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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 the PK of DRV[1] (**Figure 1**)
  - Intake with food increases the bioavailability of DRV compared to the fasted state. DRV/r should be taken with food, however, the type of food does not affect systemic exposure to DRV/r[2,3] (**Figure 2**)
  - DRV 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 pathway.[4] Net effect of DRV/r is CYP3A inhibition
  - *In vivo* binding of plasma proteins by DRV is greater than 95% (mostly alpha1-acid glycoprotein [AAG])[5]
  - No relationship between PK/pharmacodynamics and efficacy or safety has been seen at the recommended dose of 600/100mg bid in treatment-experienced HIV-infected patients[6]
  - Due to lack of dose proportionality in DRV PK 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), etravirine (TMC125), enfuvirtide (ENF), tenofovir (TDF), didanosine (ddI), TMC278, atorvastatin (AVS), omeprazole (OME), ranitidine (RAN), sildenafil (SIL), clarithromycin (CLA), sertraline (SER), paroxetine (PAR), ethinyl estradiol (EE), and norethindrone (NE); methadone (*R*-MTD), ketoconazole (KTZ), pravastatin (PRA), and digoxin (DIG)
  - Maraviroc and elvitegravir (EVG) PK-interaction studies were conducted by Abel et al[7] and Mathias et al[8], respectively
  - Effect on exposure (AUC) is presented as the least squares mean ratio

Results

- The interactions between DRV/r and other drugs are summarized in **Table 1**

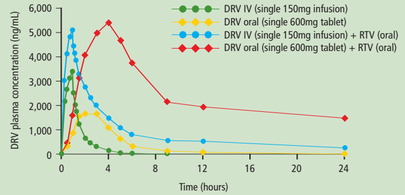

Figure 1. Mean DRV plasma concentration-time profiles

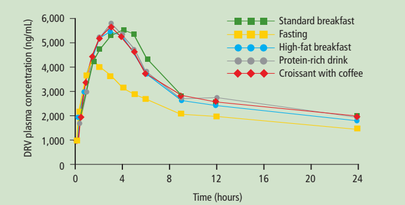

Figure 2. DRV plasma concentration follow fasting conditions and various fed states

Conclusions

- Drug interactions with DRV/r are well characterized and manageable
- DRV/r can be combined with many agents with no DRV/r dose adjustments
- Atorvastatin, pravastatin, sildenafil, digoxin, and maraviroc may require dose adjustments
- Combining DRV/r with LPV/r or SQV/r is not recommended
- Additional contraception should be used when oral contraceptives are combined with DRV/r

Table 1. Interaction of DRV with other drugs

Drug		Effect on exposure (AUC)				Dosing recommendation				
		Co-administered drug		DRV						
Drug*	Dosage	LS mean ratio % (90% CI)	PK	LS mean ratio % (90% CI)	PK	No dose adjustment of DRV or co-administered drug	Modify dose or schedule of co-administered drug	Co-administration not recommended	Dosing recommendation summary	References
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‖	600mg qd	1.21 (1.08-1.36)	↑	0.87 (0.75-1.01)	↓	●				Sekar V et al, Antivir Ther 2007;12:509–514
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
TMC278††	150mg qd	2.30 (1.98-2.67)	↑	0.89 (0.81-0.99)	↓	●			Effect of DRV/r on TMC278 PK at 75mg qd is not expected to be clinically significant	van Heeswijk R et al. ICAAC 2007, abstract H1042
NRTIs										
TDF‖	300mg qd	1.22 (1.10-1.35)	↑	1.21 (0.95-1.54)	↑	●				Hoetelmans R et al, IAC 2004, abstract TUPEB4634
ddI§	400mg qd	0.91 (0.75-1.10)	↓	1.01 (0.95-1.07)	↔	●				Sekar V et al, IAS 2007, abstract WEPEB012
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 standard dose by 50%	Abel S et al, IWCPHIV 2007, abstract 55
Integrase inhibitor										
EVG/r§	125/100mg qd	1.10 (0.99-1.12)	↑	0.89 (0.82-0.96)	↔	●				Mathias A et al, IAS 2007, abstract TUPDB03
Other drugs										
AVS‖	40mg qd (AVS alone) 10mg qd (AVS + DRV/r)	0.85 (0.76-0.97)	↑	ND	ND		●		When co-administration is required, start with the lowest possible dose of AVS with careful monitoring. A gradual dose increase of AVS may be considered based on clinical response	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, and 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 25mg 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 contraceptive measures 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 is recommended and dose titration of SER may be required	Sekar V et al, HIV8 2006, abstract P295
PAR†	20mg qd	0.61 (0.56-0.66)	↓	1.02 (0.95-1.10)	↔	●			No change in dosing. Clinical monitoring is recommended and dose titration of PAR may be required	Sekar V et al, HIV8 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. An increase in methadone dosage may be considered based on the clinical response	Sekar V et al, HIV8 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, and monitor digoxin concentrations	Sekar V et al, ASCPT 2007, abstract PII-104

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; ND = no data available; SD = single dose; ENF (enfuvirtide; T-20): sparse blood sampling (1-2) samples at each time point; *study participants were healthy volunteers except for the drug interaction studies with LPV/r, NVP, and ENF, which were conducted in HIV-infected subjects; †not recommended based on 40% reduction in C_{min} levels for DRV; ‡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, **800/100mg qd); ††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; 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; HIV8 = International Congress on Drug Therapy in HIV Infection; IAC = International AIDS Conference; IAS = International AIDS Society; ICAAC = Interscience Conference on Antimicrobial Agents and Chemotherapy; 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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Data in the poster body have been updated since the abstract was originally submitted.

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This poster is available on-line at www.tibotec.com.