Pharmacokinetics of reduced dose darunavir/ritonavir

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Background

- Darunavir/ritonavir (DRV/r) is an essential HIV drug for salvage regimen but it is expensive in resource limited settings (RLS).
- There is extensive evidence that Asians have higher protease inhibitor plasma concentrations than Caucasians while taking the same dose.[1-5]
- It is currently unknown whether this is also true for DRV/r in Asian population.
- We therefore evaluated the pharmacokinetic (PK) profiles of reduced dosed DRV/r in well-suppressed HIV-1-infected Thai adults.

Materials & Methods

- Thai HIV-1 infected adults aged > 18 years with HIV RNA < 50 copies/mL who were on DRV/r 600/100 mg twice daily (BID) as a part of their second line or salvage regimens for > 4 weeks underwent 12-hour PK
- PK sampling before, and at 1, 2 ,4, 6, 8, 10 and 12 hours post dosing.
- After 12-hour PK, DRV/r dose was reduced to DRV/r 600/100 mg once daily (QD) dose for another 4 weeks and then 24-hour PK was performed.
- Plasma concentrations were measured by validated HPLC method.
- PK parameters were calculated using WinNonlin software.
- Statistical analysis was carried out using Stata version 10. To accommodate both within-patient and between-patient variability, a repeated-measures generalized estimating equation/random effects model was used for comparing the PK parameters of the two dose groups.

Results

- Baseline characteristic of patients is shown in table 1
- Twenty-one subjects were enrolled (67% male) with a median age of 40 years and median body weight (BW) and BMI of 58.1 kg and 21.5 kg/m^2, respectively.
- The median duration of DRV/r use was 2 (IQR 1.9-2.1) years.
- All subjects took tenofovir disoproxil fumarate (TDF) plus either lamivudine or zidovudine as a backbone.
- All previously failed NNRTI/NRTI; 1 patient had PI failure but none of them had DRV mutation

Table 1: Baseline characteristics

Gender Male: Female	14:7
Median (IQR) age (years)	40 (37-44)
Median (IQR) Body weight (kg.)	58.1 (53.5-61)
Median (IQR) height (cm)	162 (157-172)
Median (IQR) BMI (kg/m^2)	21.5 (19.8-23.5)
Median (IQR) CD4 cell count (cell/mm^3)	339 (288-535)
n(%) of patients with HIV RNA < 50 copies/mL	21(100)
Median (IQR) SGPT (U/L)	27(18-40)
Median (IQR) serum creatinine(mg/dl)	0.9 (0.8-0.9)

- The PK data is shown in table 2, figure 1 and figure 2
- Mean (SD) values for DRV/r 600/100 mg BID were 46.9 (29.8) h.mg/L for AUC_{0-12}, 6.8 (1.3) mg/L for C_{max} and 2.2 (1.0) mg/L for C_{trough}. For DRV/r 600/100 mg QD mean (SD) AUC_{0-24}, C_{max}, C_{trough} were 62.49 (19.4) h.mg/L, 7.2 (2.1) mg/L and 0.9 (0.5) mg/L, respectively.
- AUC, C_{trough} and C_{min} were statistically significant between 2 doses. However, C_{max} was comparable.
- None of the subjects on 600/100mg BID vs. 4 subjects (19%) on 600/100mg QD had C_{trough} values below the protein-binding adjusted IC50 of PI-resistant virus (0.55 mg/L) for PI resistance

Table 2. Geometric mean (% coefficient of variation (%CV)) for pharmacokinetic parameter for darunavir and ritonavir

Pharmacokinetic parameter	Drug DRV/RTV (600/100) BID (N=21)	DRV/RTV (600/100) QD (N=21)	P-Value
Darunavir			
AUC_{0-24} (mg.h/L)	94.03 (1.42)	59.55 (2.31)	<0.01
C_{max} (mg/L)	6.72 (18.03)	6.90 (19.40)	0.75
C_{min} (mg/L)	1.87 (86.43)	0.61 (36.56)	<0.01
C_{trough} (mg/L)	1.94 (83.64)	0.82 (22.86)	<0.01
T_{max} (h)*	2 (2-4)	2 (2-4)	0.71
Half life (h)	6.06 (25.63)	10.56 (15.37)	<0.01
CL/F (L/h)	12.76 (10.47)	10.08 (13.67)	0.02
Ritonavir			
AUC (mg.h/L)	11.29 (12.73)	4.62 (34.33)	<0.01
C_{max} (mg/L)	0.83 (20.48)	0.52 (35.24)	0.01
C_{min} (mg/L)	0.19 (75.95)	0.04(55.67)	<0.01
C_{trough} (mg/L)	0.21 (69.90)	0.05(87.8)	<0.01
T_{max} (h)*	2 (1-4)	4 (1-6)	0.45
Half life (h)	4.31 (38.98)	6.51 (21.94)	0.01
CL/F (L/h)	17.72 (8.11)	21.65 (7.33)	0.13

*Median (IQR)

- In multivariate analysis, there was statistically non significant association of age, sex, BW, and RTV concentrations on AUC, C_{max}, and C_{trough} of DRV/r.
- Table 3: Compared to Caucasian study data (n=14 for DRV/r 600/100 BID[6] and n=7 for DRV/r 800/100 QD)[7], the PK profiles of our subjects were comparable to those data.
- All subjects had HIV RNA <50 copies/mL at 1 months after low dose DRV/r and no any grade II-IV AEs reported.

Figure 1 Median darunavir and ritonavir concentration-time curves, with bar indicating interquartile range (IQR)

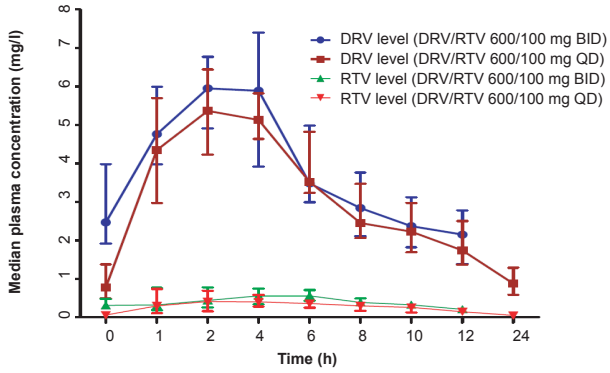

Figure 2 Individual Darunavir C_{trough} concentration between Darunavir/ritonavir 600/100 mg BID and darunavir/ritonavir 600/100 mg QD

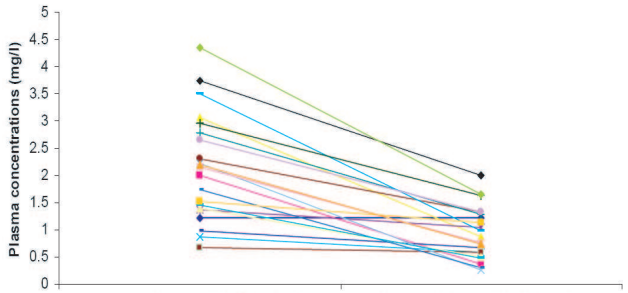

Table 3. Comparison the pharmacokinetic parameter for darunavir (mean (SD)) in patients receiving different dose of darunavir/ritonavir (DRV/r) between Thai and non-Thai

pharmacokinetic parameter	DRV/r 600/100 mg BID Thai (N=21)	DRV/r 600/100 mg BID non-Thai[6] (N=14)	P-value	DRV/r 600/100 mg QD Thai (N=21)	DRV/r 800/100 mg QD non-Thai[7] (N=7)	P-value
AUC (mg.h/L)	98.1 (29.8)	42.98 (12.67) for AUC $_{0-12hr}$ 85.96 for AUC $_{0-24hr}$	0.16	62.49 (19.4)	61.11(22.5)	0.85
C_{max} (mg/L)	6.8 (1.3)	5.6 (1.1)	0.01	7.2 (2.1)	5.26 (1.58)	0.01
C_{min} (mg/L)	2.1 (0.98)	2.25 (8.34)	0.94	0.8 (0.5)	1.07 (3.61)	0.74
C_{trough} (mg/L)	2.2 (1.0)	2.26 (1.35	0.88	0.9 (0.5)		-
T_{max} (h)	2.4 (1.2)	4.0 (1.5-6.0)	0.01	2.7 (1.5)		-
$T_{1/2}$ (h)	6.7 (3.7)		-	11.9 (7.3)	14.4 (5.17)	0.28
CL/F (L/h)	13.2 (3.7)		-	10.6 (3.7)		-

Conclusions

Thai HIV-infected adult who were on standard DRV dosing with 100mg ritonavir boosting had adequate DRV AUC_{0-12}, C_{max} and C_{trough}. Furthermore, the PK of DRV/r 600/100 mg QD from our subjects seem to be similar to those Caucasian on DRV/r 800/100 QD. The regimen was well tolerated. Our data suggest that Asian adults may have slightly higher DRV concentrations for once daily dose.

References

1. Ananworanich J, et al. Antivir Ther 2005;10(6):761-7.
2. Avihingsanon A, et al. Clin Pharmacol Ther 2009;85(4):402-8.
3. Boyd MA, et al. HIV Med 2005;6:410-20.
4. van der Lugt J, et al. Antivir Ther 2009;14(7):1001-4.
5. van der Lugt J, et al. AIDS 2009;23(9):1176-9.
6. DeJesus E, et al. Antivir Ther. 2010;15(5):711-20.
7. Boffito M, et al. HIV Clin Trials. 2008 Nov-Dec;9(6):418-27.

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