

Evaluation of the Drug Interaction between Rifabutin and Efavirenz in Patients with HIV Infection and Tuberculosis

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Background. Because of drug-drug interactions mediated by hepatic cytochrome P450, tuberculosis treatment guidelines recommend an increase in rifabutin from 300 mg to 450 or 600 mg when combined with efavirenz-based antiretroviral therapy. To assess this recommendation, rifabutin and efavirenz pharmacokinetic parameters were investigated.

Methods. Plasma concentrations of rifabutin were determined as a baseline control in 15 patients with tuberculosis and human immunodeficiency virus (HIV) infection who were treated with rifabutin 300 mg and isoniazid 15 mg/kg (up to 900 mg) twice weekly. Rifabutin, isoniazid, and efavirenz concentrations were determined after a median of 21 days (interquartile range, 20–34 days) of daily efavirenz-based antiretroviral therapy with twice-weekly rifabutin 600 mg and isoniazid 15 mg/kg.

Results. The mean rifabutin area under the concentration-time curve (AUC_{0-24}) increased 20% from the baseline value (geometric mean, 5.0 vs. 4.2 $\mu\text{g}^*\text{h}/\text{mL}$; ratio of geometric means, 1.2 [90% confidence interval, 1.0–1.4]). Also, the mean efavirenz AUC_{0-24} in the 15 patients taking concomitant rifabutin 600 mg twice-weekly was 10% higher than that in 35 historical subjects with HIV infection who were not taking rifabutin. Efavirenz-based antiretroviral therapy was effective; HIV load decreased 2.6 log copies/mL, and the median CD4^+ T cell count increased from 141 to 240 cells/ mm^3 after a median of 21 days of efavirenz-based antiretroviral therapy. No statistically significant differences in isoniazid pharmacokinetic parameters were found.

Conclusions. The rifabutin dose increase from 300 mg to 600 mg was adequate to compensate for the efavirenz drug interaction in most patients, and no drug interaction with isoniazid was detected. Efavirenz therapy administered at a standard 600-mg dose achieved adequate plasma concentrations in patients receiving intermittent rifabutin and isoniazid therapy, was generally well tolerated, and demonstrated potent antiretroviral activity.

Significant drug-drug interactions mediated by cytochrome P450 isoforms are reported between the rifamycins (a class of drugs that plays an essential role in antituberculosis therapy) and many drugs used to

treat patients with HIV infection [1–4]. However, the potency of different rifamycins as CYP3A4 inducers varies, with rifampin being the strongest and rifabutin the least potent [5]. In a study of healthy volunteers, rifabutin 300 mg daily appeared to have little or no effect on efavirenz concentrations [6], but rifabutin concentrations were reduced by efavirenz (the mean maximum rifabutin concentration decreased by 29%, and the mean area under the concentration time-curve [AUC_{tau}] decreased by 37%). On the basis of pharmacokinetic simulations, treatment guidelines recommend that, for combination therapy, the dose of rifabutin should be increased from 300 mg to 450 or 600 mg and the dose of efavirenz should remain unchanged at 600 mg [7, 8].

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To evaluate these recommendations, we characterized the 2-way pharmacokinetic interactions between efavirenz and rifabutin in HIV-infected patients with tuberculosis. To do so, rifabutin plasma concentrations were measured in 15 patients treated with an intermittent rifabutin-containing antituberculosis regimen before and after starting efavirenz-based antiretroviral therapy. We also determined isoniazid pharmacokinetic parameters in the absence of and in the presence of efavirenz. Most patients were coenrolled in the Tuberculosis Trials Consortium (TBTC)/US Public Health Service Study 23, which was designed as an observational trial to evaluate the efficacy and tolerability of a standard rifabutin-based regimen for treatment of HIV-related tuberculosis [9].

PATIENTS AND METHODS

Experiment design. Patients with HIV infection and tuberculosis were enrolled into this pharmacokinetic study during the 2-drug phase of tuberculosis treatment (generally, during months 3–6 of therapy). Most (13 of 15) patients in this pharmacokinetic study were coenrolled in TBTC Study 23 [9], and 11 of 15 patients were enrolled from 1 TBTC site. Before initiation of antiretroviral therapy, baseline pharmacokinetic sampling occurred after rifabutin 300 mg and isoniazid 15 mg/kg up to 900 mg had been administered 2 times per week for at least 2 weeks as part of continuation-phase therapy of tuberculosis. Treatment was then initiated with efavirenz 600 mg daily and 2 nucleoside reverse-transcriptase inhibitors, together with rifabutin 600 mg twice weekly and isoniazid 15 mg/kg twice weekly. The second pharmacokinetic samples were obtained after at least 2 weeks of efavirenz-based antiretroviral therapy (median duration, 21 days [interquartile range, 20–34 days] after initial samples were obtained). Efavirenz was taken at 8 A.M. during the 5 days before the second pharmacokinetic study to facilitate testing by available nursing and laboratory staff.

Exclusion criteria for the study were previous use of any nonnucleoside reverse-transcriptase inhibitor or concomitant use of a second nonnucleoside reverse-transcriptase inhibitor, a protease inhibitor, or any medication with the potential to significantly alter the concentrations of efavirenz or rifabutin [7, 10]. With a cohort of 14 subjects, it was estimated that the study power was 0.82 to detect a 10% change in the mean efavirenz area under the concentration-time curve (AUC_{0-24}). The case histories of 3 patients with serious adverse events were reviewed (by W.B., A.V., and D.B.) without knowledge of the pharmacokinetic data, and the events were classified as definitely, probably, possibly, or not associated with drug therapy by means of a graded toxicity scale adapted from the AIDS Clinical Trials Group. An historical control group for comparison of efavirenz pharmacokinetics previously participated

in phase I and phase II studies [10]. Institutional review boards at the Centers for Disease Control and Prevention and at each participating TBTC site approved the pharmacokinetic study, and signed informed consent was obtained from all patients.

Sample collection and drug analyses. Blood samples were collected just before observed doses were administered and then 1, 3, 5, 7, 9, and 21 h after rifabutin and isoniazid were administered, which was 2, 4, 6, 8, 10, 12, and 24 h after efavirenz was administered. Patients took rifabutin while fasting (no food was consumed ≥ 2 h before and ≥ 1 h after drug administration); efavirenz was taken with food. Standard techniques were used to determine plasma drug concentrations with validated high-pressure liquid chromatography analyses of isoniazid [11], rifabutin and its 25-desacetyl metabolite, and efavirenz [12].

Statistical and pharmacokinetic analyses. The primary study objective was to compare the pharmacokinetics of rifabutin 600 mg twice per week in combination with efavirenz 600 mg daily with the pharmacokinetics of rifabutin 300 mg twice per week without efavirenz. Analyses of the AUC_{0-24} were performed using noncompartmental techniques (WinNonlin, version 4; Pharsight). Drug exposure of AUC intervals were as follows: rifabutin, AUC_{0-24} ; efavirenz, AUC_{0-24} ; and isoniazid, AUC_{0-12} . Rifabutin is known to have an extended terminal elimination phase [13], and because it was not possible to accurately calculate rifabutin's terminal elimination half-life with our sampling scheme, it is not reported. However the partial AUC of rifabutin was reported as AUC_{0-24} , because findings were similar between AUC_{0-21} and AUC_{0-24} , and it was useful to report comparable partial areas as described in other pharmacokinetic studies [14]. AUC_{0-24} was calculated by addition of the AUC_{0-21} and AUC_{21-24} (obtained by extrapolating to 24 h using the estimated half-life).

Data analyses were performed using SAS software (SAS Institute). For binomial data, differences between groups were determined using χ^2 analysis or Fisher's exact test. Pharmacokinetic data were reported as arithmetic (\pm SD) and geometric means and as ratios of the geometric means (90% CI), and comparison of paired data was performed by means of a paired t test. Comparisons between arithmetic mean values (\pm SD) of efavirenz pharmacokinetic parameters in this study and historical data were conducted, but between-study statistical comparisons were not performed. If a normal distribution was rejected by the Shapiro-Wilk statistic, or if variances of different groups were unequal and natural logarithm transformation improved the validity of the analyses, t test was performed with natural log-transformed results. Natural log-transformed data were back transformed to the original scale to obtain the geometric mean and 90% CI. Differences between groups were considered to be statistically significant at the level of $P < .05$.

RESULTS

Subjects. The demographic and clinical characteristics of the 15 patients with HIV infection and tuberculosis are listed in table 1. Patients at baseline had significant immunodeficiency with low CD4⁺ T cell counts and high HIV loads. A historical control group used for comparison of efavirenz pharmacokinetics included 35 patients with HIV infection but without tuberculosis. The 35 control subjects had a mean age of 38 years (range, 20–67 years), a mean body weight of 77 kg (range, 50–123 kg), an approximate mean CD4⁺ T cell count of 318 cells/mm³ (range, 10–973 cells/mm³), and a log plasma HIV-1 RNA load of 4.64 copies/mL (range, 2.27–6.30 copies/mL) (Sanjeev Kaul, Bristol-Myers Squibb, personal communication).

Interaction of rifabutin, 25-desacetyl rifabutin, and isoniazid pharmacokinetics with efavirenz-based antiretroviral therapy. Patients receiving rifabutin 600 mg and efavirenz had a somewhat higher rifabutin AUC_{0–24}, compared with the same patients receiving rifabutin 300 mg alone (geometric mean, 5.0 vs. 4.2 μg*h/mL; ratio of geometric means, 1.2 [90% CI, 1.0–1.4]) (table 2). Previously, it was determined that the rifabutin AUC_{0–24} was <4.5 μg*h/mL in 5 (83%) of 6 patients with tuberculosis failure or relapse with acquired rifamycin-resistant mycobacteria, compared with 33 (35%) of 94 patients without tuberculosis failure or relapse (*P* = .03, Fisher's exact test) [14]. In the present study, with similar methodology, the rifabutin AUC_{0–24} was <4.5 μg*h/mL in 5 (33%) of 15 patients receiving rifabutin 600 mg and efavirenz-based antiretroviral therapy, compared with 11 (73%) of 15 patients receiving rifabutin 300 mg at baseline without efavirenz. The peak concentration was significantly higher in patients receiving efavirenz, compared with patients who were not (0.6 μg/mL vs. 0.4 μg/mL; ratio of geometric means, 1.6 [90% CI, 1.2–2.0]). Of note, the AUC_{0–24} of the 25-desacetyl rifabutin metabolite was significantly lower in patients receiving efavirenz cotherapy, compared with patients who were not receiving efavirenz at baseline (table 2 and figure 1B). No significant differences in isoniazid pharmacokinetic parameters were found between results of baseline and follow-up studies.

Efavirenz pharmacokinetics in patients receiving intermittent rifabutin therapy. The AUC_{0–24} at steady state of daily efavirenz therapy coadministered with rifabutin (600 mg twice weekly) approximated the efavirenz AUC_{0–24} in HIV-infected patients who did not also have tuberculosis. Although between-study statistical comparisons were not performed, the arithmetic mean (±SD) of efavirenz AUC_{0–24} in the present study of 203 ± 86 μmol*h/L slightly exceeded the mean AUC_{0–24} of 184 ± 73 μmol*h/L in the HIV-infected control subjects (table 2).

Changes in immune markers in patients with tuberculosis who were receiving antiretroviral therapy. The HIV load de-

Table 1. Demographic and clinical characteristics of 15 patients with HIV infection and tuberculosis (TB) enrolled in the rifabutin-efavirenz interaction study.

| Characteristic | Value |
|---|------------------|
| Age, median years (IQR) | 36 (26–48) |
| Male sex | 13 (87) |
| Race/ethnicity | |
| Black | 3 (20) |
| White, Hispanic | 7 (47) |
| White, non-Hispanic | 5 (33) |
| Homeless within past year | 3 (20) |
| Injection drug use within past year | 4 (27) |
| Alcohol abuse within past year | 7 (47) |
| Body mass index at TB diagnosis, median (IQR) | 21.5 (20.5–22.5) |
| Site of involvement | |
| Pulmonary only | 8 (53) |
| Extrapulmonary and pulmonary | 6 (40) |
| Presence of cavitation on chest radiograph | 4 (27) |
| Bilateral lung involvement on chest radiograph | 4 (27) |
| CD4 ⁺ T cell count, median cells/mm ³ (IQR) | |
| At baseline PK sampling session | 141 (80–360) |
| After efavirenz-based ART ^a | 240 (119–360) |
| HIV RNA load | |
| At baseline PK sampling session, median log copies/mL (IQR) | 5.0 (4.3–5.3) |
| After efavirenz-based ART ^a | 2.4 (2.0–3.1) |

NOTE. Data are no. (%) of patients, unless otherwise indicated. ART, antiretroviral therapy; IQR, interquartile range; PK, pharmacokinetic.

^a ART was comprised of efavirenz and 2 nucleoside analogue reverse-transcriptase inhibitors (lamivudine [13 patients], zidovudine [7 patients], stavudine [6 patients], didanosine [3 patients], or zalcitabine [1 patient] in combinations recommended by contemporaneous guidelines). Of note, rifabutin and rifampin decrease the zidovudine area under the concentration-time curve by 32% and 47%, respectively [15, 16].

creased 2.6 log copies/mL and the median CD4⁺ T cell count increased from 141 to 240 cells/mm³ after a median of 21 days of efavirenz-based antiretroviral therapy (table 1).

Serious adverse events while receiving combination of rifabutin and efavirenz-based antiretroviral therapy. Grade 3 or 4 adverse events occurred in 3 patients during the study period. One patient had an event that was classified as definitely due to study therapy. In this patient, clinical symptoms of withdrawal from cocaine and heroin occurred 5 days after the start of daily efavirenz, zidovudine, and lamivudine therapy and a change in rifabutin dosage from 300 to 600 mg twice weekly. The patient was treated with an opiate agonist and continued to receive efavirenz-based antiretroviral therapy and rifabutin 600 mg twice weekly. Two weeks after the adverse event, samples were obtained for pharmacokinetics analysis, and high rifabutin AUC_{0–24} (13.9 μg*h/mL) was demonstrated. Events in the other 2 patients (asymptomatic neutropenia [ab-

Table 2. Pharmacokinetic parameters of efavirenz, rifabutin, rifabutin desacetyl metabolite, and isoniazid in HIV-infected patients with tuberculosis.

| Drug parameter, time of pharmacokinetic sampling or study group | GM | P ^a | Ratio of steady-state to baseline GMs (90% CI) | AM ± SD |
|---|-------|----------------|--|-------------|
| Rifabutin | | | | |
| AUC ₀₋₂₄ , μg*h/mL | | | | |
| Steady state | 4.98 | .10 | 1.20 (1.00-1.44) | 5.46 ± 2.73 |
| Baseline | 4.15 | | | 4.32 ± 1.37 |
| Peak concentration, μg/mL | | | | |
| Steady state | 0.64 | .008 | 1.58 (1.22-2.04) | 0.70 ± 0.26 |
| Baseline | 0.41 | | | 0.44 ± 0.16 |
| 25-desacetyl rifabutin | | | | |
| AUC ₀₋₂₄ , μg*h/mL | | | | |
| Steady state | 0.43 | .01 | 0.64 (0.48-0.84) | 0.59 ± 0.69 |
| Baseline | 0.68 | | | 0.85 ± 0.80 |
| Peak concentration, μg/mL | | | | |
| Steady state | 0.058 | .59 | 0.90 (0.65-1.25) | 0.07 ± 0.05 |
| Baseline | 0.064 | | | 0.12 ± 0.25 |
| Isoniazid | | | | |
| AUC ₀₋₁₂ , μg*h/mL | | | | |
| Steady state | 28.6 | .30 | 0.96 (0.87-1.04) | 33.8 ± 18.3 |
| Baseline | 29.9 | | | 36.0 ± 21.0 |
| Peak concentration, μg/mL | | | | |
| Steady state | 7.0 | .80 | 1.03 (0.91-1.17) | 7.8 ± 3.4 |
| Baseline | 6.8 | | | 7.7 ± 3.4 |
| Half-life, h | | | | |
| Steady state | 2.7 | .24 | ... | 3.2 ± 1.9 |
| Baseline | 3.2 | | | 3.6 ± 1.7 |
| Efavirenz | | | | |
| AUC ₀₋₂₄ , μmol*h/L | | | | |
| Present study | ... | | ... | 203 ± 86 |
| Historical subjects | ... | | ... | 184 ± 73 |
| Peak concentration, μmol/L | | | | |
| Present study | ... | | ... | 14.1 ± 3.8 |
| Historical subjects | ... | | ... | 12.9 ± 3.7 |
| Trough concentration, μmol/L | | | | |
| Present study | ... | | ... | 6.0 ± 3.8 |
| Historical subjects | ... | | ... | 5.6 ± 3.2 |

NOTE. Baseline pharmacokinetic sampling was performed after administration of rifabutin 300 mg and isoniazid twice weekly without antiretroviral therapy. Steady-state pharmacokinetic sampling was performed after at least 2 weeks (median duration, 21 days; interquartile range, 20-34 days) of treatment with efavirenz 600 mg daily and 2 nucleoside analogue reverse-transcriptase inhibitors administered together with rifabutin 600 mg and isoniazid 15 mg/kg (up to 900 mg) twice weekly. AM, arithmetic mean; AUC, area under the concentration-time curve; GM, geometric mean.

^a By paired *t* test.

solute neutrophil count, 640 neutrophils/mm³] and elevated pancreatic enzyme levels) were classified as probably associated with drug therapy, although drug concentrations were not high, compared with concentrations in other patients.

DISCUSSION

This study suggests that the recommended rifabutin dose adjustment (from 300 mg to 600 mg) when rifabutin is coadministered with efavirenz is appropriate, and concentrations of both rifabutin and efavirenz appeared to be adequate and rea-

sonably well-tolerated in most patients. The therapeutic window of rifabutin for treatment of tuberculosis has not been defined, but lower plasma concentrations of rifabutin were associated with tuberculosis treatment failure or relapse in association with acquired rifamycin resistance among patients with HIV infection and tuberculosis [14]. In that study, the rifabutin AUC₀₋₂₄ was <4.5 μg*h/mL in 5 (83%) of 6 patients with tuberculosis treatment failure or relapse associated with acquired rifamycin resistance, compared with 33 (35%) of 94 patients with tuberculosis treatment failure or relapse and with-

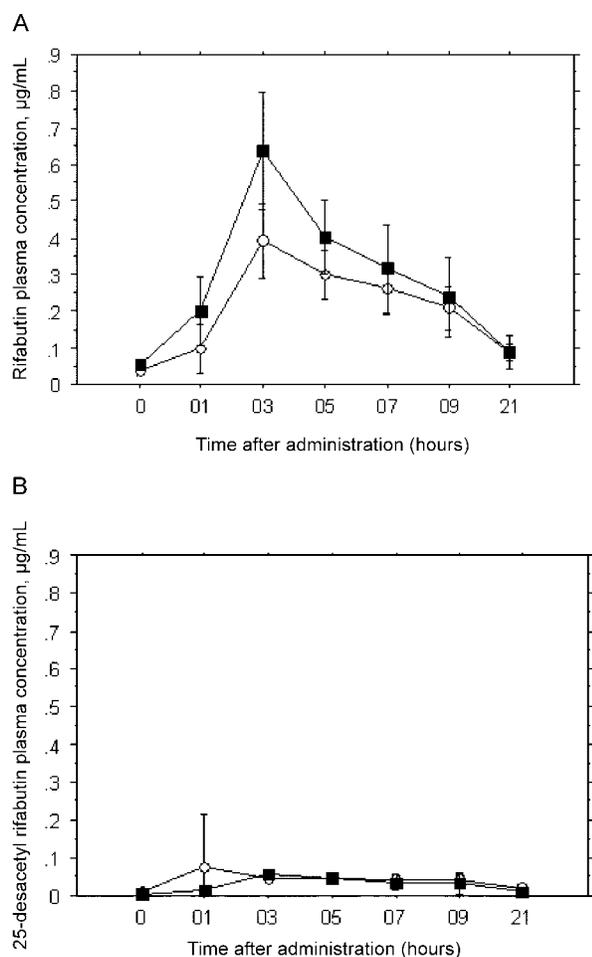


Figure 1. Mean rifabutin (A) and 25-desacetyl rifabutin (B) plasma concentrations-versus-time plots for patients with HIV-related tuberculosis who received an oral dose of rifabutin 300 mg without antiretroviral therapy (circles) and rifabutin 600 mg with efavirenz-based antiretroviral therapy (squares) for 15 patients who each underwent 2 pharmacokinetic analysis sessions. Bars, mean values (95% CIs).

out acquired rifamycin resistance ($P = .03$, by Fisher's exact test) [14]. In the current study, the rifabutin AUC_{0-24} was $<4.5 \mu\text{g}\cdot\text{h}/\text{mL}$ in 33% of patients shortly after the increase of the rifabutin dose to 600 mg and the initiation of efavirenz-based antiretroviral therapy, compared with 73% of the same patients receiving rifabutin 300 mg with no antiretrovirals. Comparable results to these were obtained for other patients with HIV infection and tuberculosis enrolled in a parallel pharmacokinetic substudy (data not shown) [14]. These data support current treatment recommendations that the rifabutin dose should be increased from 300 mg to 600 mg when administered with efavirenz 600 mg once daily [7, 8]. Although our study evaluated patients receiving a twice-weekly dose of rifabutin, the same dose adjustment (from 300 mg to 600 mg) is advisable for patients receiving a more frequent rifabutin dosage (as is

recommended for persons with a $CD4^+$ T cell count of <100 cells/ mm^3).

Both rifabutin and the 25-desacetyl metabolite appear to be metabolized, in part, through cytochrome P450-catalyzed oxidation. Previous studies have demonstrated that administration of clarithromycin, fluconazole, or ritonavir (all of which are inhibitors of cytochrome P450) result in greater AUCs and peak concentrations of both rifabutin and the 25-desacetyl rifabutin metabolite [17–19]. Furthermore, oxidation in vitro of desacetyl rifabutin was reported with cytochrome P450 preparations from human liver specimens and enterocyte microsomes [20]. In the present study, at baseline, before the initiation of efavirenz therapy, the mean AUC_{0-24} of the microbiologically-active, desacetyl metabolite was only 16% of the mean rifabutin AUC_{0-24} . The desacetyl rifabutin AUC_{0-24} significantly decreased with efavirenz treatment, a finding compatible with efavirenz induction of cytochrome P450 metabolism of the rifabutin metabolite.

Plasma concentrations of efavirenz achieved in the presence of rifabutin and isoniazid appeared to be adequate. First, patients in this study had excellent initial virologic and immunological responses to efavirenz-based antiretroviral therapy: the HIV load decreased by 2.6 log copies/mL, and the median $CD4^+$ T cell count increased 70% to 240 cells/ mm^3 after a median 21 days of combination antiretroviral therapy. Second, the efavirenz concentrations achieved in patients in this study were similar to those in historical HIV-infected control subjects who received daily efavirenz 600 mg in the absence of rifabutin (efavirenz was administered with food in both studies). Moreover, the efavirenz concentrations achieved in the present study were greater than those associated with successful therapy in previous studies [21–23]. Joshi et al. [23] reported that a trough (24-h) efavirenz concentration of $<3.5 \mu\text{mol}/\text{L}$ was associated with antiretroviral failure (63% vs. 21%). Lopez-Cortes et al. [24] described trough efavirenz concentrations of $<3.5 \mu\text{M}$ in 7 (88%) of 8 patients receiving daily treatment with rifampin and efavirenz 600 mg (median efavirenz dose, 9.7 mg/kg) and in 9 (56%) of 16 patients receiving daily treatment with rifampin and efavirenz 800 mg (median efavirenz dose, 15.7 mg/kg). In the present study, patients received a median efavirenz dose of 8.8 mg/kg, with trough efavirenz concentrations of $<3.5 \mu\text{mol}/\text{L}$ found in only 1 (7%) of 15 patients. The patient with a low trough efavirenz concentration was administered 10.5 mg/kg of efavirenz and had a good short-term (35-day) response to efavirenz-based antiretroviral therapy, with a decrease in the log plasma HIV-1 RNA load from 5.7 to 2.8 copies/mL and an increase in the $CD4^+$ cell count from 75 to 240 cells/mL.

In the current study, patients were permitted to take efavirenz with food (the mean caloric intake for 11 patients was 2625 kJ

[46 g fat, with 32% of the calories from fat]). In a previous study of a single 600-mg dose of efavirenz, a high-fat and high-calorie meal (3742 kJ and 54 g fat, with 54% of the calories from fat) was associated with a mean increase in the efavirenz $AUC_{0-\infty}$ of 22% and a mean increase in the peak efavirenz concentration of 39% [10]. The group of 35 patients infected with HIV, who served as historical control subjects for efavirenz concentrations in this study, also were administered efavirenz with food (Sanjeev Kaul, Bristol-Myers Squibb, personal communication). The manufacturer presently recommends that efavirenz be taken on an empty stomach, because a higher efavirenz concentration with food "may lead to an increase in frequency of adverse events" [10, p. 5]. In the present study, the proportion of patients with grade 3 or 4 adverse events was similar to the proportion observed in previous trials of efavirenz involving patients with HIV infection [25, 26]. However, the risk of intolerance due to higher efavirenz concentrations should be balanced against the risk of low efavirenz concentrations secondary to rifamycin-drug interactions.

This pharmacokinetic study has several important limitations. First, the distribution of our sampling scheme (24 h) was not sufficient to estimate accurately some pharmacokinetic parameters, such as rifabutin half-life. Second, the duration of the follow-up period (2 months beyond the last pharmacokinetic sampling) was too short to rigorously evaluate the durability of efavirenz-based antiretroviral therapy. However, the robustness of the findings suggests that the sampling format and the study design were sufficient to detect relevant trends in pharmacokinetic parameter values. This study was not conducted during the initial phase of tuberculosis treatment, when the drug pharmacokinetics may differ or the toxicity of multidrug treatment may be greater. Furthermore, residual confounding by measured or unmeasured variables is possible. Therefore, the data require validation in a larger group. A final limitation of the study is that the findings are limited to the United States and Europe, where rifabutin is available; rifampin is the only available rifamycin in many countries with high rates of HIV infection and tuberculosis.

In summary, the increase in the rifabutin dose from 300 mg to 600 mg was adequate to compensate for the drug interaction with efavirenz in most patients. However, additional studies are needed to characterize optimal treatment regimens for patients with HIV infection and tuberculosis, because the majority of patients receiving rifabutin 300 mg without HAART and a minority of patients who had recently started HAART had rifabutin concentrations that were associated with tuberculosis treatment failure or relapse when rifabutin was administered twice weekly. Current guidelines propose using daily tuberculosis therapy, at least for the first 2 months of treatment, for patients with advanced HIV disease [7]. In the present study, no drug interaction with isoniazid was detected. Furthermore,

standard efavirenz dosage of 600 mg daily achieved adequate plasma concentrations during intermittent rifabutin therapy and was generally well tolerated. The combination of efavirenz and 2 nucleoside reverse-transcriptase inhibitors in the presence of rifabutin and isoniazid demonstrated potent antiretroviral activity.

MEMBERS OF THE CONSORTIUM

The participating clinical sites (principal investigators and study coordinators; numbers of patients enrolled) were University of Texas Health Science Center in San Antonio/South Texas Veterans Health Care System (Marc Weiner, Melissa Engle, and Victoria Rodriguez; 11), University of British Columbia Health Center (Mark Fitzgerald, Eduardo Hernandez, and Banafsheh Peyvandi; 2), Los Angeles County/University of Southern California Medical Center (Brenda Jones, Claudia Silva, and Maria Brown; 1), and Johns Hopkins University School of Medicine (Richard Chaisson, Timothy Sterling, Kristina Moore, and Judith Hackman; 1).

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