5th International Workshop on Clinical Pharmacology of HIV Therapy – Rome 2004

Posters – L. Akagi

RTV Daily + SQV BID

- Can Ritonavir Once Daily Boost Saquinavir Twice Daily?
- A Pilot Study

- A Luber[1], D Anderson[1] R Stryker[1], A Hill[2], C Peloquin[3], M Boffito[4], P Ruane[1]
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Objective

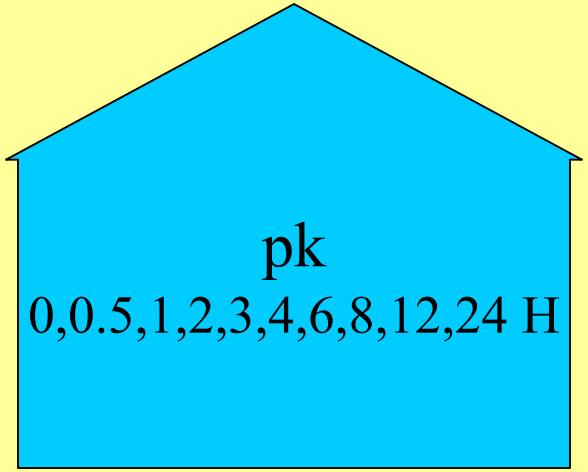
- Evaluate effects on RTV on SQV (hgc) pharmacokinetics, 12 hours after RTV dosing

Methods

- 1 site, ‘proof-of-concept PK study
- Eligibility:
  - HIV positive
  - Trt naïve/STI > 6 months
  - CD4 > 200 cells/mm^3
  - No concomitant medications contraindicated with RTV
  - Normal renal, hepatic, hematological function

PK Sampling

SQV 1600 mg/RTV 100 mg OD
Days 1- 14



PK Sampling cont.

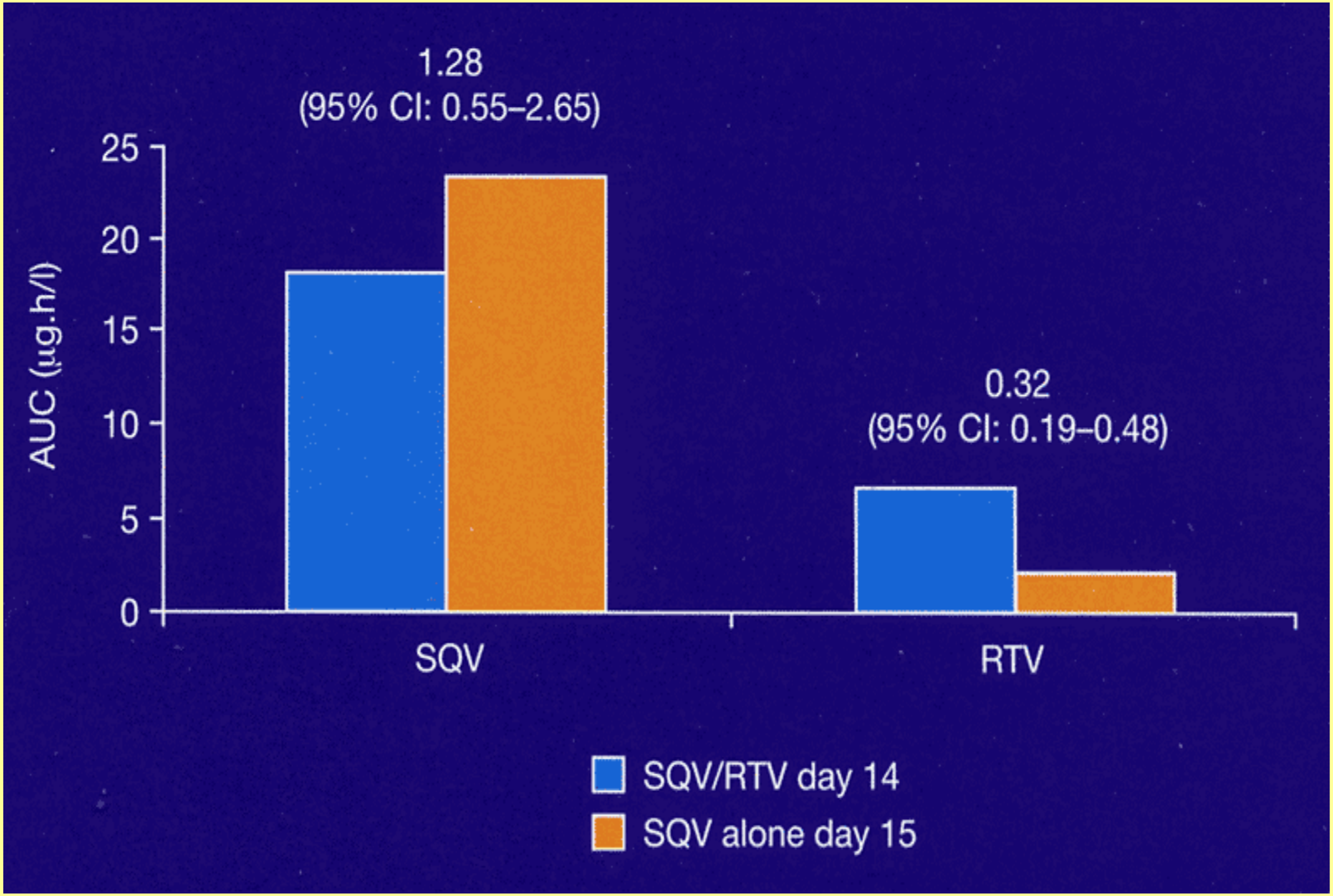
DAY 15
SQV 1600 mg/RTV 100 mg OD SQV 1600 mg OD
0 4 8 12 16 20 24

pk
PM dose: 0,0.5,1,2,3,4,6,8,12

Results

N = 6 male pts; none with AIDS diagnosis

- 3 = Trt naïve
- 3 = STI (2-6 yr)
- Age (med) = 35 yr (28-44)
- CD4 (med) = 498 (456-605) cells/mm3
- pVL (med) = 30,596 (297-422,424) c/mL


1.28
(95% CI: 0.55–2.65)
0.32
(95% CI: 0.19–0.48)
AUC (µg.h/l)
25
20
15
10
5
0
SQV
RTV
SQV/RTV day 14
SQV alone day 15

Discussion

- Suggests that RTV can boost a 2nd dose of SQV 12 post RTV dose
- Limitations:
  - Small number of subjects studied
  - 2nd SQV dose not at ss
  - Food intake not controlled

  F/U pk of 20 pts underway to confirm findings

Conclusion

- Small pilot study SQV exposures maintained 12-24 hours post RTV dosing
- Validation of results in a larger study may allow for RTV to be dosed less frequently and/or at a lower total daily dose (ie reduced pill count, toxicity, cost)

Effect of CYP3A4 Inhibitors on the Pharmacokinetics of CCR5 Antagonist UK-427,857 in Healthy Volunteers

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Objective

- Investigate the effect of CYP3A4 inhibitors ketoconazole and saquinavir (Fortovase®) on the ss pharmacokinetics of UK-427,857

Methodology

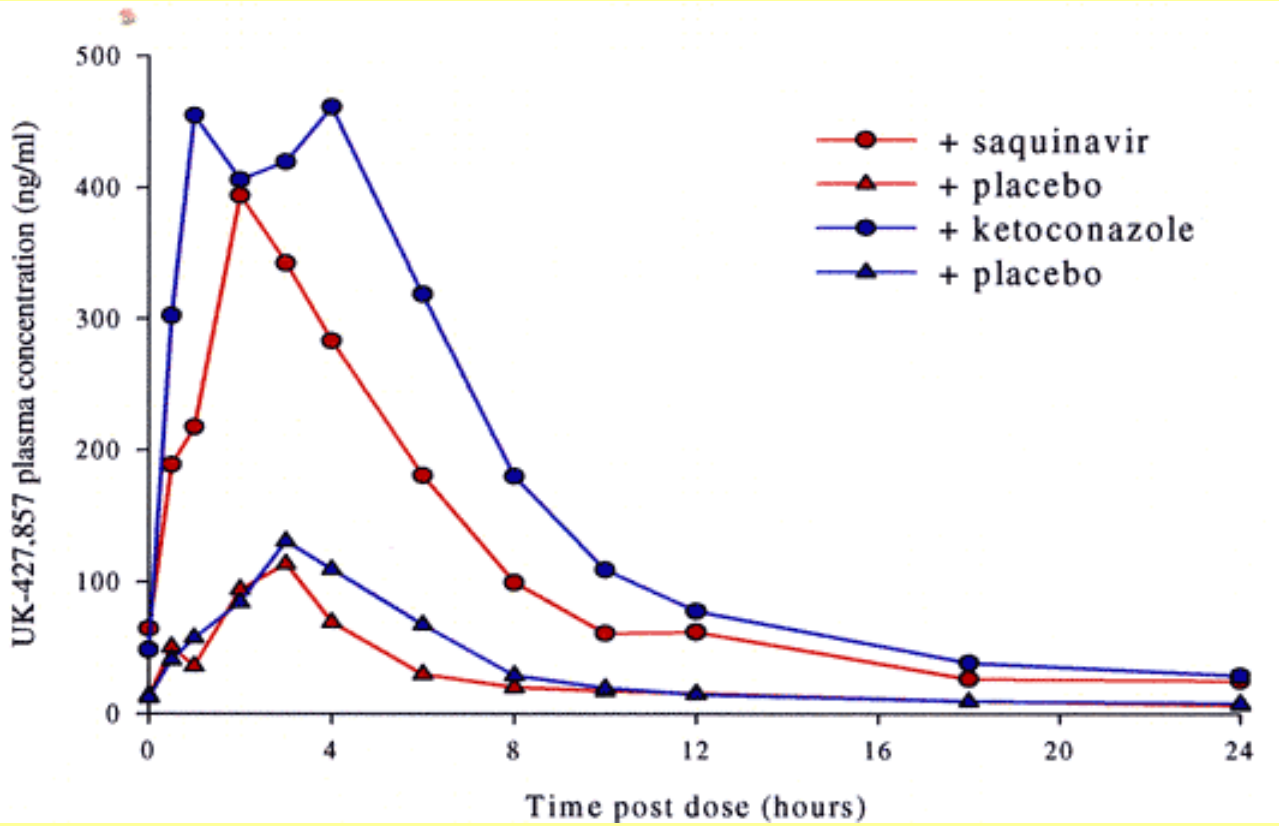
- Open, placebo-controlled, randomized study
- 2 cohorts of 12 healthy male volunteers aged 18-43 yr

Methodology cont.

- Day 1-7 of both study periods, all subjects received 100 mg BID UK-427,857.
- Cohort 1 also received SQV 1200 mg/placebo TID on days 1-9
- Cohort 2 also received ketoconazole 400 mg/placebo QD on days 1-9

Results

Treatment	AUC_{tau} (ng.h/ml)	C_{max} (ng/mL)	T_{max} (h)	$t_{1/2}$ (h)
UK-427,857 + saquinavir	2068	434	2.6	15.7
UK-427,857 + placebo	487	131	2.4	16.1
UK-427,857 + ketoconazole	3096	524	2.9	14.2
UK-427,857 + placebo	619	155	3.3	17


500
400
300
200
100
0
UK-427,857 plasma concentration (ng/ml)
0
4
8
12
16
20
24
Time post dose (hours)
+ saquinavir
+ placebo
+ ketoconazole
+ placebo

Conclusions

- Co-administration of UK-427,857 with ketoconazole and saquinavir resulted in similar increases in Cmax
- Co-administration of UK-427,857 with ketoconazole resulted in a slightly higher increase in AUC_{tau} vs saquinavir

Saquinavir Hard Gel (SQV-HG)/Ritonavir (RTV) Pharmacokinetics (PK): Effect of High Fat Meals, Plasma Concentration, Diurnal Variation and Intrapatient Variability

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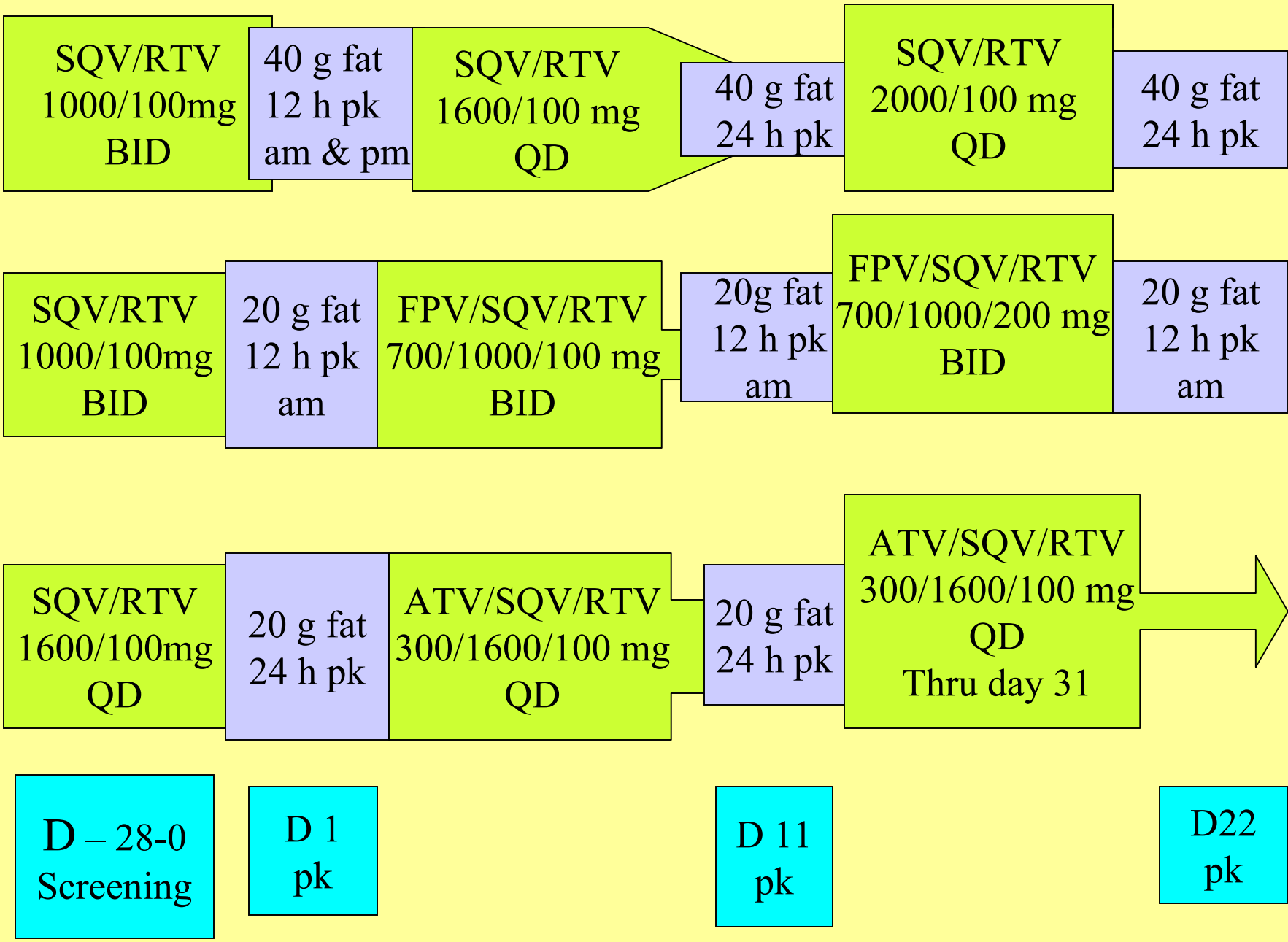
Objective

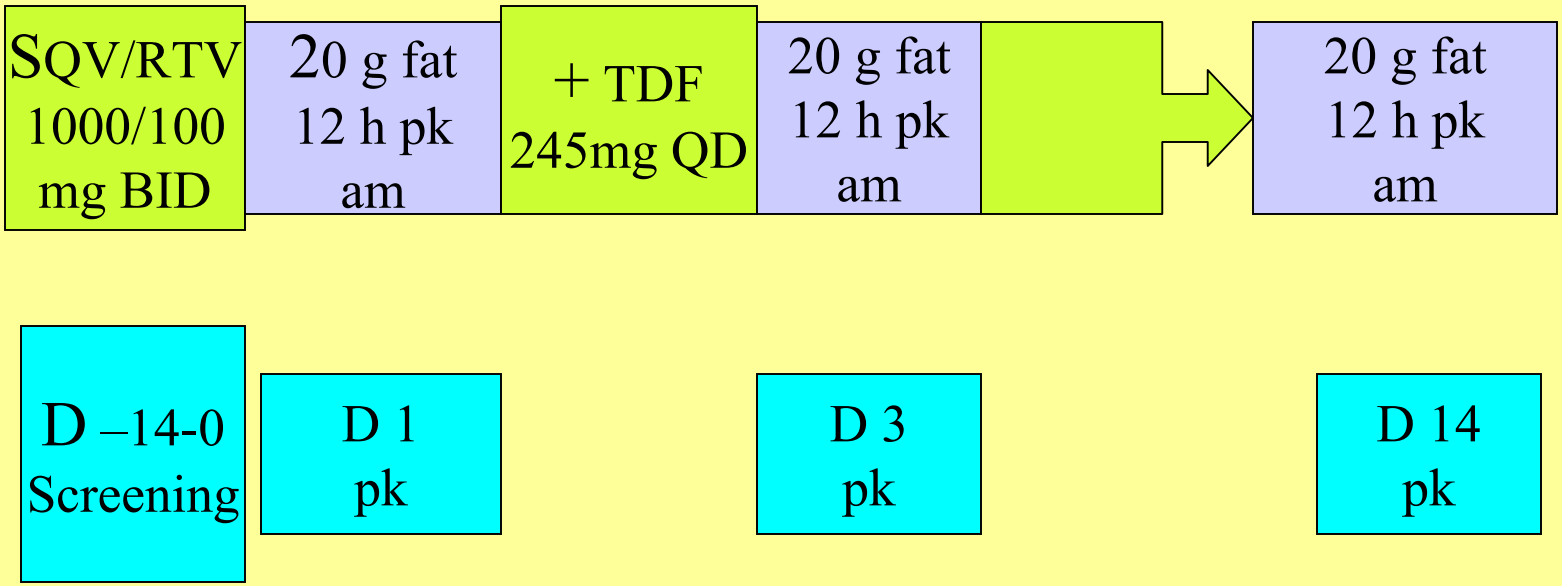
Assess intrapatient variability and diurnal variations on pk parameters for SQV-hg/RTV 1000/100 mg bid

Assess the effect of high-fat (40g) or low-fat (20g) meal on pk parameters for 1000mg/100 mg bid and 1600mg/100 mg qd administration

Methods

- Pk data from 4 different studies
- Study 1 recruited 18 patients
- Study 2 recruited 10 patients from study 1
- Study 3 recruited 8 patients from study 1
- Study 4 recruited 16 patients


SQV/RTV 1000/100mg BID
40 g fat 12 h pk am & pm
SQV/RTV 1600/100 mg QD
40 g fat 24 h pk
SQV/RTV 2000/100 mg QD
40 g fat 24 h pk
SQV/RTV 1000/100mg BID
20 g fat 12 h pk am
FPV/SQV/RTV 700/1000/100 mg BID
20g fat 12 h pk am
FPV/SQV/RTV 700/1000/200 mg BID
20 g fat 12 h pk am
SQV/RTV 1600/100mg QD
20 g fat 24 h pk
ATV/SQV/RTV 300/1600/100 mg QD
20 g fat 24 h pk
ATV/SQV/RTV 300/1600/100 mg QD Thru day 31
D – 28-0 Screening
D 1 pk
D 11 pk
D22 pk


SQV/RTV 1000/100 mg BID
20 g fat 12 h pk am
+ TDF 245mg QD
20 g fat 12 h pk am
20 g fat 12 h pk am
D –14-0 Screening
D 1 pk
D 3 pk
D 14 pk

Effect of SQV-hg/RTV Administration Following a High fat (40g) or low fat (20g) Standard Meal

			GMR (40g/20g)
SQV-hg/RTV 1000/100mg BID (n=10)	SQV	$AUC_{0\text{-}12}$ (ng.h.ml)	0.63 (0.37-1.19)
		C_{max} (ng/ml)	0.59 (0.37-1.06)
		C_{trough}(ng/ml)	0.53 (0.24-1.26)
	RTV	$AUC_{0\text{-}12}$ (ng.h.ml)	0.89 (0.64-1.42)
SQV-hg/RTV 1600/100 mg QD (n=8)	SQV	$AUC_{0\text{-}24}$ (ng.h.ml)	1.18 (0.71-1.89)
		C_{max} (ng/ml)	1.14 ((0.75-1.75)
		C_{trough} (ng/ml)	1.11 (0.49-2.38)
	RTV	$AUC_{0\text{-}24}$ (ng.h.ml)	1.26 (0.69-2.15)

Dirunal Variation in SQV-hg/RTV PK

		GMR Night/Day
SQV	$AUC_{0\text{-}12h}$	0.97 (0.80-1.43)
	Cmax (ng/ml)	0.88 (0.71-1.42)
	Ctrough (ng/ml)	**2.25 (1.39-4.50)**
RTV	$AUC_{0\text{-}12h}$	0.89 (0.78-1.15)
	Cmax (ng/ml)	0.83 (0.70-1.22)
	Ctrough (ng/ml)	**1.66 (1.40-2.38)**

Intrapatient Variability in SQV-hg/RTV pk

	SQV			RTV		
	$AUC_{0\text{-}12h}$	C_{max}	C_{trough}	$AUC_{0\text{-}12h}$	C_{max}	C_{trough}
Median %CV (range)	33 (9-57)	23 (10-53)	40 (3-94)	22 (9-42)	22 (10-41)	30 (7-57)

Discussion

- NS diff AUC,C_{max}, C_{trough} for SQV or RTV with SQV-hg/RTV 1000/100 mg or 1600/100 mg post std meal with 20 or 40 g fat
- SQV and RTV C_{trough} increased approximately 2 x (pm dose of SQV-hg/RTV 1000/100 mg BID vs am dose)
- High intrapatient variability for SQV and RTV (SQV-hg/RTV 1000/100 mg bid)

Conclusions

- SQV-hg/RTV exposure not affected by amt of fat in a meal
- Significant diurnal variation in C_{trough} and wide intrapatient variability in C_{max}, AUC, and C_{trough} observed with SQV-hg/RTV 1000/100 mg BID

Atazanavir (ATV) pharmacokinetics when combined with amprenavir (APV) in highly experienced HIV-positive patients

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Introduction

Data on ATV PK plasma levels collected on healthy volunteers shows Cmin values ranging from 149 to 219 ng/mL; Cmax ranging from 2918 to 5867 ng/mL, and AUC ranging from 18590-33500 ng.h/mL

Atazanavir (ATV) in combination with Amprenavir (APV) has a virological additive effect and may be a suitable double PI-RTV sparing regimen, but no data on ATV plasma levels are available with this combination

The aim of this study was to examine the pharmacokinetics of ATV when given in combination with APV in heavily pre treated HIV-positive patients.

Methods

HIV-positive patients included in the Atazanavir Expanded Access Program (AI424900) were evaluated as out-patients at the Clinic of Infectious Diseases, San Raffaele Hospital, Milan, Italy.

All the patients received an NRTI backbone, excluding any NNRTIs or other drugs potentially capable of interfering with the cytochrome P450 enzymatic system.

Serial blood samples for steady-state atazanavir analyses were collected after two or more week of treatment as follows: before the morning administration and then 1, 2, 3, 6, 8 and 24 h post-dosing.

C_{trough} values were collected at different time points and were analysed to evaluate intrapatient variability.

Plasma ATV concentrations were measured using a validated HPLC method with UV detection. A liquid-liquid extraction was performed from alcaline plasma. The LOQ was 20 ng/ml.

The ATV concentration-time data were analysed using a non-compartmental technique (P-Pharm Computer program).

Results

- Thirty-two subjects were included in this study, 22 male and 10 female, median age (range) 41 (35-57)
- Baseline median (range) CD4 cell count was 258 (29-918), baseline median (range) plasma HIV-RNA level was 4,6 (1,7-6 $\log_{10}$)
- Twelve heavily pre treated HIV-positive patients on treatment failure received ATV 400 mg q.d in combination with APV 600 mg b.i.d (six patients) or 1200 mg q.d (six patients), nine of whom were treated concomitantly with TDF; 20 patients received ATV as a single PI (12 in combination with TDF).
- To date, full PK ATV parameters were obtained in the 19 patients, 12 receiving ATV+APV and seven receiving ATV as single PI. Data are shown in Table 1-2 and Figure 1.
- To date, ATV trough levels were evaluated in the 32 patients included in this study. Data are shown in Table 3.
- Table 4 shows the intra-patient variability of ATV C_{trough} evaluated in 19 patients with a repeated trough ATV plasma level.

Figure 1: PK of ATV in patients treated with ATV+APV+TDF (9 pts), ATV+APV (3 pts), ATV+TDF (5 pts), ATV (2 pts)

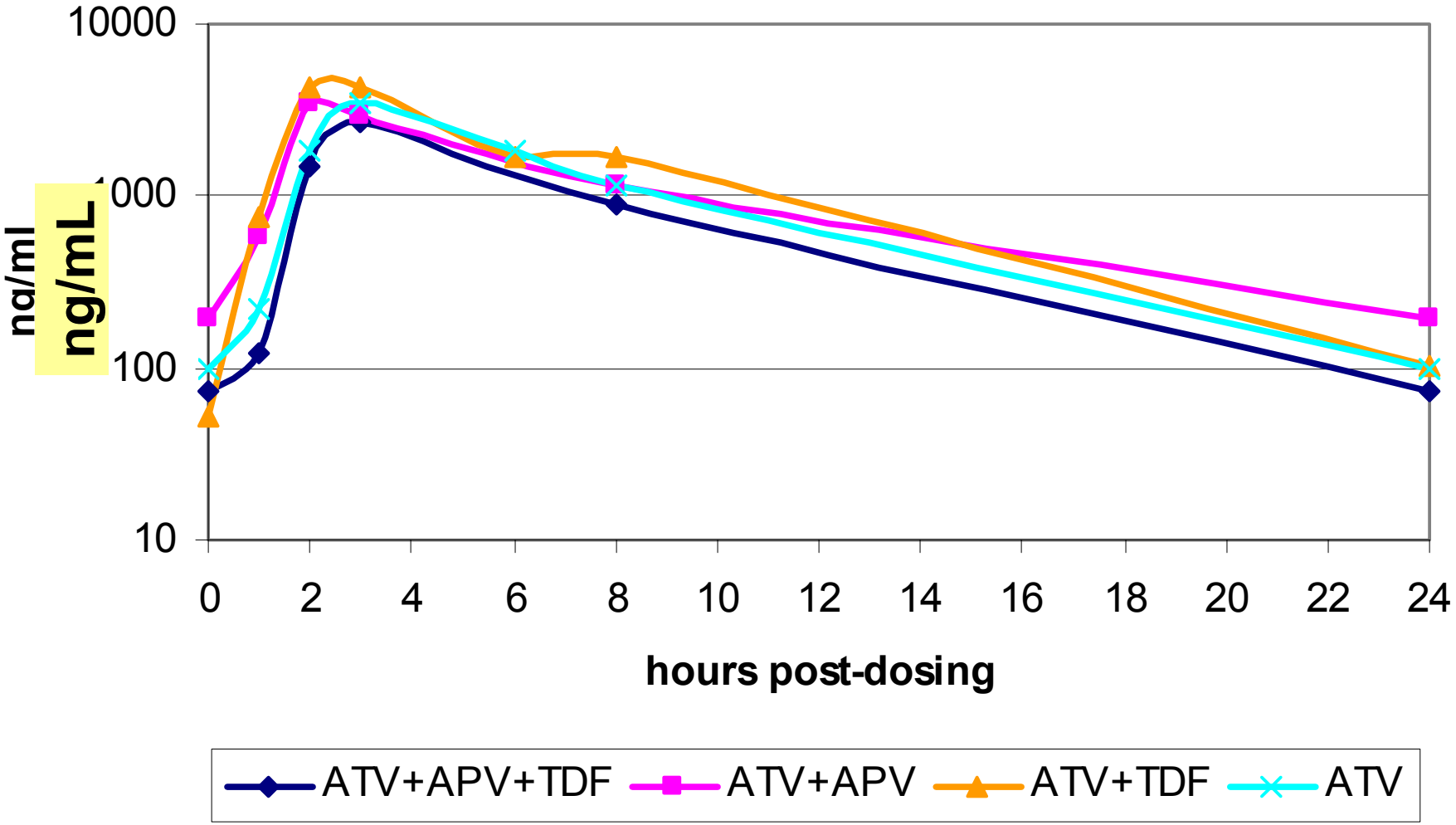

Table 1: Median (ranges) full PK parameters
in 19 patients treated with ATV+APV and ATV as single PI

		Ctrough (ng/ml)	Cmax (ng/ml)	Cl/F (L/h/kg)	AUC (ng.h/ml)
ATV	n= 7	70 (20-950)	5170 (3420-6100)	183 (154-277)	33400 (18000-58840)
ATV+APV	n=12	81 (33-284)	2990 (910-4190)	256 (200-619)	23980 (9230-31420)

Table 2: Median (ranges) full PK parameters in 19 patients treated with ATV±APV with or without TDF

		Ctrough (ng/ml)	Cmax (ng/ml)	Cl/F (L/h/kg)	AUC (ng.h/ml)
ATV	with TDF (n=5)	53 (20-950)	5260 (3660-6020)	184 (154-278)	33400 (18000-58840)
	No TDF (n=2)	135	5170	188	34000
ATV+APV	with TDF (n=9)	73 (0-128)	2850 (910-3790)	370 (260-440)	17030 (12950-23600)
	No TDF (n=3)	196 (114-284)	3500 (2940-4190)	200 (184-253)	25670 (25490-28030)

Table 3: Median (range) ATV trough values in 32 patients treated with ATV±APV with or without TDF

	No. of samples	C_{trough} (mcg/ml)
ATV+TDF N*=12	28	109 (20-950)
ATV N*=8	9	200 (66-584)
ATV+APV+TDF N*=9	18	73 (0-418)
ATV+APV N*=3	4	213 (114-284)

* Number of patients

Table 4: Intrapatient variability of ATV C_{trough} in 19 patients treated with ATV+APV+TDF or ATV+TDF

	No.of samples	CV% (range)
ATV+TDF n=11	22	30 (2-91)
ATV+APV+TDF n=8	16	51 (11-141)

Conclusions

ATV PK parameters did not significantly differ in patients treated with ATV+APV or ATV as single PI

Higher ATV C_{trough} intra-patient variability was observed in the patients treated with ATV+APV

When ATV is combined with TDF we did not observe statistically significant differences among the group studied, although ATV PK parameters seem to be lower in both TDF containing groups