Effects of Atazanavir/Ritonavir or Fosamprenavir/Ritonavir on the Pharmacokinetics of Rosuvastatin

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Background: Rosuvastatin (RSV) is a potent statin with a lower potential for drug interactions. However, recent data have revealed unexpected increases in RSV concentrations with lopinavir/ritonavir. The objective is to study the pharmacokinetic interaction of RSV with atazanavir/ritonavir (ATV/RTV) or fosamprenavir/ritonavir (FPV/RTV).

Methods: In a prospective pharmacokinetic drug interaction study, six HIV-seronegative, healthy adult volunteers received single 10-mg doses of RSV at baseline and after 6 days of ATV/RTV and FPV/RTV, with 6-day washout periods. Plasma concentrations of RSV and its metabolites, N-desmethyl-RSV and RSV-lactone, were measured by using a internally validated tandem mass spectrometric (LC-MS/MS) method over 24 hours.

Results: Compared to baseline, the area under the plasma concentration-time curve ($AUC_{0\text{-}24h}$) and maximum plasma concentration (C_{max}) of RSV increased by 213% and 600%, respectively, and the time to reach C_{max} was shorter (1.75 h vs. 2.91 h) when given with ATV/RTV ($P < 0.05$). However, coadministration with FPV/RTV did not significantly affect the pharmacokinetics of RSV. The $AUC_{0\text{-}24h}$ of N-desmethyl-RSV was not significantly affected by either combinations, but that of RSV-lactone increased ($P < 0.05$) by 61% and 76% after coadministration with ATV/RTV and FPV/RTV, respectively.

Conclusion: ATV/RTV significantly increases the plasma concentrations of rosuvastatin, most likely by increasing rosuvastatin's oral bioavailability. Dose limitations of RSV with ATV/RTV may be needed.

Key Words: rosuvastatin, atazanavir, fosamprenavir, ritonavir, pharmacokinetics, drug interaction

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The treatment of human immunodeficiency virus (HIV) infection with potent highly active antiretroviral therapy (HAART) has dramatically reduced morbidity and mortality. As prognosis improves with chronic use of HAART, management of antiretroviral-associated dyslipidemia will continue to pose a significant challenge to even experienced clinicians as use of lipid-lowering agents is often complicated by significant and often unpredictable drug-drug interactions with antiretroviral agents.

While drug-drug interactions with protease inhibitors (PIs) are predictable and now well-known for statins that are substrates of cytochrome P450 (CYP450) 3A4 (ie, simvastatin, lovastatin, and atorvastatin), drug interactions between PIs and statin drugs that are non-CYP450 3A4 substrates [ie, pravastatin and rosuvastatin (RSV)] have not been well defined. Pravastatin has historically been one of a few statins of choice that is theoretically less likely to result in clinically relevant drug interactions.[1] However, one study showed an unexpected elevation (23–400%) in pravastatin concentrations when coadministered with darunavir/ritonavir, whereas another study reported and an increase of 33% in the plasma concentration of the drug when coadministered with lopinavir/ritonavir (LPV/RTV).[2,3] In contrast, other pharmacokinetic studies with saquinavir/ritonavir and nelfinavir have shown a reduction in the pravastatin area under the plasma concentration-time curve (AUC) by approximately 50%.[4,5] Although the mechanism of these interactions have yet to be determined, these studies further highlight the need for individual evaluation of statin-PI combinations for potential drug interactions.

The high-potency statin rosuvastatin (RSV) has been an attractive option for treatment of dyslipidemia in the setting of HAART because 90% of RSV is eliminated in the feces unchanged and only 10% undergoes biotransformation via CYP2C9 (Fig. 1).[6] Additionally, pilot data have suggested low-dose (i.e., 10 mg) RSV may be safe and effective in HIV-infected patients on PI-based HAART.[7] However, that study did not include patients who were on atazanavir/ritonavir (ATV/RTV) or fosamprenavir/ritonavir (FPV/RTV). While the

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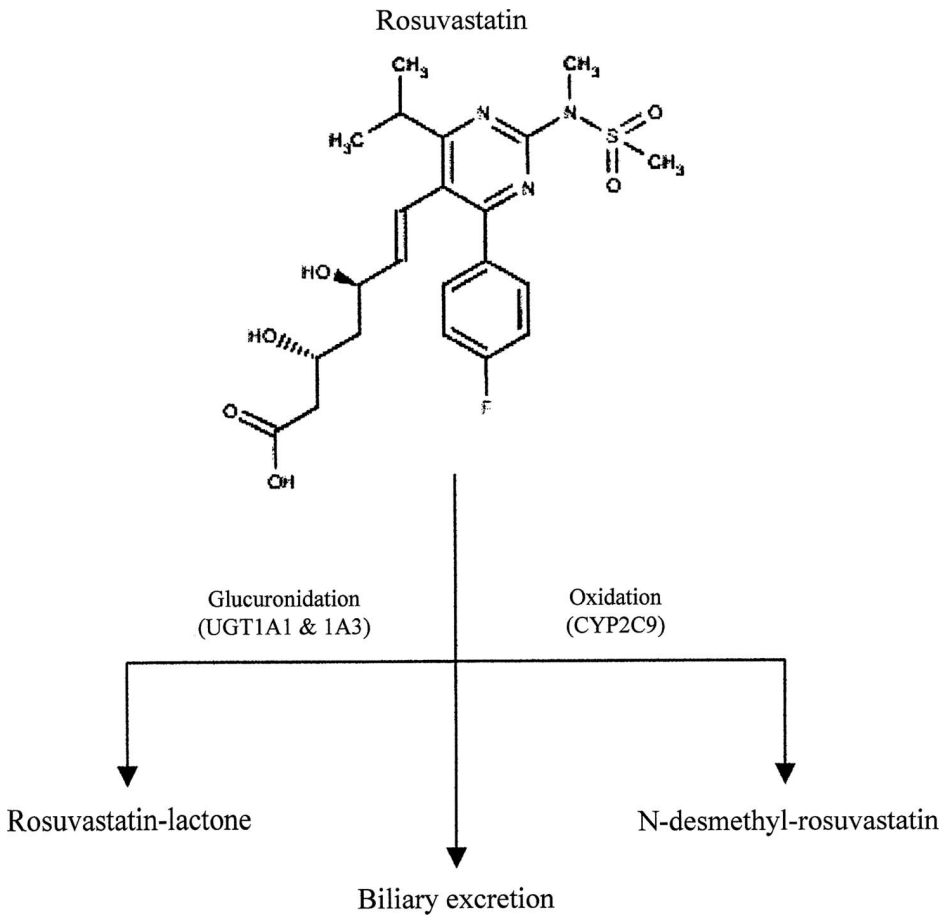

FIGURE 1. Rosuvastatin elimination pathways. UGT = UDP-glucuronosyltransferase; CYP = cytochrome. Structure from United States National Library of Medicine's ChemIDplus advanced, accessed March 17, 2008.

mechanism is not yet known, recent studies showed substantial increases in RSV plasma concentrations when coadministered with LPV/RTV.[8,9] Based on these previous studies that underscore the unpredictable nature of statin-PI interactions, we aim to examine the pharmacokinetics of RSV and metabolites when coadministered with two commonly prescribed ritonavir-boosted PIs, ATV/RTV and FPV/RTV, at steady-state in order to determine if potential for drug interaction exists.

METHODS

This was a single-center, prospective study that was conducted in healthy, adult HIV-seronegative volunteers at the Clinical Research Unit (CRU) at the Dallas VA Medical Center in Dallas, Texas. All procedures were done in accordance with the ethical standards of the institutional review boards for all participating institutions and with the Helsinki Declaration of 1975, as revised in 2000.

Subjects

Healthy, HIV-seronegative volunteers >18 years of age were eligible to participate in this study after signing a written informed consent. The inclusion criteria for females of childbearing potential were a negative urine pregnancy test and willingness and ability to use a reliable method of birth control for the duration of the study. Exclusion criteria included: HIV test positive per enzyme-linked immunosorbent assay, creatinine clearance <30 mL/min using the Cockcroft-Gault equation, positive urine pregnancy test, total bilirubin >2.0 mg/dL, alanine aminotransferase or aspartate aminotransferase ≥3 times the upper limit of normal, liver/kidney disease, or use of any form of antacid, lipid lowering medications, or known inhibitors and/or inducers of glucuronidation and/or CYP2C8/9 and 3A4.

Study Design

On day 0, the subjects arrived at 6:30 AM, had intravenous (IV) catheters placed and baseline blood drawn. At 7:00 AM, the subjects received a standardized light meal (320 calories, 61 grams of carbohydrates, 10 grams of fat, 4 grams of protein) along with a single dose of RSV 10 mg by mouth. The use of 10 mg of RSV was chosen because this was the dose previously used in the pilot study of RSV and PI by Calza and colleagues.[7] In addition, the use of a single-dose object plus multidose precipitant design for evaluation of a potential drug interaction was based on the guidance from the US Food and Drug Administration and other similar pharmacokinetic studies.[7,10] A standardized light meal was implemented to remove any potential confounding effects of meal variation on the pharmacokinetic analysis, reflecting real-world clinical practice and as indicated by the prescribing

recommendations for ATV. The prescribing recommendations for RSV and FPV indicate that food would have no impact on their absorption and could be given without regard to food.

Blood samples (10 mL) were then taken at 0, 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, and 24 h following RSV administration. The subjects then underwent a 6-day washout period. On day 7, subjects started taking ATV/RTV 300/100 mg by mouth every morning with food to achieve steady state concentrations. On day 14, subjects arrived at 6:30 AM and compliance to ATV/RTV was assessed using pill counts. Subsequently, they underwent a similar procedure as on day 0, and a single dose of RSV 10 mg was taken along with the final dose of ATV/RTV 300/100 mg by mouth after a standardized meal. Is there anyway to avoid the use of this word again since it was just used above?… maybe Start sentence like this… "Blood samples were then taken again as described above." Subsequently, blood samples were taken as described above. The subjects then underwent another 6-day washout period. On day 21, subjects started taking FPV/RTV 700/100 mg by mouth twice daily with food to achieve steady state concentrations. On day 28, the subjects received their standardized light meal along with one dose of RSV 10 mg by mouth and their penultimate dose of FPV/RTV 700/100 mg by mouth, followed by collection of blood samples.

To maintain steady state levels of the FPV/RTV throughout the pharmacokinetic analysis period of 24 h, subjects received their final oral dose of FPV/RTV at 7:00 PM (12-hour time point). Six days of PI administration was deemed appropriate for achieving steady state given that the half-lives of ATV, FPV, and RTV were 8.6 hours, 7.7 hours, and 3 to 5 hours, respectively.[11–13] Compliance to all prescribed study medication was assessed using telephone follow-up and pill counts.

Sample Analysis

Buffered plasma samples (0.1 mL) treated with lithium heparin anticoagulant were analyzed for RSV, N-desmethyl-RSV, and RSV-lactone at AstraZeneca (Wilmington, DE) using an internally validated tandem mass spectrometric (LC-MS/MS) method (data on file, technique details are proprietary information of Astra Zeneca). The analytes were extracted from plasma by supported liquid extraction. After evaporation under nitrogen, the residue was reconstituted and analyzed. The ranges of standard curves were 0.0200 to 20.0, 0.100 to 10.0, and 0.0500 to 10.0 ng/mL for RSV, N-desmethyl-RSV, and RSV-lactone, respectively. The lower limit of rosuvastatin quantification was 0.02 ng/mL. The within and between run precision and accuracy for RSV, N-desmethyl RSV, and RSV-lactone were <8% (percentage of RSD) and between 87.3 to 109% (percentage of actual value), respectively.

Data Analysis

Noncompartmental analysis (WinNonlin 4.1, Cary, NC) was used to estimate the AUC during the sampling period of 24 hr ($AUC_{0\text{-}24h}$) by the linear (ascending concentrations) and log-linear (descending concentrations) trapezoidal method, maximum plasma concentration (C_{max}), and the time to reach C_{max} (T_{max}) for the drug and its metabolites. Six patients were needed to be enrolled in order to achieve a power of 80% based on an alpha of 0.05 and an expected increase in the AUC and C_{max} of at least 50% (Minitab 14, Minitab Inc., State College, PA). A crossover design was used in order to reduce the variability and better control for any confounders between analyses. The statistical differences between the treatments were tested (StatView, Calabasas, CA) using repeated-measure ANOVA with Fisher's post-hoc analysis, using an alpha level of 0.05 and accounting for multiple comparisons. Data are presented as means ± SD.

RESULTS

Six (3 males, 3 females) healthy volunteers were enrolled and completed all aspects of the study. Their mean age and body mass index were 28 ± 0.5 years and 24.5 ± 2.8

TABLE 1. Pharmacokinetic Parameters (Mean ± SD) of Rosuvastatin and Its Metabolites After a Single Dose of the Drug Administered Alone (Baseline) and After Multiple Doses of ATV/RTV or FPV/RTV

				*P*value		
Parameter	**Rosuvastatin* (baseline)**	**Rosuvastatin + ATV/RTV**	**Rosuvastatin + FPV/RTV**	**Baseline vs. Rosuvastatin + ATV/RTV**	**Baseline vs. Rosuvastatin + FPV/RTV**	**Rosuvastatin + ATV/RTV vs. Rosuvastatin + FPV/RTV**
Rosuvastatin						
AUC_{0-24} (ng*h/mL)	14.0 ± 9.9	43.8 ± 27.9	15.1 ± 8.3	0.001	0.86	0.001
C_{max} (ng/mL)	1.90 ± 1.48	13.3 ± 9.7	2.76 ± 1.36	0.002	0.76	0.004
T_{max} (h)	2.91 ± 1.20	1.75 ± 0.27	2.50 ± 1.18	0.039	0.41	0.159
N-desmethyl rosuvastatin						
AUC_{0-24} (ng·h/mL)	3.07 ± 1.71	4.11 ± 2.79	2.07 ± 1.05	0.135	0.148	0.009
C_{max} (ng/mL)	0.345 ± 0.179	0.899 ± 0.585	0.320 ± 0.144	0.005	0.877	0.004
T_{max} (h)	4.33 ± 0.81	2.16 ± 0.93	2.58 ± 1.11	<0.0001	0.0001	0.177
Rosuvastatin-lactone						
AUC_{0-24h} (ng·hr/mL)	5.45 ± 1.77	8.87 ± 3.59	9.62 ± 3.09	0.004	0.001	0.442
C_{max} (ng/mL)	0.442 ± 0.140	1.20 ± 0.72	0.825 ± 0.363	0.001	0.054	0.053
T_{max} (hr)	5.00 ± 1.09	2.25 ± 0.88	4.33 ± 1.50	0.001	0.319	0.008

Rosuvastatin = 10 mg by mouth × 1 dose for each arm; ATV/RTV = atazanavir/ritonavir 300/100 mg qd × 6 days; FPV/RTV = fosamprenavir/ritonavir 700/100 mg bid × 6 days.

kg/m^2, respectively. Five out of six patients were white and one patient was of Asian descent.

The plasma concentration-time courses of RSV and its two metabolites at baseline and after coadministration with ATV/RTV or FPV/RTV are depicted in Figure 1 and relevant pharmacokinetic parameters are listed in Table 1. When coadministered with ATV/RTV, all the estimated kinetic parameters of RSV were significantly altered (Table 1). There was a 600% (P = 0.002) increase in the RSV C_{max}, which occurred at a substantially shorter T_{max} (1.75 h vs. 2.91 h; P = 0.039; Table 1 and Fig. 2) compared to baseline. Additionally, the $AUC_{0\text{-}24h}$ of RSV increased 213% (P = 0.001) with ATV/RTV coadministration. As for the metabolites, although ATV/RTV coadministration resulted in a higher C_{max} (P = 0.005) and a shorter T_{max} ($P < 0.0001$) for N-desmethyl-RSV, the 34% increase in the $AUC_{0\text{-}24h}$ of the metabolite but did not reach statistical significance (Table 1). However, all of the changes in the kinetic parameters of RSV-lactone as a result of ATV/RTV coadministration were significant and in the same direction as that of the changes in the parent drug (higher AUC and C_{max} and shorter T_{max}; Table 1).

When coadministered with FPV/RTV, the plasma concentration-time profile (Fig. 1) and pharmacokinetic parameters (Table 1) of RSV remained unaltered, compared with baseline. As for the metabolites, only the T_{max} of N-desmethyl-RSV was shorter and the AUC and C_{max} of RSV-lactone significantly increased as a result of FPV/RTV coadministration (Fig. 2 and Table 1).

The study drugs were well tolerated, resulting in no missed doses or discontinuations. Sixty-seven percent of the patients experienced mild jaundice while on ATV/RTV, which was expected.

DISCUSSION

Recently, van der Lee et al. showed that RSV was effective in lowering cholesterol in HIV-infected patients treated with LPV/RTV.[9] However, the steady-state minimum plasma concentrations of RSV in these patients were on average 60% higher than those reported in healthy volunteers. The authors suggested that more research was needed in this area. The study presented here provides the first comprehensive pharmacokinetic data for RSV and its metabolites after coadministration of this statin with two commonly prescribed and preferred initial PIs used in HIV-infected patients. In agreement with recent studies on the interaction of RSV with LPV/RTV,[8,9] our data also show a substantial increase in the plasma concentrations of RSV after coadministration with ATV/RTV (Fig. 2 and Table 1). In contrast to the effect of ATV/RTV on RSV concentrations, the coadministration with another PI combination, FPV/RTV, did not significantly affect the pharmacokinetics of RSV and only had minor effects on the lactone metabolite.

The mechanisms responsible for the observed 3-fold increase in the $AUC_{0\text{-}24h}$ of single-dose (10 mg) RSV when the drug is coadministered with ATV/RTV (Table 1) are not known from our study. Rosuvastatin is known to have a low oral bioavailability of 20% due to both an incomplete absorption (50%) and a significant first pass effect (63%) in the liver.[6] The major pathway for the elimination of RSV

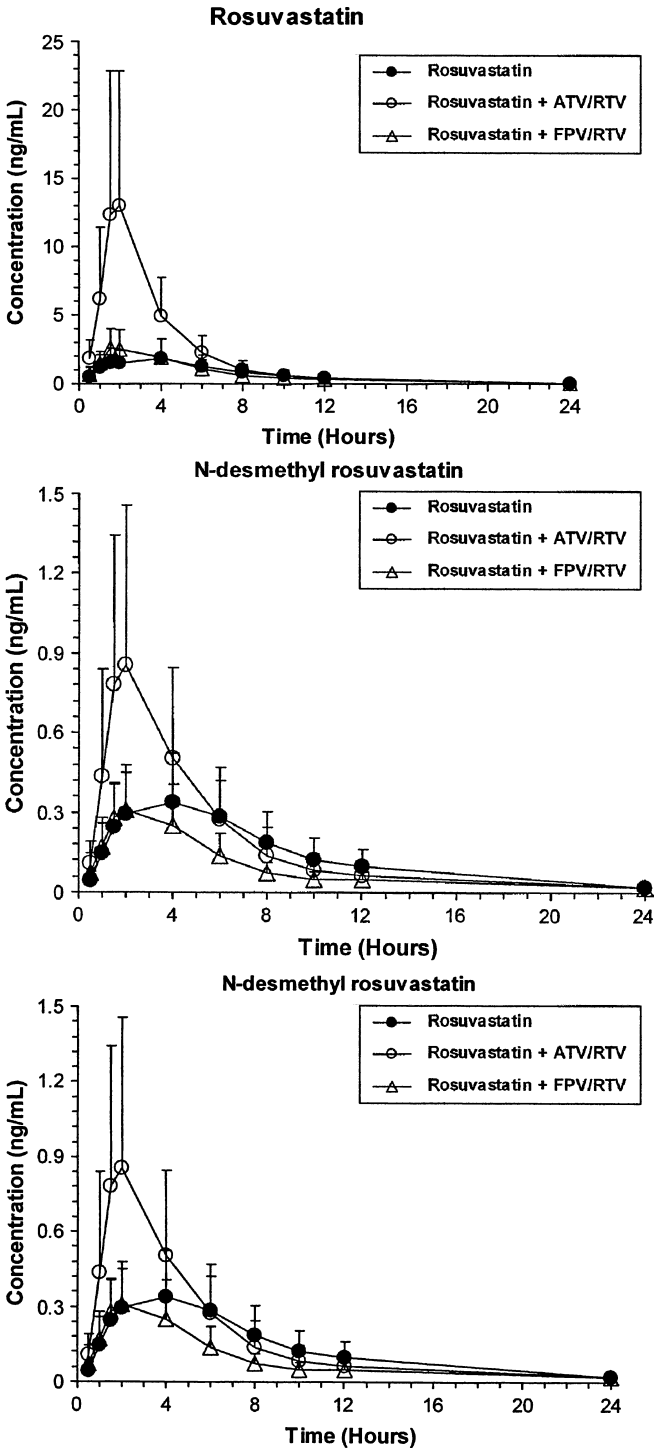

FIGURE 2. Plasma concentration-time profiles for rosuvastatin and its metabolites at baseline, with ATV/RTV and with FPV/RTV. All data reported as mean ± SD. Rosuvastatin was given as 10 mg by mouth × 1 dose for each arm. ATV/RTV = atazanavir/ritonavir; FPV/ATV = fosamprenavir/ritonavir.

appears to be excretion of parent drug or its glucuronide into the bile, with CYP450-mediated hepatic metabolism and renal clearance playing only a minor role. Therefore, the substantial

increase in the AUC of RSV (Table 1) might be explained by an increase in the extent of absorption and/or a decrease in the biliary excretion of the drug.

A recent study that utilized a membrane vesicular drug-transport model showed that RSV is a substrate for BCRP and not MDR1 (ABCB1) or MRP-2 (ABCC2).[14] While BCRP transporters are found on breast cancer cells, they are also found in many other places, including the apical surfaces of enterocytes and the bile canalicular membrane of hepatocytes, where they can influence bioavailability and efflux of drugs out of the body.[15–17] Interestingly, recent in vitro data have also shown ATV and amprenavir (APV; active moiety of FPV) to be inhibitors of BCRP, with ATV being a more potent inhibitor than APV.[18] Therefore, it is plausible that ATV inhibits BCRP-mediated enteric and/or biliary efflux of RSV and thus allows for a greater extent of absorption and/or a decrease in the biliary excretion of the drug. This hypothesis might also explain the observed increase in the concentrations of RSV metabolites after ATV/RTV coadministration (Table 1).

Another potential mechanism for a reduction in RSV excretion might be inhibition of hepatic uptake of RSV via OATP1B1 (found only in the liver) by ATV.[19] While inhibition of OATP1B1 by ATV is not known, indinavir (another PI) has been shown to inhibit OATP1B1 and also shares similar pharmacologic properties with ATV (ie, unconjugated hyperbilirubinemia).[20] In addition, a previous drug-interaction study where RSV was coadministered with gemfibrozil (a known inhibitor of OATP1B1) showed similar effects on RSV pharmacokinetic parameters (increased AUC and C_{max} and earlier T_{max}), as seen with our study.[21]

Because the administration of RSV and ATV/RTV occurred at the same time, it is possible that inhibition of biliary BCRP or hepatic uptake of RSV by ATV, if it happens, is more likely to occur during the absorption phase of the drug, when portal concentrations of ATV are expected to be high. Therefore, all three proposed mechanisms (increase in the extent of absorption and/or decrease in the hepatic uptake and/or biliary excretion) would be expected to affect predominately the oral bioavailability of the drug, rather than its systemic elimination. This, as well as the other proposed mechanisms, would need further evaluation for confirmation of such effects. Moreover, the pharmacodynamic impact of such an increase in RSV concentrations (ie, lipid-lowering efficacy as well as toxicity) remains unknown and warrants further attention.

While there were expected increases in the metabolites of RSV after ATV/RTV administration because of higher availability of RSV, there was also a significant increase in the AUC of RSV-lactone after coadministration of RSV with FPV/RTV in the absence of any effects on the AUC of the parent drug (Table 1). The increase in the AUC of RSV-lactone, which is a product of spontaneous rearrangement of RSV-glucuronide, may be due to induction of glucuronosyl transferase activity by chronic doses of RTV in the FPV/RTV regimen.[22,23] The lack of difference in the AUC of the lactone metabolite between the ATV/RTV and FPV/RTV regimens, despite higher availability of RSV in the presence of former (Table 1), could be explained by ATV's well known inhibition of UGT1A and/or a potential dose-dependent greater degree of UGT induction with the higher-dose RTV boosting used in the FPV regimen.[24] Future mechanistic studies are needed to validate these proposed mechanisms.

It may be argued that the significantly higher exposure to RSV after ATV/RTV regimen (Fig. 2) may be due to a reduction in the glucuronidation of RSV by the UGT1A inhibitory activity of ATV[25] in the intestine and/or the liver. However, if this were the only mechanism for the interaction, one would expect a simultaneous reduction in the plasma concentrations of RSV-lactone, which is derived from the RSV glucuronide. Therefore, although ATV-mediated inhibition of RSV glucuronidation may be contributing to the overall interaction in our study, the simultaneously higher plasma concentrations of RSV and RSV-lactone after ATV/RTV administration (Fig. 1) cannot be explained only on the basis of this mechanism.

Our findings are clinically relevant since in real-world clinical practice many patients will take most, if not all, of their medications simultaneously. The administration method in our study reflects the current prescribing recommendations and remained consistent throughout phases of our study. Since RSV and ATV/RTV are administered once daily, it is theoretically possible that separating the two medications from each other by 12 hours could result in a lesser effect on absorption. The efficacy of either drug is not primarily determined by the time of day of administration. While many statins with shorter half-lives are recommended to be given at bedtime for maximal cholesterol synthesis inhibition, the long half-life (about 19 hours) of RSV allows it to be administered at any time of day. Whether this is true or if steady state levels of both drugs would influence this interaction is not known and would need to be evaluated.

To date, there has been only one pilot study on the use of RSV in 16 HIV+ patients on PI-based HAART, which suggested that RSV 10 mg daily was safe and effective.[7] However, this study did not include patients on ATV/RTV or FPV/RTV. This pilot data, along with favorable safety profile and pharmacokinetic/dynamic characteristics have made RSV an attractive option in HIV+ patients on PIs. Unfortunately, our data with ATV/RTV and recently published data with LPV/RTV would suggest that the unexpected increases in RSV concentrations could put patients at greater risk of adverse drug events, such as myopathy and/or rhabdomyolysis. The 3-fold increase in AUC seen with ATV/RTV (Table 1) would suggest that the maximum dose of RSV with ATV/RTV might be 10-20 mg. This is similar to current RSV prescribing recommendations which limit the dose to a maximum of 10 mg if used with LPV/RTV due to a 5-fold increase in the AUC and 2-fold increase in C_{max}.

CONCLUSION

This study showed a significant increase in the rate and extent of oral bioavailability when RSV was coadministered with ATV/RTV but not with FPV/RTV. The coadministration of RSV and ATV/RTV led to a 3-fold increase in $AUC_{0\text{-}24h}$, thus suggesting that the maximum dose of RSV in the presence of ATV/RTV should be lower. The mechanism for this unexpected pharmacokinetic interaction or its effect on RSV safety and efficacy is not known at this time. However,

based on our data, it would appear that coadministration of RSV with FPV/RTV may be a safe combination.

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