

# Similar Changes in Metabolic Parameters of Darunavir and Atazanavir, Each Co-administered With Low-dose Ritonavir in Healthy Volunteers

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## Abstract

**Background:** This study evaluated the effects of once-daily darunavir (DRV; PREZISTA™) coadministered with low-dose ritonavir (DRV/r), which is the dosing being studied in antiretroviral-naïve adults and atazanavir/r (ATV/r) on metabolic parameters in HIV-negative volunteers.

**Methods:** In Session 1 (Days 1 through 7), all volunteers received ritonavir 100mg daily. In Session 2 (Days 8 through 28), either DRV/r 800/100mg daily (n=25) or ATV/r 300/100mg daily (n=24) was added. Lipids, glucose, and insulin were measured under fasting conditions. Short-term safety and tolerability were also evaluated.

**Results:** Forty-nine male subjects were enrolled; 45 subjects (DRV/r n=22, ATV/r n=23) completed the study. Four (8%) subjects discontinued: 2 on DRV/r due to adverse events (AE), one from each group withdrew consent. After 7 days on ritonavir, triglycerides increased 30mg/dL and other lipid parameters showed little change. During DRV/r or ATV/r treatment, mean lipid and glucose levels showed minimal change from Day 7, and no Grade 3 or 4 lipid or glucose elevations were reported. Mean insulin levels decreased by  $\geq 1$  mU/L for DRV/r and increased slightly for ATV/r between Days 7 and 28. Adding DRV decreased ritonavir exposure by 14%; adding ATV increased ritonavir exposure by 69%. AEs that occurred in  $\geq 2$  volunteers in either group during Session 2 included diarrhea, urticaria, jaundice, and headache.

**Conclusions:** In HIV-negative volunteers, low-dose ritonavir led to rapid increases in triglycerides. Addition of DRV or ATV to low-dose ritonavir resulted in small and comparable changes in lipid and glucose parameters. Both treatments were well-tolerated with few AEs.

## Introduction

- Darunavir (DRV [PREZISTA™]) is a protease inhibitor (PI) that has significant *in vitro* antiretroviral (ARV) activity against both wild-type virus and multidrug resistant HIV-1 strains<sup>1</sup> (Figure 1).
- DRV coadministered with low-dose ritonavir (RTV; DRV/r) has been approved in the United States, Canada, Russia, Argentina, Switzerland, Australia, and the European Union for the treatment of HIV infection in ARV treatment-experienced adult patients at a recommended dose of 600/100mg bid.
- In POWER 1 and 2, descriptive analyses showed no apparent relationship between DRV 800mg qd and lipid adverse events or disorders of glucose metabolism in treatment-experienced HIV-infected patients.<sup>2</sup>
- Once-daily (qd) dosing of DRV/r is currently being studied in ARV-naïve adults.
- DRV plasma concentrations over 24 hours are favorable after qd dosing. Integrated 24-week data from pharmacokinetic substudies of DRV/r 800/100mg qd in POWER 1 and 2 show that trough levels of DRV remain above target concentrations for both resistant and wild-type viruses (Figure 1).
- This study (TMC114-C159) evaluated the effects of once-daily DRV/r and atazanavir/r (ATV/r) on lipid and glucose metabolism in HIV-negative volunteers.

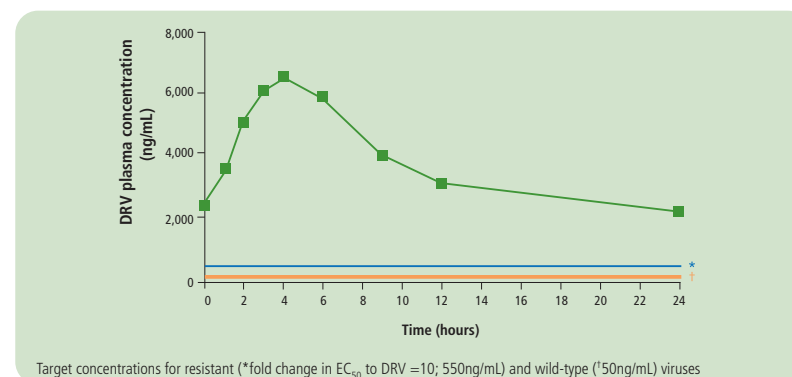


Figure 1. DRV/r 800/100mg qd: DRV plasma concentration-time profile.<sup>3</sup>

## Methods

- Forty-nine HIV-negative healthy male volunteers between 18 and 55 years were enrolled.
  - Exclusion criteria: fasting glucose  $\geq 110$ mg/dL, fasting triglycerides  $\geq 200$ mg/dL, fasting total cholesterol  $\geq 240$ mg/dL, or fasting low-density lipoprotein [LDL] 160mg/dL at baseline (Division of AIDS [DAIDS] Table for Grading the Severity of Adult and Pediatric Adverse Events).
- In Session 1 (Days 1 through 7), all volunteers received RTV 100mg qd (Figure 2).

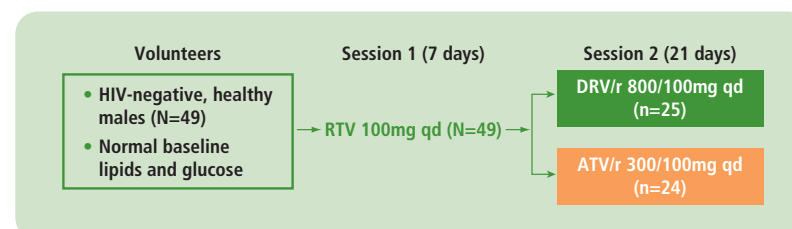


Figure 2. Study design.

- In Session 2 (Days 8 through 28), volunteers received either DRV/r 800/100mg qd or ATV/r 300/100mg qd.
- All treatments were administered within 10–15 minutes of completing a breakfast standardized for lipid, carbohydrate and protein content.
- Study duration was limited to 28 days as changes in the metabolic effects of PIs in patients and in healthy volunteers occur rapidly following initiation of treatment and continue essentially unchanged.
- The primary statistical analysis was based on change from Day 7 to Day 28 to compare lipid and glucose parameters for DRV/r versus ATV/r.
- Descriptive statistics were presented for change from baseline (Day -1) to Day 7 and from baseline (Day -1) to Day 28 to evaluate the absolute changes associated with RTV alone and subsequent treatment with DRV/r or ATV/r.
- RTV pharmacokinetics were assessed on Day 7 (after administration of RTV alone) and on Day 21 (following co-administration of DRV or ATV).

- Demographics were similar between treatment groups (Table 1).

Table 1. Demographics and patient disposition.

Demographics	DRV/r (n=25)	ATV/r (n=24)
Male, n (%)	25 (100)	24 (100)
White, n (%)	18 (72)	19 (79)
Median age, years (min; max)	25 (18; 47)	31 (18; 53)
Median weight, kg (min; max)	73 (50; 99)	73 (54; 84)
Median body mass index, kg/m <sup>2</sup> (min; max)	23 (18; 27)	22 (19; 27)
<b>Patient disposition</b>		
Completed study, n (%)	22 (88)	23 (96)
Discontinued, n (%)	3 (12)	1 (4)
Adverse event (AE), n (%)	2 (8)	0
Withdrew consent, n (%)	1 (4)	1 (4)

- Lipids (including total cholesterol, HDL, LDL, and triglycerides [TGs]), glucose and insulin levels were measured under fasting conditions.
- Safety and tolerability were evaluated.

## Results

- Forty-five subjects completed the study (DRV/r n=22; ATV/r n=23).
- Four subjects (8%) discontinued; 2 in the DRV/r group due to adverse events (AEs) and 1 from each group due to withdrawal of consent.
- Following 7 days of RTV treatment, on average, TGs increased by 30mg/dL and total cholesterol decreased by 1mg/dL (Table 2).

Table 2. Mean changes from baseline (Day -1) for lipid and glucose parameters after treatment with RTV alone and DRV/r or ATV/r.

Parameter (mg/dL)	Mean changes from baseline (mean $\pm$ SE)					
	Actual values at baseline (Day -1)		After treatment with RTV alone (Day 7)		After treatment with DRV/r or ATV/r (Day 28)	
	DRV/r	ATV/r	DRV/r	ATV/r	DRV/r	ATV/r
HDL	62.9 $\pm$ 2.5	52.3 $\pm$ 1.7	-7.3 $\pm$ 1.3	-4.9 $\pm$ 0.9	-10.3 $\pm$ 1.7	-5.4 $\pm$ 1.3
LDL	99.7 $\pm$ 4.9	118.5 $\pm$ 5.8	7.8 $\pm$ 2.6	1.2 $\pm$ 2.7	14.1 $\pm$ 3.8	5.8 $\pm$ 3.9
Total cholesterol	164.2 $\pm$ 4.7	173.8 $\pm$ 6.3	1.3 $\pm$ 3.3	-3.0 $\pm$ 3.3	7.5 $\pm$ 4.7	-2.6 $\pm$ 3.7
Triglycerides	74.5 $\pm$ 5.9	73.7 $\pm$ 6.1	31.3 $\pm$ 6.8	29.2 $\pm$ 5.9	41.1 $\pm$ 8.3	44.6 $\pm$ 7.8
Glucose	88.8 $\pm$ 1.6	89.0 $\pm$ 1.6	-5.6 $\pm$ 1.6	-5.6 $\pm$ 1.7	-7.1 $\pm$ 1.5	-8.0 $\pm$ 1.5
Insulin (mU/L)	6.3 $\pm$ 0.5	5.7 $\pm$ 0.5	0.4 $\pm$ 0.4	0.8 $\pm$ 0.5	-0.7 $\pm$ 0.4	1.1 $\pm$ 0.6

SE = standard error

- During DRV/r or ATV/r treatment, mean lipid and glucose levels showed minimal change from Day 7. No Grade 3 or 4 lipid or glucose elevations were reported during Session 2, as shown in Figure 3, and illustrated in Figure 4a–4e.

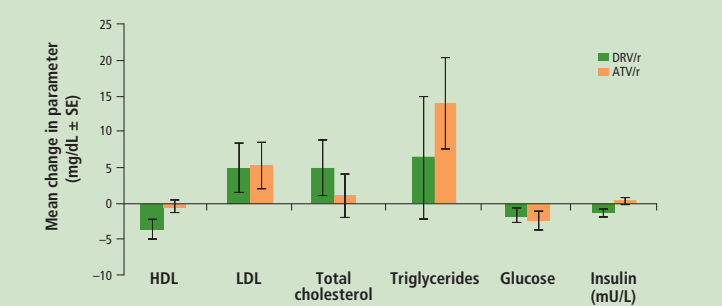


Figure 3. Mean change in lipid and glucose parameters from Day 7 to Day 28 following treatment with DRV/r or ATV/r.

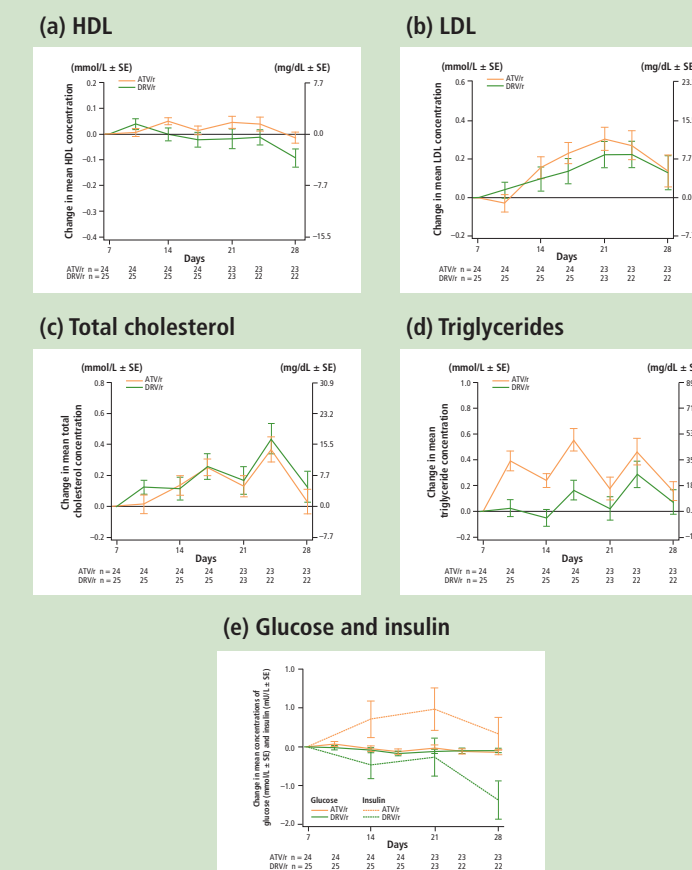


Figure 4. Mean changes over time from Day 7 to Day 28 for (a) HDL, (b) LDL, (c) total cholesterol, (d) triglycerides, and (e) glucose and insulin during treatment with DRV/r or ATV/r (Days 8–28).

- RTV pharmacokinetics:
  - Mean RTV plasma concentration–time profiles were comparable for both treatment groups during treatment with RTV alone (Figure 5).
  - Adding DRV decreased RTV exposure by 14%. Adding ATV increased RTV exposure by 69%.

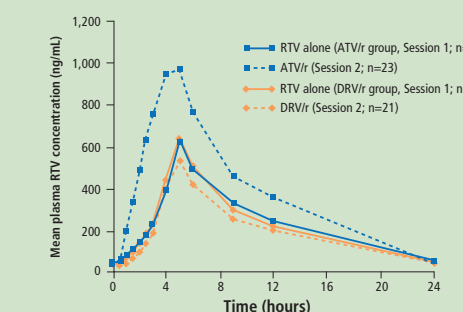


Figure 5. Mean RTV plasma concentration–time profiles over the dosing interval during treatment with RTV alone and DRV/r and ATV/r.

- Treatment with DRV/r and ATV/r was generally well tolerated.
- No serious AEs or AEs related to laboratory parameters were reported for either group.
- AEs occurring in at least 2 volunteers during Session 2 are shown in Table 3. AEs leading to discontinuation were one case each of Grade 2 and Grade 3 urticaria.

Table 3. AEs (regardless of severity or causality) reported in at least 2 volunteers during Session 2.

Volunteers, n (%)	DRV/r (n=25)	ATV/r (n=24)
Any AE	9 (36)	5 (21)
Headache	3 (12)	0
Diarrhea	1 (4)	2 (8)
Urticaria	2 (8)	0
Jaundice	0	2 (8)

## Conclusions

- In this phase I study in HIV-negative healthy volunteers:
  - The addition of DRV or ATV to RTV resulted in similarly small changes in lipid and glucose parameters.
  - No Grade 3 or 4 lipid or glucose elevations were reported during DRV/r or ATV/r treatment.
  - RTV alone resulted in rapid increases in TG.
  - Co-administration of ATV to low-dose RTV resulted in significant increases in exposure to RTV.
  - Both treatments were well tolerated with few AEs.

## References

- De Meyer S, et al. *Antimicrob Agents Chemother* 2005;49:2314–21.
- Sekar V et al. 13th Conference on Retroviruses and Opportunistic Infections; February 5–9, 2006; Denver, CO, USA. Poster J-121.
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