

INTRODUCTION

✓ Using the association lopinavir/r (LPV/r) plus amprenavir (APV) in multi-experienced patients is of a growing interest but needs to be validated in terms of pharmacokinetic profile, safety and efficacy

✓ LPV/r and APV are both metabolized by CYP3A4

✓ Ritonavir (RTV) present in LPV/r is a potent inhibitor of CYP3A4

✓ RTV is an inducer of CYP3A4

Drug-drug interactions are complex and are difficult to predict when more than 2 protease inhibitors (PI) are involved.

PATIENTS AND METHOD

- ✓ 21 patients received the association APV / RTV (600 / 100 mg bid)
- ✓ 3 patients received the association APV / RTV (750 / 100 mg bid)
- ✓ 9 patients received the association APV / LPV/r (600 / 400/100mg bid)
- ✓ 13 patients received the association APV / LPV/r (750 / 400/100 mg bid)

- ✓ Retrospective study from May 2000 to May 2001
- ✓ Data from 46 HIV-1 infected patients were analyzed:
 - 40 men / 6 women
 - median age = 43 years (31 - 60)

✓ Plasma Cmin of LPV and APV (10-12 hours post ingestion) were measured by a validated HPLC method.

- ✓ 75 plasma samples were analyzed:
 - 24 for LPV/r plasma measurement
 - 51 for APV plasma measurement:
 - ⇒ 24 from patients on APV/LPV/r
 - ⇒ 27 from patients on APV/RTV

RESULTS

Table 1: Amprenavir Cmin according to the dose and the drug associated

	APV Cmin 600mgx2 (ng/ml)		APV Cmin 750mgx2 (ng/ml)	
	with RTV 100 mg x 2	with LPV/r 3 gélules x 2	with RTV 100 mg x 2	with LPV/r 3 gélules x 2
n (samples)	23	10	4	14
Mean +/- sd	2049+/-1216	938+/-461	1608+/-188	1585+/-998
Median	1772	859*	1655	1108**
Range	783 - 6746	573-2069	1341-1783	761 - 4034
CV %	59	49	12	63

* p=0,004 **p=0,215 (Mann-Whitney test)

Figure 1: Distribution of APV Cmin for the different combination

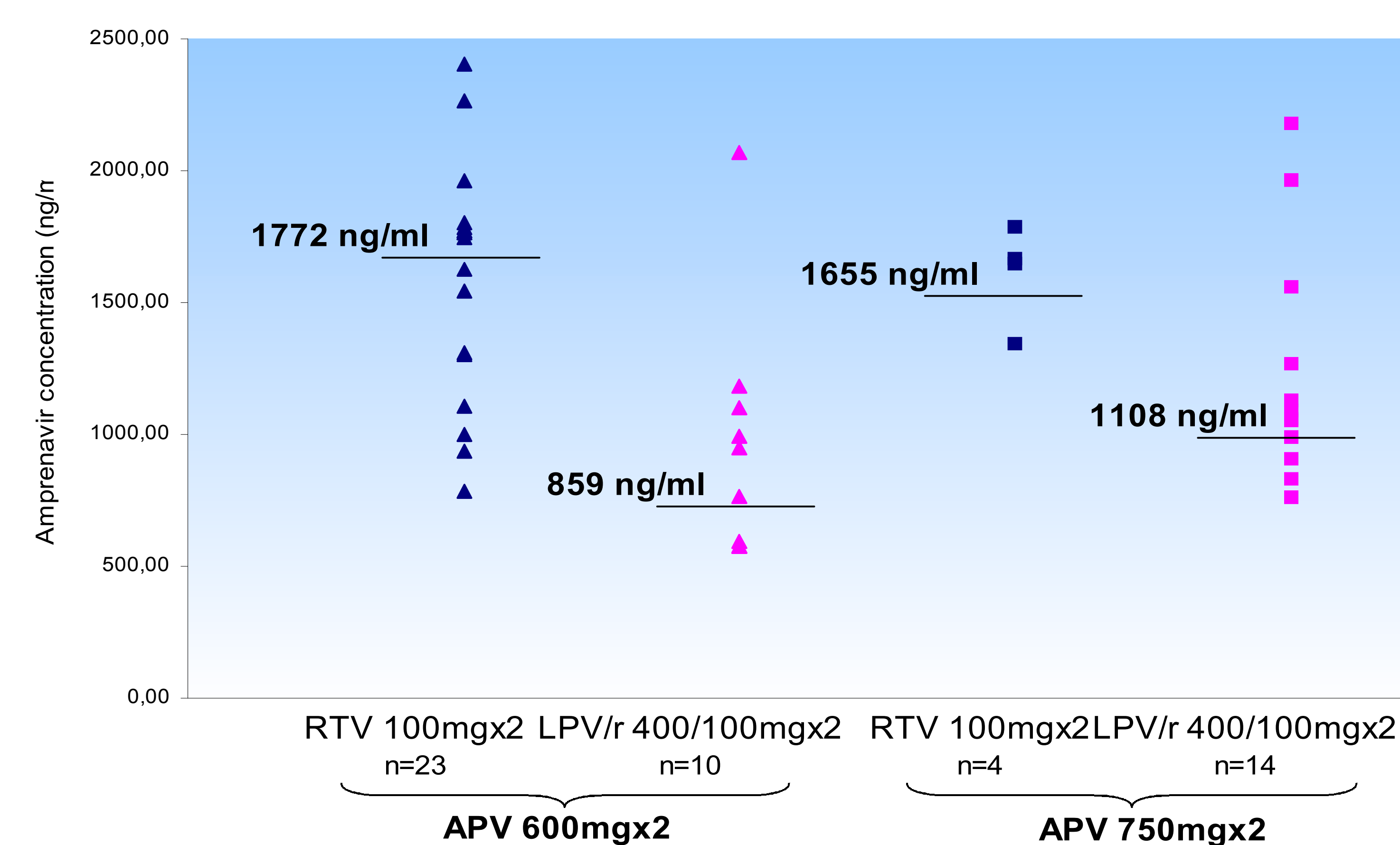


Figure 2: Distribution of LPV Cmin according to the APV dose associated

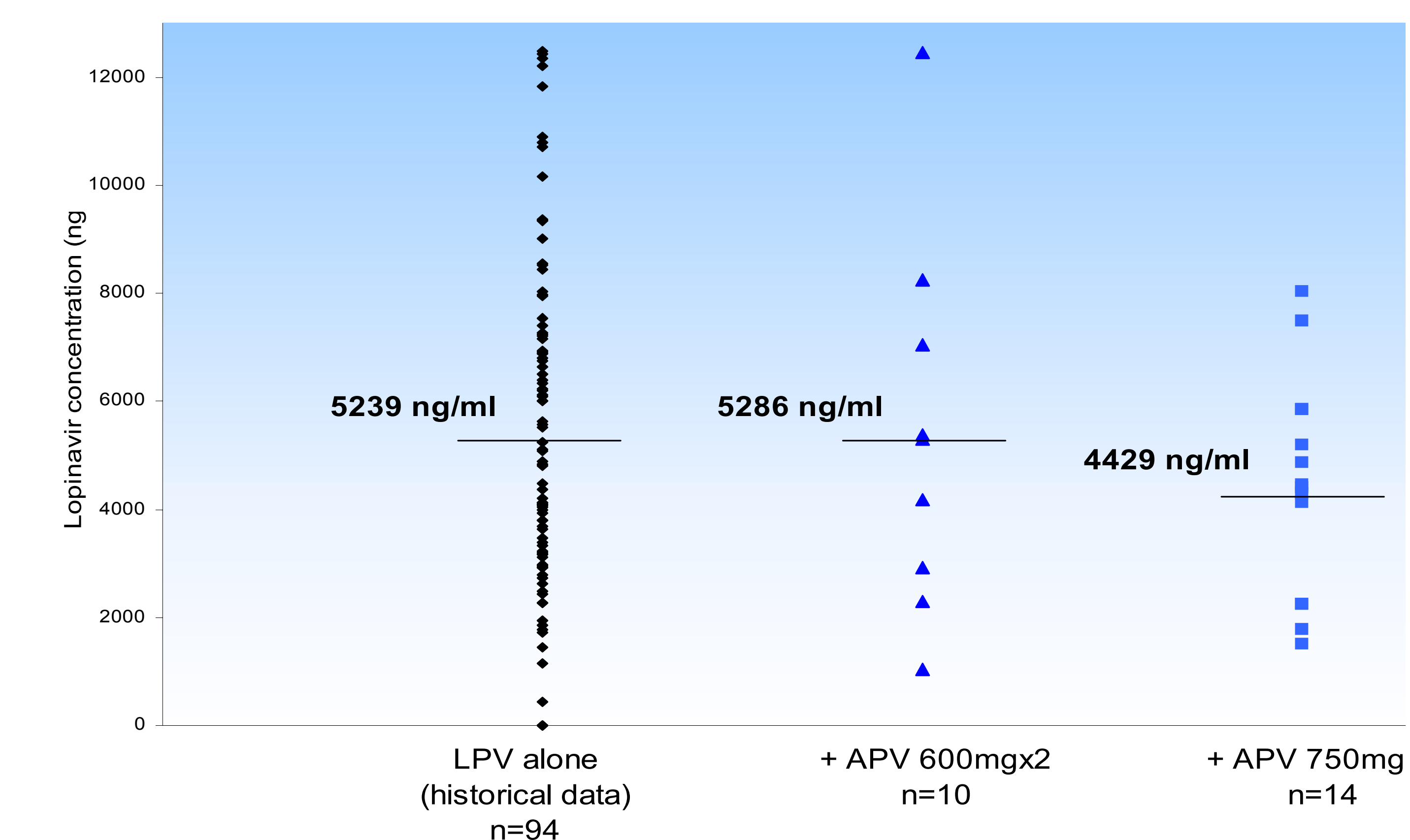


Table 2: Lopinavir Cmin according to the APV dose associated

	LPV Cmin 400/100 mg x2 (ng/ml)		
	LPV alone (historical data)	with APV 600 mg x2	with APV 750 mg x2
n (samples)	94	10	13
Mean +/- sd	5778+/-3072	5425+/-3478	4450+/-2002
Median	5239	5286	4429
Range	436 - 14092	1034 - 12444	1515 - 8016
CV %	53	64	45

DISCUSSION

✓ Median APV Cmin decreased from 51% and 33% for 600mgx2 and 750mgx2, respectively when APV is associated with LPV/r.

✓ Median APV Cmin was statistically lower when associated with LPV/r (p=0.004) as compared with RTV.

✓ Interindividual variability observed, is comparable between the different combination (APV/RTV and APV/LPV/r).

✓ Median LPV Cmin were comparable between patients treated with different doses of APV and similar to that observed with LPV/r given alone.

CONCLUSION

✓ Pharmacokinetic of LPV/r plus APV, in salvage therapy showed a decreased of the median APV Cmin, compared to patients treated by the association APV plus RTV 600 or 750/100mg bid. However, 85% of the patients taking APV/LPV/r had a median APV Cmin up to 3-fold the Cmin usually observed with the standard 1200 mg twice daily regimen (mean 280 ng/ml). In contrast, LPV Cmin was not affected by the association with APV, whatever the dose.

✓ Multiple drug-drug interaction, including more than 3 PI, substrate and/or inhibitor and/or inducer of CYP3A4, could not always be predicted because of the multiple molecular mechanisms involved. Moreover, because of the wide interindividual variability observed, APV Cmin could be either efficient or in few cases subtherapeutic. The minimal pharmacokinetic interaction between APV and LPV/r reported here does not appear to be clinically relevant. However, determination of APV and LPV/r Cmin is highly recommended when these 3 PI are associated, to determine an inappropriately high or low concentration and allow dose adjustment according to the clinical and virologic status of each patient.

✓ Further studies are required to evaluate the efficacy and the tolerance of the regimen.