

# Pharmacokinetics of Lopinavir in HIV-1 infected children

Hegoburu MS<sup>1</sup>; Curras V<sup>1</sup>; Höcht C<sup>1</sup>; Niselman V<sup>2</sup>; Mecikovsky D<sup>3</sup>; Bologna R<sup>3</sup>; Rubio MC<sup>1</sup>; Schaiquevich P<sup>4</sup>; Bramuglia GF<sup>1</sup>

<sup>1</sup>Cátedra de Farmacología, Facultad de Farmacia y Bioquímica, UBA

<sup>2</sup>Cátedra de Matemática, Facultad de Farmacia y Bioquímica, UBA

<sup>3</sup>Servicio de Control Epidemiológico e Infectología , Hospital de Pediatría Garrahan

<sup>4</sup> Unidad de Farmacocinética Clínica, Hospital de Pediatría Garrahan

Buenos Aires, Argentina

# Introduction

- Lopinavir is a protease inhibitor that can be administered in different pharmaceutical forms (syrup or tablets), co-administered with another PI, ritonavir, used as a booster, leading to less fluctuation of lopinavir levels in blood.
- Therapeutic drug monitoring of antiretroviral (ARV) is useful in treating HIV-1 infected children because pharmacokinetics of several ARV drugs differ in this population compared to adults. Moreover maturation of different organs involved in absorption and metabolism could be related to changes in pharmacokinetics of ARV drugs during child growth.

# Objectives

- Previous works have shown a great interindividual variability of lopinavir levels in children treated with lopinavir/ritonavir.
- The aim of our work was to study the lopinavir levels in HIV-1 infected children treated with different oral formulations of lopinavir/ritonavir and to study different co-variables that could be involved in pharmacokinetic variability of lopinavir in the pediatric population.

# Methods

- **Patients**

72 pediatric patients treated with lopinavir/ritonavir (Kaletra<sup>®</sup>, Abbott capsules, tablets or solution) were included. During routine clinical practice, lopinavir levels were determined from blood drawn before the administration of the next dose of lopinavir (C<sub>min</sub>) and between 1 and 4 hours after dose administration (C<sub>1</sub>). Dosage regimen was 12/3 mg/kg for those weighing 7-15 kg and 10/2.5 mg/kg for those weighing 15-40 kg twice daily. Demographic data, dose regimen, sampling times and co-medication were also registered.

We define sub therapeutic level when C<sub>min</sub> is lower than 1 µg/ml.

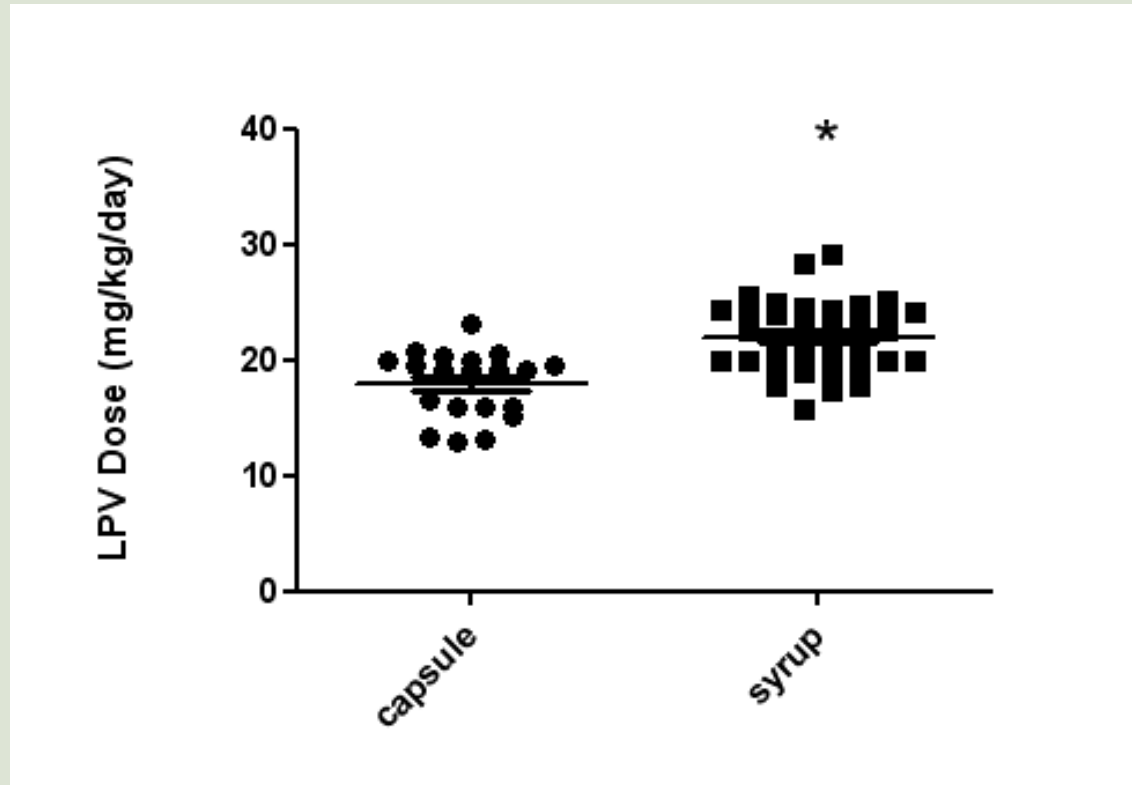
- **Analytical Method**

Lopinavir plasma concentrations were determined by HPLC method with UV detection (210 nm) after liquid-liquid extraction with ethyl ether. This method was validated over the range of 0.05-20 mg/l.

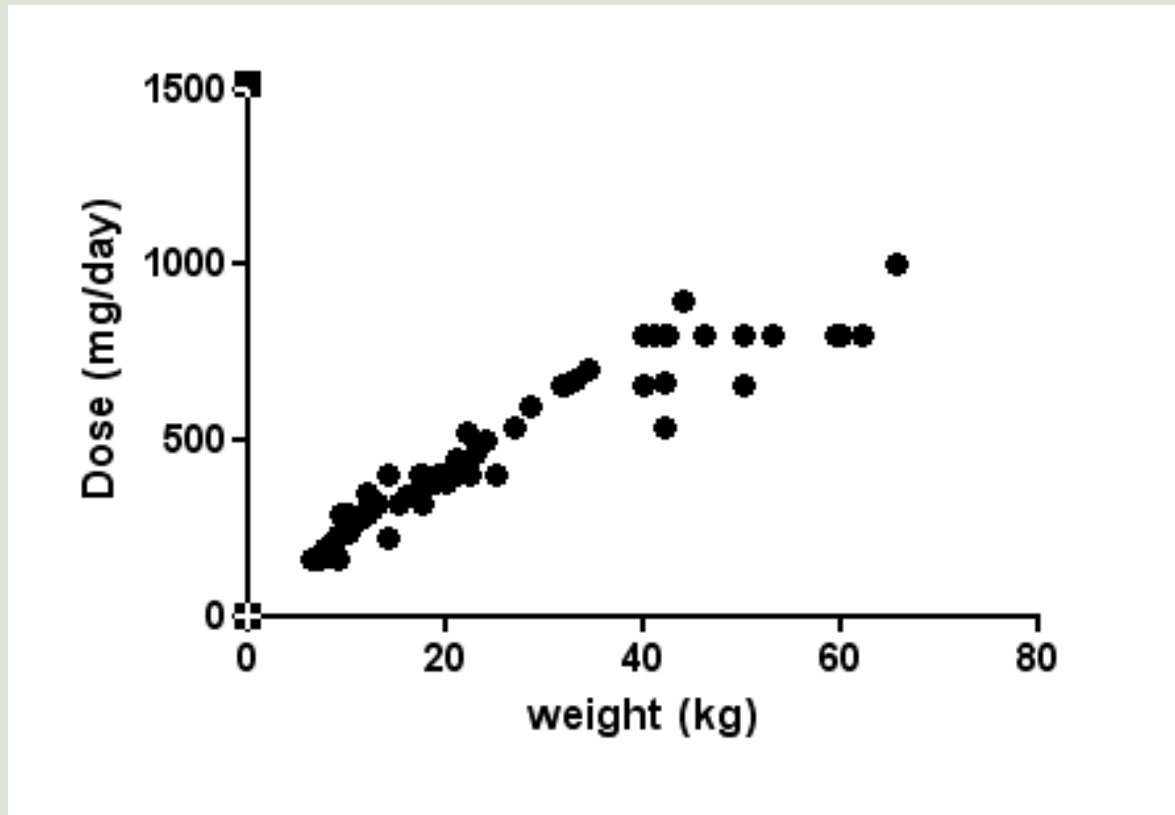
# Results

|                                 |                     |
|---------------------------------|---------------------|
| <b>Gender</b>                   |                     |
| Male                            | 33                  |
| Female                          | 39                  |
| <b>Age</b>                      | 4months-19years old |
| <b>Weight (kg)</b>              | 6,8 - 65,5          |
| <b>Plasma concentration (n)</b> | Cmin (70) C1 (45)   |
| Sub therapeutic                 | Cmin (17)           |
| <b>HAART</b>                    |                     |
| NRTI + PI                       | 68                  |
| NRTI + NNRTI + PI               | 4                   |
| <b>Previous exposure to PI</b>  |                     |
| Naïve                           | 31                  |
| Experienced                     | 41                  |

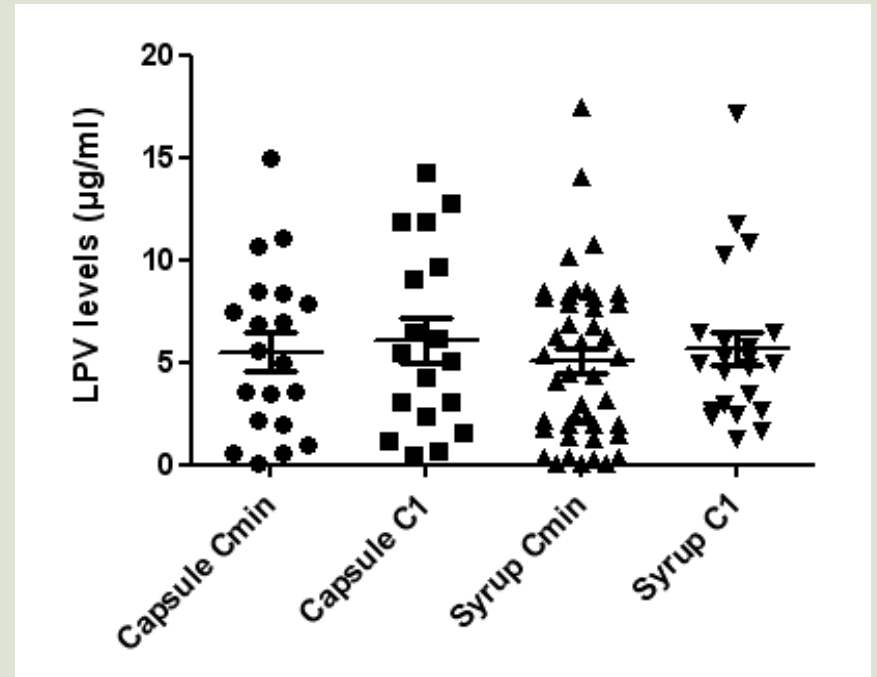
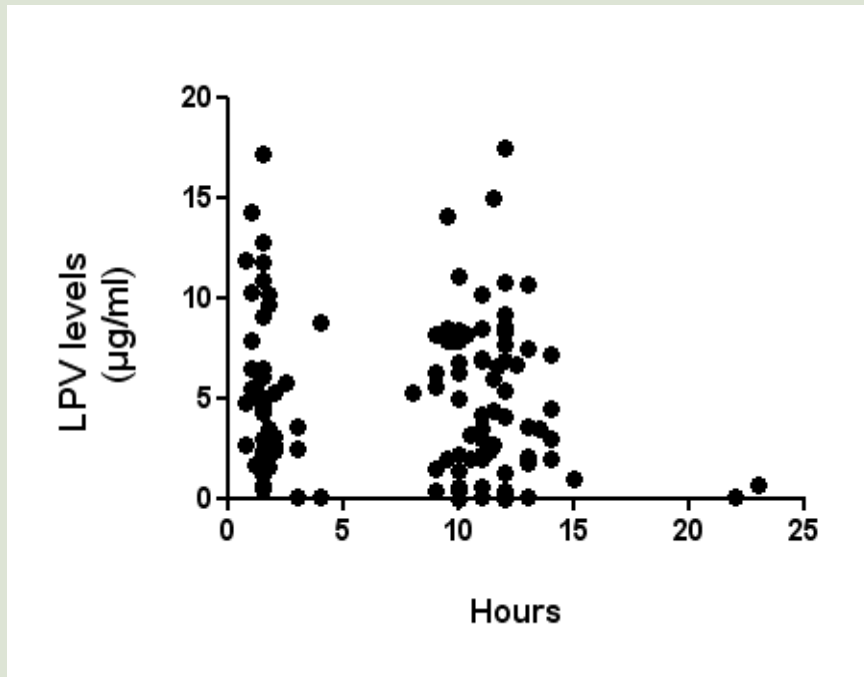
# Results



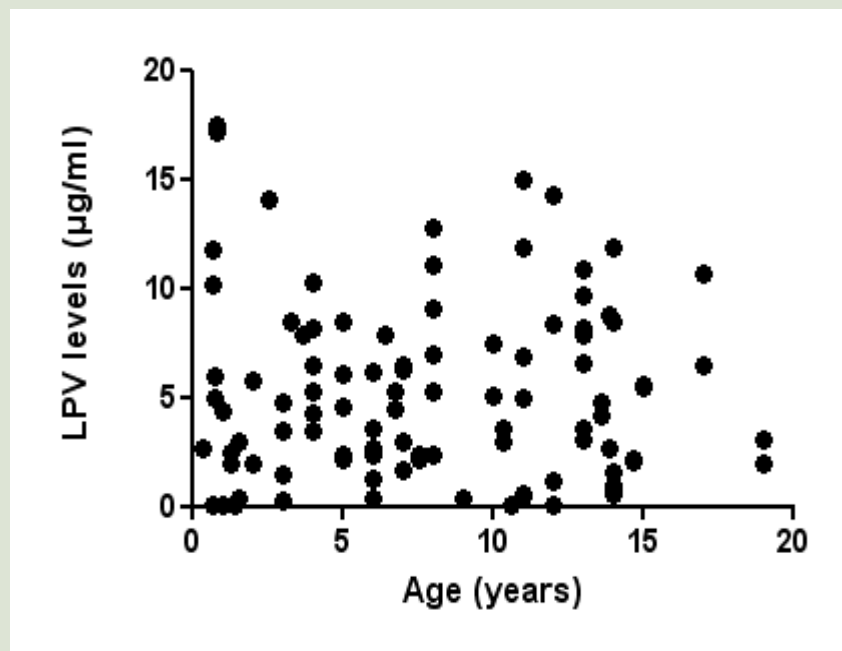
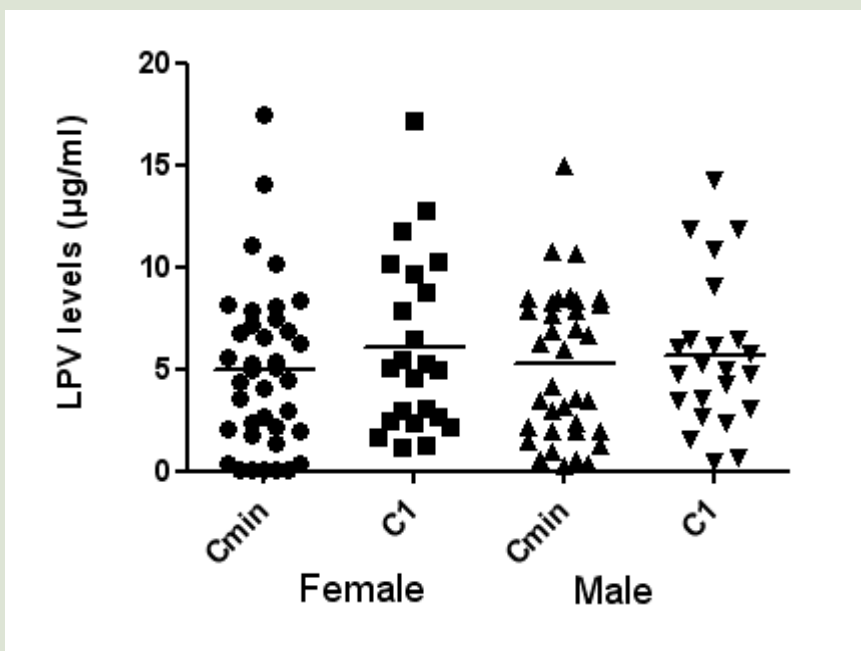
# Results



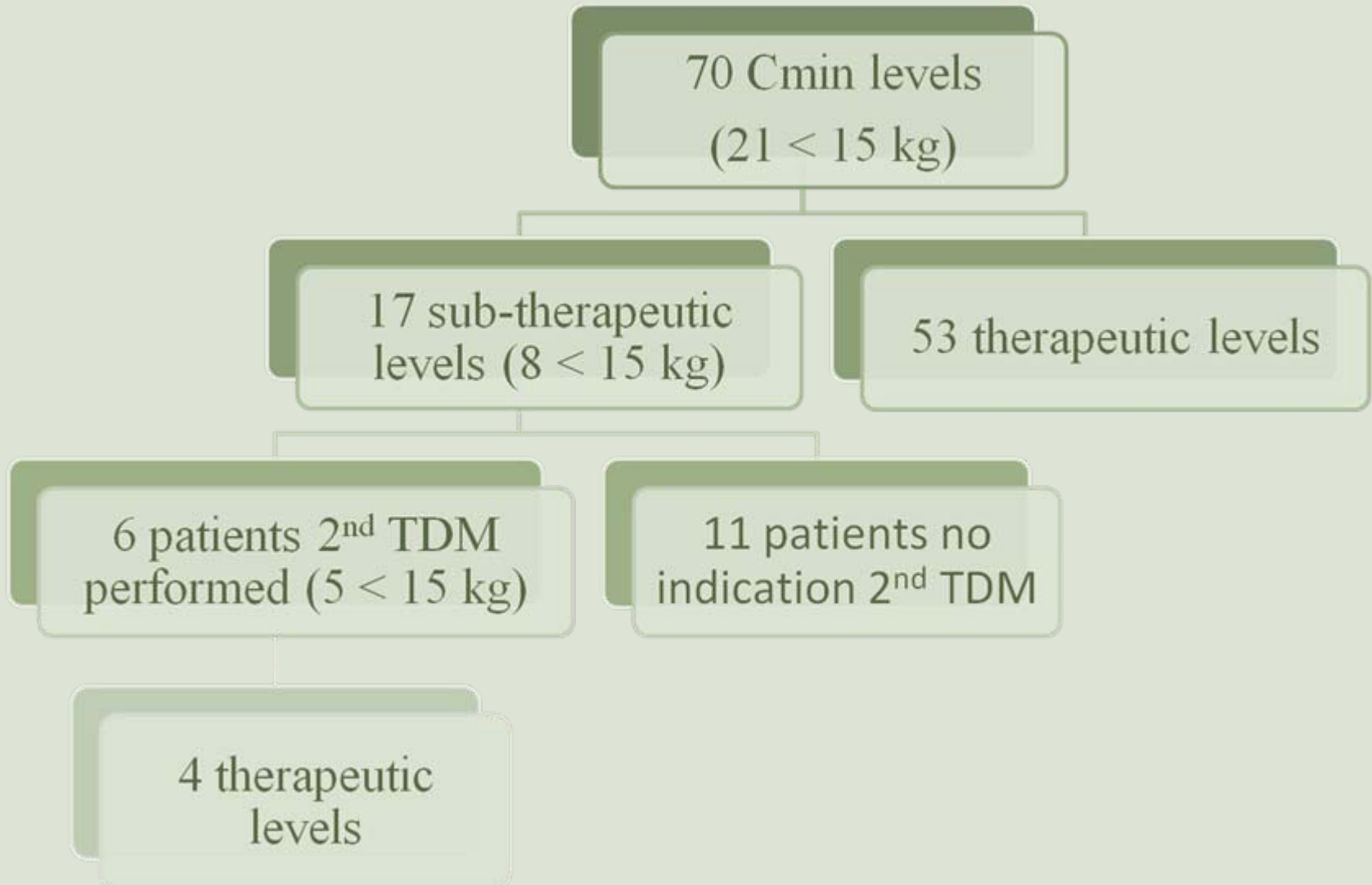
# Results



# Results



# Results



# Results

| patient | 1 <sup>st</sup> TDM | Possible reason                        | Indications                  | 2 <sup>nd</sup> TDM |
|---------|---------------------|--|------------------------------|---------------------|
| 1       | <0.05 µg/ml         | Bowel infection/Absorptive dysfunction | Dose modified                | <0.05 µg/ml         |
| 2       | 0.09 µg/ml          | ?                                      | Dose modified                | 9.13 µg/ml          |
| 3       | <0.05 µg/ml         | Drug interaction                       | TB treatment modified        | 2 µg/ml             |
| 4       | 0.06 µg/ml          | Drug intolerance/non compliance        | Dose not modified            | <0.05 µg/ml         |
| 5       | 0.08 µg/ml          | Suspected non compliance               | Support adherence strategies | 1.32 µg/ml          |
| 6       | 0.06 µg/ml          | Suspected non compliance               | Support adherence strategies | 6.23 µg/ml          |

# Discussion

- A great inter-individual variability of lopinavir levels was observed (CV Cmin: 74,6%, C1: 65,7%).
- Lopinavir levels did not show statistical significant differences following administration of different formulations.
- There was no a correlation between plasma levels of lopinavir and age or gender.
- Cmin levels  $< 1 \mu\text{gr}/\text{ml}$  : 38%  $<15 \text{ kg}$  vs 18%  $>15\text{kg}$
- The great variability of lopinavir levels together with the detection of sub-therapeutic levels (non compliance, drug interaction, other reasons) could make TDM advisable in children who are treated with lopinavir/ritonavir in order to optimize ARV treatment.