

**Poster 660, Abstract L-161**

**Lopinavir/ritonavir parameters of systemic exposure in HIV-infected children following BID or QD administration**

**Raffaella Rosso\*<sup>1</sup>, Antonio Di Biagio<sup>1</sup>, Chiara Dentone<sup>1</sup>, Matteo Bassetti<sup>1</sup>, Antonio Ferrazin<sup>1</sup>, Guido Castelli Gattinara<sup>2</sup>, Alessandra Viganò<sup>3</sup>, Marzia Merlo<sup>3</sup>, Carlo Giaquinto<sup>4</sup>, Osvalda Rampon<sup>4</sup>, and Dante Bassetti<sup>1</sup>**

Infectious Diseases Clinic, University of Genoa, Genoa, Italy<sup>1</sup>; Bambin Gesù Children's Hospital, Rome, Italy<sup>2</sup>; Luigi Sacco Hospital, Milan, Italy<sup>3</sup>; and University of Padua, Padua, Italy<sup>4</sup>

**Address for correspondence:**

Raffaella Rosso, MD  
Infectious Diseases Clinic, San Martino Hospital  
Padiglione 26, Piano -2  
Largo Rosanna Benzi, 10  
16132 Genoa, Italy  
Phone +39 010 5555134  
Fax + 39 010 3537680  
Raffaella.Rosso@unige.it

**Background:** There is evidence that adherence to HAART predicts and is related to the virological and clinical response to therapy. Although not proven, it is likely that adherence and quality of life will be improved using once daily (QD) regimens in HIV-infected adults. Few studies have shown the efficacy and safety of a QD regimen in HIV infected-children and adolescents. Current guidelines recommend to treat HIV-infected children with the same principles of treatment used in adults and include lopinavir/ritonavir (LPV/r) in first-line antiretroviral regimens for naïve children. LPV/r has been developed as a twice-daily (BID) drug, however, it is under debate whether QD

regimen may be used in naive adults patients. Pharmacokinetics and pharmacodynamic characteristics of LPV/r have not been properly defined in children.

The study was designed to examine pharmacokinetics of QD vs BID of LPV in HIV-infected children.

### **Methods:**

This open-label prospective, comparative clinical trial was conducted at 3 large Italian Hospital. Subjects included in this study were children  $> 2$  and  $\leq 14$  years old with vertically acquired HIV-1 infection. There was no CD4+ cell count or plasma HIV-RNA levels restriction (table 1). All were naïve to protease inhibitors (PIs).

Patients received LPV/r at dosage of 230/57.5 mg/m<sup>2</sup> BID or 460/115 mg/m<sup>2</sup> QD. LPV/r was associated to 2 NRTIs or 1 NRTI + 1 NNRTI on the basis of previous antiretroviral regimens and of drug resistance test (when available). In children receiving NNRTI, dosage of LPV/r was adjusted according to US DHHS: doses has been of 300/75mg/m<sup>2</sup> BID and 600/150 mg/m<sup>2</sup> QD.

### **Sample collection and processing**

Blood samples (5-7 mL) were drawn in tubes containing EDTA before a morning dose of LPV/r (C min) and 1 h, 2 h e 4 h (C max) after administration of the morning dose; plasma was separated by centrifugation, and stored at  $-20^{\circ}\text{C}$ . LPV through plasma levels were obtained after at least 4 week of treatment.

### **Analytical methods**

LPV concentrations in plasma were determined by a high-pressure liquid chromatography assay (HPLC) developed and validated in Pharmacokinetic Lab. The HPLC analysis used a reverse-phase C18 analytical column and a mobile phase consisting of a gradient with 15-mM phosphate buffer (pH 5,75)-acetonitrile and UV monitoring. The analysis was via UV detection at 210 nm using a reversed-phase column.

### **Results:**

The variability of PK parameters was extremely high. Cmin resulted lower with the QD regimen with respect to the one observed with BID regimen ( $p < 0.05$ , Mann-Whitney U test). Cmax were not significantly different. Analysis of the correlation between BMI and pharmacokinetics parameters did not reveal any significant correlation (BMI and Cmax,  $p = 0.4043$ ; BMI and Cmin  $p = 0,3919$ ) (Tab. 2, Fig. 1,2).

### **Discussion and conclusion:**

QD of LPV/r dosing regimen can achieve similar C<sub>min</sub> and C<sub>max</sub> concentrations observed in the BID pediatric pharmacokinetics studies (C<sub>max</sub> 8.2 ± 2.9, C<sub>min</sub> 3.4 ± 2.1 µg/ml). Those concentrations may be sufficient to inhibit the replication of wild type virus in most of the children. Therefore, a clinical trial of QD LPV/r in children is warranted.

### **Bibliografia**

- Gortmaker SL, Hughes M, Cervia J, et al. Effect of combination therapy including protease inhibitors on mortality among children and adolescents infected with HIV-1. *N Engl J Med* 2001; 345:1522-1528
- U.S. DHHS. Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection November 30, 2004
- Resino S, Bellon JM, Ramos J T, et al. Positive virological outcome after lopinavir/ritonavir salvage therapy in protease inhibitor-experienced HIV-1-infected children: a prospective cohort study. *J Antimicrob Chemother* 2004;54:921-31
- Back D, Flexner C. Therapeutic Drug Monitoring: its use in the care of patients with HIV infection. The ART of HIV Management Series. *Abbott Laboratories*, 2002

We would like to thank **all children and parents**.

Financial Support: **Abbott SpA**

**Table 1. Demographics at PK analysis**

Number of children	28
Gender (females)	17
Race	4 Hispanic, 5 Black, 19 Caucasian
Age median (years)	9.25, range: 3.5-14
CDC class	2 N2, 2 A2, 3 B1, 3 B2, 4 B3,3 C2,11 C3
Length of therapy with LPV/r (months)	18.5, range: 4-44
Weight (median)	24.9 Kg, range: 8.3-39.0
BMI (median)	16.51, range: 7.68-21.64
Median CD4+ (cell/mm <sup>3</sup> )	450, range: 4-1452
Median CD4 (%)	20, range: 1-35
Median viral load (copies/mL)	121,500, range: 3,900-1,900,000

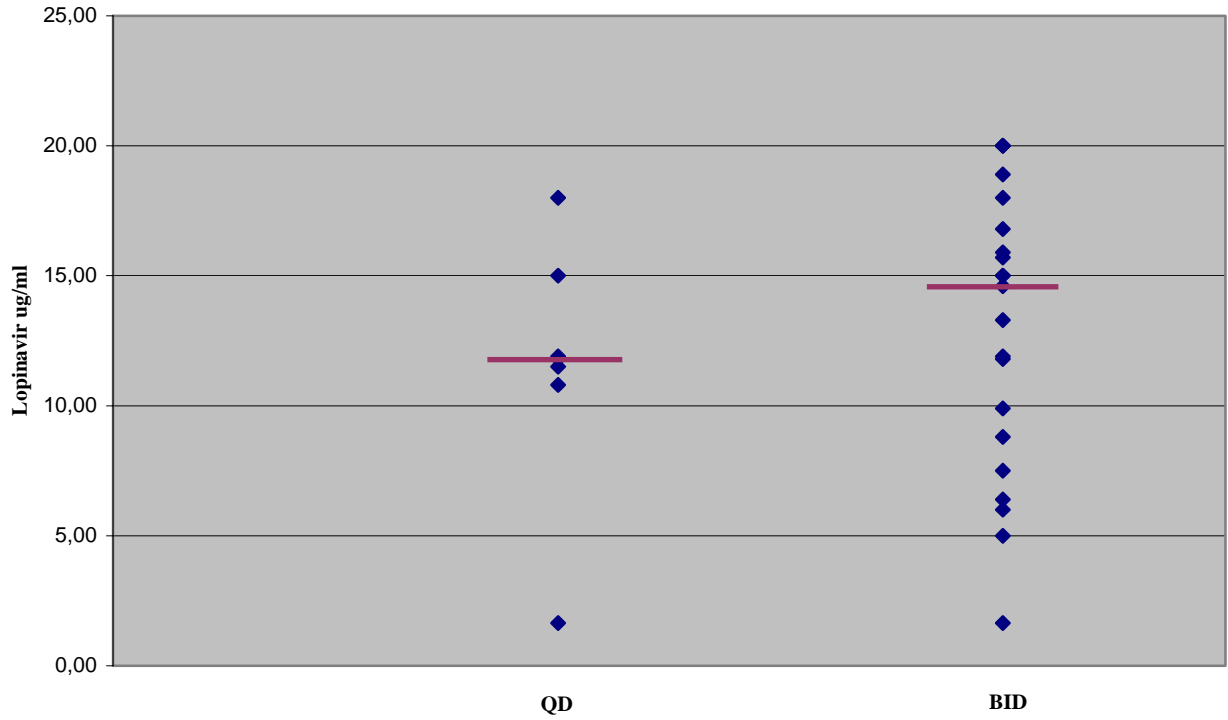
**Table 2. Peak and trough plasma concentrations**

<b>ONCE DAILY</b>	Median	mean	SD	range
Cmax	11.80	11.52	5.04	10.80-18.00
Cmin	1.59	4.30	5.07	0.00-9.00

<b>BID</b>	Median	mean	SD	range
Cmax	14.60	12.96	5.45	1.65-20.00
Cmin	7.90	9.32	5.49	0.00-20.00

**Fig. 1**

**Lopinavir plasma peak levels QD vs BID**  
(Median values: 11.80 vs 14.60  $\mu\text{g/ml}$ )



**Fig. 2**

**Lopinavir plasma trough levels QD vs BID**  
(median: 1.59 vs 7.90  $\mu\text{g/ml}$ )

