MAJOR ARTICLE

Pharmacokinetic Evaluation of Rifabutin in Combination with Lopinavir-Ritonavir in Patients with HIV Infection and Active Tuberculosis

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Background. Human immunodeficiency virus (HIV)–associated tuberculosis is difficult to treat, given the propensity for drug interactions between the rifamycins and the antiretroviral drugs. We examined the pharmacokinetics of rifabutin before and after the addition of lopinavir-ritonavir.

Methods. We analyzed 10 patients with HIV infection and active tuberculosis in a state tuberculosis hospital. Plasma was collected for measurement of rifabutin, the microbiologically active 25-desacetyl-rifabutin, and lopinavir by validated high-performance liquid chromatography assays. Samples were collected 2–4 weeks after starting rifabutin at 300 mg thrice weekly without lopinavir-ritonavir, 2 weeks after the addition of lopinavir-ritonavir at 400 and 100 mg, respectively, twice daily to rifabutin at 150 mg thrice weekly, and (if rifabutin plasma concentrations were below the normal range) 2 weeks after an increase in rifabutin to 300 mg thrice weekly with lopinavir-ritonavir. Noncompartmental and population pharmacokinetic analyses (2-compartment open model) were performed.

Results. Rifabutin at 300 mg without lopinavir-ritonavir produced a low maximum plasma concentration (C_{max}) in 5 of 10 patients. After the addition of lopinavir-ritonavir to rifabutin at 150 mg, 9 of 10 had low C_{max} values. Eight patients had dose increases to 300 mg of rifabutin with lopinavir-ritonavir. Most free rifabutin (unbound to plasma protein) C_{max} values were below the tuberculosis minimal inhibitory concentration. For most patients, values for the area under the plasma concentration–time curve were as low or lower than those associated with treatment failure or relapse and with acquired rifamycin resistance in Tuberculosis Trials Consortium/US Public Health Service Study 23. One of the 10 patients experienced relapse with acquired rifamycin resistance.

Conclusion. The recommended rifabutin doses for use with lopinavir-ritonavir may be inadequate in many patients. Monitoring of plasma concentrations is recommended.

Rifabutin is used for human immunodeficiency virus (HIV)–associated tuberculosis because hepatic microsomal enzyme induction is lower than that observed for rifampin [1, 2]. Unlike rifampin, some rifabutin and most of its partially active 25-desacetyl-rifabutin metabolite (hereafter, *desacetyl-rifabutin*) are cleared by CYP3A4. Thus, rifabutin plasma concentrations can be increased by HIV protease inhibitors [3]. Low plasma concentrations of isoniazid and rifabutin are associated with poor outcomes, at least with intermittent therapy [4, 5]. Also, elevated rifabutin plasma concentrations are associated with arthralgia, leukopenia, and anterior uveitis [1, 2]. Low lopinavir trough concentrations secondary to rifabutin induction could compromise virological and clinical responses [6]. Healthy volunteer data suggest that 300 mg of rifabutin daily can be reduced to 150 mg thrice weekly in the presence of lopinavir-ritonavir [7]. We undertook the present pharmacokinetic study to examine this bidirectional drug interaction in the clinical setting.

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METHODS

Design

This was an open-label, nonrandomized study. The primary objective was to determine the pharmacokinetics of rifabutin and lopinavir-ritonavir. Secondary objectives were to determine the short-term safety and tolerability of rifabutin plus lopinavir-ritonavir and HIV and tuberculosis clinical responses. This institutional review board–approved study was performed at A. G. Holley State Hospital in Florida. Eligibility requirements were provision of informed consent, confirmed diagnosis of HIV infection and tuberculosis, mycobacterial isolates susceptible to rifamycins, ability to tolerate appropriate tuberculosis therapy for 2 weeks, and no receipt of highly active antiretroviral therapy (HAART) at enrollment. Exclusion criteria were aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level $\geqslant$5 times the upper limit of normal (ULN), bilirubin level $\geqslant$3 times the ULN, creatinine level $\geqslant$3 times the ULN, hemoglobin level $\leqslant$7.0 mg during receipt of erythropoietin, fasting triglyceride level $\geqslant$750 mg/dL, intolerance to tuberculosis medications, fasting glucose level $\geqslant$250 mg/dL, and pregnancy.

Complete histories were taken, physical examinations were performed, and laboratory testing was done. Patients began rifabutin at 300 mg thrice weekly plus isoniazid, pyrazinamide, and ethambutol. At visit 1 (week 2–4), steady-state rifabutin concentrations were measured at 0, 2, 4, 8,12, 24, and 48 h after observed doses. New signs or symptoms, intercurrent illness, concurrent medications, adherence, and adverse events were recorded. Patients were switched to rifabutin at 150 mg thrice weekly and lopinavir-ritonavir (400 and 100 mg, respectively, twice daily), plus tenofovir and emtricitabine were started. At visit 2 (week 4–5), a new steady-state assessment was done, and extra plasma aliquots (4 and 8 h) were obtained for rapid rifabutin analysis.

At visit 3 (week 6–7), baseline assessments were repeated. Rifabutin concentrations at 4 and 8 h were evaluated. The 4-h concentration generally captures the maximum plasma concentration (C_{max}), and the 8-h concentration captures delayed absortion (8 h $\geqslant$ 4 h). The normal range for the rifabutin C_{max} value in our laboratory is 0.30–0.90 μg/mL [2, 8]. If both concentrations were $\leqslant$0.30 μg/mL, rifabutin was increased to 300 mg thrice weekly, and patients returned in 2 weeks for another pharmacokinetic study. Grade 3 or 4 adverse drug reactions (per the National Institute of Allergy and Infectious Disease Division of AIDS 2004 grading scale) were considered significant.

Pharmacokinetic and Statistical Analyses

Noncompartmental analysis. Blood was promptly centrifuged; plasma was harvested and frozen until analysis. Concentrations of rifabutin, its desacetyl metabolite, and lopinavir were determined using validated high-performance liquid chromatography assays [5]. Noncompartmental analyses (WinNonlin 4; Pharsight) were used to determine the C_{max}; the time of C_{max} (T_{max}); the area under the plasma concentration–time curve from 0 to 12 h ($AUC_{0\text{-}12}$), to 24 h ($AUC_{0\text{-}24}$), to 48 h ($AUC_{0\text{-}48}$), and to infinity ($AUC_{0\text{-}\infty}$); the elimination rate constant (K_{el}), and the elimination half-life ($t_{1/2}$).

Model-based analysis. A 2-compartment open model was chosen. Population pharmacokinetic parameters of Gatti were tested with the General Modeling, Bayesian Fitting program within the USC*PACK group of programs [9]. The fit was not adequate, so we proceeded to new models. Our laboratory's quality control assay error pattern was used for modeling done with the Nonparametric Adaptive Grid (NPAG) program [10, 11]. Models included the absorption rate constant (K_a; h^{-1}), K_{el} (h^{-1}), the volume of distribution (V_c/F, where F is absolute bioavailability; liter), and 2 intercompartmental rate constants (K_{12} and K_{21}; h^{-1}).

Goodness of fit was assessed on the basis of the log-likelihood test, plots of predicted versus observed concentrations, and R^2 values. Predictive performance was assessed using the weighted mean error for bias and the bias-adjusted weighted mean square error for precision. The remaining pharmacokinetic parameters were calculated using standard equations. JMP statistical software, version 6.0.3 (SAS Institute), was used to assess associations between pharmacokinetic parameter estimates and demographic variables for further model building. Free drug (unbound to plasma protein) AUC values were calculated by multiplying the individual AUC values by a free fraction of 15% [11].

Microbiological analysis. Susceptibility to rifabutin was confirmed for all patient samples. Clinical tests to determine minimum inhibitory concentrations (MICs) for rifabutin and desacetyl-rifabutin are not routine. We measured MICs for laboratory strain H37Rv plus 10 clinical isolates by means of the BACTEC 460 instrument (Becton Dickenson). Free drug AUC/MIC ratios were calculated using median values. For rifabutin, the bioequivalence function of WinNonlin 4 software compared periods 1 and 2. Standard definitions of bioequivalence were used (rifabutin plus lopinavir-ritonavir AUC and C_{max} within 80%–125% of those for rifabutin alone).

RESULTS

Patient Characteristics

Eleven patients were screened and 10 were enrolled from October 2006 through June 2008. One patient was excluded (because of hepatitis). Eight were men, 8 were African American, and 2 were white; and all were born in the United States. The median age was 33.5 years (range, 24–50 years), the median weight was 74 kg (range, 55–118 kg), and the median body mass index (calculated as the weight in kilograms divided by

Table 1. Rifabutin Pharmacokinetic Parameters from Noncompartmental Analyses

Parameter	Visit 1 (n = 10)	Visit 2 (n = 10)	Visit 3 (n = 8)
C_{max}, μg/mL	0.30 (0.15–0.55)	0.23 (0.04–0.32)	0.37 (0.09–0.58)
T_{max}, h	4.0 (2.0–8.0)	4.0 (2.0–6.0)	4.0 (2.0–4.0)
AUC_{0-24}, μg·h/mL	2.71 (1.39–3.98)	2.97 (0.60–4.67)	4.36 (1.73–6.09)
AUC_{0-48}, μg·h/mL	3.33 (1.75–5.43)	4.42 (0.96–7.48)	6.89 (3.13–8.16)

NOTE. Data are median (range). AUC_{0-24}, area under the plasma concentration–time curve from 0 to 24 h; AUC_{0-48}, area under the plasma concentration–time curve from 0 to 48 h; C_{max}, maximum plasma concentration; T_{max}, time of C_{max}.

the square of height in meters) was 23.1 (range, 18.0–34.3). Nine patients had pansusceptible tuberculosis, and one had an isolate resistant to isoniazid (0.1 μg/mL).

Noncompartmental Analysis

Rifabutin. All patients had measurable rifabutin concentrations at 48 h (C_{48}) (Table 1). Rifabutin C_{max} values were somewhat lower with lopinavir-ritonavir ($P = .069$). AUC_{0-48} values increased with lopinavir-ritonavir, increasing further with 300-mg doses ($P < .001$ and $P = .003$, respectively). Nine of 10 patients had visit 2 rifabutin concentrations of ≤0.30 μg/mL; 8 were given higher rifabutin doses, and 1 was withdrawn (see the section on adverse events below). The median rifabutin $t_{1/2}$ value increased 81% at visit 2, whereas oral clearance (CL/F) decreased 71% (both significant). The median volume of distribution (V_z/F) decreased by 43% (not significant).

Metabolite. All patients had measurable metabolite concentrations at 48 h during visits 2 and 3, but only 5 during visit 1 (Table 2). Metabolite C_{max} values were somewhat higher after lopinavir-ritonavir was started. C_{48} and AUC_{0-48} values both increased after lopinavir-ritonavir was started and increased further with 300-mg doses ($P < .001$ for both). Because the metabolite is partially active microbiologically, total rifabutin activity might include rifabutin plus metabolite (Table 3). AUC_{0-24} and AUC_{0-48} values increased after lopinavir-ritonavir was started and increased further with 300-mg doses ($P < .001$ for both).

Matched pairs are shown in Figures 1 and 2 for rifabutin and in Figure 3 for metabolite. Rifabutin C_{max} values dropped 19% after a change from 300 mg of rifabutin to 150 mg plus lopinavir-ritonavir. Two patients had considerably lower C_{max} values. All but 1 patient had a lower AUC value after the change to 150 mg. Although desacetyl-rifabutin C_{max} values generally increased, concentrations remained small. In contrast, several patients had large increases in metabolite AUC_{0-48} values.

Bioequivalence without and with lopinavir-ritonavir. The C_{max} value for 150 mg of rifabutin (plus lopinavir-ritonavir) was 81% of that with 300 mg rifabutin alone and failed to show bioequivalence. The 150-mg AUC_{0-48} value was 134% of that with 300 mg and failed to show bioequivalence (geometric least squares mean).

Model-Based Analysis

Two-compartment open model. A NPAG 2-compartment open model without covariates adequately described the data. Removing very low concentrations during the absorption lag phase improved the model fit. Weight explained 29% of the variability in volume ($P = .111$), so modeling was done with volume in liters per kilograms. The result had similar log likelihood, less bias, and improved precision. For rifabutin at 300 mg thrice weekly alone, the median pharmacokinetic values were as follows: K_a, 0.27 h^{-1}; V/F, 8.34 L/kg; K_{el}, 0.27 h^{-1}; K_{12}, 0.19 h^{-1}; and K_{21} 0.035 h^{-1}. For comparison, Gatti values were as follows: K_a, 0.20 h^{-1}; V/F, 4.44 L/kg; K_{el}, 0.26 h^{-1}; K_{12}, 0.26 h^{-1}; and K_{21}, 0.057 h^{-1} [9]. Additional pharmacokinetic and pharmacodynamic parameters are shown in Table 4. The plot of predicted versus observed concentrations had an R^2 value of 0.95, low bias (−0.11), and high precision (0.87).

Simulations with the model output. WinNonlin simulations using median NPAG parameter estimates closely approximated the original data. Simulations were performed with 150, 300, and 450 mg of rifabutin thrice weekly and daily doses. Daily dosing produced day 1 C_{max} values of 0.15, 0.30, and 0.45 μg/mL, respectively, and day 5 C_{max} values of 0.18, 0.35, and 0.53 μg/mL (C_{max} accumulation ratio, 1.17). Also, the simulations produced day 1 $AUC_{0-\infty}$ values of 2.00, 3.99, and 5.99 μg·h/mL, respectively.

Simulations of pharmacodynamics. We simulated rifabutin at 300 mg thrice weekly relative to the MIC (median, 0.06 μg/mL). The total (bound plus free) rifabutin C_{max}/MIC ratio was 5 (0.30 to 0.06 μg/mL). However, with a free fraction of 15%, the free rifabutin C_{max} of 0.05 μg/mL was only 84% of the MIC. Using a MIC of 0.06 μg/mL, free rifabutin C_{max}/MIC ratios at visits 1, 2, and 3 were 0.75 (range, 0.38–1.38), 0.56 (0.10–0.80), and 0.93 (0.23–1.45), respectively. At visit 1, only 1 patient had a free C_{max}/MIC ratio >1; none were >1 at visit 2, whereas 3 of 8 were >1 at visit 3. These values are low;

Table 2. Desacetyl-rifabutin Pharmacokinetic Parameters from Noncompartmental Analyses

Parameter	Visit 1 (n = 10)	Visit 2 (n = 10)	Visit 3 (n = 8)
C_{max}, μg/mL	0.06 (0.01–0.17)	0.09 (0.05–0.12)	0.14 (0.07–0.21)
T_{max}, h	4.0 (2.0–8.0)	6.0 (0.0–8.0)	4.0 (2.0–6.0)
AUC_{0-24}, μg·h/mL	0.49 (0.07–1.52)	1.54 (0.91–2.35)	2.54 (1.08–3.69)
AUC_{0-48}, μg·h/mL	0.60 (0.09–2.69)	2.70 (1.39–4.23)	4.95 (1.84–6.05)

NOTE. Data are median (range). AUC_{0-24}, area under the plasma concentration–time curve from 0 to 24 h; AUC_{0-48}, area under the plasma concentration–time curve from 0 to 48 h; C_{max}, maximum plasma concentration; T_{max}, time of C_{max}.

Table 3. Combined Area under the Plasma Concentration–Time Curve Values for Rifabutin plus Desacetyl-Rifabutin (Combined Rifamycin Exposure)

Parameter	Visit 1 (n = 10)	Visit 2 (n = 10)	Visit 3 (n = 8)
AUC_{0-24}, $\mu g \cdot h/mL$	3.45 (1.71–4.58)	4.36 (1.51–6.74)	7.31 (2.81–9.78)
AUC_{0-48}, $\mu g \cdot h/mL$	4.54 (2.27–6.20)	7.01 (2.35–11.70)	11.88 (4.97–14.13)

NOTE. Data are median (range). AUC_{0-24}, area under the plasma concentration–time curve from 0 to 24 h; AUC_{0-48}, area under the plasma concentration–time curve from 0 to 48 h.

for concentration-dependent drugs such as the rifamycins, higher ratios should be more effective.

Metabolite in Vitro

The rifabutin MIC for the laboratory strain H37Rv was 0.03 μg/mL, and the desacetyl-rifabutin MIC was at the border of 0.03–0.06 μg/mL, consistent with the findings of Ungheri et al [13]. Three rifampin-resistant clinical isolates also were resistant to rifabutin and desacetyl-rifabutin at all concentrations tested. This experiment demonstrated cross-resistance between rifampin and rifabutin and showed that desacetyl-rifabutin did not have unique activity in the absence of rifabutin activity. For clinical isolates, the rifabutin MIC was 0.06 μg/mL (range, 0.03–0.25 μg/mL), and the desacetyl-rifabutin MIC was 0.09 μg/mL (0.03–0.50 μg/mL). MIC pairs are shown in Table 5. For 5 of the 7 isolates, the desacetyl-rifabutin MIC was at least twice that of rifabutin. Therefore, for most clinical isolates the metabolite was less active than rifabutin.

Lopinavir Pharmacokinetics

Ten patients had lopinavir concentrations measured at visit 2, and 8 has them measured at visit 3. Lopinavir concentrations were similar at visits 2 and 3. The visit 2 median C_{max} value was a 8.20 μg/mL (range, 6.68–15.39 μg/mL); the C_{12} value was 5.15 μg/mL (3.57–10.69 μg/mL), and the AUC_{0-12} value was 80.54 $\mu g \cdot h/mL$ (52.77–147.04 $\mu g \cdot h/mL$). The visit 3 C_{max} value was 9.55 μg/mL (3.01–14.31 μg/mL); the C_{12} value was 3.80 μg/mL (0.15–8.19 μg/mL), and the AUC_{0-12} value was 87.55 $\mu g \cdot h/mL$ (19.06–135.93 $\mu g \cdot h/mL$). The exception was patient 2, who had a C_{max} value of 3.01 and a C_{12} value of 0.15 μg/mL on visit 3, with an a AUC_{0-12} value of 19.06 $\mu g \cdot h/mL$. The apparent elimination $t_{1/2}$ decreased from visit 2 (median, 7.8 h [6.41–16.45 h]) to visit 3 (median, 5.03 h [1.65–13.06 h]) in 6 of the 8 patients. The published target for treatment-experienced patients is >4 μg/mL [6]. At visit 2, 3 of 10 patients had C_{12} values between 3.50 and 4.00 μg/mL. At visit 3, 3 of 8 patients had C_{12} values <4 μg/mL; 4 had values between 2.90 and 4.00 μg/mL, plus the very low value noted above.

Adverse Events

Two patients developed grade 2 neutropenia (absolute neutrophil count, 750–999 cells/mm^3). One patient had neutropenia before the study and had an absolute neutrophil count of 800 cells/mm^3 on day 14 of rifabutin therapy at 300 mg; the other patient developed neutropenia (absolute neutrophil count, 900 cells/mm^3) on day 21 of rifabutin therapy at 150 mg with lopinavir-ritonavir. Both patients responded to filgrastim.

Two patients (one of whom had hepatitis C) had grade 2 elevations in liver enzyme levels (ALT or AST concentration 2.6–5.0 times the ULN). None of the 10 patients developed uveitis or arthralgia.

Two patients developed diarrhea. One had grade 2 diarrhea that lasted 1 week. Stool culture results were negative, and he completed therapy. The other patient developed grade 3 diarrhea that lasted 25 days; at one point the patient required intravenous fluids. All stool culture results were negative. He refused HAART because of gastrointestinal intolerance and was withdrawn from study; his symptoms resolved. Two additional patients experienced immune reconstitution inflammatory syndrome.

Response to Tuberculosis Treatment

All patients were considered to be cured of tuberculosis. All patients received a 4-drug regimen (isoniazid, rifabutin, pyrazinamide, and ethambutol) during hospitalization, except for one with tuberculosis meningitis, who received cycloserine instead of pyrazinamide. Importantly, one patient receiving rifabutin, isoniazid, pyrazinamide, and ethambutol experienced relapse with acquired rifamycin resistance. At visits 1 and 2,

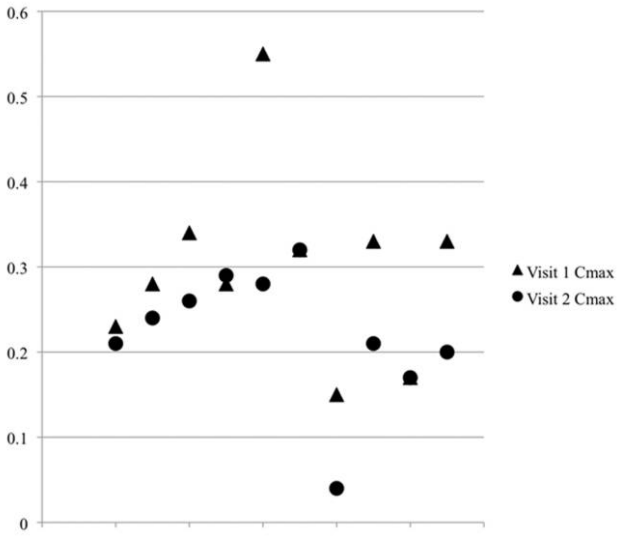

Figure 1. Visit 1 and 2 maximum plasma concentration (C_{max}) values for rifabutin (*Y*-axis; μg/mL), matched vertically by patient (*X*-axis).

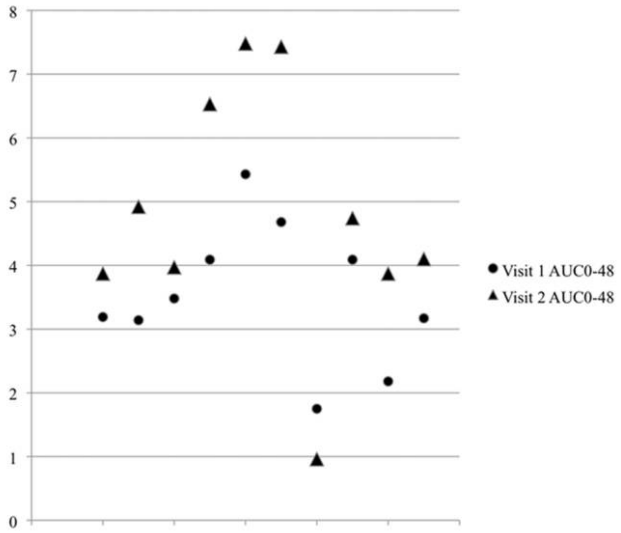

Figure 2. Visit 1 and 2 area under the plasma concentration–time curve from 0 to 48 h (AUC_{0-48}) values for rifabutin (*Y*-axis; $\mu g \cdot h/mL$), matched vertically by patient (*X*-axis).

this patient had the second lowest rifabutin and des-rifabutin C_{max} and AUC_{0-48} values (Figures 1 and 3, second from right), with correspondingly low pharmacodynamic parameters. This patient weighed 118 kg and had a body mass index of 34.3.

Response to HIV Treatment

All patients responded to HAART. The mean baseline CD4 cell count was 133 cells/mm^3 (range, 11–370 cells/mm^3), and the mean baseline viral load was 5.41 $\log_{10}$ copies/mL (4.64–5.87 $\log_{10}$ copies/mL). After 4 weeks of HAART, the mean CD4 cell count was 202 cells/mm^3 (45–473 cells/mm^3), and the mean viral load was 3.05 $\log_{10}$ copies/mL (2.20–3.81 $\log_{10}$ copies/mL). The mean increase in CD4 cell count was 69 cells/mm^3 (28–183 cells/mm^3), and the mean drop in viral load was 2.36 $\log_{10}$ copies/mL (1.77–2.92 $\log_{10}$ copies/mL).

DISCUSSION

Dose adjustment of rifabutin from 300 mg thrice weekly to 150 mg thrice weekly (with lopinavir-ritonavir) generally kept the rifabutin C_{max} and AUC values in a similar range. The visit 1 median rifabutin C_{max} value was at the low end of the normal range (0.30 μg/mL), and 5 patients had values below normal [2, 8, 12]. After changing to 150 mg of rifabutin (plus lopinavir-ritonavir), 7 of 10 patients showed a decreased C_{max} value. Also, with 300 mg of rifabutin (plus lopinavir-ritonavir), only 3 patients had total rifabutin C_{max} values of 0.45 μg/mL or greater, the C_{max} value associated with favorable outcomes in Tuberculosis Trials Consortium (TBTC)/US Public Health Service Study 23A [5]. For concentration-dependent rifamycins, low C_{max} values are undesirable [2, 8, 12, 14, 15]. In contrast, excepting one patient, AUC values increased after the dose change. The relative importance of C_{max} versus AUC as a pharmacodynamic variable for rifabutin has not been studied. For rifampin, C_{max} was most predictive in a hollow-fiber model, whereas AUC was most predictive in a mouse model [8, 14]. Our study lacks individual MICs, so we cannot extend the pharmacodynamic analysis to C_{max}/MIC or to AUC/MIC for individual patients.

Both the rifabutin and metabolite MICs showed 8-fold variability. Using our MIC of 0.06 μg/mL, the simulated total rifabutin C_{max}/MIC ratio was 5, but the simulated free rifabutin C_{max}/MIC ratio was only 0.84. At no time was the simulated free rifabutin concentration above the MIC. Only simulated 450-mg doses 5 times weekly produced free rifabutin concentrations at or slightly above the MIC for part of the dosing interval. Rifampin and rifapentine are highly concentration dependent in their activity, and rifabutin has the same mechanism of action [2, 12, 14, 15]. Thus, predictions of continuous free rifabutin concentrations beneath the MIC are disturbing.

The visit 1 median total rifabutin AUC_{0-24} value of 2.71 was less than the TBTC Study 23 value of 3.2 associated with ARR. Even the visit 1 maximum AUC_{0-24} value of 3.98 $\mu g \cdot h/mL$ was closer to the TBTC Study 23 ARR value of 3.2, rather than the 5.2 value associated with good outcomes [5]. Thus, standard starting doses of 300 mg of rifabutin (in this case, thrice weekly) are potentially inadequate for HIV-positive patients. With lopinavir-ritonavir and rifabutin doses of 150 mg, the rifabutin AUC_{0-24} value of 2.97 $\mu g \cdot h/mL$ remained less than the TBTC

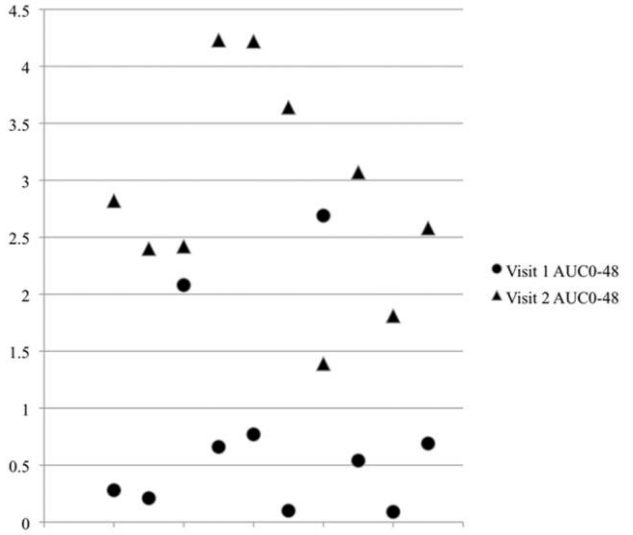

Figure 3. Visit 1 and 2 area under the plasma concentration–time curve from 0 to 48 h (AUC_{0-48}) values for desacetyl-rifabutin (*Y*-axis; $\mu g \cdot h/mL$), matched vertically by patient (*X*-axis).

Table 4. Summary of Individual Nonparametric Adaptive Grid Pharmacokinetic Parameters for Rifabutin

Parameter	Median (range)
K_a, h^{-1}	0.28 (0.11–0.39)
Abs $t_{1/2}$, h	2.51 (1.78–6.30)
K_{el}, h^{-1}	0.27 (0.12–0.72)
$t_{1/2}$, h	2.57 (0.97–5.59)
V_c/F, L/kg	8.08 (2.18–23.13)
V_c/F, L	658 (159–2733)
CL/*F*, L/h	167 (79–355)
K_{12}, h^{-1}	0.19 (0.01–1.01)
K_{21}, h^{-1}	0.040 (0.005–1.000)
V_t, L	3846 (27–30,460)
CL_d, L/h	138 (27–296)
R^2 (individual fit)	0.98 (0.48–0.99)
C_{max} (NCA), μg/mL	0.30 (0.15–0.55)
Free C_{max} (NCA), μg/mL	0.04 (0.02–0.08)
Free C_{max}/MIC (NCA)	0.75 (0.38–1.37)
$AUC_{0-\infty}$, $\mu g \cdot h/mL$	1.79 (0.85–3.78)
Free $AUC_{0-\infty}$, $\mu g \cdot h/mL$	0.27 (0.13–0.57)
Free $AUC_{0-\infty}$/MIC	4.48 (2.11–9.44)

NOTE. Abs $t_{1/2}$, absorption half-life; $AUC_{0-\infty}$, area under the plasma concentration–time curve from 0 h to infinity; CL_d, intercompartmental distribution clearance; C_{max}, maximum plasma concentration; CL/*F*, oral clearance; *F*, absolute bioavailability; K_{12} and K_{21}, intercompartmental rate constants; K_a, absorption rate constant; K_{el}, elimination rate constant; MIC, minimum inhibitory concentration; $t_{1/2}$, elimination half-life; NCA, noncompartmental analysis; V_c, pharmacokinetic volume of the central or plasma compartment; V_t, volume of peripheral or tissue compartment.

Study 23 ARR value of 3.2 [5]. Only 3 of 10 patients had visit 2 rifabutin AUC_{0-24} values >4 $\mu g \cdot h/mL$, and none reached 5.2. Thus, the standard adjusted rifabutin dose of 150 mg thrice weekly (with lopinavir-ritonavir) is potentially inadequate for HIV-positive patients. In 1989, after a study of HIV-positive patients, Skinner et al concluded that "because of the low and unpredictable bioavailability of rifabutin, it may be necessary to either monitor concentrations in plasma or consider alternate dosage forms" [16, p 1241]. Their recommendation should be heeded.

Our simulations show that a rifabutin dose of 450 mg 5 times weekly would be needed to frequently achieve the C_{max} and AUC values associated with clinical and microbiological success in TBTC Study 23 [5]. Regardless of the milligram dose chosen, daily dosing should be considered, since most companion drugs (isoniazid, pyrazinamide, and ethambutol) are cleared long before rifabutin [17, 18]. With thrice-weekly dosing of all tuberculosis drugs, sub-MIC rifabutin concentrations are present for 3 days each week, unaccompanied by other tuberculosis drugs. Such a scenario favors the selection of drug resistance. One of our patients experienced relapse with ARR tuberculosis, as did 8 (5%) of 169 patients in TBTC Study 23. This is significant. It is unacceptable for our primary rifamycin-based regimen for patients with tuberculosis receiving HAART to routinely generate rifamycin-resistant tuberculosis.

The addition of lopinavir-ritonavir clearly increased the concentrations of the desacetyl-rifabutin metabolite. Although the C_{max} increased by a median of 50%, metabolite concentrations remained small. Importantly, desacetyl-rifabutin frequently was ⩾2-fold less potent than the parent rifabutin. Therefore, the increase in desacetyl-rifabutin AUC values seen after the addition of lopinavir-ritonavir may not compensate for the concurrently low rifabutin AUC values.

The relative contribution of rifabutin or the desacetyl-rifabutin metabolite (or other metabolites not measured here) to rifabutin-associated adverse drug reactions is not clear [2, 12, 19]. It is clear that exposure to the metabolite increases after the addition of lopinavir-ritonavir. Doses of 300 mg thrice weekly plus lopinavir-ritonavir show further increases, as would the simulated daily doses of 300 to 450 mg of rifabutin. Although increased rifabutin doses clearly seem indicated to increase efficacy and reduce ARR, they might increase the incidence of anterior uveitis, arthralgia, skin discoloration, and cytopenia. Fortunately, one can monitor for these adverse reactions, which typically are reversible. One cannot monitor for impending ARR, which, once it occurs, is not reversible.

Lopinavir concentrations generally were similar at visits 2 and 3. The target for treatment-experienced patients is >4 μg/mL, and 8 of 18 measurements were below this value. Therefore, the standard dose of lopinavir-ritonavir may be too small for treatment-experienced patients receiving rifabutin. We recommend measuring rifabutin and lopinavir plasma concentrations in patients receiving this drug combination. Consideration should be given for daily rifabutin treatment, and this should be studied prospectively. Patients should be monitored closely for response to treatment and for adverse drug reactions.

Limitations of this study include its small sample size. One patient experienced relapse with ARR, but the study was not designed as an efficacy trial, and we lack long-term outcomes for the other patients. We did not measure rifabutin metabolites other than desacetyl-rifabutin. Tenofovir is known to produce

Table 5. Rifabutin and Desacetyl-Rifabutin Minimum Inhibitory Concentration (MIC) Values for Rifabutin-Susceptible Isolates

Isolate	MIC		Fold difference
	Rifabutin	Desacetyl-rifabutin	
1	0.06	0.12	2
2	⩽0.03	0.06	⩾2
3	0.12	>0.50	>4
4	0.25	>0.50	>2
5	0.06	0.06	0
6	0.06	0.12	2
7	0.06	0.06	0

unexpected drug interactions and may have contributed to changes in rifabutin and metabolite concentrations [3]. Finally, our data do not address the potential efficacy or safety of the simulated daily rifabutin doses of 300–450 mg.

In conclusion, 300 or 150 mg of rifabutin thrice weekly plus lopinavir-ritonavir twice daily produced low rifabutin plasma concentrations, similar to those associated with ARR in TBTC Study 23 [5]. Adjustment of the rifabutin dose to 300 mg thrice weekly (plus lopinavir-ritonavir) increased the rifabutin and desacetyl-rifabutin concentrations and generally was well tolerated. Simulations suggest that doses as high as 450 mg daily may be required to achieve free rifabutin concentrations above the MIC while avoiding the long periods of sub-MIC rifabutin monotherapy. The efficacy and safety of these alternative rifabutin regimens need to be studied. In the interim, we recommend (as did Skinner et al in 1989 [16]) monitoring rifabutin concentrations in HIV-positive patients. Patients may also benefit from the measurement of lopinavir concentrations.

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