

Darunavir in Combination With Other Medications: Pharmacokinetic Interactions

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Introduction

- We present data on pharmacokinetic (PK) interactions between darunavir (DRV; PREZISTA™) co-administered with low-dose ritonavir (RTV; DRV/r) and other medications commonly used in HIV-infected patients
- The PK profile of DRV is well-characterized:
 - Co-administration with RTV improves PK of DRV¹ (Figure 1)
 - Intake with food increases the bioavailability of DRV versus fasted state. DRV/r should be taken with food, and the type of food does not affect systemic exposure to DRV/r.^{2,3} (Figure 2)
 - The elimination half-life (12-15 hours)⁴ in the presence of low-dose RTV supports once- and twice-daily dosing
 - DRV is primarily metabolized by the CYP3A4 pathway⁴
 - In vivo* binding of plasma proteins by DRV is greater than 95% (mostly alpha1-acid glycoprotein [AAG])⁵
 - Lack of relationships between PK/pharmacodynamic (PD) efficacy and safety has been demonstrated at the recommended dose of 600/100mg bid in treatment-experienced HIV-infected patients⁶
 - Due to lack of dose proportionality in DRV PKs and significant overlap in DRV concentrations between doses, similar results are expected for DRV/r 600/100mg bid and 800/100mg qd

Methods

- Clinical studies were conducted to evaluate the effects of co-administering DRV/r with a variety of drugs based on both *in vitro* findings and theoretical considerations for potential PK interactions
- In a series of phase I studies, DRV/r was co-administered with the following commonly used medications to assess the potential PK interactions:
 - Atazanavir (ATV), indinavir (IDV), lopinavir/r (LPV/r), saquinavir/r (SQV/r), efavirenz (EFV), nevirapine (NVP), TMC125, tenofovir (TDF), atorvastatin (AVS), omeprazole (OME), ranitidine (RAN), sildenafil (SIL), clarithromycin (CLA), sertraline (SER), paroxetine (PAR), oral contraceptives (OC) ethinyl estradiol (EE) and norethindrone (NE); methadone (R-MTD), ketoconazole (KTZ), pravastatin (PRA), and digoxin (DIG)

Results

- The interaction of DRV/r with other drugs is summarized in Table 1

Conclusions

- DRV/r can be combined with many agents without DRV/r dose adjustments
- Some co-administered agents may require dose adjustments (AVS, PRA, DIG, and maraviroc)
- Combining DRV/r with LPV/r or SQV/r is not recommended
- Drug interactions with DRV/r are well characterized and manageable

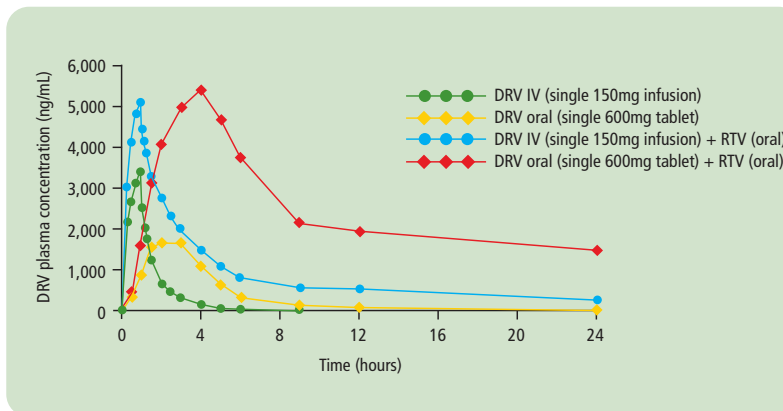


Figure 1. Mean plasma concentration-time profiles

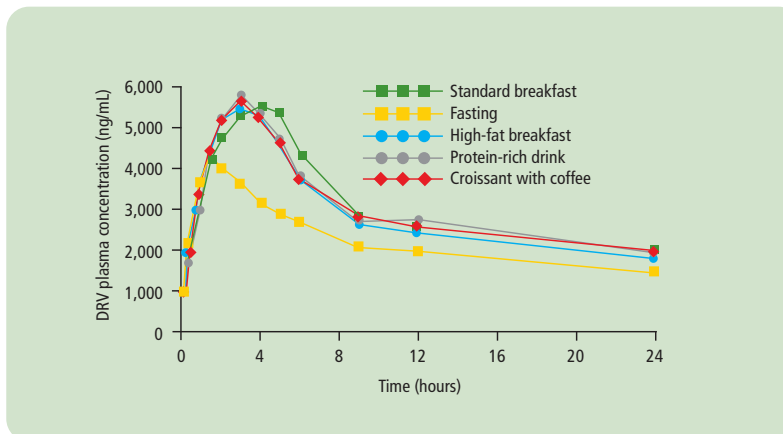


Figure 2. DRV plasma concentration follow fasting conditions and various fed states

References

- Sekar V et al. 7th International Workshop on Clinical Pharmacology of HIV Therapy; April 20-22, 2006; Lisbon, Portugal. Poster 86.
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- PREZISTA prescribing information. Available at www.tibotec.com
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- Sekar V et al. 16th International AIDS Conference; August 13-18, 2006; Toronto, Canada. Poster TUPE 0078.

Data in Table 1 were corrected on June 5, 2007.

Table 1. Interaction of DRV with other drugs

Drug	Dosage	Effect on exposure (AUC)				Dosing recommendation			Dosing recommendation summary	References
		Co-administered drug		DRV		No dose adjustment of DRV or co-administered drug	Modify dose or schedule of co-administered drug	Co-administration not recommended		
		LS mean ratio % (90% CI)	PK	LS mean ratio % (90% CI)	PK					
PIs										
ATV/r*	300/100mg bid	1.08 (0.94-1.24)	↔	1.03 (0.94-1.12)	↔	●				Sekar V et al, EAC 2005, abstract PE4.3/4
SQV/r*	1,000/100mg bid	0.94 (0.76-1.17)	↔	0.74 (0.63-0.86)	↓		●			Sekar V et al, IDSA 2006, abstract 959
LPV/r**	400/100mg bid	1.09 (0.86-1.37)	↑	0.62 (0.53-0.73)	↓		●			Sekar V et al, ICAAC 2006, abstract A-0367
IDV/r*	800/100mg bid	1.23 (1.06-1.42)	↑	1.24 (1.09-1.42)	↑	●				Sekar V et al, ISHEID 2006, abstract PP4.15
NNRTIs										
EFV ⁵	600mg qd	1.21 (1.08-1.36)	↑	0.87 (0.75-1.01)	↓	●				Sekar V et al, IWCPHIV 2007, abstract 55
NVP*#	200mg bid	1.27 (1.12-1.44)	↑	1.24 (0.97-1.57)	↑	●				Sekar V et al, IDSA 2006, abstract P956
TMC125 [†]	100mg bid	0.63 (0.54-0.73)	↓	1.06 (1.00-1.13)	↔	●				Boffito M et al, CROI 2006, abstract 675C
NRTI										
TDF ⁵	300mg qd	1.22 (1.10-1.35)	↑	1.21 (0.95-1.54)	↑	●				Hoetelmans R et al, IAC 2004, abstract TuPeB4634
Fusion inhibitor										
ENF ^{†#}	90mg bid	ND	ND	ND**	↔	●				Sekar V et al, IWCPHIV 2006, abstract P54
Entry (CCR5) inhibitor										
Maraviroc	150mg bid	4.05 (2.94-5.59)	↑	ND [§]	↔		●		Decrease maraviroc dose by 50%	Abel S et al, IWCPHIV 2007, abstract 55
Other drugs										
AVS ⁵	40mg qd (AVS alone) 10mg qd (AVS + DRV/r)	0.85 (0.76-0.97)	↑	ND	ND		●		Start with lowest dose of AVS and titrate as necessary	Hoetelmans R et al, ICAAC 2004, abstract H-865
PRA [†]	40mg SD	1.81 (1.23-2.66)	↑	ND	ND		●		When co-administration is required, start with lowest possible dose of PRA, titrate to achieve desired clinical effect, & monitor safety	Sekar V et al, IWCPHIV 2007, abstract 54
OME*	20mg qd	ND	ND	1.04 (0.96-1.13)	↔	●				Sekar V et al, IWCPHIV 2005, abstract 2.10
RAN*	150mg bid	ND	ND	0.95 (0.90-1.01)	↔	●				Sekar V et al, IWCPHIV 2005, abstract 2.10
SIL*	100mg qd (SIL alone) 25mg qd (SIL + DRV/r)	0.97 (0.86-1.09)	↑	ND	↔		●		Single dose not exceeding 25 mg SIL in 48 hours	Sekar V et al, ICAAC 2006, abstract A-0369
OC [†] (EE) (NE)	0.035mg qd 1.0mg qd	0.56 (0.50-0.63) 0.86 (0.75-0.98)	↓ ↓	ND ND	↔ ↔		● ●		Alternate/additional contraceptives recommended	Sekar V et al, ICAAC 2006, abstract A-0368
CLA*	500mg bid	1.57 (1.35-1.84)	↑	0.87 (0.75-1.01)	↔	●			No change in dosing of CLA (except for renal impairment according to the package insert for Biaxin)	Sekar V et al, ASCPT 2006, abstract PI-61
SER*	50mg qd	0.51 (0.46-0.58)	↓	0.98 (0.84-1.14)	↔	●			No change in dosing. Clinical monitoring and dose titration of SER is recommended	Sekar V et al, ICDTHIV 2006, abstract P295
PAR*	20mg qd	0.61 (0.56-0.66)	↓	1.02 (0.95-1.10)	↔	●			No change in dosing. Clinical monitoring and dose titration of PAR is recommended	Sekar V et al, ICDTHIV 2006, abstract P295
KTZ*	200mg bid	3.12 (2.65-3.68)	↑	1.42 (1.23-1.65)	↑		●		No change in dosing (maximum dose KTZ 200mg qd)	Sekar V et al, IDSA 2006, abstract P960
R-MTD [†]	55-200mg qd	0.84 (0.78-0.91)	↓	ND	ND	●			No prior methadone dose adjustment needed, however, patients should be monitored for opiate abstinence syndrome	Sekar V et al, ICDTHIV 2006, abstract P294
DIG [†]	0.4mg qd	1.77 (0.90-3.50)	↑	ND	ND		●		When co-administration is required, start with lowest possible dose, titrate to achieve desired clinical effect, & monitor digoxin concentrations	Sekar V et al, ASCPT 2007, abstract PII-104

ND = no data available; SD = single dose; LS mean ratio = least squares mean ratio; % increase/decrease in exposure may be calculated from LS mean ratio; ie, LS mean ratio of 1.81 is equivalent to 81% increase in exposure; ENF (enfuvirtide; T-20): sparse blood sampling (1-2) samples at each time point; **DRV PK in the presence of ENF compared to without ENF are found to be not different; DRV/r dose (*400/100mg bid, *600/100mg bid, *1200/100mg bid, *300/100mg bid); †maraviroc data includes 1 patient with extremely low maraviroc concentrations; ‡although no statistical analysis was performed, DRV PK was measured and compared to historical data and was found to be similar—there was no apparent effect of maraviroc on DRV PK; §study conducted with HIV-infected subjects; reference definitions: ASCPT = Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics; CROI = Conference on Retroviruses and Other Infections; EAC = European AIDS Conference; IAC = International AIDS Conference; ICAAC = Interscience Conference on Antimicrobial Agents and Chemotherapy; ICDTHIV = International Congress on Drug Therapy in HIV Infection; IDSA = Infectious Diseases Society of America Conference; ISHEID = International Symposium on HIV and Emerging Disease; IWCPHIV = International Workshop on Clinical Pharmacology of HIV Therapy

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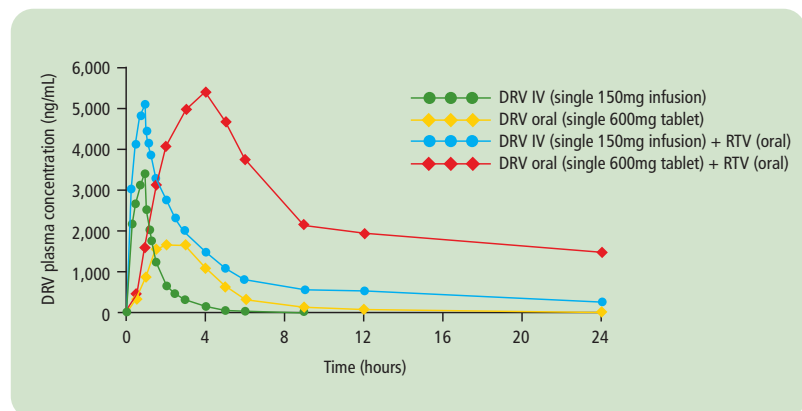


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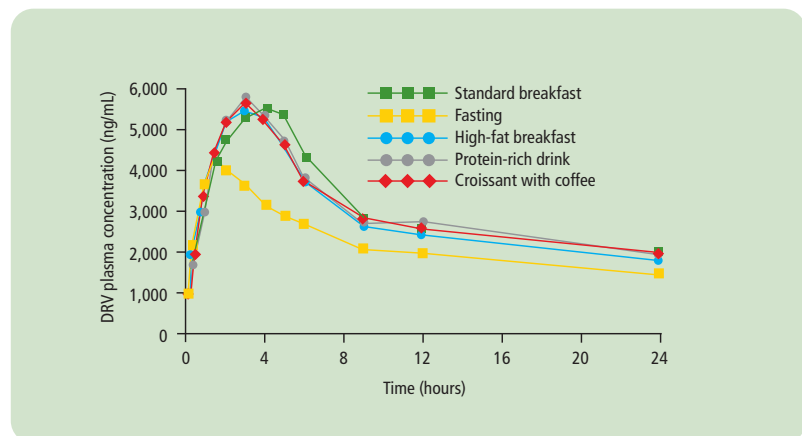


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	●		Sekar V et al, ICAAC 2006, abstract A-0367
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●		Start with lowest dose of AVS and titrate as necessary	Hoetelmans R et al, ICAAC 2004, abstract H-865
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		No change in dosing of CLA (except for renal impairment according to the package insert for Biaxin)	Sekar V et al, ASCPT 2006, abstract PI-61
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●		When co-administration is required, start with lowest possible dose, titrate to achieve desired clinical effect, & monitor digoxin concentrations	Sekar V et al, ASCPT 2007, abstract PII-104

1 is equivalent to 81% increase in exposure; ENF (enfuvirtide; T-20): sparse blood sampling (1-2) samples at each time point; **DRV PK in the presence of ENF compared to without ENF are found to be not different; statistical analysis was performed, DRV PK was measured and compared to historical data and was found to be similar—there was no apparent effect of maraviroc on DRV PK; #study conducted with HIV-infected subjects; European AIDS Conference; IAC = International AIDS Conference; ICAAC = Interscience Conference on Antimicrobial Agents and Chemotherapy; ICDTHIV = International Congress on Drug Therapy in HIV Infection; ology of HIV Therapy