Darunavir/ritonavir increases rosuvastatin concentrations but does not alter lipid-lowering effect in healthy volunteers

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Updated Abstract*

Background: Treatment of dyslipidemia in HIV-infected persons may be limited by drug-drug interactions between antiretroviral agents and HMG-CoA reductase inhibitors. We hypothesize that DRV/RTV increases the concentration of rosuvastatin (ROS) when co-administered.
Methods: HIV seronegative volunteers were randomized to receive ROS 10 mg/day or DRV/RTV 600/100 mg twice daily for 7 days followed by a 7 day washout then crossover to other arm for 7 days. After another 7 day washout they received all 3 medications for 7 days. At baseline we obtained fasting lipids and on Days 7, 21 and 35 fasting lipids were obtained along with pharmacokinetic (PK) samples at 0, 1, 2, 4, 8, 12 and 24 hours post-dose. Statistical analyses of the maximum concentration (C_{max}), elimination half-life and area under the curve (AUC) were done using a non-compartmental model comparing the geometric means.
Results: Twelve subjects completed all PK visits. The geometric mean AUC_{0-24} of ROS before and after administration of DRV/RTV showed a significant increase (109 vs. 161 ng*hr/mL, P=0.003), representing a 1.48 fold change. C_{max} significantly increased 2.44 fold (P<0.001) but the elimination half-life did not change (P=0.176). DRV and RTV AUC, C_{max}, and elimination half-lives did not change, respectively. The baseline median LDL-C was 108 mg/dL with no significant difference in the median change in LDL-C with ROS alone compared to ROS+DRV/RTV (-22 mg/dL vs. -19 mg/dL, P<0.001). There were no significant adverse events attributable to the drug-drug interaction.
Conclusions: Co-administration of DRV/RTV significantly increased ROS AUC and C_{max} without changing the elimination half-life. ROS did not significantly affect the PK of DRV but had minor effects on the PK of RTV. Lipid-lowering effects of ROS are not clinically significantly altered in the presence of DRV/RTV despite higher concentrations of ROS.

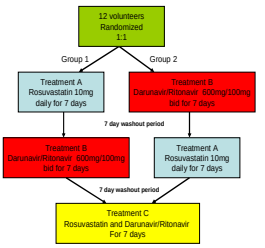
Introduction

- Dyslipidemia and atherosclerosis are important problems in persons with HIV infection.
- A mainstay of prevention for coronary atherosclerosis are HMG-CoA reductase inhibitors (Statins).
- Rosuvastatin (ROS) has been proven to lower the risk of mortality as primary and secondary prevention in persons without HIV infection (JUPITER, NEJM, 2008).
- However, complex drug-drug interactions remain a common problem with Statins and two of the major classes of antiretrovirals , non-nucleoside reverse transcriptase inhibitors and protease inhibitors (PIs).
  - Saquinavir/ritonavir increase simvastatin concentrations by 3079%.
  - Saquinavir/ritonavir decreases pravastatin concentrations by 50%.
  - Darunavir/ritonavir increases pravastatin concentrations by 81%.
  - Lopinavir/ritonavir increases ROS concentrations by 110%.

  (Fichtenbaum, AIDS, 2002; Sekar, 8th IWOCP, 2007, Abstract; Kiser, JAIDS, 2008)
- We hypothesized that DRV/RTV would increase the concentration of ROS.

Study Methods

- Inclusion of healthy, HIV seronegative volunteers.
  - Age: 18-60 years
  - Body Mass Index (BMI) < 36
- Medication doses:
  - DRV 600 mg / RTV 100 mg twice daily.
  - ROS 10 mg once daily.
- Blood drawn on days 7, 21 & 35 – Time 0, 1, 2, 4, 6, 8, 12 & 24
- Additional blood draws on days 8, 9, 22, 23, 36 and 37.
- Lipid levels were measured after a 12 hour fast at baseline, day 7, day 21, day 35 and day 45
- ROS, DRV and RTV concentrations were measured by validated LC-MS/MS.



Objectives and Statistical Analyses

- The primary objective was to determine the systemic exposure of each agent alone and in combination as measured by the area-under-the-curve (AUC), maximum concentration (C_{max}) and elimination half-life ($t_{1/2}$).
- Secondary objectives included the levels of lipids with exposure to each treatment alone and in combination and the short-term safety.
- Rosuvastatin, darunavir and ritonavir PK analysis was performed using non-compartmental analysis using WinNonlin 5.2 (Pharsight Inc.). The C_{max} and minimum concentration (C_{min}) were determined visually.
- Primary analysis of AUC, C_{max}, and C_{min} were done after log transformation. Effects were measured using appropriate paired tests reporting geometric means and 90% confidence intervals.

Study Population (N=12)

Median Age	25 years
25-75% interquartile	(23-49)
Gender	
Female	50%
Male	50%
Median BMI	27.9 kg/m^2
25-75% interquartile	(24.2-30.5)
Race/Ethnicity	
White, non-Hispanic	91.7%
Asian	8.3%

Results

Figure A – Rosuvastatin Concentrations

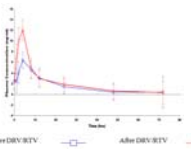


Figure B – Darunavir Concentrations

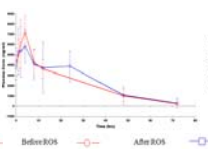


Figure C – Ritonavir Concentrations

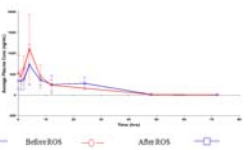


Table 1 – Geometric Means for $AUC_{0-\tau}$ (ng*hr/mL)

Parameters	Monotherapy	Combination therapy	Fold change	P value
Rosuvastatin (90% CI)	108.96 (83.85-141.60)	161.24 (124.62-208.59)	1.48 (1.04-2.10)	0.003
Darunavir (90% CI)	154910 (134648-178238)	165963 (137088-200909)	1.07 (0.85-1.34)	0.53
Ritonavir (90% CI)	8645 (6362-11746)	11140 (8970-13836)	1.29 (0.90-1.84)	0.27

Table 2 – Geometric means for C_{max} (ng/mL)

Parameters	Monotherapy	Combination therapy	Fold change	P value
Rosuvastatin (90% CI)	6.70 (5.26-8.53)	16.32 (11.78 to 22.61)	2.44 (1.65 to 3.59)	<0.001
Darunavir (90% CI)	7536 (6775-8383)	6544 (5642-7591)	0.87 (0.73 to 1.03)	0.07
Ritonavir (90% CI)	980 (690-1392)	666 (498-890)	0.68 (0.44 to 1.05)	0.06

Table 3 – Median lipids in mg/dL (25-75% interquartile ranges)

Parameter	Baseline	DRV-RTV	ROS	All Drugs
Cholesterol	202 (148-212)	192 (172-221)	151 (114-163)	159 (138-168)
HDL-C	48 (42-58)	44 (34-50)	47 (43-51)	43 (37-47)
LDL-C	108 (89-133)	115 (85-148)	85 (55-96)	80 (69-101)
Triglycerides	99 (54-181)	114 (80-230)	78 (39-118)	123 (66-175)
non-HDL-C	141 (101-161)	152 (118-172)	104 (67-115)	114 (89-124)

Table 4 – Change in values and percentages of lipids (mg/dL)

Parameter	BL → ROS	BL → DRV-RTV	BL → All drugs	BL → ROS versus BL → All Drugs†
Cholesterol	**-49 (-30%)***	11 (5%)	**-33 (-23%)***	**11 (10%)***
HDL-C	-1 (-2%)	**-8 (-20%)***	**-7 (-16%)***	**-6 (-13%)***
LDL-C	**-32 (-40%)***	2 (3%)	**-25 (-30%)***	5 (12%)
Triglycerides	-43 (-8%)	17 (14%)	8 (3%)	**54 (56%)***
non-HDL-C	**-41 (-43%)***	**19 (12%)***	**-26(-26%)***	**16 (24%)***

*P<0.05; †Paired comparisons of mean values, all other paired comparisons are median values.

Additional Pharmacokinetic Measures

- There were no significant differences between the C_{min} of darunavir or ritonavir when rosuvastatin was added (data not shown).
- There was no difference in the elimination half-life of darunavir, ritonavir or rosuvastatin when the agents were combined (data not shown).

Safety Analysis

- 17 subjects exposed to drug.
  - 3 subjects had treatment limiting AEs; 1 subject withdrew consent after day 7; and 1 subject was withdrawn for a protocol violation.
- Subjects with AEs – Drug was discontinued (n=3)
  - Each had a Grade 1 skin rash that was attributed to darunavir/ritonavir and resolved within 7 days off drug.
- Subjects with AEs – Drug was continued (n=8)
  - Grade 1 GI intolerance (n=5)
  - Grade 1 Headache (n=3)
  - Muscle weakness associated with respiratory illness and fatigue (n=1)
- No significant laboratory abnormalities.

Summary

- DRV/RTV results in a 1.48 and 2.44 fold ↑ in AUC and C_{max} for ROS, respectively.
- The elimination half-life for ROS did not change with DRV/RTV administration.
- There was no significant change in DRV or RTV concentrations with ROS use.
- There were few adverse events with co-administration of all three agents.
- The effects of ROS on certain lipid fractions (Cholesterol, HDL-C, triglycerides and non-HDL-C) were modified by the presence of DRV/RTV.

Conclusions & Implications

- ROS should be used at lower doses with caution in combination with DRV/RTV.
- The magnitude of the drug interaction effect on ROS is slightly less than previously reported for LPV/RTV (Kiser, JAIDS, 2007).
- Alterations in the beneficial lipid effects of ROS when used with DRV/RTV are mild and likely to be of minimal clinical significance.
- The mechanism of the interaction could be based upon the alteration in the transport of ROS though further studies are needed to confirm or refute this hypothesis.