIC of 0.5 mg/L is more than tripled for 1500 mg LFX compared to 750 mg LFX dose. Peloquin et al³⁰ in their earlier PopPK study of LFX, Gatifloxacin, and MXF revealed that the most favorable PK results were seen with LFX in the study population. This observation, the evidence that LFX has less risk for QT interval prolongation⁴² than MXF, and the findings of less LFX resistance when using the WHO critical concentrations, suggest LFX-based regimens are more preferable in the treatment of MDR-TB in Ethiopia. Deshpande et al¹⁹ recently identified that 1500 mg LFX confers equivalent effect to MXF 800 mg/day using HFS-TB in tandem with Monte Carlo Experiment, artificial intelligence-based analyses, and Probit models of clinical data. Cr, which affected CL of LFX, may be an important covariate in the therapeutic drug monitoring (TDM) of LFX. This is expected since LFX undergoes significant renal clearance and hence the renal function can affect drug clearance.⁴³ Cr clearance was shown to be a covariate that influences LFX clearance in other studies as well.³⁰

Delayed drug absorption and erratic concentration-time curves for some concentrations were observed in our study. It may be related to the food and drink intake behavior of patients before and during the investigation, as the patients were ambulatory and there was no food and drink restrictions. On the day of PK sampling, pre-dose blood samples were drawn in a fasting state while they received their daily dose after breakfast (under direct observation of the medical staff). However, the drug adherence information prior to the PK testing day was dependent on self-report of the patients. Therefore, non-adherence to the drug regimen could be a likely reason for some of the observed erratic concentration-time curves. Variable patterns of adherence to prescribed treatment are common and yet underestimated factors to sub-therapeutic plasma concentrations of TB drugs. Adverse drug effects and individual patient-related factors (psychiatric illness, substance use, and homelessness) increase the risk for variation in patterns of adherence.⁴⁴ The other possible reason for the sub-therapeutic plasma concentrations may be a long storage time before the bioanalysis. It has been suggested that plasma sample storage time should also be regarded as an equally prominent covariate as age or gender and need to be included in epidemiological studies involving drugs in plasma. Repeated freeze-and-thawing of a sample during sample storage could affect data quality by interfering with peak detection.^{45,46}

These findings support the importance of testing drug susceptibility and the potential benefit of follow-up TDM to determine if higher doses achieve targeted exposures. A further clinical study based on this work could be designed around higher starting doses of LFX and MXF, *gyrA* sequencing to determine no/low/high level resistance more rapidly than MIC testing, and measurement of serum drug concentrations by a limited sampling strategy performed at steady-state. Those patients not achieving target AUC₀₋₂₄ or those with mutations consistent with low-level resistance could be triaged for a further dose/exposure optimization or exchange of the FQ drug class. Barriers to TDM include higher costs of specialized equipment and preserving the cold chain for analysis,^{47–54} yet assays under development, such as those using dried blood spots or saliva, promise to deliver drug concentration testing closer to the point-of-care. Lastly, more rigorous PopPK analyses to determine the optimal starting dose, if performed at local or regional levels, may be able to determine a setting-specific dose that could mitigate the routine need for TDM.^{55–57}

Limitations

This was an observational study of MDR-TB patients in a programmatic treatment course. Many aspects which may affect the study result were not strictly controlled in the present study unlike in an interventional trial. Moreover, although our sample size is adequate for PopPK for a population with similar covariate distribution, it may not be representative of all Ethiopian MDR-TB patient populations. Incomplete MIC profile of the clinical isolates from the study subjects is also a limitation of this study. Bacterial killing and suppression of resistance depend on the concentration of unbound drug. However, for PTA calculations, raw drug concentrations were used to calculate the area under the concentration-time curve over 24 h.

Conclusion

The total plasma exposure in Ethiopian MDR-patients for both LFX and MXF is relatively lower than reports from previous studies in other settings. LFX demonstrated a more proportionate increase in the PTA required for the maximum mycobacterial kill with dose, whereas resistance prevention target was better achieved by higher dose of MXF. Cr and BMI are likely important covariates to consider for further interventional studies of dose increase or TDM to establish the optimal dose and plasma exposures of both drugs in Ethiopian patients.

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Disclosure

The authors report no conflicts of interest in this work.

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