Pharmacokinetics of \textit{para}-Aminosalicylic Acid in HIV-Uninfected and HIV-Coinfected Tuberculosis Patients Receiving Antiretroviral Therapy, Managed for Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis

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The emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) \textit{Mycobacterium tuberculosis} prompted the reintroduction of \textit{para}-aminosalicylic acid (PAS) to protect companion anti-tuberculosis drugs from additional acquired resistance. In sub-Saharan Africa, MDR/XDR tuberculosis with HIV coinfection is common, and concurrent treatment of HIV infection and MDR/XDR tuberculosis is required. Out of necessity, patients receive multiple drugs, and PAS therapy is frequent; however, neither potential drug interactions nor the effects of HIV infection are known. Potential drug-drug interaction with PAS and the effect of HIV infection was examined in 73 pulmonary tuberculosis patients; 22 (30.1%) were HIV coinfected. Forty-one pulmonary MDR or XDR tuberculosis patients received 4 g PAS twice daily, and in a second crossover study, another 32 patients were randomized, receiving 4 g PAS twice daily or 8 g PAS once daily. A PAS population pharmacokinetic model in two dosing regimens was developed; potential covariates affecting its pharmacokinetics were examined, and Monte Carlo simulations were conducted evaluating the pharmacokinetic-pharmacodynamic index. The probability of target attainment (PTA) to maintain PAS levels above MIC during the dosing interval was estimated by simulation of once-, twice-, and thrice-daily dosing regimens not exceeding 12 g daily. Concurrent efavirenz (EFV) medication resulted in a 52% increase in PAS clearance and a corresponding >30% reduction in mean PAS area under the concentration curve in 19 of 22 HIV-\textit{M. tuberculosis}-coinfected patients. Current practice recommends maintenance of PAS concentrations at $\geq$1 $\mu$g/ml (the MIC of \textit{M. tuberculosis}), but the model predicts that at only a minimum dose of 4 g twice daily can this PTA be achieved in at least 90% of the population, whether or not EFV is concomitantly administered. Once-daily dosing of 12 g PAS will not provide PAS concentrations exceeding the MIC over the entire dosing interval if coadministered with EFV, while 4 g twice daily ensures concentrations exceeding MIC over the entire dosing interval, even in HIV-infected patients who received EFV.

In sub-Saharan Africa, an estimated 79% of tuberculosis (TB) patients are also coinfected with human immunodeficiency virus (HIV), and approximately 50% of AIDS-associated death is TB related (1); concurrent treatment with combination chemotherapy against both infections is the standard of care (2). Complicating this high prevalence of \textit{M. tuberculosis}-HIV coinfections, multidrug-resistant (MDR) and extensively drug-resistant (XDR) \textit{Mycobacterium tuberculosis} strains are reaching epidemic proportions (3, 4). MDR \textit{M. tuberculosis} is resistant to at least the two first-line drugs, isoniazid and rifampin, while XDR \textit{M. tuberculosis} is additionally resistant to fluoroquinolone and at least one of three second-line injectable drugs (4). XDR \textit{M. tuberculosis} is associated with a high early mortality among HIV-infected individuals (5), and the scarcity of effective treatment options against MDR and XDR \textit{M. tuberculosis} caused the reintroduction of second-line TB drugs, including \textit{para}-aminosalicylic acid (PAS).

PAS is a second-line antimycobacterial agent generally reserved for treatment of XDR TB (6) and for management of complicated forms of MDR TB but is notorious for gastrointestinal intolerance, including nausea, vomiting, abdominal cramping, and diarrhea (7, 8). Current recommendations for dosing of PAS are based on the supposition that, as PAS is bacteriostatic, it is thus necessary to maintain PAS concentrations above the MIC of approximately 1 $\mu$g/ml (9) throughout a dosing interval; current recommendations suggest a dosage of 8 to 12 g PAS daily in two or three divided doses. However, in early studies conducted by the British Medical Research Council, PAS was used at a dosage of 20 g in four divided dosages (10). When accompanied by streptomycin, PAS therapy was associated with a 5-year mortality of 19% (10). This rate can be compared with a mortality of 80% reported for some series of XDR HIV-associated TB (11).

For nearly 2 decades, a granular slow-release form of PAS (\textit{para}-aminosalicylic acid delayed-release granules [PASER granules]) has been available and has been found to cause less intolerance in several studies in TB patients and healthy volunteers (12, 13). This formulation still provides PAS concentrations exceeding...
pharmacokinetic analysis were collected at predose and 1, 2, 3, 4, 5, 6, 8, and 12 h after 4 g twice daily and at predose and 1, 2, 3, 4, 6, 8, 12, and 24 h after 8 g once daily. To prevent early PAS release in the stomach, doses were routinely taken with acidic food or beverages. Patients received breakfast an hour after dosing. These studies were conducted according to the principles of the South African Guidelines for Good Clinical Practice and were approved by the Ethics Committee for Human Research of Stellenbosch University (N09/08/212; M12/01/006). The protocols conformed to the Declaration of Helsinki and subsequent amendments.

**Bioanalytical method.** The concentrations of PAS were quantified using a validated high-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay as previously described (14). The analysis of quality control samples reported good reproducibility with coefficient of variation of ±5% and accuracy, with between-sample differences not exceeding 2.5%. The lower limit of quantification was 0.01 µg/mL. All of the observed drug concentrations were above this limit.

**Pharmacokinetic analysis.** The nonlinear mixed-effects modeling of PAS disposition in *M. tuberculosis*-HIV-coinfected patients was performed using NONMEM (version 7.2) with first-order conditional estimation and with η interaction. The one-compartment model with first-order absorption with lag time or transit compartment followed by first-order absorption (15, 16) or mixed Michaels-Menten and first-order absorption (17) was explored for the steady-state concentration-time profiles of patients who were administered 8 g PAS once daily or 4 g PAS twice daily. The final structural model was parameterized on the PK parameters: transit rate constant (Ktr) with 3 transit compartments, apparent oral clearance (CL/F), and the apparent volume of distribution (V/F).

The relative bioavailability parameter (F) assumed the value of 1. Exponential interindividual variability terms were included in the pharmacokinetic parameters. Interoccasion variability was introduced to both the apparent oral clearance and transit rate constant: \( P_{ij} = P \times \exp(\eta_{P} + \kappa_{P} j) \), where \( P \) represents the mean parameter value and \( \eta \) and \( \kappa \) describe interindividual and interoccasion (within an individual) variability and were assumed to be independently and normally distributed, both with zero mean and variances of \( \sigma_{P}^{2} \) and \( \sigma_{P}^{2} \), respectively. The subscript \( i \) represents the individual, and \( j \) represents the occasion for the individual. Dummy variables were introduced to distinguish separate occasions, where 1 designated the first occasion wherein individuals received the first 4-g twice-daily regimen, 2 indicated the second 4-g twice-daily regimen, and 3 was used for the 8-g once-daily regimen. All three occasions were consolidated to determine the interoccasion variability. The residual variability, which is a composite of the other unexplained errors, was estimated by a mixture of additive and proportional error models.

Covariates that were evaluated for their potential effect on PAS disposition included the following: total body weight, age, HIV status, gender, race, and comedictions. The concomitant medications were evaluated individually for their effects on PAS disposition. Dummy variables consisting of 0 and 1 were introduced for absence and presence of drug, respectively. The hypothesis testing to discriminate among alternative hierarchical structural models was based on the \( P \) values for the forward inclusion and backward elimination at 0.05 and 0.01, respectively. After the covariate screening determined that EFV has a significant effect on PAS pharmacokinetics, EFV effect was tested on the apparent oral clearance.

The covariate model for the EFV effect on the apparent oral clearance was based on the following: \( \text{TV}_{\text{CL/F}} = \theta_{1} \times \exp(\theta_{2} \times I_{\text{COV}}) \), where \( \theta_{1} \) is the typical value (TV) for the population CL/F, \( \theta_{2} \) is the exponential factor to adjust for the population CL/F in concomitant EFV medication, and \( I_{\text{COV}} \) represents the indicator function for the presence or absence of concomitant EFV. The dose effect of EFV could not be evaluated, as all patients who received EFV had a 600-mg oral once-daily dose.

The HIV status of the individual was also evaluated. The three additional HIV-seropositive individuals who were not on antiretroviral therapy containing EFV were included in the category for HIV status. The
TABLE 1 Characteristics of 73 patients enrolled in studies of the pharmacokinetics of para-aminosalicylic acid in tuberculosis patients with and without HIV infection

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (% of total or range)</th>
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<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>No. of males</td>
<td>39 (53.4)</td>
</tr>
<tr>
<td>No. of females</td>
<td>34 (46.6)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>17 (23.3)</td>
</tr>
<tr>
<td>Mixed</td>
<td>56 (76.7)</td>
</tr>
<tr>
<td>Median wt, kg</td>
<td>56 (33–86)</td>
</tr>
<tr>
<td>Median ht, m</td>
<td>1.7 (1.5–1.8)</td>
</tr>
<tr>
<td>Median BMI, kg m⁻²</td>
<td>20 (14–35)</td>
</tr>
<tr>
<td>Median age, yr</td>
<td>33 (18–64)</td>
</tr>
<tr>
<td>Median creatinine clearance, ml/min</td>
<td>87 (35 to &gt;150)</td>
</tr>
<tr>
<td>Median serum creatinine, μmol/liter</td>
<td>72.5 (44–152)</td>
</tr>
<tr>
<td>No. with concurrent disease</td>
<td></td>
</tr>
<tr>
<td>MDR TB</td>
<td>58 (79)</td>
</tr>
<tr>
<td>XDR TB</td>
<td>15 (21)</td>
</tr>
<tr>
<td>Total HIV infected</td>
<td>22 (30.1)</td>
</tr>
<tr>
<td>HIV infected and receiving efavirenz</td>
<td>19 (26.0)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; HIV, human immunodeficiency virus; TB, tuberculosis; MDR, multidrug resistant; XDR, extensively drug resistant; CV, coefficient of variation.

RESULTS

Patient characteristics. The patients’ characteristics and administration of concomitant drugs are listed in Tables 1 and 2. Forty-one patients were recruited in the 4-g twice-daily study and 32 patients in the crossover study; data from all 73 patients were used in the analysis; 26% were HIV coinfected, 21% had XDR TB, and 79% had MDR TB.

The time course of PAS concentrations was well described by a one-compartment disposition model with its absorption described by a 3-transit-compartment in series (Fig. 1) (16). The model provided reasonable fits to the observed concentration-time profiles (Fig. 2). The large interindividual and interoccasion variability in PAS disposition resulted in a large difference between the population fit and the observed data, as shown in the upper right graph of Fig. 2. The conditional weighted residuals (CWRES) versus time and CWRES versus the population predicted PAS concentrations in Fig. 2 show that most of the data lie within 2 units of the zero ordinate. Figure 3 shows a visual predictive check of the final model stratified on concomitant efavirenz administration. The concentration profiles for both dosing regimens were simultaneously described with a single set of population PK parameter estimates (Table 3). With the excep-
tion of the first-order absorption with the lag time model, the mixed Michaelis-Menten and first-order absorption model was unstable and did not result in successful convergence, including boundary problems and undeterminable rounding of significant digits. The transit compartment model selected as the objective function was markedly lower than that of the first-order absorption with lag time model. Allometric scaling by body weight did not improve interindividual variability, resulting in no significant reduction in the minimum objective function value.

The MCMP analysis indicated that the sample size of 73, with 19 and 54 patients receiving and not receiving EFV, respectively, for the covariate analysis had 95% and 88% power at $P$ values of 0.05 and 0.01, respectively, to detect differences in PAS pharmacokinetics. Similarly, for an 80% power at a significance level corresponding to a $P$ value of 0.05, 10 and 30 individuals on PAS with or without EFV, respectively, would be sufficient to detect the EFV effect. Because of the exploratory and uncontrolled nature of the study, there was an unbalanced allocation of subjects in each treatment group. For this reason, a formal bioequivalence-type analysis was not performed. Given the sample size, however, the study was deemed sufficiently powered to detect pharmacokinetic interactions, and MCMP analysis indicated that the sample size of the present study was sufficient to detect an EFV effect with a statistical power of 95%. The other demographic variables were not influential factors of PAS pharmacokinetics.

Efavirenz interaction with PAS. During the screening for drug-drug interaction, the EFV effect in reducing PAS exposure was significant. The difference in objective function value was 8.94 from the base model, which is significant at a $P$ value of 0.01. EFV was associated with an approximately 52% increased PAS clearance in patients who took this concurrent medication. The exponential coefficient for the effect of EFV on PAS CL/F was 0.419, which translated to 1.52 in the linear scale (Table 3). The areas under the concentration-time curve (AUCs) over a day (AUC$_{0–24}$; mean ± standard deviation) for PAS without and with EFV were 875 ± 424 and 621 ± 295 mg · h/liter in the group receiving 4 g twice daily and 889 ± 493 and 625 ± 338 mg · h/liter in the group receiving 8 g once daily, respectively. The HIV-infected patients on EFV had an overall >30% reduction in PAS mean exposure.

When HIV status was evaluated as a covariate of apparent oral clearance and bioavailability, the resulting change in objective function values was -3.151, which is not significant at a $P$ value of 0.05. Adding HIV status on top of EFV effect did not result in additional reduction in objective function values. Thus, the model incorporating the EFV effect on PAS pharmacokinetic was selected.

The half-lives of PAS in the individual observed concentration-time profiles were determined using log-linear regression. Without EFV, the mean half-lives (coefficient of variation [CV]) in the 4-g twice-daily and 8-g once-daily dosing regimens were 4.09 h (50.8%) and 3.25 h (34.5%), respectively. In EFV comedication group, PAS half-lives were 2.85 h (36.2%) and 2.56 h (37.3%), respectively. The
reduction in the PAS half-life in EFV comedication group indicated that EFV effect on PAS CL/F is more likely than its effect on PAS relative bioavailability. There are some indications that EFV induction is primarily hepatic and not intestinal (22).

Monte Carlo simulations and probability of target attainment. The plasma PAS concentrations were simulated for several dosing regimens, and the resulting exposure parameters are summarized in Fig. 4. The top panels show the pharmacokinetic parameters in virtual patients who had concomitant EFV, whereas the lower panels are for those without EFV. The increase in PAS clearance in patients who were coadministered EFV was reflected in lower plasma PAS concentrations and areas under the concentration-time curve. In the computation of the free Cmin of PAS, the unbound fraction is assumed to be 50% of the total drug concentration (19). There is an overall 30% reduction in PAS exposure with EFV. These simulated profiles were used to determine the probability of achieving free PAS levels greater than the MIC against M. tuberculosis, as shown in Fig. 5.

The PTA was based on the free trough PAS concentration (fCmin) above the MICs during the entire dosing interval. When 4 g PAS every 12 h was simulated, PTA values of >90% were obtained for hypothetical MICs of 0.5 up to 5 μg/ml in virtual patients with concomitant EFV. Patients who are not taking EFV can achieve PTA values of >90% at the same dosage even with hypothetical MICs of 3 μg/ml. Higher PTAs were achieved when the dosing frequency was increased to thrice daily. With 6 g twice daily, the PTA was achieved at MICs of 3 μg/ml and 5 μg/ml with and without EFV, respectively. The once-daily dosage regimen of 6 g, 8 g, and even 12 g are at risk of not achieving PTA at a MIC of 1 μg/ml. With the exception

![Graph](http://aac.asm.org/)

**FIG 3** Visual predictive check showing the 5th, 50th, and 95th percentiles (lines) of the observed PAS concentration data (dots) and the 95% confidence intervals (shaded areas) of the percentiles based on the pharmacokinetic model stratified by concomitant efavirenz administration.

### TABLE 3 Population pharmacokinetic model parameters of the final model evaluating the pharmacokinetic interaction of para-aminosalicylic acid with efavirenza

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean value (% RSE) in final model</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Structural model parameters</strong></td>
<td></td>
</tr>
<tr>
<td>Apparent oral clearance (CL/F, liters/h)</td>
<td>9.42 (6.6)</td>
</tr>
<tr>
<td>Apparent volume of distribution (V/F, liters)</td>
<td>51.8 (6.7)</td>
</tr>
<tr>
<td>Transit rate constant (Ktr, h⁻¹)</td>
<td>0.65 (6.8)</td>
</tr>
<tr>
<td>Number of transit compartments</td>
<td>3</td>
</tr>
<tr>
<td><strong>Interindividual variability</strong></td>
<td></td>
</tr>
<tr>
<td>% CV of CL/F (σCL)</td>
<td>47.5 (9)</td>
</tr>
<tr>
<td>% CV of V/F (σV)</td>
<td>74.8 (11.9)</td>
</tr>
<tr>
<td>% CV of Ktr (σKtr)</td>
<td>43.5 (13.2)</td>
</tr>
<tr>
<td><strong>Residual variability</strong></td>
<td></td>
</tr>
<tr>
<td>Proportional residual error</td>
<td>0.269 (12)</td>
</tr>
<tr>
<td>Additive residual error (μg/ml)</td>
<td>7.90 (10.8)</td>
</tr>
<tr>
<td><strong>Covariates</strong></td>
<td></td>
</tr>
<tr>
<td>Efavirenz on CL/Fb</td>
<td>0.419 (33)</td>
</tr>
<tr>
<td>∆OFV (from baseline model)</td>
<td>-8.94</td>
</tr>
</tbody>
</table>

*Abbreviations: OFV, minimum objective function value; RSE, relative standard error.

b The covariate equation to describe the effect of efavirenz on CL/F is $CL/F = CL/F_e \times \exp(\theta_1 \times I_{E})$. 

reduction in the PAS half-life in EFV comedication group indicated that EFV effect on PAS CL/F is more likely than its effect on PAS relative bioavailability. There are some indications that EFV induction is primarily hepatic and not intestinal (22).
of the 12-g once-daily dosing without EFV, PTA for the dosage regimens were below 90% (Fig. 5, middle and right). The 5th percentiles of free PAS trough concentrations in the once-daily dosing were below 1 μg/ml for the three doses, regardless of whether EFV was coadministered.

DISCUSSION

The most important findings of this study are that PAS concentrations are reduced in HIV-infected TB patients and that concomitant administration of EFV likely plays a role in this deficit. Our population pharmacokinetic model predicts a 52% increase in PAS clearance. A corresponding reduction of 30% in mean PAS exposure was observed in M. tuberculosis-HIV-coinfected patients on EFV. To our knowledge, there has been no in vitro or animal experiment to evaluate drug interactions between second-line anti-tuberculosis and anti-retroviral therapies.

The mechanism of the drug-drug interaction between efavirenz and PAS remains to be elucidated. PAS was previously shown to be a prodrug that acts as a metabolic precursor of the folate biosynthetic pathway (23). More than 80% of absorbed PAS...
is excreted renally; the other 20% is cleared following metabolism (24). PAS is primarily metabolized by N-acetyltransferase 1 (NAT1) and to a lesser extent by NAT2 (25, 26) to form N-acetyl-p-aminosalicylates; conjugation with glycine to form p-aminosalicylic acid accounts for the remaining 25% of PAS metabolism (27). It is not clear whether efavirenz affects the NAT metabolic pathway of PAS. Efavirenz is known to affect both phase I and phase II metabolic enzymes, including induction of CYP3A4, 2B6, 2C19, UGT1A1 2B7, and bile efflux transporters and inhibition of CYP3A5, 2C9, 2C19 and UDP 1A4 and 1A9 (28–34). The effect of efavirenz on CYP3A4 was previously shown to be due to the activation of the human pregnane X receptor, which regulates the CYP3A4 transcription (35). An average 3- to 4-fold increase in CYP3A4 activity was observed at 5 to 10 μM efavirenz (35). Consequently, CYP3A4 substrates when administered with efavirenz resulted in a reduction in plasma levels of these drugs (36–38). EFV was thought to affect only the hepatic CYP3A4 enzymes and not intestinal CYP3A4 (22). One study indicated that there may be some association between efavirenz systemic exposure and NAT2 genotypes as risk factors of liver injury in M. tuberculosis-HIV patients (39). Even though that study was not designed to evaluate the effect of efavirenz on NAT2 enzymes, we hypothesize that modulation of NAT2 activities by efavirenz may contribute to toxicity of drugs and agents that are metabolized by NAT2. Given the wide variety of drug-metabolic enzymes that were shown to be affected by efavirenz, it is likely that the increase in PAS clearance could be due to NAT1 or NAT2 induction by efavirenz. This hypothesis needs to be validated clinically by evaluating the extent of increase in N,N-acetyl-PAS formation in a controlled trial, as the current study was not designed to evaluate the effect of efavirenz on the metabolism of PAS. Nonetheless, this limitation does not affect the results of the present study.

With the high rate of M. tuberculosis-HIV coinfection, drug interactions between ARV and TB drugs are increasingly documented, primarily for the first-line anti-TB drugs (40, 41). Given that EFV appears to increase PAS clearance, it is likely that PAS efficacy could be compromised when PAS is administered with EFV. In this study, Monte Carlo simulations were conducted to evaluate several dosage regimens that could achieve drug concentrations of at least 1 μg/ml throughout the dosing interval. With its primary purpose, the prevention of further resistance to companion anti-tuberculosis drugs in MDR-TB and XDR-TB patients, maintaining PAS plasma concentration above the typical MIC against M. tuberculosis at 1 μg/ml throughout the dosing interval is believed to at least maintain its bacteriostatic activity, as PAS lacks a postantibiotic effect (12, 20, 42). Our results show that HIV-M. tuberculosis-coinfected patients taking EFV are not at risk of PAS concentrations falling below 1 μg/ml in a 4-g twice-daily PAS regimen. Peloquin et al. evaluated PAS dosages of 4 g twice daily and 4 g once daily and determined that the 4-g twice-daily dosage, but not the 4-g once-daily dosage, was adequate to maintain PAS concentrations at >1 μg/ml throughout the dosing interval (7, 12). The Centers for Disease Control and Prevention recommendation for 8 g to 12 g daily in 2 or 3 equal doses (43) is consistent with our findings that equal doses equal to or greater than a daily total dose of 8 g would provide sufficient exposure above 1 μg/ml.

Several earlier studies compared once-daily and divided dosing and found that adult patients tolerated gastrointestinal side effects better with once-daily dosage regimens (44–46). Single daily dosing was also shown to be as effective as divided daily doses in both TB patients (44) and guinea pigs (47). In deciding the most appropriate PAS dose and frequency of administration, one needs to balance maintenance of a plasma concentration above 1 μg/ml and the possible risk of increased intolerance due to more frequent dosing or using higher PAS doses.

For this reason, we chose to evaluate once-daily dosing regimens, including 6 g, 8 g, and 12 g. The target attainment of at least 90% of the population maintaining greater than 1 μg/ml free PAS concentration was unlikely for the once-daily dosage regimens, except for the 12 g PAS without EFV concomitantly administered. Our study has shown that the 4-g twice-daily PAS dosage achieves a 90% PTA for fC_{min} of >1 μg/ml even with concurrent EFV in HIV-positive patients with TB. However, the once-daily dosing even at 12 g is not compatible with EFV concurrent medication. We did not simulate higher doses, so as not to go above the total daily dose recommended in the product’s package insert.

Despite the current conviction that PAS is bacteriostatic, there is evidence that PAS has bactericidal effects at higher doses probably associated with peak concentrations. Thus, Jindani et al. (48) studied the early bactericidal activity (EBA) of anti-M. tuberculosis agents by quantifying the serial reduction of CFU of M. tuberculosis in sputum of pulmonary TB patients and reported that at a single dose of 15 g in the first two treatment days, PAS caused a fall in CFU per ml sputum per day of 0.25 log_{10}/ml, a rank that is preceded only by isoniazid (48). In a study of streptomycin resistance prevention, the evaluation of PAS daily dosages of 5, 10 or 20 g divided in four doses showed that following 4 months of treatment with the highest dosage of 20 g PAS in divided doses only 4% of patients developed streptomycin resistance but the proportion increased to 21% and 47% following lower PAS dosages of 10 g or 5 g daily (49). In a subsequent study following the introduction of the more powerful drug isoniazid, it was found that a daily PAS dosage of 10 g was adequate to prevent the development of resistance to isoniazid (50). An early in vitro study also reported that low PAS concentrations only delayed the emergence of PAS resistance, but that higher concentrations suppressed the growth of resistant mutants (51). There is also recent evidence that PAS resistance occurs over a wide range of MICs (52), some of which are well within the range of the peak concentration achieved by many of our patients receiving 8 g once daily. The MICs of PAS-resistant M. tuberculosis complex strains containing mutations in the thyA gene, which encodes enzymes of the folate pathway (53), ranged from 8 to over 128 μg/ml (52). With regard to the pharmacokinetic-pharmacodynamic index of PAS, it is still debatable whether the improved action of PAS in preventing resistance in companion drugs was due to the maintenance of concentrations above the MIC or to the higher peak concentrations. In the case of isoniazid administered with the purpose of preventing resistance development of other companion TB drugs, its pharmacokinetic-pharmacodynamic index is related to the peak concentrations (54).

In conclusion, this study demonstrates a possible effect of EFV on the pharmacokinetics of PAS in HIV-infected patients with TB. An overall reduction of approximately 30% PAS exposure should be expected in HIV-infected TB patients who are on concurrent EFV. When ARV therapy contains EFV, once-daily dosing up to 12 g PAS in these patients is not recommended. If maintenance of PAS concentrations above the MIC is considered advisable, a regimen of 4 g twice daily provides sufficient pharmacodynamic coverage of a PTA above 90% over the dosing interval, and a PTA of...
100% is achieved with thrice-daily dosage regimes of 12 g/day. The possible advantages regarding increased efficacy and ease of programmatic administration of once-daily higher doses of PAS and the role of PAS deserve further exploration, particularly for the very vulnerable group of HIV-infected patients with MDR and XDR TB.

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We have no competing interests to declare.

REFERENCES


11. Fox W, Sutherland I.


