Presented at the 7th International Workshop on Clinical Pharmacology of HIV Therapy, Lisbon, April 2007, Abstract 60.

Intra-patient variability and comparison of saquinavir/ritonavir C_{trough} concentrations between HIV-infected individuals and healthy volunteers administered saquinavir mesylate 500 mg film-coated tablets (1000/100 mg twice daily).

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Comparison of PK in healthy volunteers and HIV patients

Background

- Clinical studies conducted in healthy volunteers as well as target population
- Important to recognise potential for differences in drug disposition between groups
- Pharmacokinetics (PK) of antiretrovirals may be altered compared to healthy individuals
- What are the differences between the two groups and how could they impact drug PK?

Background

- Higher gastric pH in patients
  (Welage *et al.*, 1995; *Clin Infect Dis)*
- Differences in protein binding - ↑ AAG
  (Merry *et al.*, 1996; *AIDS*)
- Greater variability in CYP3A activity
  (Slain *et al.*, 2000; *Pharmacotherapy*,
  Fellay *et al.*, 2005; *Eur J Clin Pharmacol*)
- Suppressed CYP activity due to cytokine production
  (Slain *et al.*, 2000; *Pharmacotherapy*)
- Malabsorption/diarrhoea

Background

- Saquinavir (SQV) 600 mg *tid:* C_{max} and AUC 2-2.5 times that of healthy volunteers
  (Invirase Product Information, Roche, Sept 2005)

- SQV (Fortovase) 1200 mg *tid*: Interaction with rifampicin and ketoconazole more pronounced in healthy volunteers
  (Grub *et al.,* 2001; *Eur J Clin Pharmacol*)

- Difference with ritonavir (RTV) boosting and new film-coated tablet?

Background

Drug	Comment	Reference
ATV	Data suggest ATV concentrations could be lower in HIV patients	Le Tiec *et al.,* 2005
	Significantly lower C_{min} than that reported for healthy individuals	Guiard-Schmid *et al.,* 2005
	Differential effect of PPI on ATV C_{min}	
FPV	Steady state APV PK similar between groups with or without RTV	Kim *et al.,* 2004
	No substantial differences between groups	GSK, 2006
LPV	No substantial differences between groups	Abbott, 2005
TPV	HIV status had significant effect on CL. HIV patients had higher CL, larger V and tended to have lower TPV concentrations	Yong *et al.,* 2005

Objective

Compare SQV/RTV C_{trough} of HIV-infected patients and healthy volunteers administered SQV mesylate 500 mg film-coated tablets (1000/100 mg twice daily)

Retrospective analysis of 2 SQV/RTV PK studies:

1. Healthy volunteers: SQV/RTV + omeprazole. Winston *et al.*, 2005; 10th EACS, Poster LBPE4.3/16
2. HIV-infected patients: SQV/RTV + Food. Boffito *et al.*, 2006; 7th International Workshop on Clinical Pharmacology of HIV Therapy, Poster 66

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Patients

Parameter	Healthy	HIV-infected
n	18	22
Female [n (%)]	6 (33)	5 (23)
Age (yr)	28 (18-53)	47 (39-62)
Weight (kg)	66 (59-121)	72 (58-108)
BMI (kg/m^2)	23 (19-40)	23 (20-39)
CD4 at screen (cells/mm^3)	-	456 (256-1023)
Detectable VL (copies/ml)	-	132 (48-2680)
Undetectable VL [n (%)]	-	14 (64)

- Stable on SQV/RTV-containing regimen
- Written informed consent
- Excluded: inducers/inhibitors
  clinically significant medical conditions
  lab parameters not in consensus with protocol

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Methods

SQV+OMP

HEALTHY (n=18)

PK days, 7 ml Blood:
0, 0.5, 1, 2, 3, 4, 6, 8, 10, **12** post-dose

HIV-INFECTED (n=22)

SQV+food

PK days, 7 ml Blood:
0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12 post-dose
+
C_{trough} day **7**, **10**, **13** PM, 14 AM/PM, **17**, **20** PM, 21 AM/PM

HPLC-MS/MS

C_{trough}

Comparison of C_{trough}:

Healthy *vs.* HIV day 7, 10, 13, 17, 20 (standard meal, SQV/RTV 1000/100 mg *bid* ONLY)

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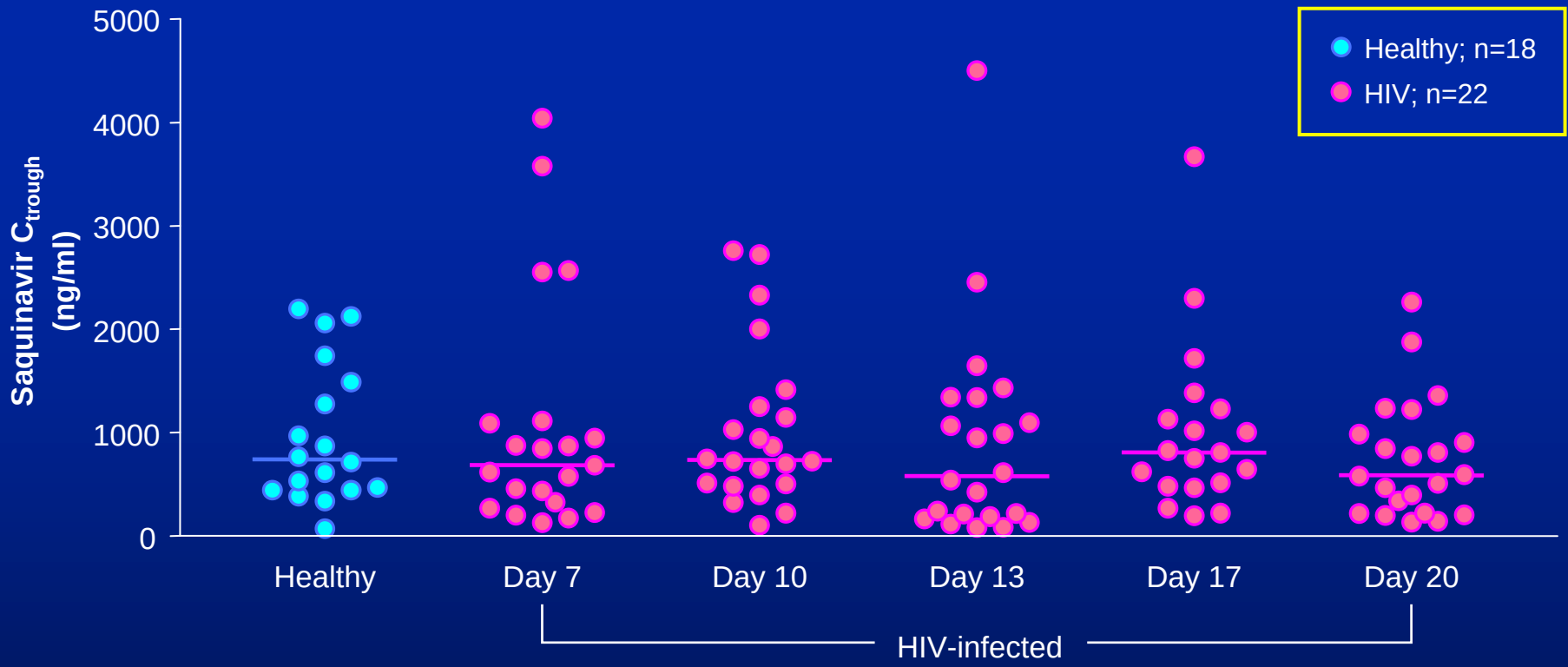
Saquinavir: comparison of C_{trough}



	Healthy	HIV				
		Day 7	Day 10	Day 13	Day 17	Day 20
C_{trough} (ng/ml)	741	686	735	577	809	587
	(71-2199)	(128-4041)	(106-2761)	(84-4502)	(197-3668)	(134-2262)
CV (%)	*70*	*105*	*75*	*114*	*82*	*77*

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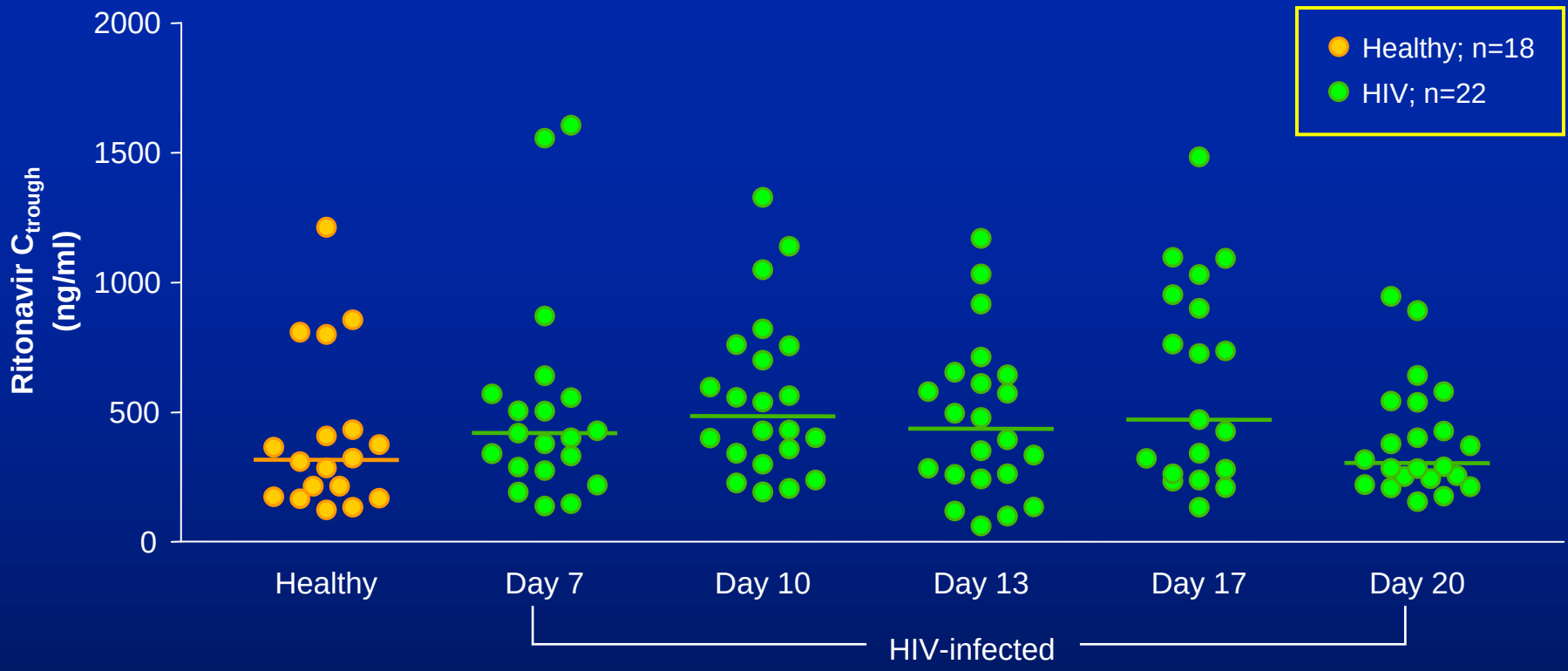
Ritonavir: comparison of C_{trough}



	Healthy	HIV				
		Day 7	Day 10	Day 13	Day 17	Day 20
C_{trough} (ng/ml)	317 (124-1214)	419 (138-2420)	485 (193-1329)	437 (61-1171)	471 (134-1484)	392 (155-947)
CV (%)	*75*	*94*	*56*	*64*	*64*	*56*

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Statistical comparison of C_{trough}

SQV / RTV	Healthy	Day 7	Day 10	Day 13	Day 17	Day 20
Healthy		0.695	0.847	0.330	0.880	0.314
Day 7	0.176		0.540	0.546	0.579	0.523
Day 10	0.054	0.552		0.219	0.971	0.207
Day 13	0.326	0.685	0.312		0.252	0.972
Day 17	0.064	0.578	0.997	0.339		0.238
Day 20	0.857	0.215	0.065	0.398	0.078	

Analysis performed by Kruskal-Wallis

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Summary of results

- First data comparing new SQV formulation boosted with RTV between HIV-infected patients and healthy volunteers
- No statistically significant differences in SQV/RTV C_{trough} between groups
- Marked inter-individual variability in concentrations

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Intra-patient variability

Background

- In some settings Therapeutic Drug Monitoring (TDM) based on 1 plasma sample
- Difficult or impractical to obtain multiple samples
- Assumes limited intra-patient variability
- Recent study defined intra-patient variability of PIs and NNRTIs through intensive sampling
- High intra-patient variability observed for PIs (Nettles *et al.*, 2006; *Clin Infect Dis*)
- SQV = 52, 55 %; RTV = 34, 43 %

Background

- Study evaluating effectiveness of TDM and adherence support
  (Khoo *et al.*, 2006; *J Aquir Immune Defic Syndr*; in press)
- Inter-patient variability of SQV: 112 %
- Median intra-patient variability of PIs: 48 %

Objective

Determine SQV/RTV intra-patient variability in HIV-infected individuals receiving SQV mesylate 500 mg film-coated tablets (1000/100 mg twice daily)

Effect of food on new formulation of SQV:

Boffito *et al.*, 2006; 7th International Workshop on Clinical Pharmacology of HIV Therapy, Poster 66

Patients and methods

- Total of 22 patients described earlier
- Intra-patient variability of SQV/RTV C_{trough} using 5 samples per patient:
  - Days 7, 10, 13, 17, 20
  - CV% = (s.d./mean conc.) x 100

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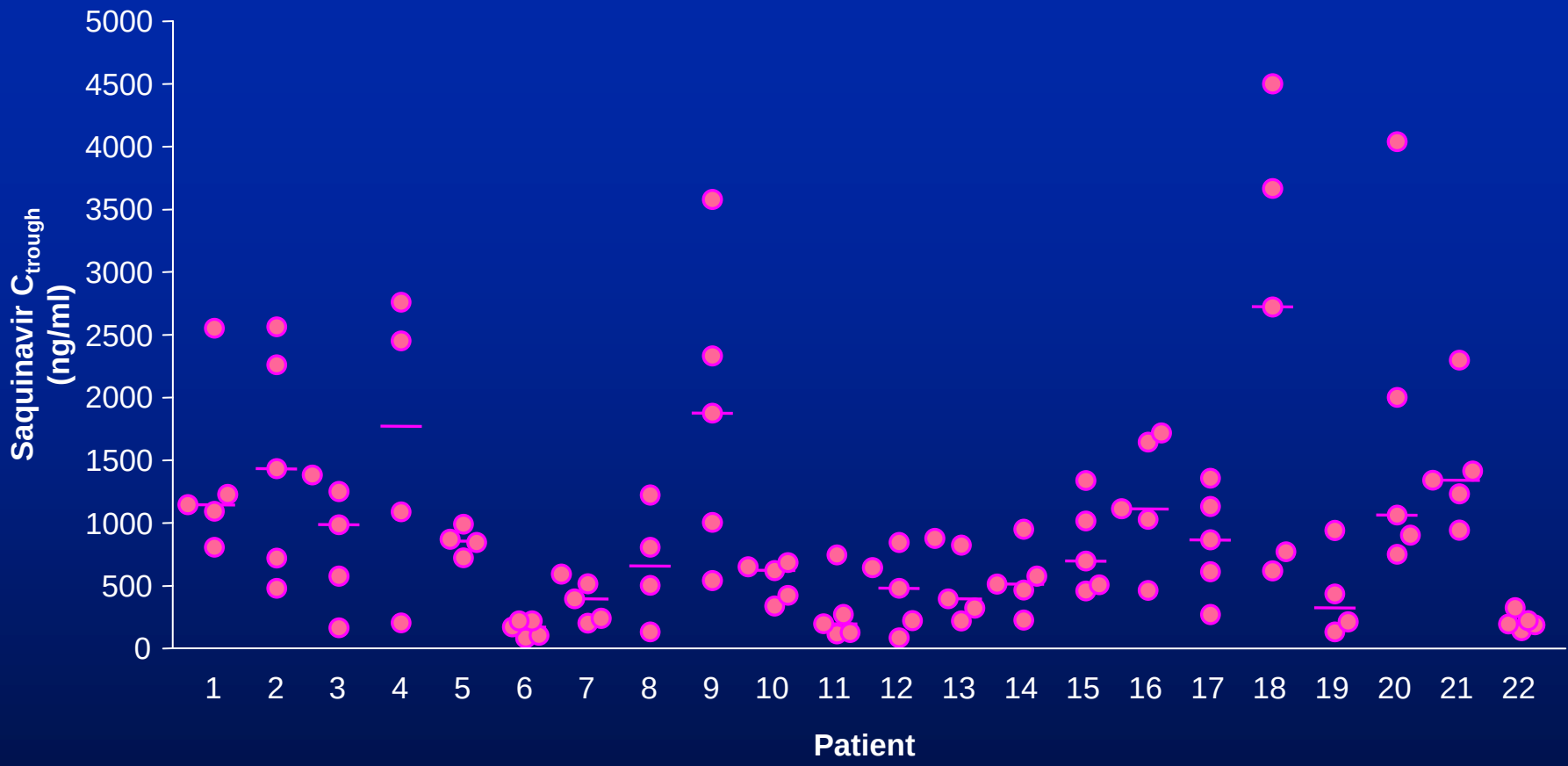
Saquinavir intra-patient variability



Median (range) intra-patient variability: 54 % (13-90)

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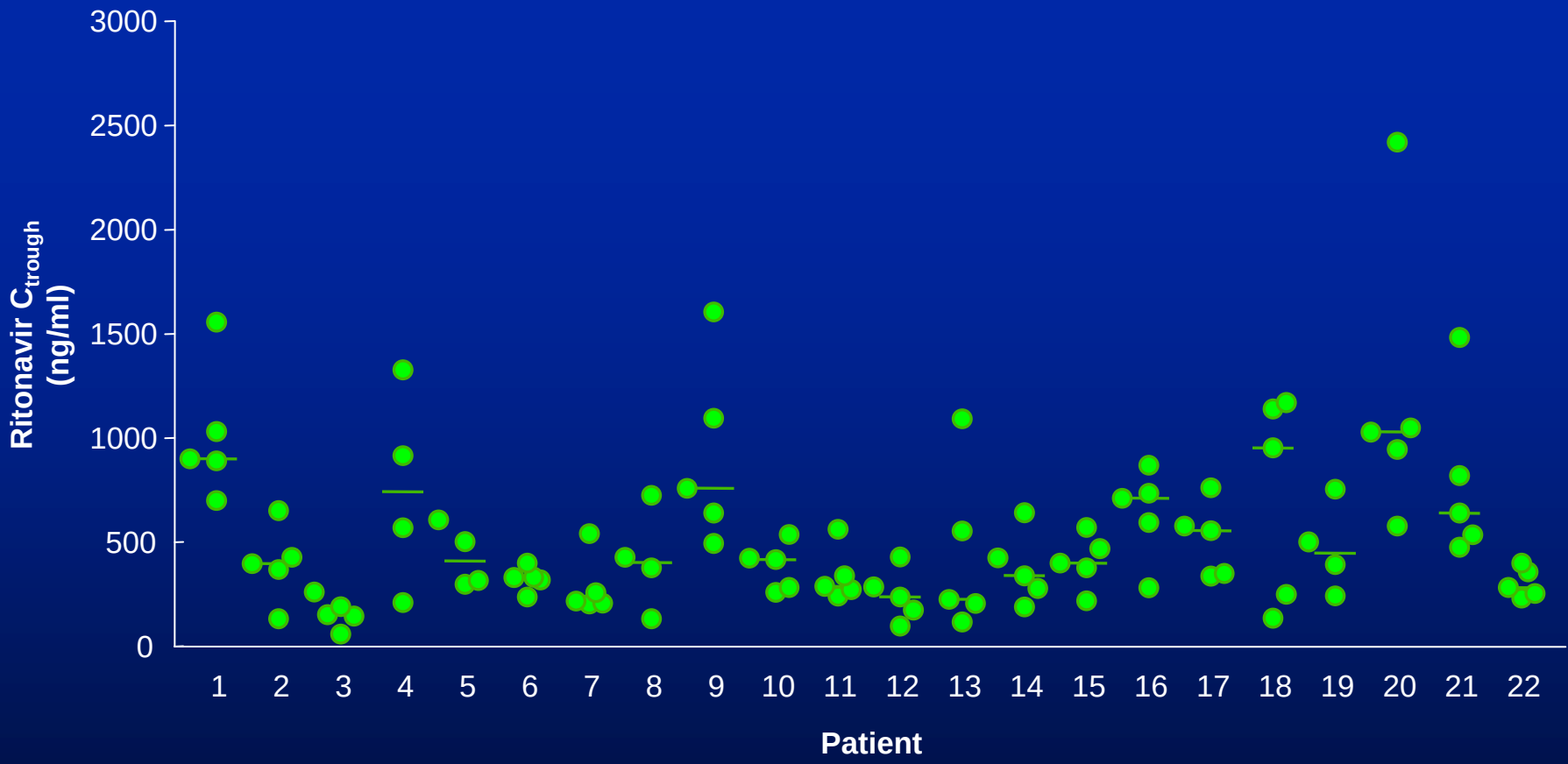
Ritonavir intra-patient variability



Median (range) intra-patient variability: 46 % (18-91)

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Summary of results

- SQV/RTV intra-patient variability of C_{trough} (5 samples) similar to values previously reported
- Intra-patient variability varies widely between individuals

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Discussion

- No differences in SQV/RTV C_{trough} between HIV patients and healthy volunteers
- Even in the context of a clinical trial there is marked inter- and intra-individual variability
  - SQV: **75-114 %** and **13-90 %**, respectively
  - RTV: **56-94 %** and **18-91 %**, respectively
- Need to understand reasons for underlying variability

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