6.1

Lopinavir/r administration

V. Micheli[1], P. Meraviglia[1],

[1] *II Department of Infectious Diseases*
L. Sacco Hospital - Milan

in HIV/HCV co-infected patients:

M. Regazzi[2], P. Villani[2], M. Schiavini[1],

[2] Laboratory of Clinical Pharmacology
IRCCS-Policlinico S. Matteo - Pavia

pharmacokinetic considerations

M. Cusato[2], P. Viganò[3], A. Cargnel[1]

[3] Azienda Ospedaliera di Legnano

OBJECTIVES

- To assess the impact of HCV infection on Lopinavir/ritonavir pharmacokinetic (PK) parameters in co-infected patients versus HIV+ control subjects.
- To identify a valuable parameter to optimize Lopinavir/ritonavir dose in this clinical setting.

PATIENTS

20 patients administered with LPV/r in steady-state status

CONTROL
HIV+
n=9

7 pts: 400/100 mg BID
1 pt: 267/67 mg BID
1 pt: 533/133 mg BID

HI
HIV/HCV+
n=11

8 pts: 400/100 mg BID
2 pts: 267/67 mg BID
1 pt: 267/67 mg BID*

The reduction of standard LPV/r dose was body weight-guided (BW<49 Kg)

*A.E.

METHODS

- All patients enrolled were judged compliant by the physician.
- 19/20 patients are on antiretroviral therapy including a backbone of 2 NRTIs. 1 pt was receiving EFV.
- Plasma samples were collected pre-dose and at 1, 2, 3, 4, 6, 8 and 12 hours (when possible) post dose.
- Lopinavir and Ritonavir plasma levels were determined by reverse-phase high-performance liquid chromatography (HPLC) according to a validated method UV-based.

  LPV/r limit of quantification= 5.0/1.0 ng/mL

Patients characteristics (1)

	CONTROL (n=9)	HI (n=11)
Age	42±7	43±5
Gender M/F	7/2	8/3
Body weight (Kg)	75.8±21.7	65.4±16.8
Body Mass Index	26±6	23±4
CDC stage A B C	 2 1 6	 - 6 5
Time of exposure (months)	12±6	14±9

Patients characteristics (2)

	CONTROL (n=9)	HI (n=11)
HIV-RNA	2.12±0.97	2.29±1.14
CD4+	292±123	354±205
AST (UI/L)	34±29	48±27
ALT (UI/L)	34±30	53±41
Tot. Bilirubin (mg/dL)	0.73±0.35	1.04±0.91
Albumine (g/dL)	4.4±0.2	4±0.6 §
Pche (mg/dL)	9,441±3,340	6,088±2,836 §

§ statistically significant

Clinical features of HIV/HCV+ pts

- All patients were HCV-RNA+
- 8 pts: mild HI
  - 2 negative
  - 3 mild hepato/splenomegaly
  - 1 mild hepatomegaly
  - 1 moderate steatosis
  - 1 mild steato/fibrosis
- 3 pts: cirrhosis

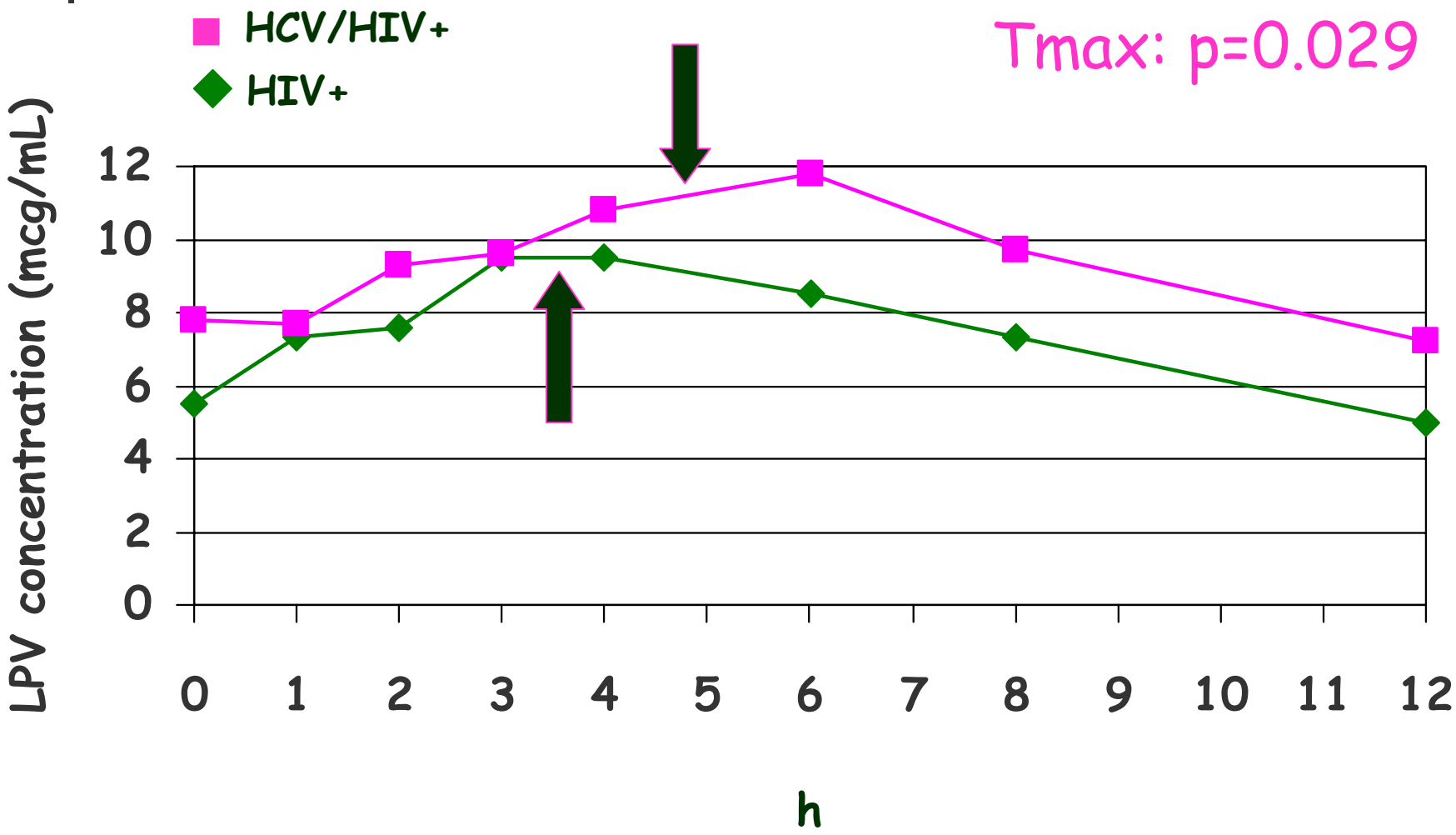
Ultrasound diagnosis

Adverse events

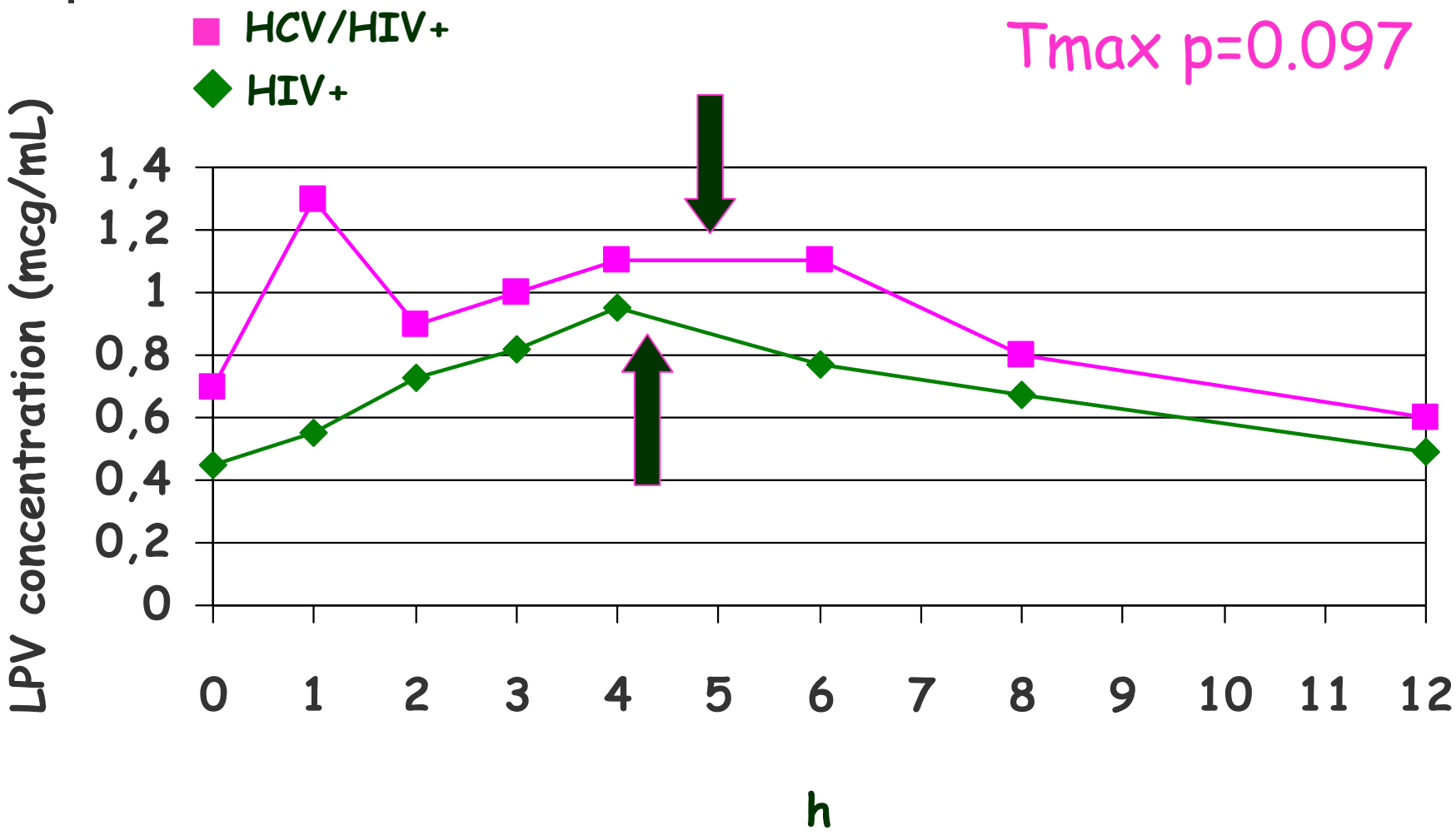
	Control (n=9)	HI (n=11)
Increase ALT/AST (grade 3)	-	1
Hyperlipemia (grade 3)	2+1	-
Diarrhea	-	1
Diarrhea and gastric pain	1	2

discontinuation of LPV for adverse events

LPV time-concentration profile

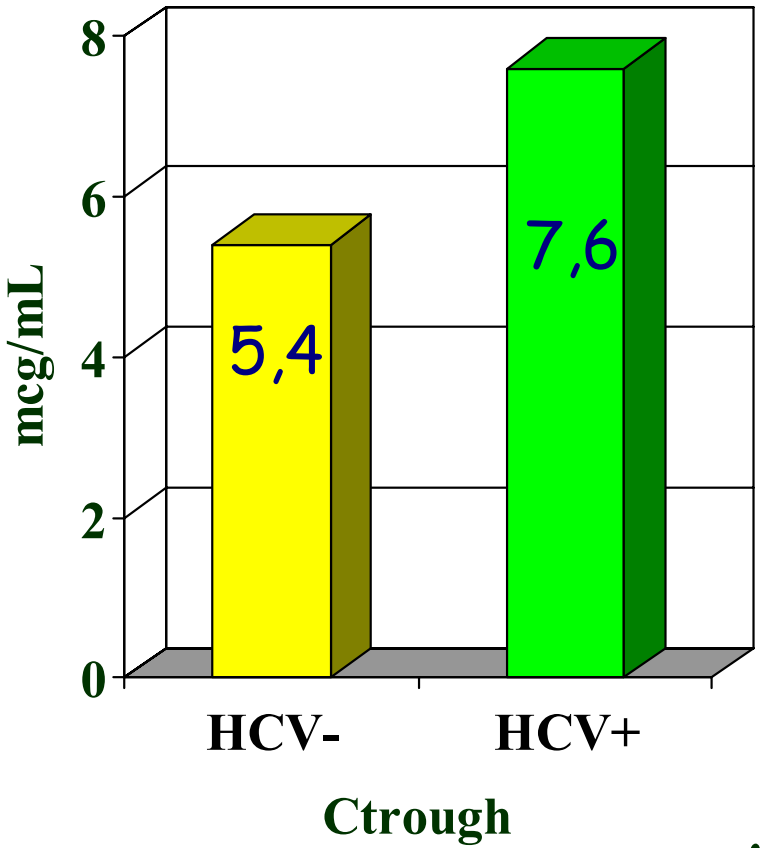


RTV time-concentration profile

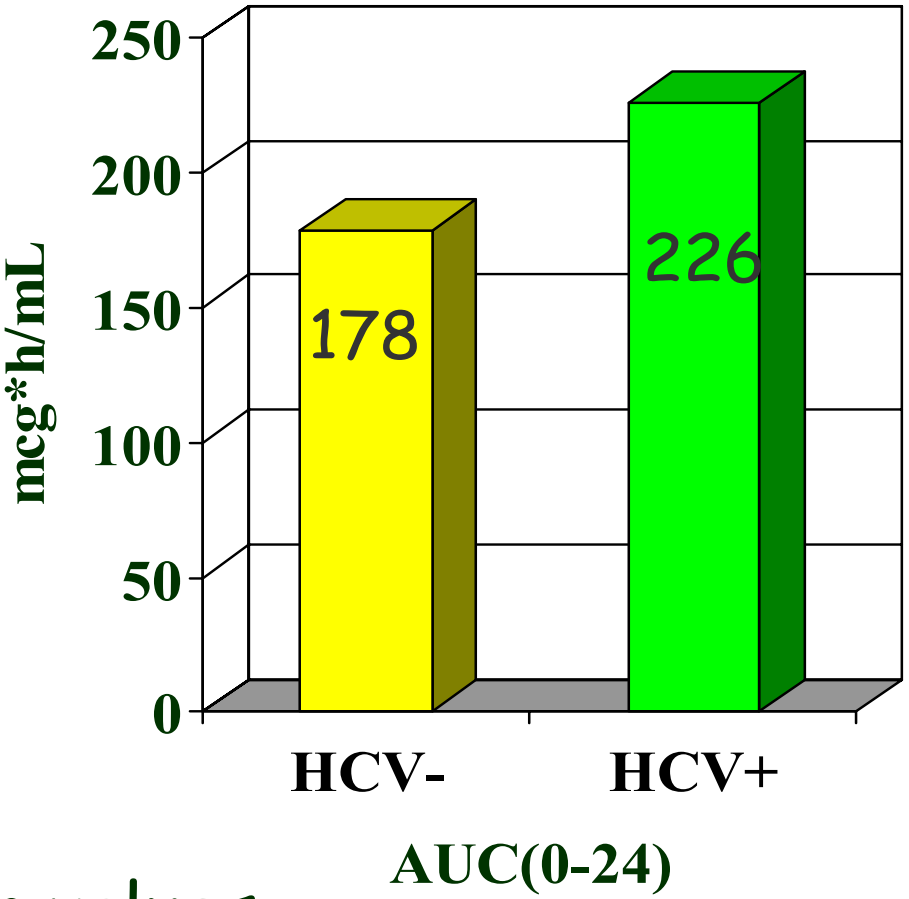


LPV: Ctrough and AUC

p=0.097



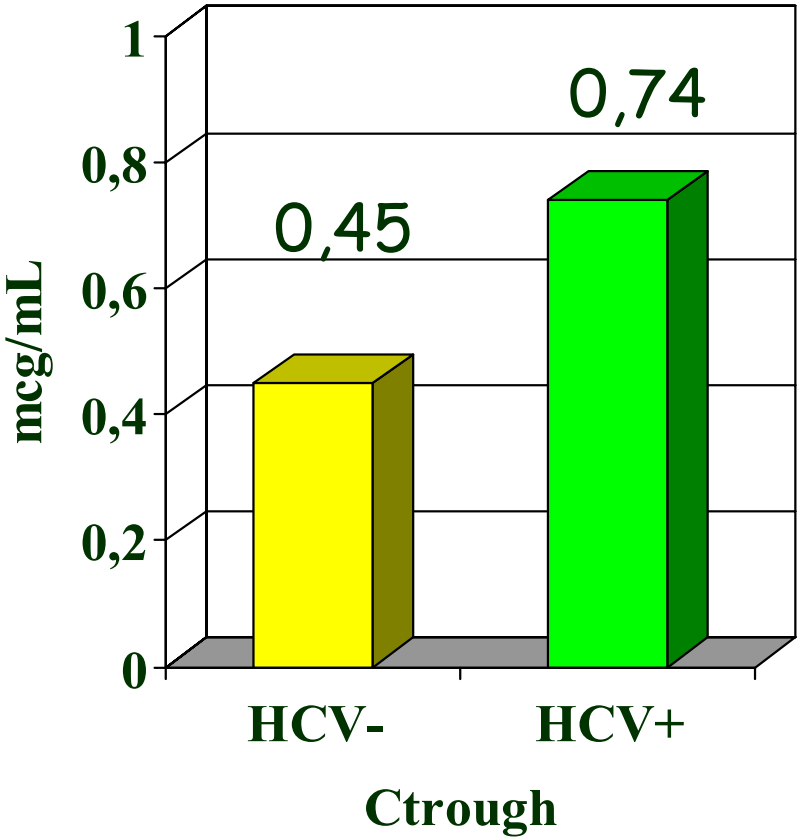
p=0.097



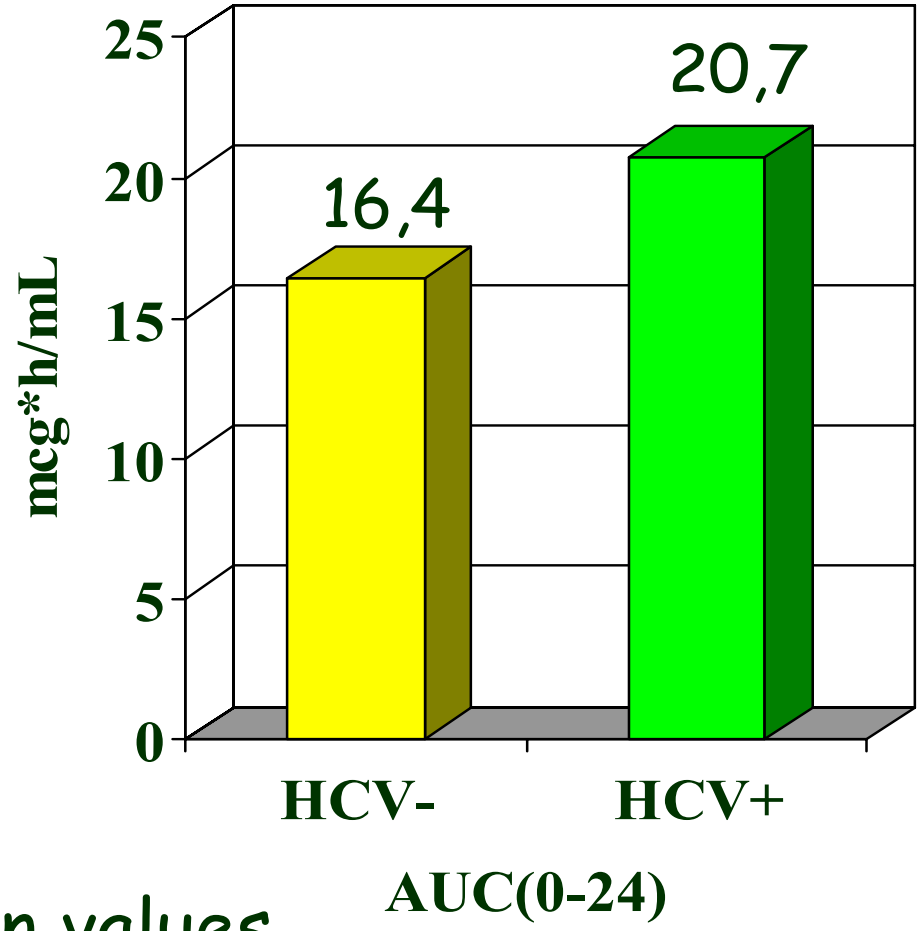
Mean values

RTV: Ctrough and AUC

p=0.08

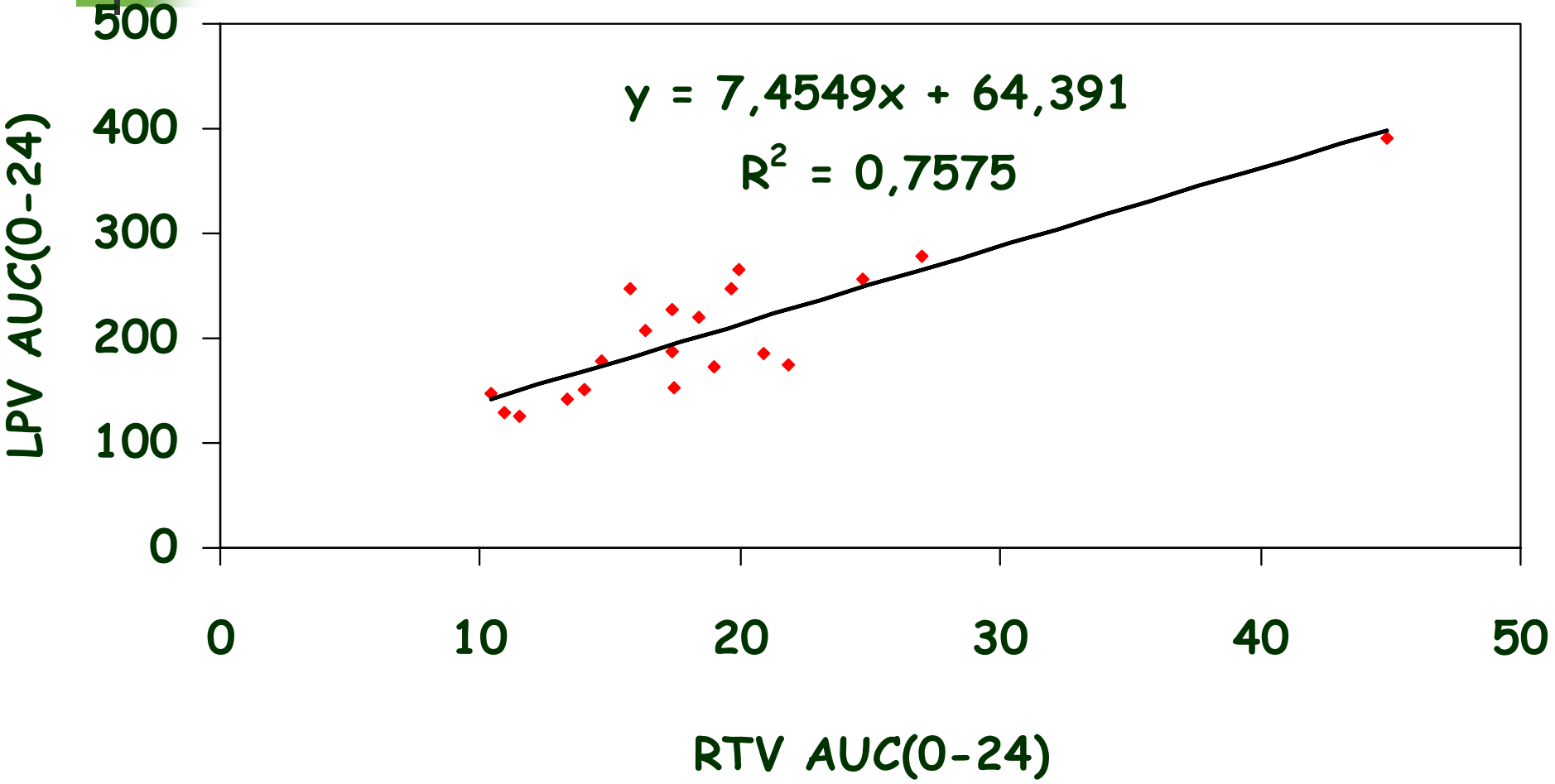


p=0.09



Mean values

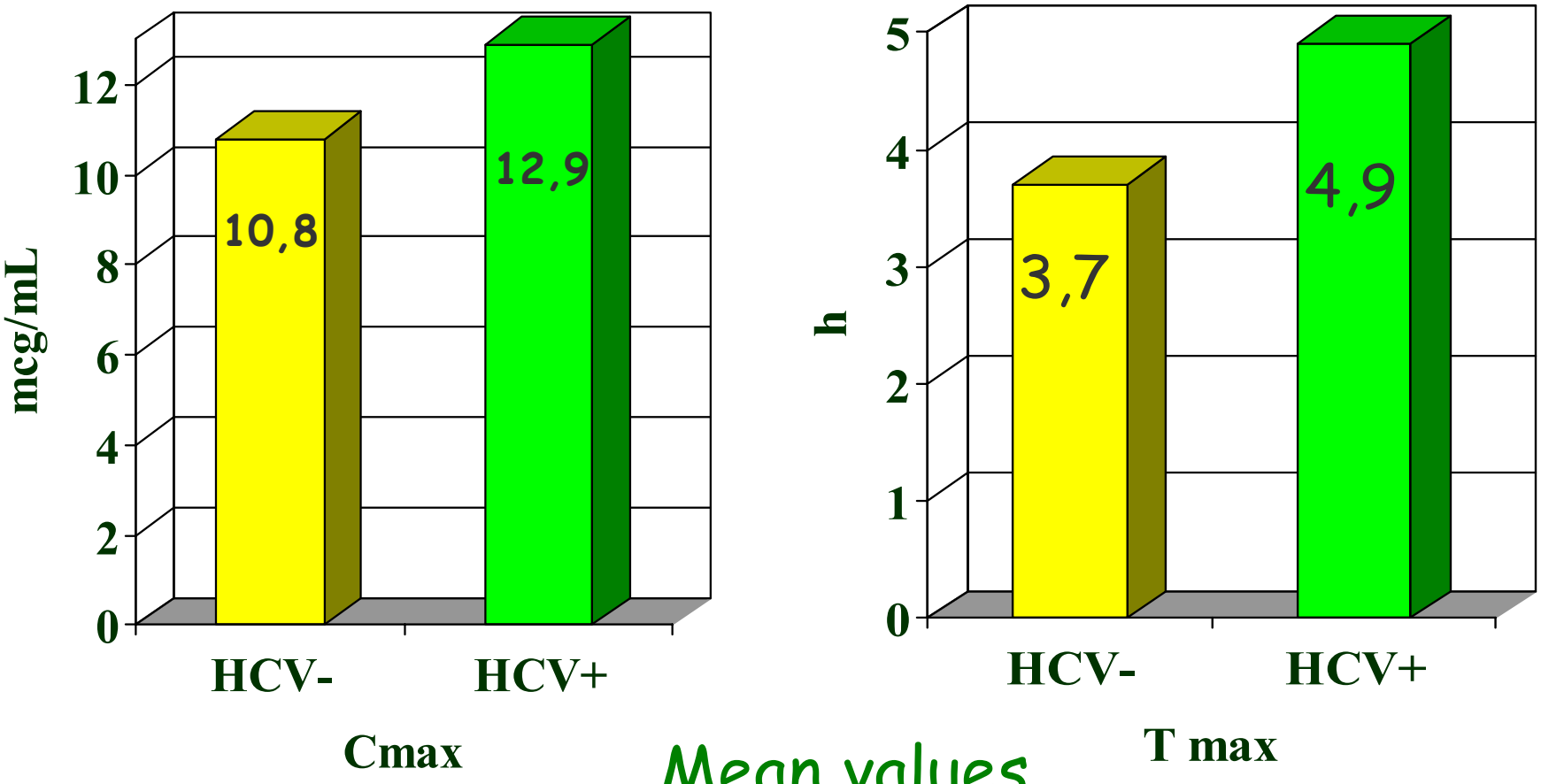
Relationship between LPV AUC_{0-24} and RTV AUC_{0-24}



LPV: Cmax and Tmax

p=0.06

p=0.029

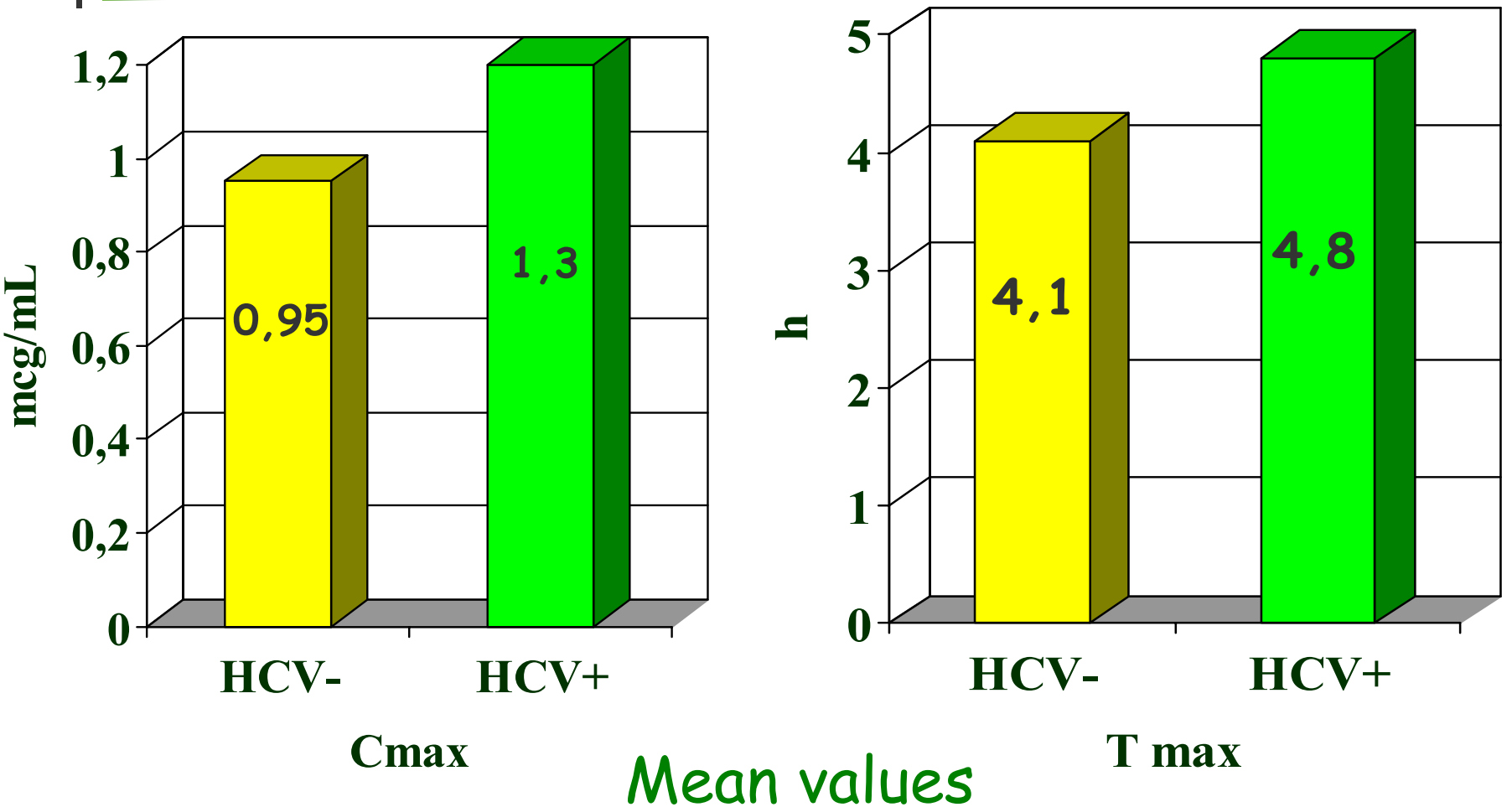


Mean values

RTV: Cmax and Tmax

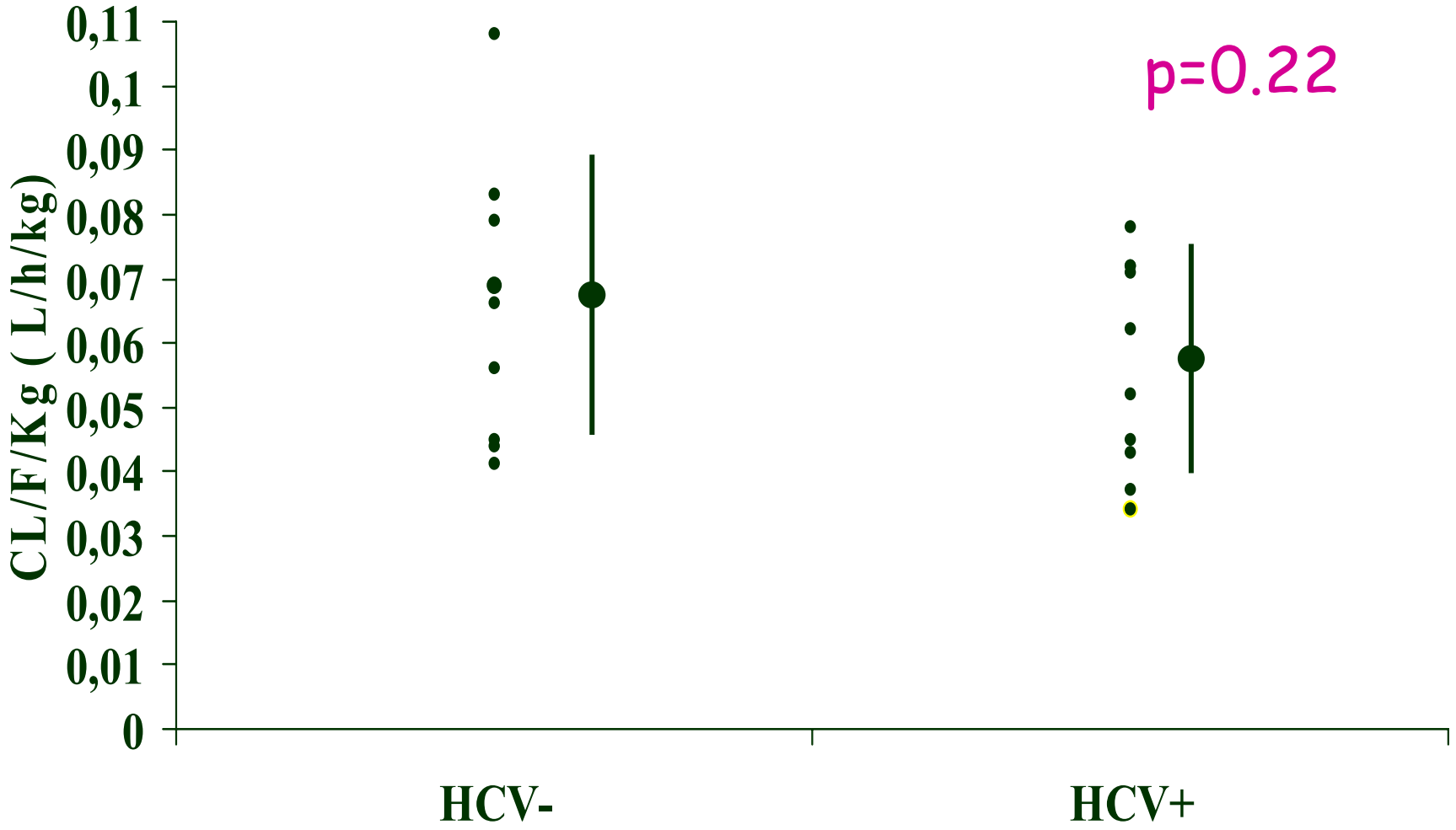
p=0.01

p=0.097

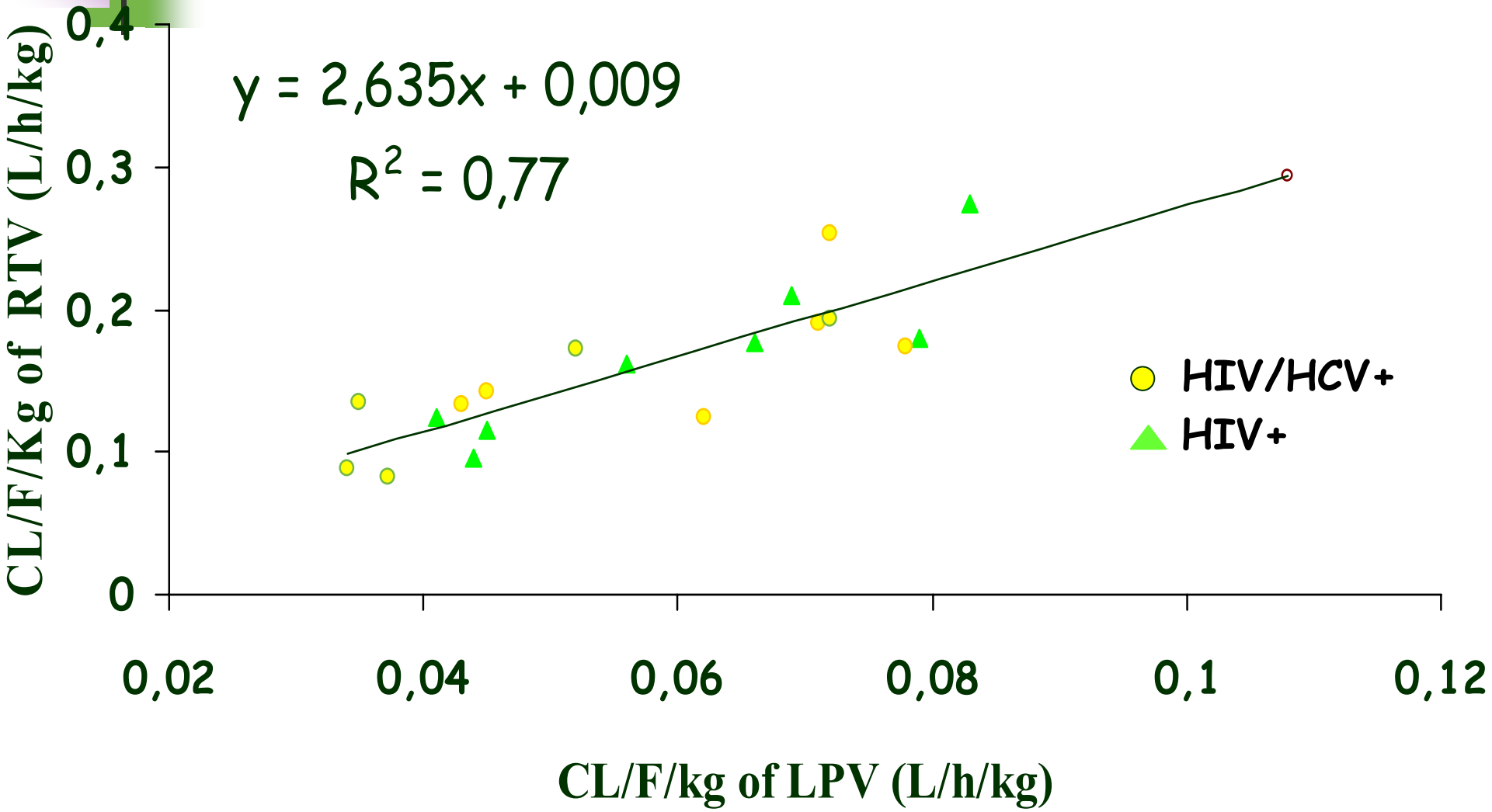


Mean values

LPV CL/F/kg distribution mean ± SD



Relationship between oral clearance (CL/F/Kg) of RTV and LPV



LPV RESULTS	CONTROL	HI	p
Dose/Kg (mg)	10.7±2.2	11.5±2.2	0.42
C_{trough} (µg/mL)	5.4±2.2	7.6±3.6	0.097
C_{max} (µg/mL)	10.8±1.8	12.9±3.3	0.06
T_{max} (hours)	3.7±1.0	4.9±1.3	0.029
AUC_{0-24} (µg*h/mL)	178.1±46.9	225.7±70.6	0.097
CL/F/Kg (L/h/Kg)	0.066±0.022	0.055 ±0.017	0.22

CONCLUSION (1)

- Our data confirmed previous evidences about an increase of LPV AUC_{0-24} in patients HIV/HCV co-infected (27% vs 30% of Arribas study).
- The correlation between LPV oral clearance and RTV oral clearance is an index of the metabolic capacity of the patient.
- We didn't find any correlation with adverse events onset and LPV pk parameters.

CONCLUSION (2)

- The delay in Tmax in HIV/HCV co-infected pts is probably correlated with a reduction in drugs absorption rate, causing LPV C_{trough} higher than in HIV+ control subjects.
- Our preliminary data don't support a dose adjustment in HIV/HCV pts starting an antiretroviral regimen including LPV/r.
- A dose adjustment is recommended on the basis of low both body weight and BMI, independently of HCV status.