Determination of rifabutin dosing regimen when administered in combination with ritonavir-boosted atazanavir

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Objectives: Treatment of HIV/tuberculosis (TB) co-infected patients is complex due to drug–drug interactions for these chronic diseases. This study evaluates an intermittent dosing regimen for rifabutin when it is co-administered with ritonavir-boosted atazanavir.

Patients and methods: A randomized, multiple-dose, parallel-group study was conducted in healthy subjects and these subjects received a daily dose of rifabutin 150 mg (n = 15, reference group) or a twice weekly dose with atazanavir 300 mg/ritonavir 100 mg once daily (n = 18, test group). Serial blood samples were collected at steady-state for pharmacokinetic analysis. Modelling and simulation techniques were utilized, integrating data across several healthy subject studies. This study is known as Study AI424-360 and is registered with Clinical-Trials.gov, number NCT00646776.

Results: The pharmacokinetic parameters (Cmax, AUC 24avg and Cmin) for rifabutin (149%, 48% and 40% increase, respectively) and 25-O-desacetyl rifabutin (6.77-, 9.90- and 10.45-fold increases, respectively) were both increased when rifabutin was co-administered with atazanavir/ritonavir than rifabutin 150 mg once daily alone. The study was stopped because subjects experienced more severe declines in neutrophil counts when rifabutin was given with atazanavir/ritonavir than alone. A post-hoc simulation analysis showed that when rifabutin 150 mg was given three times weekly with atazanavir/ritonavir, the average daily exposure of rifabutin was comparable to rifabutin 300 mg once daily, a dose necessary for reducing rifamycin resistance in HIV/TB co-infected patients.

Conclusions: The benefits to HIV/TB co-infected patients receiving rifabutin 150 mg three times weekly or every other day may outweigh the risks of neutropenia observed here in non-HIV-infected subjects, provided that patients on combination therapy will be closely monitored for safety and tolerability.

Keywords: HIV, tuberculosis, drug–drug interactions, pharmacokinetics, clinical trials

Introduction

Approximately half a million HIV-related tuberculosis (TB) deaths occurred in 2008, accounting for a quarter of the global HIV/AIDS mortality, and TB is the leading cause of death among people living with HIV in Africa.1 HIV/TB co-infected patients are 20–30 times more likely to develop TB than those without HIV.1 HIV infection significantly increases the risk of progression from latent to active TB in patients infected with Mycobacterium tuberculosis.2 Due to the high incidence of TB among patients with advanced HIV disease, antiretroviral therapy is often initiated in patients who also require simultaneous treatment for TB.3 Rifampicin is the basis of the treatment regimen for patients with active TB. However, it is often not a treatment option for patients with HIV/TB co-infection due to its potent inductive effect on cytochrome P450 3A4 (CYP3A4).4 Rifabutin, another antimycobacterial agent used to treat TB and Mycobacterium avium complex, induces CYP3A4 to a much lesser degree than rifampicin and therefore is the preferred treatment for HIV/TB co-infected patients, particularly when used with protease inhibitors (PIs).5 Rifabutin is metabolized by cholinesterase and CYP3A4 resulting in the generation of its major metabolite, 25-O-desacetyl rifabutin, which has equal activity in vitro compared with rifabutin, and accounts for ~10% of the antimicrobial activity of rifabutin in vivo. 25-O-desacetyl rifabutin is also metabolized by CYP3A4. In HIV/TB co-infected patients receiving highly active antiretroviral therapy, especially ritonavir-boosted PIs, the plasma concentrations of rifabutin and the active
ClinicalTrials.gov, number NCT00646776. Review Board #08-101) and all participants gave written informed consent. This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP).

Rifabutin 150 mg is administered twice weekly in combination with atazanavir/ritonavir. A previous clinical trial compared the regimen of rifabutin 150 mg given three times daily alone to that from rifabutin 150 mg once daily when given alone. This study examined the pharmacokinetic parameters of rifabutin 150 mg twice weekly when dosed with atazanavir 300 mg/ritonavir 100 mg versus rifabutin 150 mg once daily alone in healthy subjects. However, additional data from clinical studies in HIV/TB co-infected patients indicated that rifamycin resistance was more likely to develop in patients receiving intermittent rifabutin treatment, and rifabutin exposure levels similar to those achieved at a 300 mg daily dose may be necessary to reduce the risk of rifampicin resistance. Therefore, additional simulation analysis was performed to further examine the regimen of rifabutin 150 mg given three times weekly with atazanavir 300 mg/ritonavir 100 mg once daily.

Patients and methods

Study design and treatment

This was an open-label, randomized, multiple-dose, parallel-group, Phase 1 study in healthy subjects. Based on the high rate of adverse events associated with rifabutin exposure in prior studies conducted in healthy subjects, a parallel design (as opposed to a crossover design) was chosen for this study in order to minimize the duration of rifabutin exposure to any given subject. Subjects in the reference group received an oral dose of rifabutin 150 mg once daily on days 1–10, while subjects in the test group received an oral dose of rifabutin 150 mg twice weekly in combination with atazanavir/ritonavir 300 mg/100 mg once daily on days 1–17. The analysis compared the exposure of rifabutin and the total exposure level of rifabutin plus 25-O-desacetyl rifabutin when rifabutin 150 mg is administered twice weekly in combination with atazanavir/ritonavir with rifabutin 150 mg administered once daily and rifabutin 300 mg once daily (extrapolated from the 150 mg once daily data). This study was conducted in accordance with the Declaration of Helsinki and the research protocol was approved by the relevant Institutional Review Board/Independent Ethics Committee (New England Institutional Review Board #08-101) and all participants gave written informed consent. This study is known as Study AI424-360 and is registered with ClinicalTrials.gov, number NCT00646776.

Study population

Subjects were required to be between the ages of 18 and 50 years and have a body mass index between 18 and 32 kg/m². Women of childbearing potential were not pregnant or nursing, had used contraception for at least 1 month prior to dosing with study medication. Subjects were excluded if they had any significant acute or chronic illness, current or recent gastrointestinal disease or surgery that could impact the absorption of the study drug, history of haemolytic disorders, acute or chronic pancreatitis, positive blood screen for hepatitis C antibody, hepatitis B surface antigen or HIV viral RNA or HIV-1/2 antibody, absolute leucocyte or neutrophil count less than the lower limit of normal or a history of any drug allergy.

Fifteen subjects were randomized to rifabutin 150 mg once daily and 18 subjects were randomized to rifabutin 150 mg twice weekly administered with atazanavir 300 mg/ritonavir 100 mg once daily.

Blood sampling and bioanalytical analysis

Serial blood samples were collected on day 10 at pre-dose (0) and 1, 2, 3, 4, 6, 8, 12 and 24 h post-dose for subjects receiving rifabutin 150 mg once daily and on days 11 and 15 at pre-dose (0) and 1, 2, 3, 4, 6, 8, 12, 24, 48 and 72 h post-dose for subjects receiving rifabutin 150 mg twice weekly plus atazanavir 300 mg/ritonavir 100 mg. Pre-dose samples were also collected on days 6 and 8 for subjects receiving rifabutin 150 mg once daily and on days 4 and 8 for subjects receiving rifabutin 150 mg twice weekly plus atazanavir 300 mg/ritonavir 100 mg. All blood samples were analysed using validated liquid chromatography tandem mass spectrometry during the period of known stability. The linear range was 2–800 ng/mL for rifabutin and 25-O-desacetyl rifabutin, 10–10,000 ng/mL for atazanavir and 5–5000 ng/mL for ritonavir.

The coefficient of variances (CVs) for between-run and within-run were ≤5.67% and ≤17.53%, respectively, for rifabutin and ≤7.06% and ≤11.81%, respectively, for 25-O-desacetyl rifabutin. The within-run variability was ±6.2% and ±9.2% for atazanavir and ritonavir, respectively. Since sample analysis was conducted on a single run, between-run variability was not determined for atazanavir and ritonavir.

Pharmacokinetic analysis and simulations

Plasma rifabutin, 25-O-desacetyl rifabutin, atazanavir and ritonavir concentrations versus actual sampling time data were analysed by a non-compartmental method using Kineticca version 4.4.1 (Thermo Electron Corp., Philadelphia, PA, USA). Steady-state pharmacokinetic parameters (Cmax, AUC24h, and Cmin) were derived from plasma concentration–time data for rifabutin, 25-O-desacetyl rifabutin, atazanavir and ritonavir. AUC24h (sum of rifabutin and metabolite 25-O-desacetyl rifabutin) and metabolite-to-parent ratio were estimated. A population pharmacokinetic model was developed to describe the disposition of rifabutin and 25-O-desacetyl rifabutin when co-administered with atazanavir or with or without ritonavir and described elsewhere. Since rifabutin 150 mg three times weekly with atazanavir 300 mg/ritonavir 100 mg once daily may be necessary to decrease the risk of rifabutin resistance and rifabutin treatment failure, its exposure was simulated based on a pharmacokinetic model that was developed using data presented here and existing historical data following co-administration of rifabutin 150 mg (once daily or twice weekly) and atazanavir given with and without ritonavir in healthy subjects. Simulations were performed for rifabutin and active metabolite concentration–time profiles for 100 subjects receiving rifabutin 150 mg three times weekly and atazanavir 300 mg/ritonavir 100 mg once daily. Non-compartmental analyses of the simulated profiles were conducted and a summary of exposure parameters for rifabutin and the sum of rifabutin plus active metabolite were obtained.

Statistics

The effect of atazanavir/ritonavir on the pharmacokinetics of rifabutin was assessed by an analysis of variance (ANOVA) performed on the log AUC24h, log Cmax, and log Cmin of rifabutin for the regimens of rifabutin with and without atazanavir/ritonavir. Point estimates and 90% confidence intervals (CIs) of treatment differences on the log scale were exponentiated to obtain estimates on the original scale. Similar analyses were conducted for AUCtot of rifabutin and 25-O-desacetyl rifabutin; no adjustments were made for multiplicity. The effect of atazanavir/ritonavir on
the pharmacokinetics of the active metabolite, 25-O-desacetyl rifabutin, was evaluated using similar analyses. The pharmacokinetic parameters of \( \text{AUC}_{\text{24avg}}, C_{\text{min}} \) and \( C_{\text{max}} \) for atazanavir and ritonavir were compared with historical data pooled from studies AI424-113, AI424-114 and AI424-115 (data on file) and similar analyses were performed. Geometric means and coefficients of variation are reported for \( \text{AUC}_{\text{24avg}}, C_{\text{min}} \) and \( C_{\text{max}} \).

**Safety**

Safety assessments were based on a review of adverse event reports and changes in vital signs, electrocardiograms, physical examinations and clinical laboratory tests. The incidence of treatment-emergent adverse events was tabulated and reviewed for potential significance and clinical importance.

**Results**

**Demographics**

Eighty-two percent (27/33) of the subjects were male, the mean (SD) age of the subjects was 36 (7) years, the mean (SD) weight was 80.3 (13.5) kg and the mean (SD) body mass index was 26.4 (3.3) kg/m². These characteristics were similar between the treatment arms. There were almost equal numbers of Caucasians (42%, \( n = 14 \)) and African Americans (45%, \( n = 15 \)) in the study, but more Caucasians \( (n = 9, 60\%) \) were in the reference group and more African Americans \( (n = 12, 67\%) \) were in the test arm.

**Disposition**

Of the 33 subjects that received treatment, 15 received 150 mg once daily (reference arm) and 18 received rifabutin 150 mg twice weekly with atazanavir/ritonavir 300 mg/ritonavir 100 mg once daily (test arm). One discontinuation occurred due to nausea in the reference arm and 13 discontinuations occurred in the test arm. These discontinuations included nine due to adverse events (five due to pyrexia, three due to neutropenia and one due to both pyrexia and neutropenia). The remaining four discontinuations were at the investigators’ discretion due to mild or moderate neutropenia. This study was terminated early for safety reasons.

**Pharmacokinetics of rifabutin**

The pharmacokinetic dataset of the test arm for rifabutin and its metabolite included a total of seven subjects, with two subjects who received all the rifabutin doses, but only 15 of the 17 doses of atazanavir/ritonavir. The pharmacokinetic dataset for atazanavir and ritonavir included two additional subjects in the test arm. These two subjects discontinued the rifabutin treatment early (on day 11 and day 14) and thus were only included in the atazanavir/ritonavir analysis, not in the rifabutin or 25-O-desacetyl rifabutin analysis.

The mean plasma concentrations of rifabutin and 25-O-desacetyl rifabutin over time are shown in Figure 1(a) and Figure 1(b), respectively, for both arms of the study. As shown in Table 1, the pharmacokinetic parameters \( (C_{\text{max}}, \text{AUC}_{\text{24avg}} \text{ and } C_{\text{min}}) \) for rifabutin and 25-O-desacetyl rifabutin were all higher when rifabutin was co-administered with atazanavir/ritonavir than when it was administered alone, indicating that atazanavir/ritonavir increased the rifabutin exposure as expected. These increases were similar to those observed with other PIs.6–9 Administration of rifabutin 150 mg twice weekly with atazanavir/ritonavir resulted in a 48% and 40% increase in the \( \text{AUC}_{\text{24avg}} \) and \( C_{\text{min}} \) of rifabutin, respectively (Table 1). In addition, the 90% CI of the geometric mean ratios (rifabutin 150 mg twice weekly with atazanavir/ritonavir over 150 mg rifabutin once daily) for rifabutin \( C_{\text{max}}, \text{AUC}_{\text{24avg}} \text{ and } C_{\text{min}} \) were all >1 (Table 1). Co-administration of atazanavir/ritonavir greatly increases the exposures of rifabutin’s active metabolite 25-O-desacetyl rifabutin.

**Pharmacokinetic simulation of rifabutin**

The simulation results (Table 2) showed that the \( C_{\text{max}}, \text{AUC}_{\text{24avg}} \) and \( C_{\text{min}} \) of rifabutin are similar to those of rifabutin 300 mg once daily administered alone, while the total \( \text{AUC}_{\text{24}} \) of the sum of rifabutin and its active metabolite was higher. In addition, the

![Figure 1](https://academic.oup.com/jac/article-abstract/66/9/2075/770341/fig1)

**Figure 1.** Mean (SD) plasma concentration of rifabutin (a) and 25-O-desacetyl rifabutin (b) over time for both treatment regimens, rifabutin 150 mg once daily (day 10, \( n = 14 \)) and rifabutin 150 mg twice weekly with atazanavir 300 mg/ritonavir 100 mg once daily (day 11, \( n = 9 \) and day 15, \( n = 7 \)).
amount of time the rifabutin concentration is above the established MIC decreases the risk of rifabutin resistance and treatment failure. This time (% CV) was also simulated and showed that the rifabutin concentration was above the MIC (0.07 μM) for 136 h/week (24) when given at 150 mg three times (N=100) weekly versus 95.6 h/week (40) when given twice weekly (N=7), both in combination with atazanavir 300 mg/ritonavir 100 mg.

**Pharmacokinetics of atazanavir and ritonavir**

The pharmacokinetic parameters of atazanavir and ritonavir were compared with historical values (Table 3). While the atazanavir C\text{max} and AUC values were comparable to historical observations, atazanavir C\text{min} was about 25% lower when administered with twice weekly rifabutin. Similarly, the pharmacokinetic parameters of ritonavir were also reduced by rifabutin during the co-administration regimen.

**Safety**

Both arms of the study experienced declines in neutrophil counts and these declines were more severe with treatment of rifabutin and atazanavir/ritonavir than rifabutin alone, which led to premature termination of the test arm. In the test arm, two subjects experienced decreases in neutrophil counts (0.97×10^3 and 0.44×10^3 cells/μL, on days 14 and 11, respectively) that were considered to be serious adverse reactions; additional treatment was not necessary because they resolved on their own after discontinuation of the study drugs. Four subjects discontinued due to mild/moderate neutropenia in the setting of an overall trend toward neutrophil declines that were greater than anticipated; their neutrophil counts at discontinuation were 1.63×10^3 cells/μL on day 11, 1.77×10^3 cells/μL on day 11, 0.87×10^3 cells/μL on day 11 and 1.61×10^3 cells/μL on day 12.

The most frequently observed adverse events, pyrexia and decreased neutrophil count, each occurred in seven (21.2%) subjects overall and are known effects of rifabutin. During this study, the incidence of moderate neutropenia (1.5×10^3 cells/μL) was 7% and 44% in the reference and test arms, respectively, and the incidence of severe neutropenia (<0.5×10^3 cells/μL) was 0% and 11%, respectively, resulting in premature termination of the test arm.

As shown in Figure 2, no relationship was found between the maximum decrease of the absolute neutrophil count from baseline and the rifabutin C\text{max}, 25-O-desacetyl rifabutin C\text{max} and AUC\text{tot}. Linear regression for C\text{max}, AUC\text{24avg} and C\text{trough} for rifabutin and 25-O-desacetyl rifabutin as well as AUC\text{tot} versus absolute neutrophil maximum decrease from baseline were examined (data not shown). All the R^2 values from these regression analyses were <0.45, indicating the lack of relationship between the absolute neutrophil maximum decrease from baseline and pharmacokinetic parameters.

Other adverse events reported by three or more subjects included headache (15.2%), diarrhea (12.1%), pain (12.1%), chills (9.1%), jaundice (9.1%), dizziness (9.1%) and rash (9.1%). Jaundice, a known effect of atazanavir, occurred in 3 of 18 (16.7%) subjects in the test arm and did not occur in any of the 15 subjects in the reference arm. All the cases of jaundice

| Table 1. Pharmacokinetic parameters for rifabutin and 25-O-desacetyl rifabutin |
|---|---|---|---|---|
| Rifabutin | 25-O-desacetyl rifabutin | Rifabutin | 25-O-desacetyl rifabutin |
| geometric means (CV%) | geometric means (CV%) | geometric means (CV%) | geometric means (CV%) |
| ratios (B/A) of geometric means | ratios (D/C) of geometric means | ratios (B/A) of geometric means | ratios (D/C) of geometric means |
| C\text{max} (ng/mL) | 158.9 (30) | 100 mg OD (B) (n=7) | 155.9 (30) |
| AUC\text{24avg} (ng.h/mL) | 1565 (32) | 100 mg OD (B) (n=7) | 1565 (32) |
| C\text{min} (ng/mL) | 28.89 (45) | 100 mg OD (B) (n=7) | 28.89 (45) |
| C\text{trough} (ng/mL) | 2.79 (46) | QD, once daily; RFB, rifabutin; ATV, atazanavir; RTV, ritonavir. | 2.79 (46) |

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Table 2. Comparison of observed and simulated pharmacokinetic parameters for rifabutin and the sum of rifabutin plus 25-O-desacetyl rifabutin

<table>
<thead>
<tr>
<th>Geometric means (CV%)</th>
<th>RFB 150 mg twice weekly + ATV 300 mg/RTV 100 mg QD (n = 7)</th>
<th>RFB 150 mg three times weekly + ATV 300 mg/RTV 100 mg QD (simulated)</th>
<th>RFB 300 mg QD (n = 13)²</th>
<th>RFB 150 mg QD (n = 14)²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rifabutin</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>( C_{\text{max}} ) (µM)ᵇ</td>
<td>0.47 (14)</td>
<td>0.43 (22)</td>
<td>0.42 (35)</td>
<td>0.19 (30)</td>
</tr>
<tr>
<td>( AUC_{24} ) (µM·h)ᶜ</td>
<td>2.73 (22)</td>
<td>3.6 (23)</td>
<td>3.90 (27)</td>
<td>1.85 (32)</td>
</tr>
<tr>
<td>( C_{\text{min}} ) (µM)ᵈ</td>
<td>0.048 (27)</td>
<td>0.06 (43)</td>
<td>0.064 (30)</td>
<td>0.034 (45)</td>
</tr>
<tr>
<td><strong>Sum of rifabutin plus 25-O-desacetyl rifabutin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( AUC_{24} ) (µM·h)ᶜ</td>
<td>4.38 (13)</td>
<td>5.9 (17)</td>
<td>4.13 (27)</td>
<td>2.00 (33)</td>
</tr>
</tbody>
</table>

QD, once daily; RFB, rifabutin; ATV, atazanavir; RTV, ritonavir.

ᵇFrom previous study AI424-033.
ᶜFor twice weekly and three times weekly schedule, \( C_{\text{max}} \) is the observed maximum concentration over the entire week.
ᵈFor twice weekly and three times weekly schedule, \( AUC_{24} \) is calculated as weekly \( AUC/7 \).

were mild in intensity and resolved within 8–9 days after stopping treatment.

**Discussion**

Rifabutin given twice weekly with atazanavir/ritonavir to healthy subjects resulted in exposures of rifabutin that were higher relative to the reference treatment used in the study, rifabutin 150 mg once daily. The reference treatment was selected based on the results reported by Gonzalez-Montaner et al., that rifabutin 150 mg once daily provided the best risk-to-benefit ratio; however, the study was conducted in HIV-negative TB-infected patients. Burman et al., reported that when HIV/TB co-infected patients were treated with antiretroviral therapy and received rifabutin twice weekly, the treatment failure rate or relapse of TB was ~5%. More importantly, among the nine patients who failed therapy, eight patients (89%) developed rifamycin resistance. In addition to highly intermittent administration of TB therapy, acquired rifamycin resistance is also associated with low baseline CD4 counts, and the incidence of TB is highest among patients with advanced HIV disease. This suggests that rifabutin 150 mg twice weekly with atazanavir/ritonavir may not be a robust treatment regimen for HIV/TB co-infected patients.

The current recommended dose of rifabutin to manage TB in HIV-infected patients is 300 mg once daily in the absence of antiretroviral therapy. Our findings suggest that when rifabutin 150 mg twice weekly is co-administered with atazanavir/ritonavir, rifabutin exposures (AUCs) are about 25%–30% lower than those seen with rifabutin 300 mg once daily. In addition, the rifabutin \( C_{\text{min}} \), following rifabutin 150 mg twice weekly with atazanavir/ritonavir (0.040 mg/L) is below the established MIC for TB (0.060 mg/L), suggesting that the risk of treatment failure will be high with twice weekly administration. Furthermore, our simulation model predicted that the co-administration of rifabutin 150 mg three times weekly with atazanavir/ritonavir would result in rifabutin AUC levels comparable to those observed when rifabutin 300 mg once daily is administered alone. Dosing rifabutin 150 mg three times weekly will likely reduce the opportunity for the development of resistance.

The addition of atazanavir/ritonavir to rifabutin not only increased the levels of rifabutin, but also the levels of its active metabolite, 25-O-desacetyl rifabutin; determining the individual contributions of rifabutin and 25-O-desacetyl rifabutin to the efficacy and tolerability of the HIV/TB treatment regimen is difficult. The role of 25-O-desacetyl rifabutin in vivo is not known, given that the tissue distribution/penetration of the metabolite is unclear. In other studies, no association between the AUC of 25-O-desacetyl rifabutin and acquired rifamycin resistance was observed. As presented here, a decrease in neutrophil count did not correlate with the exposure of rifabutin, 25-O-desacetyl rifabutin or the sum of rifabutin and 25-O-desacetyl rifabutin.

Consequently, these clinical and pharmacokinetic data support the idea that rifabutin 150 mg three times weekly administered with atazanavir/ritonavir is likely to minimize the selection of rifamycin-resistant strains compared with rifabutin 150 mg twice weekly in HIV/TB co-infected patients. However, there have been case reports of rifamycin resistance with every-other-day rifabutin dosing in combination with boosted PI therapy including atazanavir, suggesting that even rifabutin 150 mg every other day may be inadequate in patients being treated with boosted PIs.

A theoretical concern is that the dosage increase may also increase the rate of adverse events. This study was prematurely terminated because ~90% of the subjects treated with rifabutin and atazanavir/ritonavir experienced a trend toward absolute neutrophil count decline compared with ~50% treated with rifabutin only. The severity of the neutrophil decline was higher with rifabutin and atazanavir/ritonavir (six subjects with a neutrophil count <1.0×10⁹ cells/µL, two subjects with a neutrophil count <0.5×10⁹ cells/µL) compared with rifabutin (none <1.0×10⁹ cells/µL) in these non-HIV-infected subjects. However, similar safety issues have rarely been noted in HIV co-infected patients who were treated with a more frequent regimen of rifabutin (three times weekly or every other day) in combination with atazanavir/ritonavir. This may be due to the
Rifabutin 150 mg once daily
(a)
Rifabutin 150 mg twice weekly + atazanavir/ritonavir 300/100 mg once daily (b) and (c) for modulation of rifabutin (a), 5-fluorouracil (b), and allopurinol (c). Absolute neutrophil maximum decrease versus modulating parameters. Absolute neutrophil maximum decrease versus modulating parameters. Absolute neutrophil maximum decrease versus modulating parameters.

Figure 2. Relationship between neutrophils and pharmacokinetic parameters. Absolute neutrophil maximum decrease versus rifabutin C\text{max} (a), 25-O-desacetyl rifabutin C\text{max} (b), and AUC\text{tot} (c) for rifabutin 150 mg once daily (n = 14) and rifabutin 150 mg twice weekly with atazanavir 100 mg/ritonavir 100 mg once daily (n = 7).

Table 3. Pharmacokinetic parameters of atazanavir and ritonavir compared with historical controls\textsuperscript{a}.

<table>
<thead>
<tr>
<th></th>
<th>Atazanavir</th>
<th>Ritonavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>geometric means (CV%)</td>
<td>ratios (E/H) of geometric means, point estimates (90% CI)</td>
<td>ratios (F/H) of geometric means, point estimates (90% CI)</td>
</tr>
<tr>
<td>RFB 150 mg twice weekly + ATV 300 mg/RTV 100 mg QD (E) (n = 9)</td>
<td>historical controls, ATV 300 mg/RTV 100 mg QD (H)</td>
<td>historical controls, ATV 300 mg/RTV 100 mg QD (H)</td>
</tr>
<tr>
<td>C\text{max} (ng/mL)</td>
<td>5634 (16)</td>
<td>5950</td>
</tr>
<tr>
<td>AUC\text{tot} (ng.h/mL)</td>
<td>51795 (24)</td>
<td>60454</td>
</tr>
<tr>
<td>C\text{min} (ng/mL)</td>
<td>921 (49)</td>
<td>1236</td>
</tr>
</tbody>
</table>

QD, once daily; RFB, rifabutin; ATV, atazanavir; RTV, ritonavir.

\textsuperscript{a}Historical controls include subjects (n = 116) from studies AI424-113, AI424-114, and AI424-115 who were treated with atazanavir 300 mg/ritonavir 100 mg QD.

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lower exposures of rifabutin in HIV-infected patients than those observed in healthy subjects. It is also possible that HIV patients are able to tolerate rifabutin better than healthy subjects.\(^{23}\) Naiker et al.\(^{24}\) reported that rifabutin 150 mg, either three times weekly or daily, was well tolerated when co-administered with lopinavir/ritonavir in HIV/TB co-infected patients. This report also showed that the median rifabutin AUC\(_{0-24}\) following three times weekly administration with lopinavir/ritonavir was about 24% lower than that of rifabutin 300 mg daily alone. These data further support that the frequency of rifabutin dosing should not be less than 3 times per week.

A limitation of this study is that the pharmacokinetic parameters from rifabutin in healthy subjects should not be compared with those in HIV-infected individuals because it is well known that HIV patients have lower exposures to a variety of drugs, such as atazanavir, possibly due to poorer absorption.\(^{25}\) Previous studies have shown lower levels of several antimycobacterium drugs, including isoniazid, rifampicin and ethambutol, in HIV-infected patients with TB compared with levels in non-HIV-infected patients with TB.\(^{26,27}\) The pharmacokinetics of rifabutin were relatively consistent between two trials conducted in different settings and by different investigators when a standard dose of rifabutin was administrated in the absence of concomitant medications in HIV-infected patients.\(^{28,29}\) These observed pharmacokinetic values are lower than those observed in a Bristol-Myers Squibb study,\(^{20}\) consistent with observations that HIV-infected patients mal-absorb medication. Taken together, this suggests that further studies with rifabutin in combination with HIV PIs in healthy subjects should be avoided.\(^{26,27,30}\)

Administration of rifabutin did not significantly alter the exposure of atazanavir in this study. The \(C_{\text{min}}\) of atazanavir was reduced by 25%. A similar magnitude of reduction was observed when atazanavir was given with tenofovir, and the anti-HIV activity of atazanavir is not affected due to the adequate buffer in atazanavir concentrations provided by ritonavir boosting.\(^{31}\) Based on such data, the dose of atazanavir 300 mg/ritonavir 100 mg should provide sufficient drug exposure to prevent treatment failure for the HIV portion of the co-infection.

In summary, the use of atazanavir and rifabutin in non-HIV-infected subjects leads to a high rate of adverse events and discontinuations. Development of rifamycin resistance occurred in other studies when patients were given rifabutin twice weekly in combination with antiviral therapy.\(^{15}\) However, the benefits of rifabutin 150 mg three times weekly with atazanavir 300 mg/ritonavir 100 mg to HIV/TB co-infected patients may outweigh the risks of neutropenia, provided that there is close monitoring of safety and tolerability.

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### Transparency declarations

All authors report being employees and shareholders of Bristol-Myers Squibb.

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### Author contributions

J. Z. contributed to the concept and design of the study, acquisition, analysis and interpretation of the data, drafting and critical revision of the manuscript and supervision. L. Z. contributed to the concept and design of the study, acquisition, analysis and interpretation of the data and drafting and critical revision of the manuscript. M. S. contributed to the concept and design of the study, acquisition of the data and drafting and critical revision of the manuscript. J. C. was responsible for the conduct and safety of the study, analysis and interpretation of the data and critical revision of the manuscript. Y. W. contributed to the study design, analysis and interpretation of the data and drafting and revision of the manuscript. A. F. contributed to the analysis and interpretation of the data and drafting the manuscript. R. B. contributed to the concept and design of the study, analysis and interpretation of the data and critical revision of the manuscript. All authors approved the final manuscript.

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