Pharmacokinetics of First-Line Tuberculosis Drugs in Tanzanian Patients

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East Africa has a high tuberculosis (TB) incidence and mortality, yet there are very limited data on exposure to TB drugs in patients from this region. We therefore determined the pharmacokinetic characteristics of first-line TB drugs in Tanzanian patients using intensive pharmacokinetic sampling. In 20 adult TB patients, plasma concentrations were determined just before and at 1, 2, 3, 4, 6, 8, 10, and 24 h after observed drug intake with food to estimate the areas under the curve from 0 to 24 h (AUC_{0-24}) and peak plasma concentrations (C_{max}) of isoniazid, rifampin, pyrazinamide, and ethambutol. Acetylator status for isoniazid was assessed phenotypically using the isoniazid elimination half-life and the acetylisoniazid/isoniazid metabolic ratio at 3 h postdose. The geometric mean AUC_{0-24}s were as follows: isoniazid, 11.0 h · mg/liter; rifampin, 39.9 h · mg/liter; pyrazinamide, 344 h · mg/liter; and ethambutol, 20.2 h · mg/liter. The C_{max} was below the reference range for isoniazid in 10/19 patients and for rifampin in 7/20 patients. In none of the patients were the C_{max}s for pyrazinamide and ethambutol below the reference range. Elimination half-life and metabolic ratio of isoniazid gave discordant phenotyping results in only 2/19 patients. A substantial proportion of patients had an isoniazid and/or rifampin C_{max} below the reference range. Intake of TB drugs with food may partly explain these low drug levels, but such a drug intake reflects common practice. The finding of low TB drug concentrations is concerning because low concentrations have been associated with worse treatment outcome in several other studies.

The pharmacokinetic properties of tuberculosis (TB) drugs are well described, especially in Caucasian populations (1, 2). Pharmacokinetic data from East Africa are limited, especially data that are based on intensive pharmacokinetic sampling during the full dosing interval. Such intensive pharmacokinetic sampling enables an accurate assessment of the total exposure to TB drugs (area under the time-versus-plasma concentration curve from 0 to 24 h [AUC_{0-24}]) and the peak plasma concentration (C_{max}) in individual patients. Large interpatient variability in these key pharmacokinetic parameters of TB drugs generally exists (1). As a result, a proportion of patients achieve drug concentrations that are below the reference range for TB drugs. Several studies have shown that such lower exposures to TB drugs are associated with a suboptimal response (3–8) A recent study showed that pharmacokinetic variability to just a single drug in the multidrug TB drug regimen is associated with treatment failure and acquired drug resistance (9, 10).

On the other hand, unduly high exposures may cause toxicity and interruption of TB treatment. It is therefore important to have more knowledge on the pharmacokinetic properties of TB treatment in populations from East Africa, as a high TB incidence and a high TB mortality are found in this region (11). HIV infection (12–14) and malnutrition (15) have been associated with decreased plasma concentrations of TB drugs. Both are highly prevalent among East African TB patients, and therefore, low TB drug levels are to be expected in this population (11).

The objective of this study was to describe the pharmacokinetic parameters of isoniazid, rifampin, pyrazinamide, and ethambutol using intensive sampling during the full dosing interval in Tanzanian TB patients.

MATERIALS AND METHODS

Study design. We conducted an observational pharmacokinetic study at the Kilimanjaro Clinical Research Institute at the Kilimanjaro Christian Medical Centre (KCMC) in Moshi, Tanzania, using the standard two-stage approach. With this approach, individual pharmacokinetic parameters are estimated in the first stage. In the second stage, population characteristics of each parameter are derived by obtaining measures of central tendency and spread of all the subjects' individual parameters.

Study participants. Study participants were recruited from an outpatient tuberculosis treatment clinic at Mawenzi Hospital in Moshi. Adult TB patients who were in the intensive phase of treatment and who were not using medication that could interfere with TB drug plasma concentrations were eligible for participation. All participants gave written informed consent. The study was approved by the local Institutional Research Board at KCMC and by the Tanzanian National Institute of Medical Research.

Tuberculosis was treated with fixed-dose combination tablets (FDC tablets) that were manufactured by Sandoz, Mumbai, India, and are on the WHO list of prequalified medicinal products. The drugs were donated by Novartis through the WHO Global Drug Facility (GDF), which provides only high-quality drugs that meet stringent WHO standards. Pa-

tients with a body weight of less than 50 kg use three FDC tablets per day (i.e., 225 mg isoniazid, 450 mg rifampin, 1,200 mg pyrazinamide, and 875 mg ethambutol), and patients with a body weight of >50 kg use four FDC tablets per day (i.e., 300 mg isoniazid, 600 mg rifampin, 1,600 mg pyrazinamide, and 1,100 mg ethambutol) (16).

Data collection. Basic demographic and clinical information was collected from all participants, including age, sex, body weight and height (to calculate body mass index [BMI]), comorbidities (including HIV infection and hepatitis B and C), and concomitant drug use. Malnutrition was defined as a BMI of <18.5 kg/m^2 (17).

Sample collection. Pharmacokinetic sampling took place at KCMC hospital. Patients had to be on TB treatment for at least 10 days because of the expected steady state in the pharmacokinetics of the TB drugs at that point. Patients had refrained from food consumption for at least 8 h before drug intake. On the sampling day, patients took their drugs under our supervision at 8 a.m. They then had a standardized breakfast within 30 min after drug intake, which reflected the usual drug intake procedures in this population. The standardized breakfast consisted of a cup (125 ml) of tea with whole milk and sugar and either a small bowl of porridge or mandaazi, a typical East African fried pastry (analogous to a doughnut) that is rather high in fat.

Serial venous blood samples were collected just before, and at 1, 2, 3, 4, 6, 8, 10, and 24 h after observed TB drug intake. Plasma was separated and stored at −80°C immediately until transport on dry ice to The Netherlands for bioanalysis.

Bioanalysis. The plasma concentrations of isoniazid, rifampin, pyrazinamide, and ethambutol were assessed by validated high-performance liquid chromatography (HPLC) as described before (18). Isoniazid and acetylisoniazid (acetyl-INH) were measured with liquid-liquid extraction followed by ultra-performance liquid chromatography (UPLC) with UV detection. Accuracy was between 97.8% and 106.7% for isoniazid and between 98.0% and 108.9% for acetylisoniazid, depending on the concentration level. The intra- and interassay coefficients of variation were less than 13.4% and less than 3.2% (depending on the concentration), respectively, over the range of 0.05 to 15.1 mg/liter for isoniazid and less than 4.2% and less than 5.7%, respectively, over the range of 0.16 to 16.2 mg/liter for acetylisoniazid. Lower limits of quantification were 0.05 mg/liter for isoniazid and 0.16 mg/liter for acetylisoniazid. Isoniazid- and acetylisoniazid-containing samples were stable (<5% loss) for at least 12 months at −80°C.

Pharmacokinetic analysis. Pharmacokinetic evaluations were performed using noncompartmental methods in WinNonLin version 5.3 (Pharsight Corp., Mountain View, CA). The highest observed plasma concentration was defined as the C_{max} and the corresponding sampling time as the time to C_{max} (T_{max}). The log-linear period (log C versus t) was based on the last data points (at least three). The absolute value of the slope (β/2.303, in which β is the first-order elimination rate constant) was calculated using linear regression analysis. The elimination half-life ($T_{1/2}$) was calculated as 0.693/β. If the concentration at 24 h (C_{24}) was below the limit of quantification of the assay (which was often the case for isoniazid and rifampin), it was estimated based on the last measurable concentration (C_{last}) and β using the formula $C_{24} = C_{last} \cdot e^{-[\beta \cdot (24 - T_{last})]}$. The area under the plasma concentration-time curve from 0 to 24 h (AUC_{0-24}) was calculated using the linear/log-trapezoidal rule from zero up to the last concentration at 24 h. The apparent clearance of the drug (CL/F, where F is bioavailability) was calculated as dose/AUC_{0-24}, and the apparent volume of distribution (V/F) was calculated as (CL/F)/β. The reference ranges for C_{max} were 3 to 5 mg/liter for isoniazid, 8 to 24 mg/liter for rifampin, 20 to 50 mg/liter for pyrazinamide, and 2 to 6 mg/liter for ethambutol (19).

These reference ranges represent the normal C_{max}s that can be expected in adults after the standard doses of anti-TB drugs. They are based on data that were compiled from all available sources (for both healthy volunteers and TB patients) by, among others, Holdiness (1) and Peloquin (2). Subsequently, the ranges were validated in a range of phase I

studies in healthy volunteers (C. A. Peloquin, presented at the 51st Intersci. Conf. Antimicrob. Agents Chemother., Chicago, IL, 17 to 20 September 2011).

Determination of acetylator status. We determined the acetylator status phenotypically by assessing the $t_{1/2}$ of isoniazid. Participants with a $t_{1/2}$ of greater than 130 min were classified as slow metabolizers, and those with a $t_{1/2}$ of less than 130 min were classified as fast/intermediate metabolizers (21–23). As another means to assess acetylator phenotype, the metabolic ratio of acetylisoniazid concentration to isoniazid concentration at 3 h postdose was calculated. Patients with a ratio above 1.5 were considered fast/intermediate metabolizers, and patients with a ratio below 1.5 were considered slow metabolizers (21). In addition, we also explored a metabolic ratio of 0.55 at 3 h postdose as a cutoff to distinguish fast/intermediate from slow metabolizers, as this evolved from a study in African patients (23).

Statistical analysis. Most pharmacokinetic parameters were presented as geometric means. The sample size was considered too small to test for associations between patient characteristics and pharmacokinetic parameters. We tested the effect of acetylator status only on the pharmacokinetics of isoniazid. The correlations between the C_{max} and AUC_{0-24} of each of the drugs were explored using Spearman's rho correlation.

To explore the potential of limited sampling for estimating the AUC_{0-24} based on sampling early in the pharmacokinetic curve, univariate linear regression was used to determine the association between the plasma concentration at 2, 3, 4, and 6 h postdose and the AUC_{0-24} for each of the drugs. The r^2 value was presented as a measure of variance in the AUC_{0-24} that is explained by the variance in the concentration at that time point. Statistical analyses were performed in STATA version 10.1 (Stata Corp. LP, College Station, TX).

RESULTS

Twenty tuberculosis patients were enrolled for this study. All were under community-based directly observed treatment. Their median age was 38 years (interquartile range [IQR], 30 to 42 years), 15 patients (75%) were male, seven (35%) were HIV positive, and seven (35%) were considered malnourished based on their BMI (Table 1).

Descriptive pharmacokinetics. Intensive pharmacokinetic sampling took place after a median of 19 days after the start of TB treatment (range, 11 to 49 days). The pharmacokinetic parameters for isoniazid, rifampin, pyrazinamide, and ethambutol are presented in Table 2. In 10 patients (53%), the isoniazid peak plasma concentration was below the reference range (3 to 5 mg/liter). In seven patients (35%), the rifampin C_{max} was below the reference range (8 to 24 mg/liter); in five of them, the isoniazid C_{max} was also below the reference range. In none of the patients was the C_{max} of pyrazinamide or ethambutol below the reference range.

There was a positive correlation between the AUC_{0-24} and C_{max} of isoniazid (correlation coefficient, 0.68; $P = 0.001$), pyrazinamide (correlation coefficient, 0.69; $P = 0.001$), and ethambutol (correlation coefficient 0.72; $P = 0.003$) but not between those of rifampin (correlation coefficient, 0.35; $P = 0.14$).

Assessment of acetylator status. Based on the elimination half-life of isoniazid, 7 (37%) patients were fast or intermediate metabolizers and 12 (63%) were slow metabolizers. Based on the 3-hour acetyl-INH/INH ratio with a cutoff of 1.5, nine patients (47%) were fast/intermediate metabolizers and 10 patients (53%) were slow metabolizers (Fig. 1). Two patients had a discrepancy in acetylator phenotype determined by the two methods. With a cutoff of 0.55, 11 patients (58%) were fast/intermediate metabolizers and eight (42%) were slow metabolizers.

Acetylator status based on the half-life method was associated with the AUC_{0-24} and C_{max} of isoniazid. In slow metabolizers, the

TABLE 1 Characteristics of 20 tuberculosis patients in northern Tanzania

Characteristic	Value
Male sex, n (%)	15 (75)
Age, median, yr (IQR)	38 (30–42)
Body wt, mean, kg (SD)	55.7 (6.4)
BMI, mean (SD)	19.5 (2.4)
Malnutrition, n (%)[a]	7 (35)
HIV positive, n (%)	7 (35)
Type of tuberculosis, n (%)	
Pulmonary	19 (95)
Extrapulmonary	1 (5)
Concomitant drugs, n (%)	
Amoxicillin	1 (5)
Antiretroviral treatment	2 (10)
Co-trimoxazole	3 (15)
Diclofenac	3 (15)
Vitamin B complex	2 (10)
Dose, mean, mg per kg body wt (SD)	
Isoniazid	5.2 (0.46)
Rifampin	10.4 (0.91)
Pyrazinamide	27.8 (2.4)
Ethambutol	19.1 (1.7)
Acetylator status, n (%,) based on:	
INH $t_{1/2}$	
Slow	12 (63)
Fast/intermediate	7 (37)
Acetyl-INH/INH ratio with cutoff of:	
1.5	
Slow	10 (53)
Fast/intermediate	9 (47)
0.55	
Slow	8 (42)
Fast/intermediate	11 (58)

[a] Malnutrition defined as BMI of <18.5 kg/m^2.

geometric mean AUC_{0-24} was 17.2 h · mg/liter (range, 9.5 to 22.7) and the C_{max} was 3.4 mg/liter (range, 2.0 to 4.6), and in intermediate/fast metabolizers, the geometric mean AUC_{0-24} was 5.2 h · mg/liter (range 3.7 to 8.1) and the C_{max} was 2.0 mg/liter (range, 1.0 to 3.3) ($P < 0.001$ and $P = 0.01$, respectively).

Association between the 2-, 3-, 4-, and 6-h concentrations and AUC_{0-24}. The isoniazid concentrations at 2, 3, 4, and 6 h postdose were associated with AUC_{0-24}, and the r^2 value ranged from 0.91 to 0.96, meaning that 91 to 96% of the variance in the AUC_{0-24} is explained by the variance in the concentration at a particular sampling time point. For rifampin, the r^2 value was highest for the concentration at 4 h postdose (0.82). For pyrazinamide, the r^2 value was highest for the concentrations at 4 and 6 h postdose (0.84 and 0.86, respectively). For the different ethambutol concentrations, the r^2 value was low, varying from 0.40 to 0.71. This indicates that limited sampling to estimate the AUC_{0-24} may be feasible for isoniazid, rifampin, and pyrazinamide but less for ethambutol.

DISCUSSION

This report provides important data on the pharmacokinetic characteristics of isoniazid, rifampin, pyrazinamide, and ethambutol based on intensive 24-hour pharmacokinetic sampling in East African TB patients.

Half of the patients from our study had an isoniazid peak plasma concentration (C_{max}) below the reference range, and a third of patients had a rifampin C_{max} below the reference range. This may partly be explained by the breakfast that patients took within half an hour after the intake of TB drugs. This approach was chosen to mimic the real-life situation for TB patients, as most TB patients take their pills just before or with their breakfast in order to prevent or alleviate gastrointestinal adverse effects. Previous studies have shown that intake of a meal with a high fat or carbohydrate content just before drug intake decreases the rate of absorption and significantly reduces the isoniazid C_{max} by 20% to 51% (24–27). The rifampin C_{max} can be reduced up to 36% when it is taken directly after a meal (24, 28). There is no significant effect of food on the C_{max}s of pyrazinamide and ethambutol (24, 29, 30). Of note, in the current study the average T_{max} values for the TB drugs were short (about 1 h for isoniazid, rifampin, and pyrazinamide) (Table 2), indicating that the delay in absorption and a possible related decrease in C_{max} were probably limited. Furthermore, it should be noted that pharmacokinetic studies from other African countries found even higher proportions of patients with C_{max}s below the reference range for isoniazid (30% in Botswana [8, 31] and 89% in Kenya [32]) and rifampin (69% in South Africa [12], 78 to 84% in Botswana [27, 28], and 90% in Kenya [32]), despite administration of drugs on an empty stomach in the studies from Botswana and Kenya. The relatively high C_{max}s of the TB drugs in our study among African patients may also relate to the average body weight of 55.7 kg (Table 1), which is

TABLE 2 Pharmacokinetic parameters of tuberculosis drugs in 20 Tanzanian tuberculosis patients

Pharmacokinetic parameter	Value, geometric mean (minimum-maximum) for:			
	Isoniazid[a]	Rifampin	Pyrazinamide	Ethambutol
AUC_{0-24}, h · mg/liter	11 (3.7–22.7)	39.9 (27.4–68.3)	344 (209–610)	20.2 (13.4–32.0)
C_{max}, mg/liter	2.8 (1.0–4.6)	8.9 (5.9–14.8)	38.2 (29.0–50.8)	3.3 (2.2–5.8)
T_{max}, h	1.2 (0.7–2.9)	1.3 (0.9–3.0)	1.2 (0.7–3.0)	1.5 (0.9–2.2)
CL/F, liters/h	25.8 (13.0–60.5)	14.4 (8.8–21.9)	4.5 (2.6–6.5)	52 (34.3–71.3)
V/F, liters	99 (69.6–173.4)	37.3 (22.7–56.5)	40.3 (29.5–98.3)	719 (491–965)
$t_{1/2}$, h	2.9 (1.3–4.2)	1.8 (1.1–3.8)	5.5 (4.1–15.7)	9.5 (6.9–13.5)
Reference range C_{max}, mg/liter	3–5	8–24	20–50	2–6
No. (%) with C_{max} below reference range	10 (52)	7 (35)	0 (0)	0 (0)

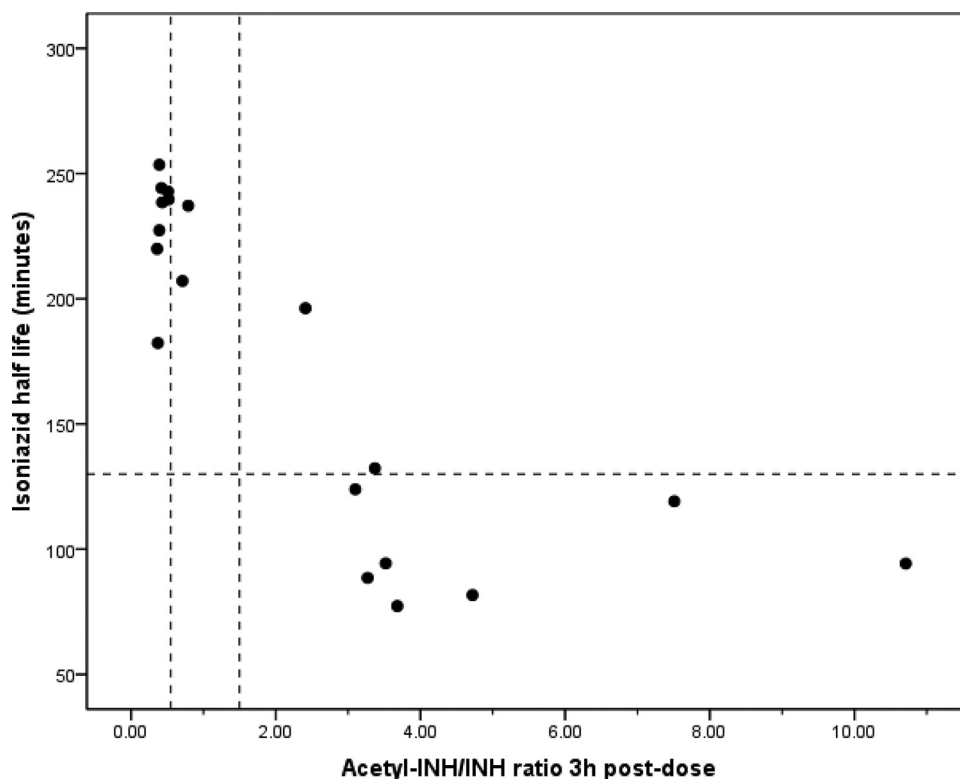[a] Isoniazid plasma concentrations were determined for only 19 patients.

FIG 1 Relationship between the acetylator status (slow versus fast/intermediate) based on two methods: the $t_{1/2}$ of isoniazid and the acetyl-INH/INH metabolic ratio in the 3-h-postdose plasma sample. Patients with a $t_{1/2}$ below 130 min (below the horizontal dashed line) were considered fast/intermediate metabolizers (17–19). Patients with an acetyl-INH/INH ratio greater than 0.55 (19) or greater than 1.5 (17) (right of the first or second vertical dashed line, respectively) were considered fast/intermediate metabolizers based on metabolic ratio. Note that phenotyping by $t_{1/2}$ and metabolic ratio resulted in discordant results (in the upper right quadrant) in 4 patients when a metabolic ratio of 0.55 was used as the cutoff, compared to 2 patients when a metabolic ratio of 1.5 was used as the cutoff.

just above 50 kg, above which 4 FDC tablets (rather than 3) are administered.

Values for total exposure (AUC_{0-24}) may be even more relevant to the efficacy of first-line TB drugs than the C_{max} (33). AUC_{0-24} values can best be compared to those recorded in Indonesian TB patients (18) and in a racially mixed population of patients in The Netherlands who used similar doses on a mg/kg basis (C. Magis-Escurra, H. M. J. Later-Nijland, J. W. C. Alffenaar, J. Broeders, D. M. Burger, R. van Crevel, M. J. Boeree, A. R. T. Donders, R. van Altena, T. S. van der Werf, and R. E. Aarnoutse, submitted for publication), as the pharmacokinetics in these studies were assessed with the same analytical methodology. Average exposures to rifampin were 39.9, 48.5, and 41.1 h · mg/liter in the Tanzanian patients, the Indonesian patients, and a mixed population, pyrazinamide AUC_{0-24} values were 344, 473, and 380 h · mg/liter, respectively, and exposures to ethambutol were 20.2, 14.4, and 23.5 h · mg/liter, respectively. Isoniazid was not measured in the Indonesian TB patients, and we used another analytical method with the mixed population (the average AUC_{0-24} was 15.2 h · mg/liter, compared to 11.0 in the current study). These comparisons show no drastically lower total exposure to TB drugs between Tanzanian patients and the Indonesian patients and the mixed population from the Netherlands.

Even though the exposure to TB drugs in Tanzanian patients may be high compared to exposure in other African studies and similar to those in other populations, a large number of patients had low plasma concentrations of isoniazid and rifampin., Several

clinical studies have pointed toward a possible association between low TB drug concentrations and poor treatment outcome (3–5). A preclinical model showed that interindividual variability in pharmacokinetics is relevant to the emergence of resistance (7), and a recent meta-analysis revealed that variability in exposure to isoniazid is associated with failure of therapy and acquired drug resistance (10). On the other hand, other studies have found no association between plasma concentrations and effect of first-line TB drugs (34, 35).

We could not readily explain the observed low isoniazid and rifampin AUC_{0-24}s and C_{max}s by patient characteristics, as the sample size was considered too small for analysis of association between patient characteristics and pharmacokinetic parameters. However, we evaluated the effect of genetic polymorphisms in N-acetyltransferase 2 (NAT2), a phase II metabolic enzyme, on the pharmacokinetics of isoniazid. Slow acetylation of isoniazid into acetylisoniazid is a homozygous recessive trait. Genotypically, homozygous fast, heterozygous fast (or intermediate), and slow acetylators are distinguished (22, 36). In our study, acetylator status was assessed phenotypically using the isoniazid elimination half-life and the acetylisoniazid/isoniazid ratio at 3 h postdose with a cutoff of 1.5. Based on these two methods, 63% or 53% of patients in our study, respectively, were slow metabolizers. This is consistent with available data showing that 50 to 60% of European (Caucasian), African, and Indian populations are slow metabolizers (37). Clearly, assessment of the acetylator status by the acetylisoniazid/isoniazid metabolic ratio at a single time point postdose

is more convenient. There was good concordance between the two methods when 1.5 was used as the cutoff for the metabolic ratio (there were 2 discordant patients). In the future, limited sampling may allow for an assessment of acetylator status as well as estimation of AUC values of TB drugs, considering the high correlation between concentrations measured in the early part of the pharmacokinetic curve and exposures to isoniazid, rifampin, and pyrazinamide. The AUC_{0-24}s and C_{max}s of isoniazid, pyrazinamide, and ethambutol were also correlated, but for rifampin no such association was found. We have considered whether this may be explained by the nonlinear, saturable pharmacokinetics of rifampin, but disproportional changes in exposure above certain concentrations are expected to affect both C_{max} and AUC_{0-24}.

In summary, this study provides pharmacokinetic data for first-line TB drugs based on intensive 24-h sampling in East African TB patients. Half of the patients had isoniazid peak plasma levels and a third had rifampin peak plasma concentrations below the reference ranges. Although the pharmacodynamics of the currently used first-line TB drugs are not entirely clear, low isoniazid and rifampin concentrations have been associated with a suboptimal treatment response. Exploring the effect, tolerability, and pharmacokinetics of higher doses of isoniazid and rifampin in African tuberculosis patients is therefore recommended.

ACKNOWLEDGMENTS

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