Interaction studies of tipranavir/ritonavir (TPV/r) with clarithromycin, fluconazole and rifabutin in healthy volunteers

Running title: tipranavir/ritonavir + clarithromycin, fluconazole or rifabutin

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Abstract

Three separate controlled, 2-period, studies in healthy volunteers assessed the pharmacokinetic (PK) interactions between tipranavir/ritonavir (TPV/r) 500/200 mg and 500 mg clarithromycin (CLR), 100 mg fluconazole (FCZ) and 150 mg rifabutin (RFB).

The CLR study was conducted in 24 subjects. The GMR (90% CI) for the effect of multiple dose TPV/r on multiple dose CLR AUC, Cmax and Cp12h were: 1.19(1.04-1.37), 0.95(0.83-1.09) and 1.68(1.42-1.98), respectively. The formation of the metabolite 14-OH-CLR was decreased by 95% and TPV AUC increased 66% compared to HIV negative historical controls.

The FCZ study was conducted in 20 subjects. The GMR (90% CI) for the effect of multiple dose TPV/r on multiple dose FCZ AUC, Cmax and Cp12h were: 0.92(0.88-0.95), 0.94(0.91-0.98) and 0.89(0.85-0.92), respectively. TPV AUC increased by 50% compared to HIV negative historical controls.

The RFB study was conducted in 24 subjects. The GMR (90% CI) for the effect of multiple dose TPV/r on single dose RFB AUC, Cmax and Cp12h were: 2.90(2.59-3.26), 1.70(1.49-1.94) and 2.14(1.90-2.41), respectively. The GMR (90% CI) for the effect of TPV/r on RFB + 25-O-desacetyl-RFB AUC, Cmax and Cp12h were: 4.33(3.86-4.86), 1.86(1.63-2.12) and 2.76(2.44-3.12), respectively. There was a 16% increase in TPV Cp12h.

In the general population, no dose adjustments are necessary when combining TPV/r and CLR or FCZ. Combining TPV/r with RFB should be done with caution, while toxicity and RFB drug levels should be monitored. Study medications were generally well tolerated in these studies.
Introduction
The treatment of human immunodeficiency virus (HIV) infected patients with highly active antiretroviral therapy (HAART) has greatly improved life expectancy over the years (14). Nevertheless, opportunistic infections in people living with HIV continue to be a threat to their health. Drug treatment of these opportunistic infections can be challenging because of the possible drug interactions between HAART and other drugs. This article presents the results of three interaction studies between tipranavir co-administered with low-dose ritonavir, and clarithromycin, fluconazole and rifabutin in healthy adult volunteers.

Tipranavir (TPV) is an approved protease inhibitor (PI) with potent activity against PI-resistant HIV-1. Tipranavir is highly plasma protein bound (99.98%) and is a substrate as well as an inducer of cytochrome P450 (CYP) 3A. (5, 18). To achieve effective plasma TPV concentrations and a twice-daily dosing regimen in treatment experienced patients, co-administration of 500 mg of TPV with 200 mg of ritonavir (TPV/r) is needed.

Clarithromycin (CLR) is a macrolide antibacterial that is used extensively by people living with HIV/AIDS. In addition to its multiple anti-bacterial effects, clarithromycin may be used for both prophylaxis and treatment of Mycobacterium avium complex infections in AIDS. Clarithromycin is a substrate and an inhibitor of cytochrome P450 CYP3A. The primary metabolite is 14-hydroxy-R-clarithromycin (14-OH-CLR) which is the most active of the CLR metabolites (1).

Fluconazole (FCZ) is routinely indicated for oropharyngeal and esophageal candidiasis, as well as for treatment of other serious systemic fungal infections in persons living with HIV. Fluconazole is cleared primarily by renal excretion with a terminal elimination half-life of approximately 30 hours. Approximately 80% of the administered dose appears in the urine as unchanged drug and 11% of the dose is excreted in the urine as metabolites (3).
Rifabutin (RFB) is an antimycobacterial agent indicated for the prevention of disseminated *Mycobacterium avium* complex (MAC) disease in patients with advanced HIV infection, or treatment of *Mycobacterium tuberculosis*. Rifabutin is both an inducer and substrate of CYP3A. Induction may cause reductions in the plasma concentrations of drugs that are metabolized by this enzyme system while inhibition of CYP3A may significantly increase plasma concentrations of rifabutin. Five rifabutin metabolites have been identified. The predominant metabolite, 25-O-desacetyl-rifabutin, has an activity equal to the parent drug and contributes up to 10% to the total antimicrobial activity (4).

The objectives for these three drug interaction studies were to investigate the pharmacokinetic effects of TPV/r on the pharmacokinetics of clarithromycin, fluconazole and rifabutin and vice versa. The secondary objective for each study was to investigate safety and tolerability of the study regimens.
Materials and Methods

These studies were conducted in HIV negative healthy male and female subjects. The study designs are summarized in Figure 1 (clarithromycin), Figure 2 (fluconazole) and Figure 3 (rifabutin).

The studies were approved by an Independent Ethics Committee, and all subjects gave written informed consent before any study related procedure could take place. All three studies were conducted at MDS Pharma Services, St. Laurent, Quebec, Canada. The studies were conducted in compliance with the ICH guidelines, the Declaration of Helsinki 1996, and the Canadian Therapeutic Product Directorate guidelines. For each study a detailed set of inclusion and exclusion criteria was defined. In general, male and female subjects (18 to 60 years of age) had to be non-smoking, in good health, have laboratory values less than or equal to Grade 1 based on the ACTG Grading Scale, have an acceptable medical history, physical examination and 12-lead ECG, a healthy chest X-ray, if deemed necessary to establish good health of subject by the investigator, able to give informed consent and adhere to the study protocol. Major exclusion criteria included: serological evidence of HBV, HCV and/or HIV infection, a seated systolic blood pressure either <100 mm Hg or >150 mm Hg; resting heart rate either <50 beats/min or >90 beats/min, pregnancy, breastfeeding, non-use of barrier contraception for females, use of hormonal contraception or hormone replacement therapy, recent participation in another drug trial, recent blood or plasma donations, use of any other drugs, and alcohol or substance abuse.

Study design: clarithromycin interaction

The subjects were administered clarithromycin 500 mg BID from study day 1 until the morning of study day 13. Twice daily TPV/r 500 mg/200 mg was initiated on study day 6 and continued until the last dose on the morning of study day 13. Study drugs were taken with 240 mL water on an empty stomach on PK study days and with a light snack on other days. Steady state pharmacokinetic profiles for clarithromycin were obtained on study days 5 and 13 (clarithromycin + TPV/r), and the effect of first dose TPV/r on clarithromycin was evaluated from pharmacokinetic profiles obtained on day 6.
(clarithromycin + first dose TPV/r). For the pharmacokinetic profiles, blood samples were obtained just before (nominal time, 0 hours) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, and 12 hours after drug intake in the morning. The effect of clarithromycin on plasma TPV was determined by comparing the TPV pharmacokinetic parameters on study day 13 to TPV data from a pharmacokinetic analysis of 68 healthy volunteers from 4 clinical studies (12, 18, 25, 29). Ritonavir concentrations were not measured in this study.

**Study design: fluconazole interaction**

The subjects were administered a loading dose of 200 mg fluconazole on study day 1 followed by a daily 100 mg fluconazole dose for the remainder of the study. On study day 7 the subjects were started on a twice daily dosing regimen with TPV/r 500 mg/200 mg. TPV/r treatment was continued until the last dose on the evening of study day 13. On study days 6, 7 and 13 pharmacokinetic sampling was done just before (nominal time, 0 hours) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12 and 24 hours after drug intake in the morning. Study drugs were taken with 240 mL water on an empty stomach on PK study days and with a light snack on other days. Steady state pharmacokinetic profiles for fluconazole were obtained on study days 6 and 13 (fluconazole + TPV/r), and the effect of first dose TPV/r on fluconazole was evaluated from pharmacokinetic profiles obtained on day 7 (fluconazole + first dose TPV/r). The effect of fluconazole on TPV was determined by comparing the tipranavir pharmacokinetic parameters on study day 13 to TPV data from a pharmacokinetic analysis of 68 healthy volunteers from 4 clinical studies (12, 18, 25, 29) Ritonavir concentrations were not measured in this study.

**Study design: rifabutin interaction**

The subjects were administered a single dose of rifabutin 150 mg on study day 1. Pharmacokinetic plasma sampling was done just before dosing (nominal time, 0 hours) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48, 72, 96, 120, and 144 hours after drug intake. On study day 8 subjects started with TPV/r 500/200 mg twice daily and continued until study day 20. On study day 14 pharmacokinetic sampling was done for tipranavir
just before dosing (nominal time, 0 hours) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, and 12 hours after the morning drug intake. On study day 15, rifabutin was given as a single dose of 150 mg in the morning with the TPV/r dose and pharmacokinetic sampling was done up to 144 hours after administration. Study drugs were taken with 240 mL water on an empty stomach on PK study days and with a light snack on other days. The effect of steady-state TPV/r on the single-dose pharmacokinetics of RFB and 25-O-desacetyl-rifabutin were determined by comparing the pharmacokinetic parameters of RFB and 25-O-desacetyl-rifabutin on study days 1 and 15. The effect of single-dose RFB on the steady-state pharmacokinetics of TPV were determined by comparing the pharmacokinetic parameters of TPV on study days 14 and 15. Ritonavir concentrations were not measured in this study.

Bioanalysis
Clarithromycin and 14-OH-CLR
A LC/MS/MS method with on-line automated extraction for the determination of clarithromycin and 14-OH-CLR in human plasma had been validated by MDS Pharma Services, Saint Laurent, Quebec, Canada. An aliquot of human plasma containing clarithromycin and 14-OH-CLR was extracted using an on-line extraction procedure. The extracted samples were analyzed with LC/MS/MS. The calibration curve ranged from 10.0 to 4011.5 ng/mL for clarithromycin and from 4.00 to 2000.43 ng/mL for 14-OH-CLR. Intra-day and inter-day accuracy and precision were ≤7.3%, ≤13.2%, ≤6.4% and ≤6.0%, respectively for clarithromycin. For 14-OH-CLR these results were ≤6.5%, ≤6.3%, ≤8.1% and ≤9.1%.

Fluconazole
Plasma samples were analyzed for fluconazole at BASi Analytics, West Lafayette, Indiana, USA, with a validated LC/MS/MS method. Fluconazole was extracted from human heparinized plasma, treated with a 10% ammonium hydroxide solution, by liquid-liquid extraction with methyl-tert butyl ether. The supernatant was blown down to dryness. The extract was reconstituted and injected into an LC/MS/MS system using a
Symmetry C18 analytical column (50x4.6 mm, 3.5 µm) with an isocratic elution from a methanol/formic acid mobile phase. The fluconazole calibration curve ranged from 0.0100 µg/mL to 10.0 µg/mL. Intra-day and inter-day accuracy and precision were ≤17.0%, ≤10.0%, ≤4.3% and ≤6.9%, respectively.

Rifabutin and 25-O-desacetyl-rifabutin
A LC/MS/MS assay was developed and validated for rifabutin and 25-O-desacetyl-rifabutin by PPD Development, Middleton, Wisconsin, USA. Briefly, plasma samples were extracted in the following manner. Extraction solvent (ethyl acetate:hexane, 60:40) and ammonium hydroxide were added to a 100 µL sample aliquot, then fortified with 20 µL of internal standard working solution. Samples were vortexed, centrifuged, and the organic layer was transferred to tubes containing a 100% butyl ether keeper solution. Samples were evaporated and the remaining residue was reconstituted with 500 µL of mobile phase and hexane was added. Samples were vortexed, centrifuged, and the hexane layer was aspirated to waste. The remaining solution was injected. The calibration curve ranged from 2.00 to 800 ng/mL for rifabutin and 25-O-desacetyl-rifabutin. Intra-day and inter-day accuracy and precision were ≤8.3%, ≤6.8%, ≤3.2% and ≤2.5%, respectively for rifabutin. For 25-O-desacetyl-rifabutin these results were ≤5.6%, ≤5.0%, ≤5.1% and ≤3.4%.

Tipranavir
Plasma samples were analyzed for tipranavir with a validated liquid chromatography tandem mass spectrometry (LC/MS/MS) method at BASi Analytics, West Lafayette, Indiana, USA. Tipranavir and the internal standard were extracted from human heparinized plasma by a two-step liquid/liquid extraction method that used an ethyl acetate/hexane mixture followed by a hexane wash. The analytes were separated and detected by an LC/MS/MS system that used a 2.0 x 30 mm Synergi Polar RP column with a formic acid/acetic acid/acetonitrile mobile phase. The high calibration curve ranged from 1,000 ng/mL to 20,000 ng/mL. The low calibration curve ranged from 25.0 ng/mL to 2,000 ng/mL. Intra-day and inter-day accuracy and precision were ≤4.9%,
≤2.4%, ≤6.8% and ≤6.1%, respectively for the high range. For the low range these results were ≤5.2%, ≤1.4%, ≤6.3% and ≤7.8%.

Pharmacokinetic analysis
Non-compartmental methods were used for pharmacokinetic analysis (WinNonlin Professional version 4.0, Pharsight Corporation, Mountain View, CA, USA). The highest observed plasma concentration was defined as Cmax, with the corresponding sampling time as Tmax. The concentration at 12 and 24 hours post dose were defined as Cp12h and Cp24. The elimination rate constant (λz) was determined by least squares linear regression analysis (log C vs t) of the last data points (n ≥ 3). The half-life (t1/2) was calculated by the equation t1/2 = ln2/λz. The area under the plasma concentration vs time curve (AUC0-∞ for rifabutin, AUC0-24h for fluconazole and AUC0-12h for tipranavir and clarithromycin) was estimated using the linear-log trapezoidal rule (linear up/log down). The apparent oral clearance (CL/F) was calculated as dose/AUC, and the volume of distribution (V) was calculated as (CL/F)/λz.

In the rifabutin study, because 25-O-desacetyl-RFB has an antimicrobial activity equal to the parent drug, the PK of both compounds will be addressed using the sum of the RFB and 25-O-desacetyl-RFB AUC0-∞, Cmax, and Cp12h, in addition to the analysis of parent and metabolite alone. Results were converted using µM equivalents (RFB, molecular weight 847.02 and 25-O-desacetyl-RFB, molecular weight 804.97).

Adverse events
Subject safety was monitored by assessment of all adverse events (AEs) at each visit, in addition to laboratory assessment of safety parameters including hematology, chemistry, liver function tests (AST, ALT, alkaline phosphatase, total bilirubin), and lipid parameters (triglycerides, cholesterol) at screening and on various days throughout the studies.
Statistical analysis

Statistical analysis was done with SAS (Release 8.2; SAS Institute Inc., Cary, NC). For clarithromycin, fluconazole, rifabutin and tipranavir, the pharmacokinetic parameters AUC, Cmax and Cp12h or Cp24 geometric means were calculated. The ratio of the geometric means of the test regimen to the reference regimen was used to assess the interaction (30). The null hypothesis was that the ratio being tested lies either below the lower boundary of relevance (0.80) or above the upper boundary of relevance (1.25). The alternative hypothesis was that the ratio lies within the relevance boundaries. The null hypothesis was tested using the methodology of two one-sided tests, i.e., the null hypothesis was rejected in favor of absence of a relevant interaction if the 90% confidence interval on the ratio was completely contained in the acceptance region of 0.80 – 1.25. The 90% confidence interval on the ratio was derived by exponentiation of the confidence interval from the logarithmic scale.

For tipranavir co-administered with clarithromycin or fluconazole, SAS Proc Multtest was used to resample tipranavir AUC\textsubscript{0-12h}, Cmax and Cp\textsubscript{12h} pharmacokinetic results from 4 healthy volunteer clinical studies (12, 18, 25, 29) and from the respective drug interaction studies. Bootstrap arithmetic means (2000 resamples) were determined and the ratio of the means of the test regimen to the reference regimen was used to assess the interaction and determine the point estimate. The 5\textsuperscript{th} and 95\textsuperscript{th} percentiles of the distribution of the ratios provided the 90% confidence interval.

The sample size for the clarithromycin and rifabutin studies was based on tipranavir data that were on file. This was done because clarithromycin within subject variation in AUC was similar to that for tipranavir whereas for rifabutin no within subject variation data was available, however between subject variation was similar to that of tipranavir. Based on this data, 18 subjects were required to ensure the studies would have a 90% power to reject both the null hypothesis that the ratio of the test mean to the standard mean is below 80% and the null hypothesis that the ratio of test mean to the standard mean is above 125%; i.e., that the test and standard are not equivalent, in favor of the alternative hypothesis that the means of the two groups are equivalent, assuming that the expected
ratio of means is 100%, the coefficient of variation for the standard is 0.133, that data will be analyzed in the log-scale at the 5% level. To ensure sufficient sample size for analysis and allowing for drop-outs, 24 subjects were recruited and entered into both studies.

For the fluconazole study data from a previous study done by Boehringer Ingelheim was used to calculate the fluconazole intra-individual coefficient of variation. Fluconazole Cmax had a higher coefficient of variation and was used for the sample size calculation. For an expected reduction of PK parameters for fluconazole of 5%, a sample size of 14 subjects was expected to result in a probability of 92% (power) that a 90% CI was included in the acceptance range of 80% – 125%. To allow for drop outs it was decided to include 20 subjects in the study.

Results
Clarithromycin Study
Twenty-four healthy volunteers (7 females and 17 males) were enrolled and completed the study. Two subjects were black and 22 were white. The mean ± SD age, weight and height for the study population was 33.2 ± 9.2 years, 75.3 ± 12.3 kg and 173.5 ± 10.5 cm, respectively.

Pharmacokinetic results for study days 10 and 13 were based on 21 subjects due to recurrent vomiting by 3 subjects. Table 1 summarizes the geometric mean ratios and 90% confidence intervals for AUC0-12h, Cmax and Cp12h for CLR, 14-OH-CLR in the presence and absence of single dose (sd) and multiple dose tipranavir (comparisons made between the different study days). Table 2 summarizes the observed values for the main pharmacokinetic parameters for the studied compounds on the different study days. Figures 4 and 5 illustrate the individual values for the 21 subjects for AUC, Cmax and Cp12 for CLR and 14-OH-CLR, before and after the addition of TPV/r to the regimen. The addition of a single dose of TPV/r to clarithromycin resulted in a 50% increase in clarithromycin Cp12h and multiple dose TPV/r resulted in a 68% increase in clarithromycin Cp12h. The Cp12h of the metabolite of clarithromycin, 14-OH-CLR, was
decreased by 61% and 95% after single and multiple doses of TPV/r, respectively. Multiple dose of TPV/r also resulted in a 97% decrease in both AUC0-12 and Cmax of 14-OH-CLR. When steady-state clarithromycin 500 mg twice-daily was co-administered with TPV/r 500/200 mg twice-daily, the TPV AUC0-12h, Cmax, and Cp12h increased 66%, 40% and 100%, respectively, when compared to the healthy volunteer historical control population (Table 1).

No serious adverse events occurred during this study. There were no discontinuations due to AEs or any other reason. The most frequently reported AEs during clarithromycin + TPV/r treatment included nausea (37.5%), loose stools (25%), headaches (25%), abdominal pain (16.7%), taste perversion (16.7%), vomiting (16.7%) and dizziness (12.5%). The majority of AEs were mild to moderate in intensity, with the majority (54.2% of subjects) in the mild class. With the exception of one subject having a grade 3 ALT level during the clarithromycin + TPV/r phase and one subject having a grade 3 lipase elevation during the clarithromycin-only phase, there were no clinically relevant laboratory abnormalities.

**Fluconazole Study**
Twenty healthy volunteers (2 females and 18 males) were enrolled and completed the study. One subject was black, 19 were white. The mean ± SD age, weight and height for the study population was 42.4 ± 11.0 years, 75.9 ± 9.5 kg and 175.7 ± 6.8 cm, respectively.

Pharmacokinetic results for fluconazole are available for 19 subjects; the results for one subject were omitted because of an anomalous Cp24 for fluconazole on study day 6. Table 3 summarizes the geometric mean ratios and 90% confidence intervals for AUC0-24h, Cmax and Cp24 for fluconazole in the comparisons made between the different study days. Table 4 summarizes the observed values for the main pharmacokinetic parameters for fluconazole and tipranavir on the different study days. Figure 6 illustrates the individual values for the 19 subjects for AUC, Cmax and Cp12 for FCZ, before and after the addition of TPV/r to the regimen.
The effect of single dose TPV/r 500/200 mg on fluconazole AUC, Cmax and Cp12h was minimal (<3%) (Table 3). After multiple dose TPV/r the decrease in fluconazole exposure was <12%. In both dosing situations the 90% confidence intervals of the GMR were within the bioequivalence limits of 0.80 – 1.25.

When steady-state fluconazole 100 mg once-daily was co-administered with TPV/r 500/200 mg twice-daily, the TPV AUC0-12h, Cmax, and Cp12h increased 50%, 32% and 69%, respectively, when compared to the healthy volunteer historical control population (Table 3).

No serious adverse events occurred during this study. There were no discontinuations due to Aes or any other reason. The most frequently observed adverse events were gastrointestinal-related (35% loose stool, 20% nausea and 15% lower abdominal pain). Dizziness (excluding vertigo that was not observed in this study) and somnolence accounted for 20% each. The majority of these events were of mild to moderate intensity with 16 subjects (80%) having mild events and 2 subjects (10%) having moderate events.

There were no clinically relevant variations from baseline in the results of laboratory tests during the co-administration of TPV/r plus fluconazole. Relative to fluconazole alone, TPV/r plus fluconazole treatment resulted in a median 2.1-fold increase in ALT and 1.5 fold increase in AST, however no clinical adverse symptoms or events were associated.

There were no relevant differences in the medians of other liver function test parameters between fluconazole alone and TPV/r plus fluconazole treatments.

**Rifabutin study**

Twenty-four healthy volunteers (4 females and 20 males) were enrolled and 20 completed the study; four subjects were discontinued due to adverse events. Twenty-two subjects were white and two were black. The mean ± SD age, weight and height for the study population was 32.8 ± 8.5 years, 73.2 ± 8.9 kg and 173.8 ± 8.6 cm, respectively.
Three subjects withdrew from the study prior to study day 15 and 1 subject withdrew from the study on study day 16. Therefore, pharmacokinetic results were available for 20 subjects for RFB and 25-O-desacetyl-RFB, while results for 21 subjects were available for TPV pharmacokinetics. Table 5 summarizes the geometric mean ratios and 90% confidence intervals for $\text{AUC}_{0-\infty}$, $\text{Cmax}$ and $\text{Cp12h}$ for tipranavir, rifabutin, 25-O-desacetyl-rifabutin, the sum of rifabutin and 25-O-desacetyl-rifabutin, in the comparisons made between the different study days. Figure 7 illustrates the individual values for the 20 subjects for $\text{AUC}$, $\text{Cmax}$ and $\text{Cp12}$ for rifabutin and its metabolite, with and without TPV/r. Table 6 summarizes the observed values for the main pharmacokinetic parameters for tipranavir, rifabutin and 25-O-desacetyl-rifabutin on the different study days. Co-administration of steady-state TPV/r with single-dose RFB caused statistically significant increases in all three primary pharmacokinetic parameters ($\text{AUC}_{0-\infty}$, $\text{Cmax}$ and $\text{Cp12h}$) for both the parent drug (RFB) and the active metabolite (25-O-desacetyl-RFB). Co-administration of single-dose RFB with steady-state TPV/r did not affect the primary TPV pharmacokinetic parameters $\text{AUC}_{0-12h}$ or $\text{Cmax}$, and caused only a small, but statistically significant 16% increase in $\text{Cp12h}$.

Eighteen subjects (75%) reported at least one AE while receiving TPV/r. The most frequently reported Aes were related to the gastrointestinal tract (reported by 14 subjects (58.4%); nausea (33.3%) and vomiting (25%)), and the central nervous system (reported by 11 subjects (45.8%); headaches (33.3%) and dizziness (12.5%)). All Aes during treatment with TPV/r were of mild to moderate DAIDS grade severity with 18 subjects (75%) reporting mild events, and 3 subjects (12.5%) reporting moderate events. Five subjects were found to have clinically relevant laboratory test abnormalities. Three subjects developed asymptomatic ≥ DAIDS grade 3 levels of ALT or AST, which led to their early discontinuation from the study. In all 3 subjects, ALT and AST levels returned to normal by a follow-up visit approximately 1 month following the end of the study. A grade 3 elevation in lipase level (on day 21) and a grade 4 elevation in PPT level (on day 8) were also reported during the study; these levels returned to normal 1 week later.
A fourth subject was discontinued due to the appearance of generalized rash, which resolved after 5 days. All the Aes that led to discontinuations occurred during the TPV/r treatment period.

DISCUSSION
This article presents three healthy volunteer studies which investigated the pharmacokinetic interaction between tipranavir co-administered with low-dose ritonavir and each of the antimicrobial drugs clarithromycin, fluconazole and rifabutin. These drug combinations are frequently needed in the treatment of HIV infected patients, and therefore pharmacokinetic drug-drug interaction studies of these combinations were warranted.

Clarithromycin study pharmacokinetics
In the clarithromycin study, it was found that clarithromycin AUC and Cp12h increased 19% and 68%, while Cmax decreased 5%, after co-administration with TPV/r at steady state. The effect of TPV/r on 14-hydroxy-clarithromycin was greater and almost completely (>95%) inhibited the formation of this metabolite. These observations are consistent with previously published results with other protease inhibitors. In an interaction study with ritonavir 200 mg tid and clarithromycin 500 mg bid, increases were seen in clarithromycin AUC, Cmax and Cmin of 77%, 31% and 182%, respectively. Also in this study, the formation of 14-hydroxy-clarithromycin was inhibited strongly (>99%) (20). In an interaction study with indinavir 800 mg tid and clarithromycin 500 mg bid, it was found that clarithromycin AUC and Cmax increased 47% and 19%, respectively, while 14-hydroxy-clarithromycin AUC and Cmax decreased by 49% and 48% (7). When combining amprenavir 1200 mg bid with clarithromycin 500 mg bid, there was only a small effect (<10%) on clarithromycin AUC, Cmax and Cp12h, however for 14-hydroxy-clarithromycin these parameters were decreased by 35%, 32% and 4%, respectively (8). In this last study it was noticed that the renal clearance of clarithromycin increased 34% when combined with amprenavir. This observation can explain the relatively low increase in clarithromycin AUC in this combination. Similarly, in the present study the relatively
low increase in clarithromycin of 19% may be the result of increased renal clearance. The changes in clarithromycin pharmacokinetics when combined with TPV/r normally will not require a dose adjustment for clarithromycin, given the wide therapeutic range of clarithromycin. However, when renal function is decreased, a decrease in the clarithromycin dose will likely be necessary to prevent supra-therapeutic drug concentrations(1).

The increase in tipranavir exposure of 66%, in comparison to the healthy volunteer historical controls, can be explained by the inhibitory effects of clarithromycin on CYP3A isozymes. For amprenavir, indinavir and ritonavir, increases in the AUC of 18%, 19% and 12%, respectively, have been reported when combined with clarithromycin (7, 8, 20).

**Fluconazole study pharmacokinetics**

In the FCZ study, co-administration of two doses of TPV/r 500/200 mg did not substantially influence the steady-state pharmacokinetics of FCZ (changes in the AUC$_{0-24h}$, $C_{max}$, and $C_{p24h}$ ≤ 3%). Co-administration of TPV/r 500/200 mg twice-daily for 7 days caused small, but statistically significant decreases in the FCZ AUC$_{0-24h}$ (-8%), $C_{max}$ (-6%), and $C_{p24h}$ (-11%). However, these minor changes are not considered to be clinically significant. The absence of a clinically relevant effect of TPV/r on FCZ pharmacokinetics can be explained by the fact that FCZ is cleared primarily by renal excretion with approximately 80% of the administered dose appearing in the urine as unchanged drug. About 11% of the dose is excreted in the urine as metabolites. FCZ has only a weak affinity of human cytochrome P450 metabolic enzymes. However, the increases in steady-state AUC$_{0-12h}$, $C_{max}$ and $C_{p12h}$ of TPV, compared to the healthy volunteer historical controls, might be explained by the inhibitory effect of FCZ on CYP3A mediated metabolism (10, 17), the main enzyme for the metabolism of both TPV and RTV.
Similarly, FCZ (at different dosages) has been shown to influence plasma concentrations of other HIV protease inhibitors. FCZ (200 mg once-daily) increased the AUC\textsubscript{0-24h} and \(C_{\text{max}}\) of RTV (200 mg every 6 hours) by 12% and 15%, respectively, in a study in eight healthy volunteers (10). The AUC\textsubscript{0-8h} and \(C_{\text{max}}\) of saquinavir (1,200 mg thrice-daily) was increased by 50% and 56%, respectively, during co-administration of FCZ (200 mg once-daily) in a small study in five HIV-1 infected patients (17). In the same study, no effect of FCZ on the pharmacokinetics of RTV (600 mg twice-daily) was observed (n=3). In a study in 11 HIV-1-infected patients, co-administration of FCZ (400 mg once-daily) and indinavir (1,000 mg thrice-daily) caused a marginally statistically significant decrease in the AUC\textsubscript{0-8h} of indinavir (-24%), with no substantial effect on \(C_{\text{max}}\) or \(C_{\text{p8h}}\) (13). The reduction of the indinavir AUC might be explained by potential interference of FCZ with indinavir absorption, or induction of certain CYP450 enzymes by FCZ.

An increase in the \(C_{\text{max}}\) (+82%) and a decrease in the CL/F (-36%) of TPV was observed during co-administration of TPV/r and FCZ compared to the results population PK analysis, suggesting that FCZ inhibited both intestinal and hepatic CYP3A enzymes. This is in agreement with the results of a previously published pharmacokinetic interaction study of oral FCZ with intravenous and oral midazolam, which is a well known substrate for CYP3A (19).

Rifabutin study pharmacokinetics

In the rifabutin study, the effect of a single 150mg dose of RFB on the steady-state pharmacokinetics of TPV (co-administered with RTV) was limited to a 16% increase in \(C_{\text{p12h}}\) with no apparent effect on AUC\textsubscript{0-12h} or \(C_{\text{max}}\). This is in line with the knowledge that RFB-mediated CYP3A induction requires approximately one week of daily drug administration (9, 22). Therefore, an RFB-dependent CYP3A induction effect was unlikely to occur since this study was limited to investigating the interactions between single-dose of RFB and steady-state TPV/r. However from several reports it seems that multiple dose rifabutin in healthy volunteers might lead to unacceptable adverse events (6, 15, 28).
When a single 150 mg dose of RFB was co-administered with TPV/r, RFB AUC$_{0-\infty}$, C$_{\text{max}}$ and C$_{p12h}$ increased 2.90-fold, 1.70-fold and 2.14-fold, respectively. Greater changes were observed for 25-O-desacetyl-RFB with the AUC$_{0-\infty}$, C$_{\text{max}}$ and C$_{p12h}$ increasing 20.71-fold, 3.20-fold and 7.83-fold, respectively, with the combined parent + metabolite AUC$_{0-\infty}$, C$_{\text{max}}$ and C$_{p12h}$ increasing 4.33-fold, 1.86-fold and 2.76-fold.

The greater effect of TPV/r on the pharmacokinetics of 25-O-desacetyl-RFB than on those for RFB can be explained by differential contribution of CYP3A to the metabolism of RFB and 25-O-desacetyl-RFB as was previously proposed (11). The change in the pharmacokinetics of RFB and 25-O-desacetyl-RFB and the ratio of metabolite:parent in the presence of TPV/r is the likely outcome of the potent inhibitory effect that RTV exerts on CYP3A activity. This inhibition of CYP3A can occur in both the intestinal wall and the liver resulting in decreased first-pass metabolism at both sites (11). The results of the present study are consistent with previously observed increases in RFB and 25-O-desacetyl-RFB in healthy volunteers receiving RFB (150 mg qd for 16 days) co-administered with RTV (500 mg q12h for 10 days) at steady-state (11). In the latter, RFB and 25-O-desacetyl-RFB AUC increased approximately 4-fold and 35-fold, respectively, when co-administered with RTV. The combined parent + metabolite AUC increased nearly 7-fold. Also, the ratio of metabolite to parent increased to approximately 77%, which compares well with the 65% increase in the present study.

The results of a clinical pharmacokinetic study in HIV+ patients without mycobacterial infection and who were receiving saquinavir 400 mg / ritonavir 400 mg demonstrated that RFB dosing every 3 days at 150 mg resulted in peak and trough concentrations that were similar to the 300 mg daily RFB dose in the absence of CYP3A inhibitors (16).

To manage the clinically important changes in the pharmacokinetics of RFB and 25-O-desacetyl-RFB when combined with TPV/r, therapeutic drug monitoring (TDM) of RFB could be useful. The expected large interpatient variability in these interactions increases the need for TDM of RFB to determine the best dose adjustment for the individual patient. TDM of RFB, including cutoff values, has been described in more detail in the
literature (21, 26, 27). Finally, patients receiving RFB with TPV/r should be closely monitored for emergence of adverse events associated with RFB therapy.

**Safety**

In terms of safety, these studies were conducted in healthy male and female subjects between 18 and 60 years of age. Consistent with previous TPV trials, the most frequently observed AEs were GI related. In general, the treatments in the clarithromycin and fluconazole studies were well-tolerated with the majority of AE’s being mild in intensity. The clinically non relevant increases in ALT and AST in the fluconazole study seem to be concordant with a report of liver toxicity being related to fluconazole use in tuberculosis treatment (23).

In the rifabutin study five subjects were found to have clinically relevant changes in laboratory measurements in this study. Three subjects developed asymptomatic Grades 3 and 4 levels of ALT and AST which led to their early discontinuation from the study. A fourth subject was discontinued due to the appearance of generalized rash. All the AEs that led to discontinuations occurred during the TPV/r treatment period. Overall, the RFB and TPV/r combination treatment was moderately tolerated.

**Conclusion**

In conclusion, when combining tipranavir with clarithromycin it should be noted that both tipranavir and clarithromycin exposure will be increased. For clarithromycin this will not cause problems in patients with a normal renal function. However, while concentration-related adverse events have not been observed in studies with TPV (2, 24), patients using clarithromycin at doses higher than 500 mg BID should be carefully monitored for signs of toxicity. The almost complete inhibition of formation of 14-OH-CLR should be taken in account when treating pathogens susceptible to this pharmacologically active metabolite. Overall, the TPV/r/CLR combination treatment was moderately-tolerated in the healthy subject population used in this study, however it is not clear if this is a result of the increase in CLR exposure.
Co-administration of TPV/r 500/200 mg twice-daily and FCZ (100 mg once-daily) does not have a clinically relevant effect on the pharmacokinetics of FCZ. Therefore, no dosage adjustment of FCZ is required when combined with TPV/r 500/200 mg. FCZ appeared to have a significant effect on the steady-state pharmacokinetics of TPV when compared to the pharmacokinetics of TPV/r alone in HIV negative people. The clinical significance of this increase in the exposure to TPV is not known, but it was previously shown that a 45.6% increased TPV exposure did not result in increased toxicity(2, 24), however clinical monitoring of patients receiving this combination is advised. No unexpected safety issues arose in this study and medications were well tolerated in these healthy volunteers.

The effect of a single 150 mg dose of RFB on the steady-state pharmacokinetics of TPV resulted in an average 16% increase in Cp12h with no effect occurring in AUC0-12h or Cmax. This small increase in trough TPV concentration does not appear to be clinically relevant. As a result of CYP3A inhibition by ritonavir, changes of clinical importance occurred in the pharmacokinetics of RFB and its active metabolite, 25-O-desacetyl-RFB. When the AUC of parent and metabolite are considered together, a greater than 4-fold increase in exposure occurred after the administration of RFB 150 mg. When RFB is co-administered with TPV/r, RFB drug levels should be monitored with TDM and the dose adjusted accordingly. In addition, patients receiving RFB with TPV/r should be closely monitored for RFB toxicity by clinical judgment and laboratory assessments.

**ACKNOWLEDGEMENTS**

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contracted research through his Institution (University of Ottawa at The Ottawa Hospital) for Boehringer Ingelheim, Pharmacia & Upjohn, and Abbott Laboratories.
**Figure 1. Clarithromycin Study Design**

<table>
<thead>
<tr>
<th>Study Day</th>
<th>1</th>
<th>2</th>
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<th>4</th>
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<tbody>
<tr>
<td>Procedure</td>
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<td>TPV/r</td>
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<td>Q</td>
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<tr>
<td>CLR</td>
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<td>B</td>
<td>B</td>
<td>B</td>
<td>Q</td>
</tr>
</tbody>
</table>

- **P** = pharmacokinetic blood sampling
- **B** = twice daily dosing
- **Q** = once daily dosing
- **TPV/r** = tipranavir/ritonavir 500/200mg
- **CLR** = clarithromycin 500mg

**Figure 2. Fluconazole Study Design**

<table>
<thead>
<tr>
<th>Study Day</th>
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<th>2</th>
<th>3</th>
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<tr>
<td>Procedure</td>
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<td>P</td>
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<tr>
<td>TPV/r</td>
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<td>B</td>
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<td>B</td>
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<tr>
<td>FCZ</td>
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<td>Q</td>
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<td>Q</td>
</tr>
</tbody>
</table>

- **P** = pharmacokinetic blood sampling
- **B** = twice daily dosing
- **Q** = once daily dosing
- **TPV/r** = tipranavir/ritonavir 500/200mg
- **FCZ** = fluconazole, 200mg on study day 1, 100mg on study days 2-13

**Figure 3. Rifabutin Study Design**

| Study Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 |
|-----------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|
| RFB       |   |   | Q |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | Q  |

- **P** = pharmacokinetic blood sampling
- **B** = twice daily dosing
- **Q** = single dose
- **TPV/r** = tipranavir/ritonavir 500/200mg
- **RFB** = rifabutin 150mg
Figure 4. Effect of first-dose (fd) (Panel A) and steady-state (ss) (Panel B) TPV/r on the pharmacokinetics of steady-state clarithromycin (CLR). The symbols and lines represent individual subjects (n=21).
Figure 5. Effect of first-dose (fd) (Panel A) and steady-state (ss) (Panel B) TPV/r on the pharmacokinetics of steady-state 14-OH-clarithromycin (CLR). The symbols and lines represent individual subjects (n=21).
Figure 6. Effect of first-dose (fd) (Panel A) and steady-state (ss) (Panel B) TPV/r on the pharmacokinetics of steady-state fluconazole (FCZ). The symbols and lines represent individual subjects (n=19).
Figure 7. Effect of steady-state TPV/r on the pharmacokinetics of single-dose rifabutin (RFB) (Panel A) and 25-O-desacetyl-rifabutin (Panel B). The symbols and lines represent individual subjects (n=20).
Table 1. Summary of mean ratios and 90% confidence intervals for clarithromycin, 14-hydroxy clarithromycin and tipranavir

<table>
<thead>
<tr>
<th></th>
<th>Mean Ratio (90% CI)</th>
<th>n</th>
<th>AUCa</th>
<th>Cmax</th>
<th>Cmina</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLR + sd TPV/r</td>
<td>CLR alone (day 5)</td>
<td>24</td>
<td>1.00 (0.91-1.11)</td>
<td>0.88 (0.78-1.00)</td>
<td>1.50 (1.31-1.71)</td>
</tr>
<tr>
<td>CLR + md TPV/r</td>
<td>CLR alone (day 5)</td>
<td>21</td>
<td>1.19 (1.04-1.37)</td>
<td>0.95 (0.83-1.09)</td>
<td>1.68 (1.42-1.98)</td>
</tr>
<tr>
<td>14-OH-CLR after CLR + sd TPV/r</td>
<td>CLR alone (day 5)</td>
<td>24</td>
<td>0.54 (0.48-0.59)</td>
<td>0.75 (0.68-0.83)</td>
<td>0.39 (0.35-0.44)</td>
</tr>
<tr>
<td>14-OH-CLR after CLR + md TPV/r</td>
<td>CLR alone (day 5)</td>
<td>21</td>
<td>0.03 (0.02-0.04)</td>
<td>0.03 (0.02-0.04)</td>
<td>0.05 (0.04-0.07)</td>
</tr>
<tr>
<td>CLAV + md TPV/r</td>
<td>historical controls</td>
<td>24 (68b)</td>
<td>1.66 (1.43-1.73)</td>
<td>1.40 (1.24-1.47)</td>
<td>2.00 (1.58-2.47)</td>
</tr>
</tbody>
</table>

aAUC0-12h and Cp12h
bHistorical controls (N=68)

Table 2. Summary of the steady-state pharmacokinetic parameters of clarithromycin and tipranavir

<table>
<thead>
<tr>
<th>Pharmacokinetic Parametersa</th>
<th>Clarithromycin</th>
<th>Tipranavir</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CLR alone (day 5) (n=24)</td>
<td>CLR + sd TPV/r (day 6) (n=24)</td>
</tr>
<tr>
<td>AUC</td>
<td>21.9 (23.0, 9.8-54.0)</td>
<td>22.0 (21.6, 13.5-48.2)</td>
</tr>
<tr>
<td>Cmax</td>
<td>2.80 (3.19, 0.91-5.79)</td>
<td>2.47 (2.27, 1.35-6.19)</td>
</tr>
<tr>
<td>Cmin</td>
<td>0.97 (1.07, 0.36-3.57)</td>
<td>1.46 (1.59, 0.76-3.17)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>1.8 (1.5, 0.0-4.0)</td>
<td>2.1 (1.5, 0.5-8.0)</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>6.1 (3.5, 4.1-16.2)</td>
<td>10.2 (9.6, 37-21.3)</td>
</tr>
<tr>
<td>Cl/F (L/h)</td>
<td>22.9 (21.7, 9.3-51.4)</td>
<td>22.7 (23.2, 10.4-37.0)</td>
</tr>
<tr>
<td>V (L)</td>
<td>201 (180, 107-1203)</td>
<td>335 (347, 158-1089)</td>
</tr>
</tbody>
</table>

aAUC0-12h; h•µg/mL for CLR; h•µM for TPV, Cmax and Cp12h; µg/mL for CLR; h•µM and µM for TPV
bExcludes 1 subject with a Tmax of 0 h
All data presented as geometric mean and (median, min – max)
Table 3. Summary of mean ratios and 90% confidence intervals for fluconazole and tipranavir

<table>
<thead>
<tr>
<th></th>
<th>Mean Ratio (90% CI)</th>
<th>n</th>
<th>AUC(^a)</th>
<th>C(_{\text{max}})</th>
<th>C(_{\text{min}})(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FCZ</td>
<td>FCZ alone (day 6) vs. FCZ + sd TPV/r (day 7)</td>
<td>19</td>
<td>0.99 (0.97-1.02)</td>
<td>0.97 (0.94-1.01)</td>
<td>0.98 (0.94-1.02)</td>
</tr>
<tr>
<td>FCZ</td>
<td>FCZ alone (day 6) vs. FCZ + md TPV/r (day 13)</td>
<td>19</td>
<td>0.92 (0.88-0.95)</td>
<td>0.94 (0.91-0.98)</td>
<td>0.89 (0.85-0.92)</td>
</tr>
<tr>
<td>TPV</td>
<td>FCZ + md TPV/r (day 13) vs. historical controls</td>
<td>20 (68(^c))</td>
<td>1.50 (1.29, 1.73)</td>
<td>1.32 (1.18, 1.47)</td>
<td>1.69 (1.33-2.09)</td>
</tr>
</tbody>
</table>

\(^{a,b}\)AUC\(_0-24\)h and Cp\(_{24}\)h for FCZ; AUC\(_0-12\)h and Cp\(_{12}\)h for TPV  
\(^c\)Historical controls (N=68)

Table 4. Summary of the steady-state pharmacokinetic parameters of fluconazole and tipranavir

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters(^a)</th>
<th>Fluconazole</th>
<th>Tipranavir</th>
<th>Tipranavir + FCZ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FCZ alone (day 6) (n=19)</td>
<td>FCZ + 2 doses TPV/r (day 7) (n=19)</td>
<td>FCZ + steady-state TPV/r (day 13) (n=19)</td>
</tr>
<tr>
<td>AUC</td>
<td>99.0 (97.1, 81.7-149.8)</td>
<td>98.2 (93.4, 79.5-136.5)</td>
<td>90.6 (90.2, 74.5-145.7)</td>
</tr>
<tr>
<td>Cmax</td>
<td>5.3 (4.9, 4.4-8.6)</td>
<td>5.1 (4.9, 4.0-7.0)</td>
<td>4.9 (4.7, 3.9-8.0)</td>
</tr>
<tr>
<td>Cmin</td>
<td>3.6 (3.5, 2.8-5.4)</td>
<td>3.5 (3.3, 2.8-5.0)</td>
<td>3.2 (3.2, 2.3-4.9)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>2.1 (2.0, 1.0-4.0)</td>
<td>2.8 (3.0, 1.5-10.0)</td>
<td>2.4 (3.0, 1.5-4.0)</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>50.8 (50.2, 30.6-74.1)</td>
<td>46.9 (44.0, 26.2-77.7)</td>
<td>46.0 (45.2, 31.6-74.3)</td>
</tr>
<tr>
<td>CI/F (L/h)</td>
<td>1.0 (1.0, 0.7-1.2)</td>
<td>1.0 (1.1, 0.7-1.3)</td>
<td>1.1 (1.1, 0.7-1.4)</td>
</tr>
<tr>
<td>V (L)</td>
<td>74.0 (72.9, 50.7-121.0)</td>
<td>68.9 (66.9, 38.8-108.4)</td>
<td>73.2 (71.1, 41.0-136.5)</td>
</tr>
</tbody>
</table>

\(^a\)AUC\(_0-24\)h (h•µg/mL), Cmax and Cp\(_{24}\)h (µg/mL) for FCZ; AUC\(_0-12\)h (h•µM), Cmax and Cp\(_{12}\)h (µM) for TPV  
All data presented as geometric mean and (median, min – max)
**Table 5.** Summary of mean ratios and 90% confidence intervals for rifabutin, 25-O-desacetyl-RFB (metabolite) and the total parent + metabolite as well as tipranavir

<table>
<thead>
<tr>
<th>Mean Ratio (90% CI)</th>
<th>n</th>
<th>AUC(^a)</th>
<th>Cmax</th>
<th>Cmin</th>
</tr>
</thead>
<tbody>
<tr>
<td>RFB</td>
<td>20</td>
<td>2.90 (2.59-3.26)</td>
<td>1.70 (1.49-1.94)</td>
<td>2.14 (1.90-2.41)</td>
</tr>
<tr>
<td>RFB metabolite</td>
<td>20</td>
<td>20.71 (17.66-24.28)</td>
<td>3.20 (2.78-3.68)</td>
<td>7.83 (6.70-9.14)</td>
</tr>
<tr>
<td>RFB + metabolite</td>
<td>20</td>
<td>4.33 (3.86-4.86)</td>
<td>1.86 (1.63-2.12)</td>
<td>2.76 (2.44-3.12)</td>
</tr>
<tr>
<td>TPV</td>
<td>21</td>
<td>1.00 (0.96-1.04)</td>
<td>0.99 (0.93-1.07)</td>
<td>1.16 (1.07-1.27)</td>
</tr>
</tbody>
</table>

\(^a\)AUC\(_{0-\infty}\) for RFB; AUC\(_{0-12h}\) for TPV; C\(_{p12h}\) for RFB and TPV

**Table 6.** Summary of the steady-state pharmacokinetic parameters of tipranavir, rifabutin and 25-O-desacetyl-rifabutin

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters(^a)</th>
<th>Tipranavir</th>
<th>Rifabutin</th>
<th>25-O-desacetyl-RFB</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>955 (980, 537-1444)</td>
<td>2217 (2157, 895-6032)</td>
<td>6441 (6206, 4160-10426)</td>
</tr>
<tr>
<td>Cmax</td>
<td>140.6 (141.1, 84.5-213.1)</td>
<td>162.0 (156.5, 55.9-435.0)</td>
<td>275.5 (283.0, 173.0-455.0)</td>
</tr>
<tr>
<td>Cmin</td>
<td>35.2 (38.8, 10.5-79.2)</td>
<td>46.7 (49.0, 23.7-116.0)</td>
<td>100.1 (99.3, 70.0-161.0)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>2.8 (3.0, 2.0-4.0)</td>
<td>3.5 (3.0, 2.0-6.0)</td>
<td>4.1 (4.0, 2.0-6.0)</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>4.7 (4.5, 2.5-8.0)</td>
<td>5.5 (5.8, 3.0-11.1)</td>
<td>65.1 (71.2, 42.5-91.6)</td>
</tr>
<tr>
<td>Cl/F (L/h)</td>
<td>0.87 (0.85, 0.57-1.54)</td>
<td>0.87 (0.47, 0.83-1.42)</td>
<td>na</td>
</tr>
<tr>
<td>V (L)</td>
<td>5.9 (6.1, 3.6-9.1)</td>
<td>4028 (4368, 1542-8638)</td>
<td>2188 (2318, 909-3205)</td>
</tr>
</tbody>
</table>

\(^a\)AUC\(_{0-\infty}\) (h*ng/mL), Cmax and C\(_{p12h}\) (ng/mL) for RFB; AUC\(_{0-12h}\) (h*µM), Cmax and C\(_{p12h}\) (µM) for TPV

All data presented as geometric mean and (median, min – max)
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