

Intracellular Pharmacokinetics of Boosted and Unboosted Atazanavir in HIV Infected Patients

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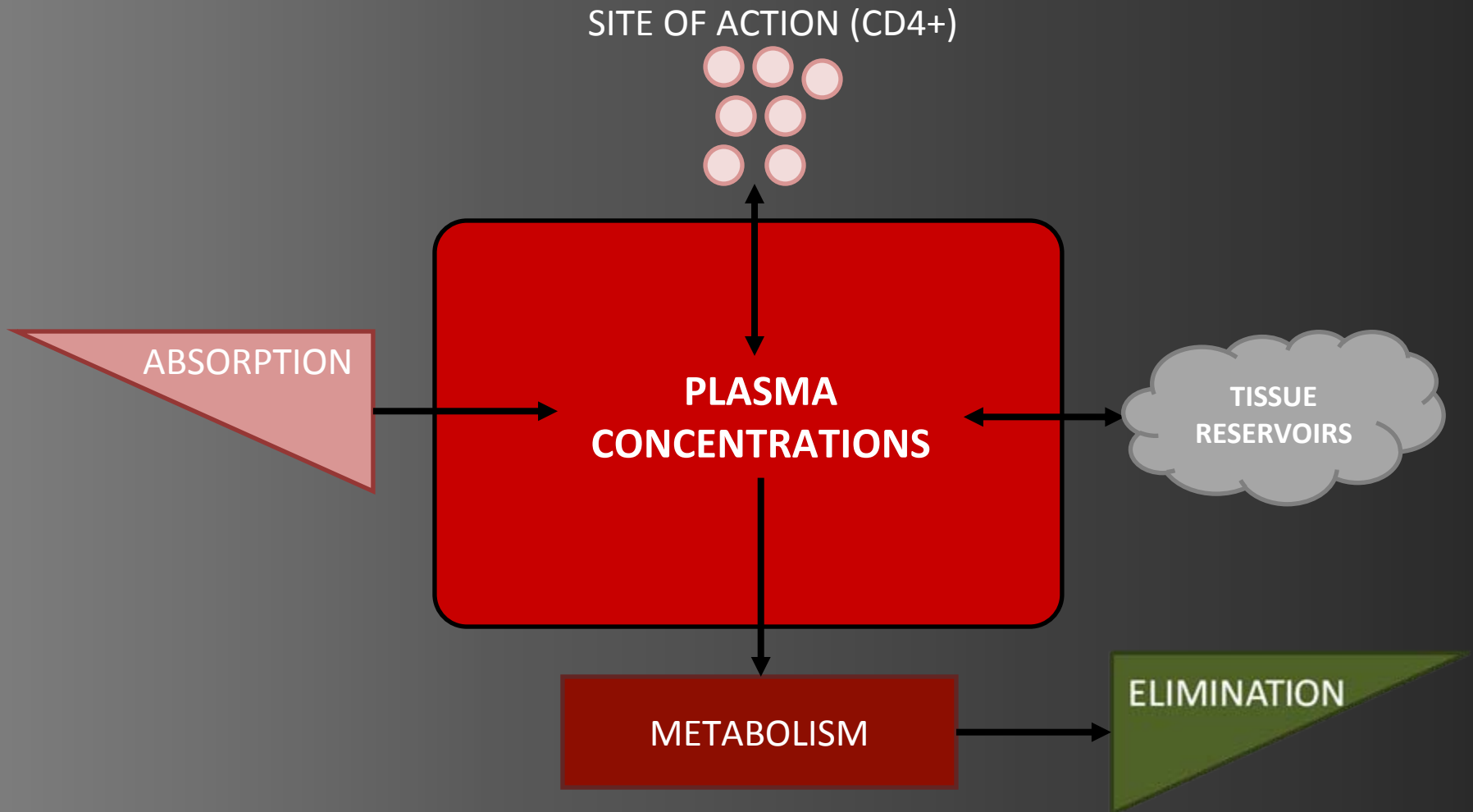
Background



- ATV is commonly administered **q.d at 300 mg** with 100 mg of RTV as a booster.
- **Unboosted ATV** (400mg q.d) could be an attractive choice for patients with **RTV-related toxicity or intolerance.**



Background



Background



Drug and dose ^a	n	Design		Plasma and intracellular pharmacokinetics				Correlation
		plasma (n _{obs} /n _{vis})	intracellular (n _{obs} /n _{vis})	parameters ^b	plasma	intracellular	ratio ^c	
PIs								
Saquinavir								
1600 mg od (+ 100 mg ritonavir)	12	4/1	4/1	AUC ₂₄	5.7–39.3 µg • h/mL	24.7–114.6 µg • h/mL	1.5–6.7	Yes (R ² =0.63)
1600 mg od (+ 100 mg ritonavir)	13	1/3	1/3	C ₂₄			1.1–8.7	Yes (R ² =0.31)
				wk 2	0.04–1.43 µg/mL	0.15–0.79 µg/mL		
				wk 4	0.04–1.97 µg/mL	0.11–0.84 µg/mL		
				wk 12	0.04–1.21 µg/mL	0.17–0.47 µg/mL		
Indinavir								
800 mg tid	10	6/1	6/1	AUC ₈	25.1 ± 4.2 µg • h/mL	7.6 ± 1.0 µg • h/mL	NR	No
				C _{trough}	10.7 ± 1.3 µg/mL	3.2 ± 0.7 µg/mL	NR	
800 mg bid (+ 100 mg ritonavir)	19	2/1	2/1	C _{trough}	NR	NR	0–20	NR
				C _{max}	NR	NR	1–5	NR
Lopinavir								
400 or 533 mg bid (+100 or 133 mg ritonavir)	38	1/2	1/2	C _{trough}				
				wk 4	0.7–5.7 µg/mL	2.9–29.0 µg/mL	1.9–3.8	Yes (R ² = 0.72)
				wk 24	0.7–7.7 µg/mL	0.1–27.5 µg/mL	1.3–3.1	No
400 mg bid (+ 100 mg ritonavir)	11	14/1	4/1	AUC ₁₂	61.8–82.8 µg • h/mL	63.1–113.8 µg • h/mL	0.7–2.1	NR

Objectives



- To evaluate ATV intracellular concentrations **in PBMC.**
- To compare the ATV concentrations between **boosted** and **unboosted** administrations .

Methods



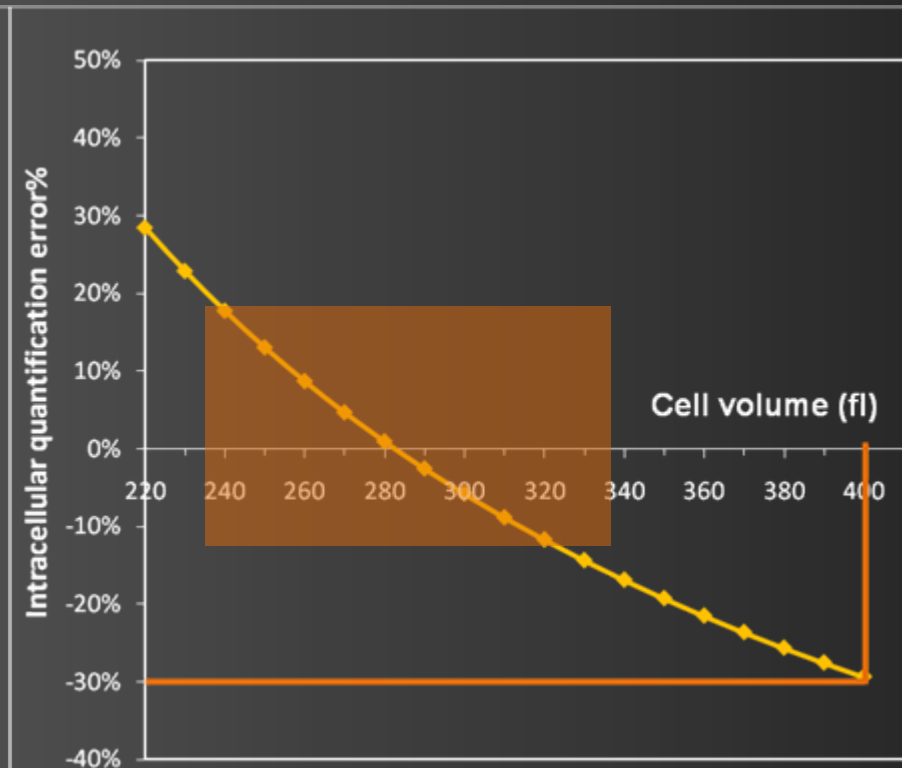
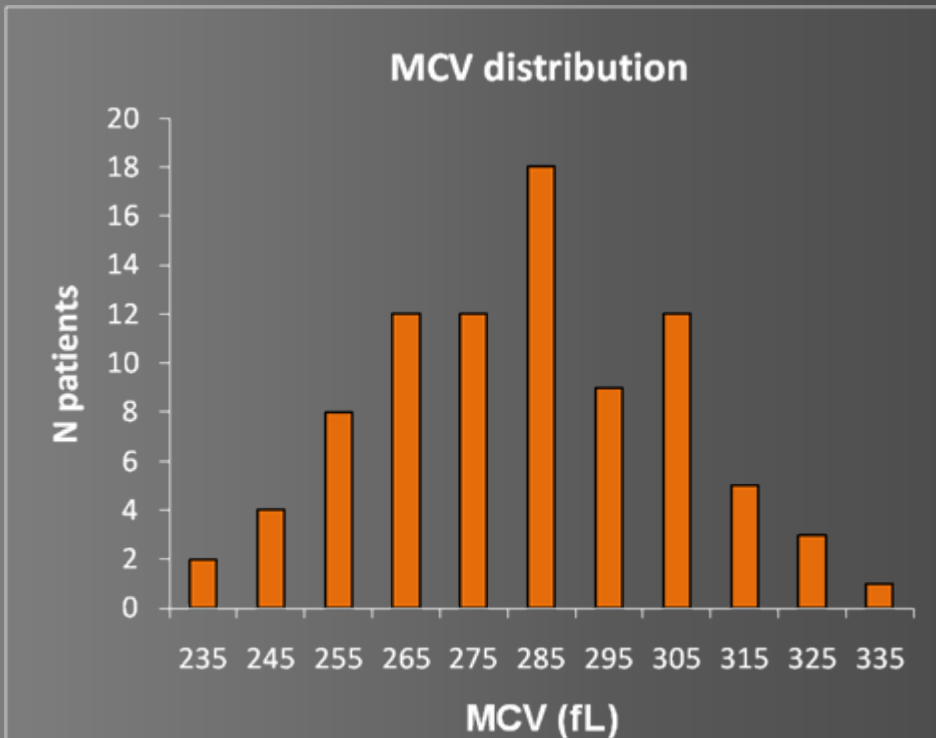
- Patients were recruited in **Turin, Italy**
- **Inclusion criteria** were:
 - Older than 18 years
 - No concomitant interacting drugs (except tenofovir)
 - Self-reported adherence more than 95%
- Plasma samples analysed by HPLC-PDA method and intracellular samples analysed by HPLC-MS method.
- Quantification of mean cellular volume (MVC) and cell count were assessed using **Coulter Counter.**
- **Ctrough** measured in samples collected **22 – 26 h after dosing**



Results

Poster 62 - Simiele et al. - **Are intracellular drug concentrations underestimated? The role of mean corpuscular volume (MCV) for a correct determination .**

$$\text{Intracellular concentrations} = \frac{\text{Amount of drugs in N cells}}{\text{MCV} \times \text{N cells}}$$



Results

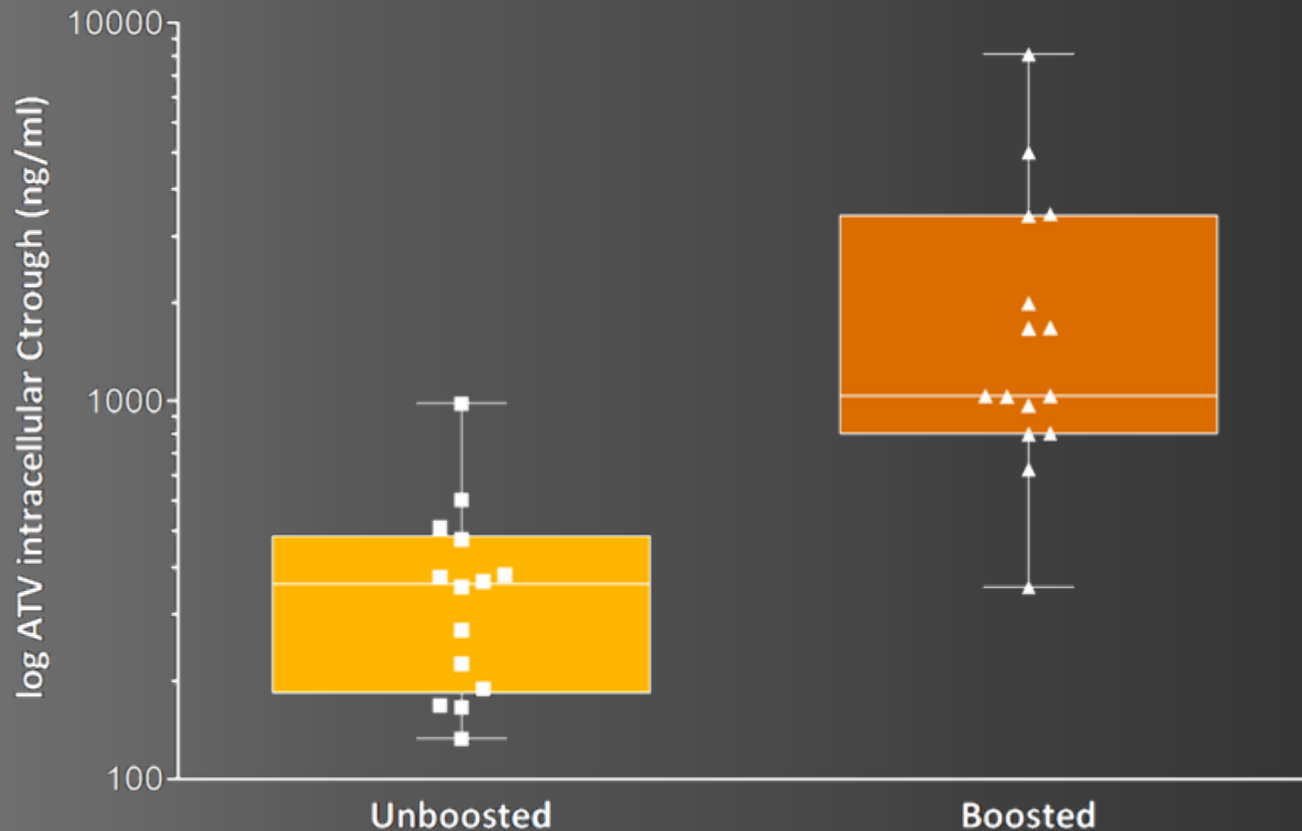


Demographic and physical characteristics		
	Unboosted	Boosted
Number of patients	14	15
Males (%)	10 (72)	11 (74)
Age, median years (IQR)	48 (43-54)	48 (37-65)
BMI, median kg/m ² (IQR)	23.5 (20.8-28.1)	24.3 (21.2-26.6)

Atazanavir concentrations **were not correlated** with any demographic factors.

Results

ATV intracellular C_{trough} **was higher** for boosted ATV compared to unboosted ATV, **328 ng/ml (168-440) versus 1032 ng/ml (819-3091), $p = 0.001$.**

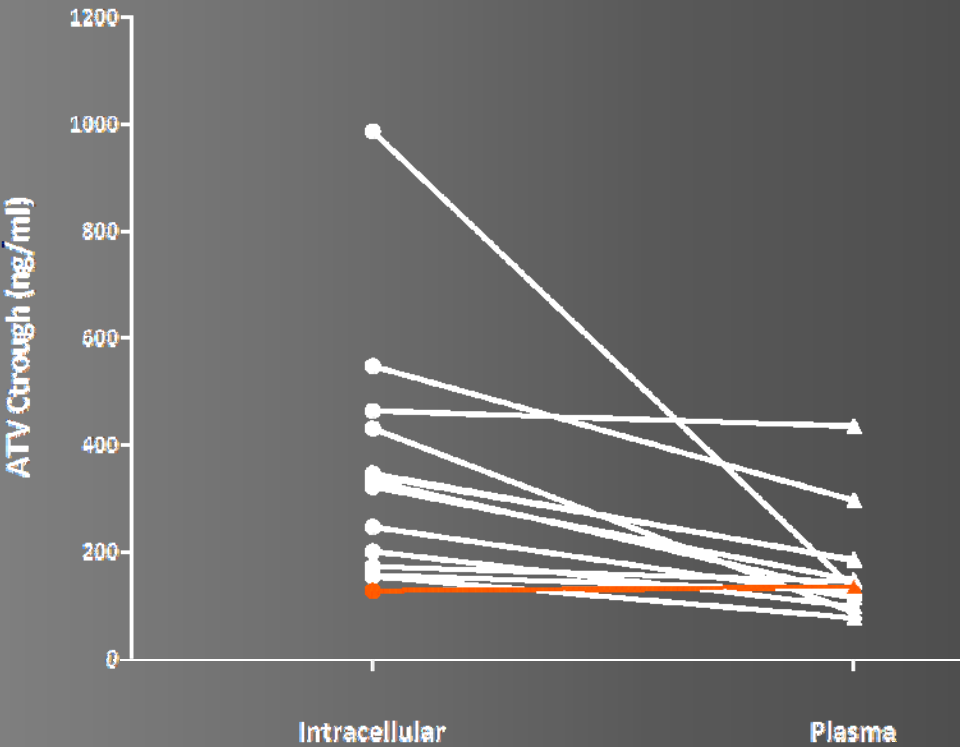


Results

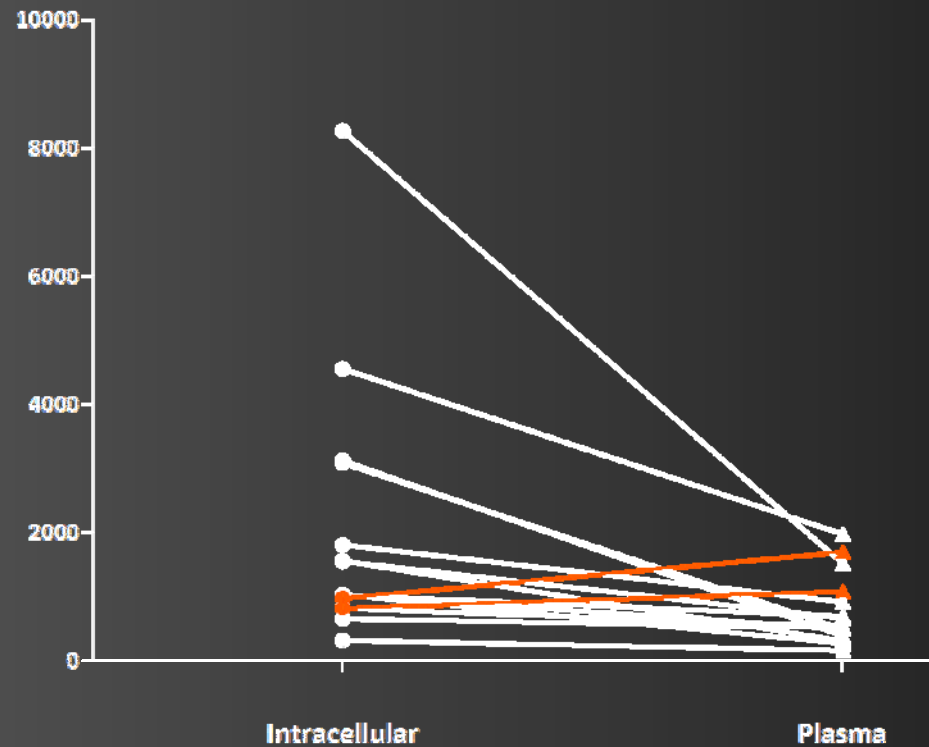


ATV intracellular C_{trough} **was higher** than plasma C_{trough} .

Unboosted



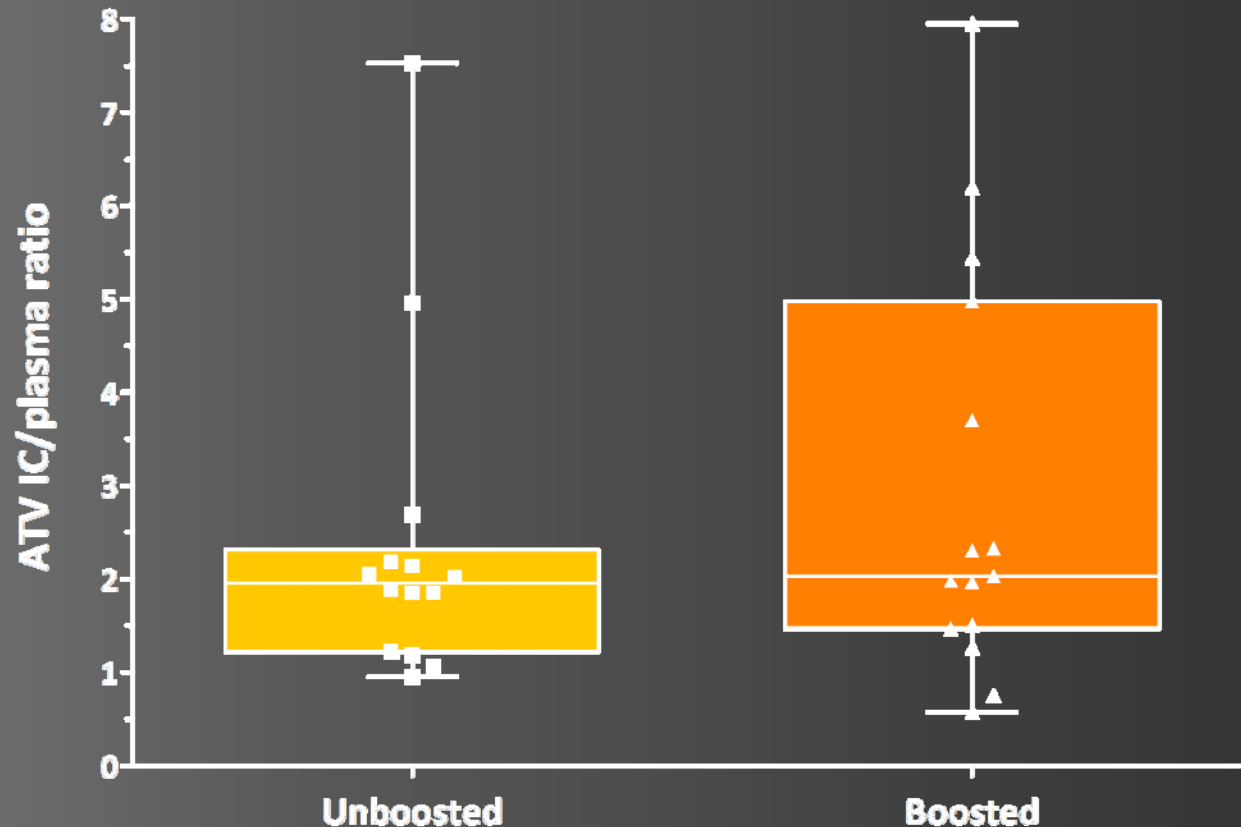
Boosted



Results



Cellular accumulation ratio was comparable between the two treatment groups, **1.9 (1.2-2.3) for unboosted ATV versus 2 (1.5-4.9) for boosted ATV.**

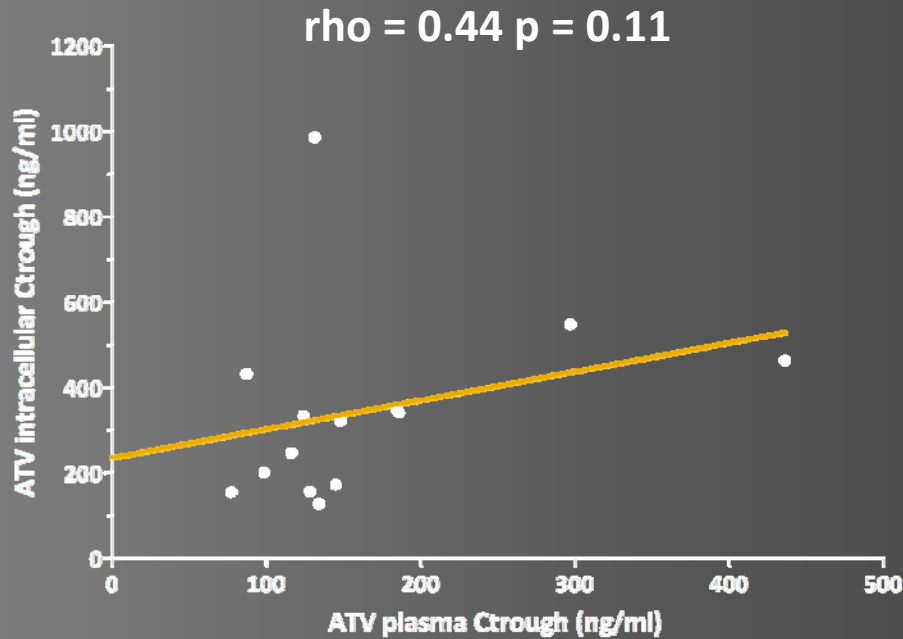


Results

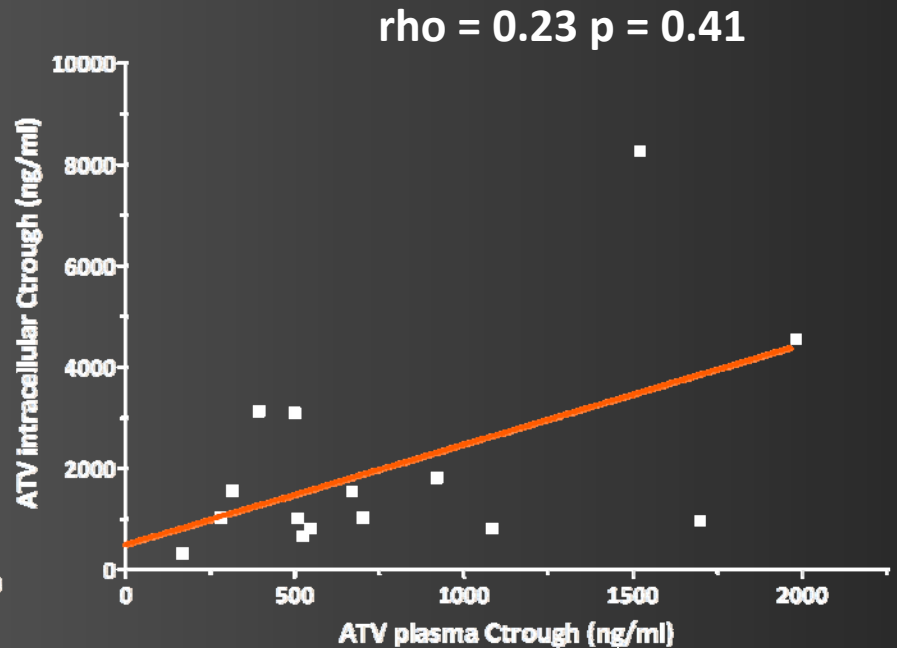


Plasma and intracellular concentrations were not statistically correlated.

Unboosted



Boosted





Summary

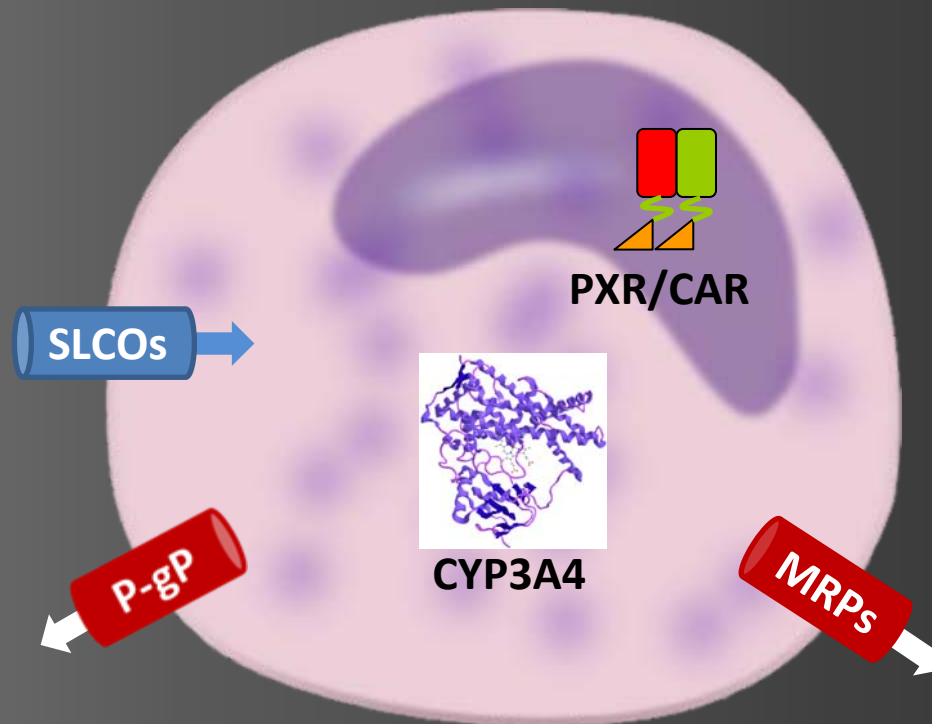
	Unboosted	Boosted
ATV intracellular Ctrough, median (IQR)	328 ng/ml (168-440)	1032 ng/ml (819-3091)
ATV plasma Ctrough, median (IQR)	132 ng/ml (111-184)	543 ng/ml (393-1081)
ATV IC/plasma ratio	1.9 (1.2-2.3)	2 (1.5-4.9)
correlation IC-plasma	rho=0.44 p=0.11	Rho 0.23 p=0.41

- **Intracellular concentrations were higher** than plasma concentrations, indicating an accumulation of ATV in PBMC.
- **Cellular drug accumulation was similar** in the two treatment groups.



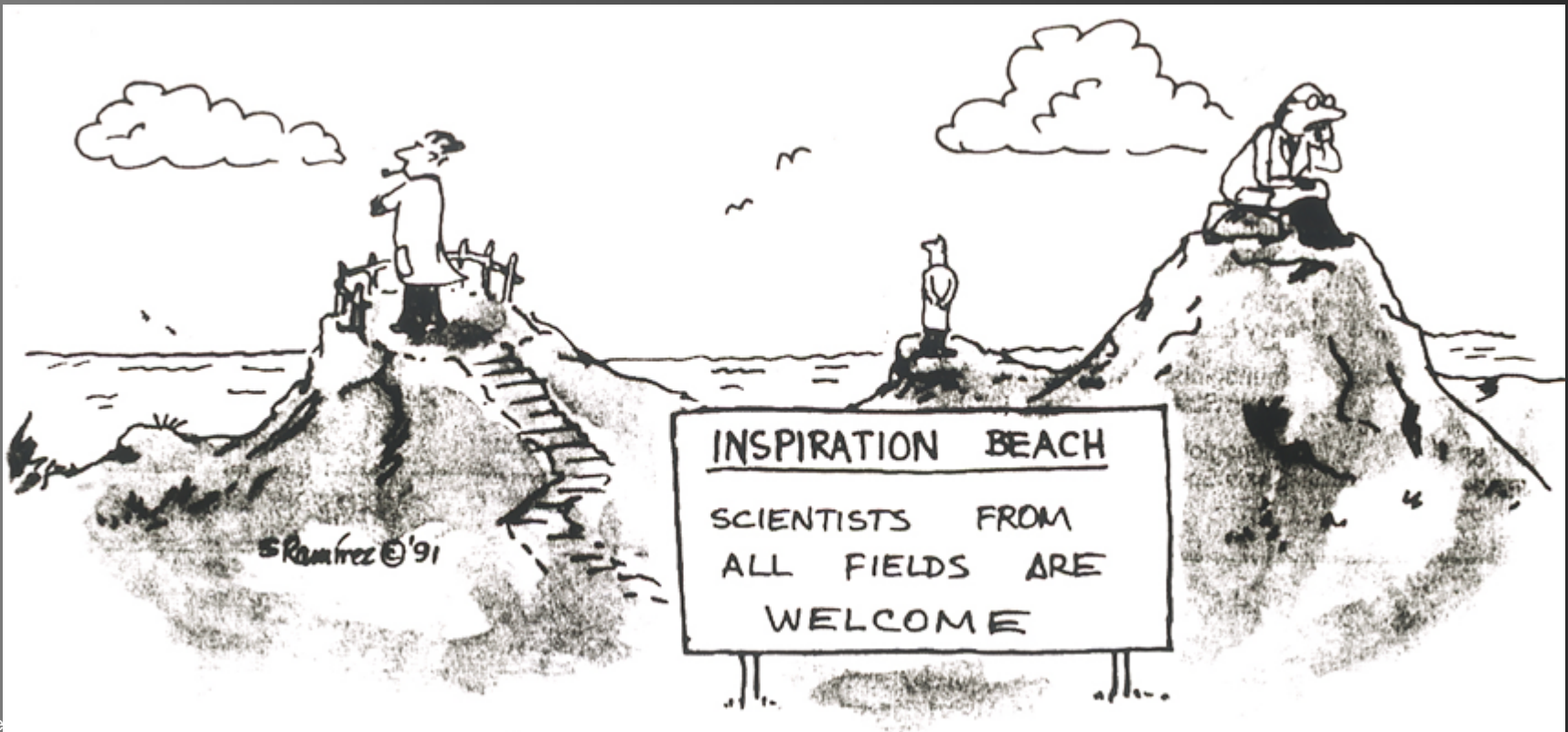
Discussion

- The **lack of a clear correlation** between plasma and intracellular concentrations suggests a potential **role for transporters**.



Discussion

- Is there a need of standardization?
 - PK variables
 - Sample size
 - PBMC count and volume



Acknowledgements



Universita' di Torino

Prof. Alessandro Sinicco
Maria Cristina Tettoni
Laura Trentini
Ilaria Motta
Letizia Marinaro
Mattia Chiesa
Maria Chiara Dominici
Lia Vizio
Samantha Pattanella
Alessio Audino

Liverpool University

Prof. David Back
Prof. Saye Khoo
Deirdre Egan
Laura Else
Neil Liptrott
Darren Moss
Wai San Kwan