# Pharmacokinetics and safety of once daily versus twice daily lopinavir/ritonavir in pediatric HIV infected patients

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## Background

Limited data are available for the use of once daily lopinavir/ritonavir in pediatric patients. This study was done to investigate the pharmacokinetics and safety of once daily lopinavir/ritonavir compared to twice daily lopinavir/ritonavir in pediatric patients.

## Methods

### Study design

This was a phase-I, open-label, cross-over pharmacokinetic study in pediatric patients. See figure 1 for details. HIV-1-infected children aged 6 months to 18 years and virologically suppressed on a lopinavir/ritonavir containing regimen, were eligible. Treatment 1 consisted of once daily lopinavir/ritonavir 460/115 mg per m2, plus 2 NRTIs. Treatment 2 consisted of twice daily lopinavir/ritonavir 230/57.5 mg per m2 plus 2 NRTIs. Patients were randomized to start with treatment 1 followed by treatment 2 or vice versa. Lopinavir/ritonavir was given as soft gel capsules or oral solution, combining of both was not permitted. After a minimum of 14 days serial blood sampling was done at the clinic. Blood samples were drawn immediately before and at 2, 4, 6, 8, and 12 hours (+24 hours for once daily treatment) after dosing.

**Figure 1. Study design**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| LPV/r BID (14 d) | → | PK | → | LPV/r QD (14 d) | → | PK |
| LPV/r QD (14 d) | → | PK | → | LPV/r BID (14 d) | → | PK |

PK = pharmacokinetics
LPV/r = lopinavir/ritonavir
14 d = 14 days

### Selection of subjects

***Inclusion Criteria:***

- HIV-infected children aged 6 months - 18 years.
- Being on LPV/r plus 2 nucleoside reverse transcriptase inhibitors (NRTI) for at least 2 weeks prior to study entry.
- At least 2 consecutive plasma HIV RNA < 400 copies/ml prior to study entry while on LPV/r containing regimen.
- CD4 lymphocyte ≥ 15% at screening.
- Written informed consent signed by parent/legal guardian.

***Exclusion Criteria:***

- Presence of protease inhibitors other than LPV/r, non-nucleoside reverse transcriptase inhibitors or investigational drugs in the current treatment regimen.
- Prior exposure to protease inhibitors, except nelfinavir.
- Presence of malabsorption, emesis or diarrhea at screening.
- Female patients of reproductive potential who are unwilling to use an effective method of contraception, or who are pregnant or breast feeding.
- Hemoglobin < 8.0 gm% at screening.
- AST > 180 IU/L at screening.
- ALT > 215 IU/L at screening.
- Ongoing/active opportunistic infections.

### Bioanalysis

Plasma lopinavir and ritonavir concentrations were analysed with a validated assay using liquid chromatography coupled to tandem mass-spectrometry. Sample pre-treatment was done using protein precipitation with methanol.

### Pharmacokinetics

Pharmacokinetic parameters including AUC, Cmax, Tmax, C12, C24, t1/2, CL/F and Vd/F were calculated with WinNonlin using non-compartmental techniques.

### Safety

Clinical data on co-medications and safety were collected as well.

## Results

### Study population

7 patients, 5 girls and 2 boys, were included in the study. Median age was 9.8 years (range 5.8 to 15.5 years). See details in Table 1. Backbone therapy consisted of d4t and ABC for 4 children, AZT and 3TC for 2 children and AZT + ABC for 1 child. Other co-medications included multivitamins (for one patient), trimethoprim-sulfamethoxazole (for one patient) and polyvisol, loratidine and fluticasone (for one patient). None of these medications are known to influence the pharmacokinetics of the study medication. Nevertheless, fluticasone is not advised to be given with ritonavir due to risk of Cushing syndrome.

**Table 1. Patient characteristics**

| | | | QD treatment | | | BID treatment | | |
|---|---|---|---|---|---|---|---|---|
| # | Gender | Age (years) | BSA (m2) | form | QD dose (mg) | BSA (m2) | form | BID dose (mg) |
| 1 | female | 9.8 | 0.98 | OS | 448/112 | 0.98 | OS | 224/56 |
| 2 | male | 11.1 | 1.54 | OS | 712/178 | 1.54 | OS | 352/88 |
| 3 | female | 7.7 | 0.91 | SGC | 400/100 | 0.92 | OS | 208/52 |
| 4 | female | 6.6 | 0.73 | OS | 336/84 | 0.76 | OS | 176/44 |
| 5 | female | 15.5 | 1.51 | SGC | 666/167 | 1.51 | OS | 347/87 |
| 6 | male | 5.8 | 0.78 | OS | 363/91 | 0.78 | OS | 182/46 |
| 7 | female | 14.3 | 1.23 | OS | 560/140 | 1.22 | OS | 280/70 |

OS = oral solution, SGC = soft gel capsules

### Pharmacokinetics

For one patient pharmacokinetic data were missing for the twice daily treatment, as IV access was not successful and the patient was discontinued from the study. See figures 2 and 3 and table 2 for lopinavir PK data. For the once daily treatment the median (range) for the lopinavir AUC24, Cmax and C24 were: 214.6 (114.2-289.2) hr*mg/L, 13.5 (8.3-17.5) mg/L and 3.4 (0.6-7.4) mg/L, respectively. For the twice daily treatment the median (range) lopinavir AUC12, Cmax and C12 were: 80.9 (23.3-135.9) hr*mg/L, 9.8 (3.4-15.2) mg/L and 5.7 (1.7-9.7) mg/L, respectively. For ritonavir median (range) AUC24, Cmax and C24 for once daily were: 13.4 (4.5-20.8) hr*mg/L, 1.1 (0.4-1.9) mg/L and 0.04 (0.01-0.20) mg/L. For twice daily ritonavir median (range) AUC12, Cmax and C12 were: 4.9 (0.4-14.2) hr*mg/L, 0.34 (0.04-1.4) mg/L and 0.12 (0.01-0.26) mg/L.

**Figure 2. Mean lopinavir concentration - time plots**

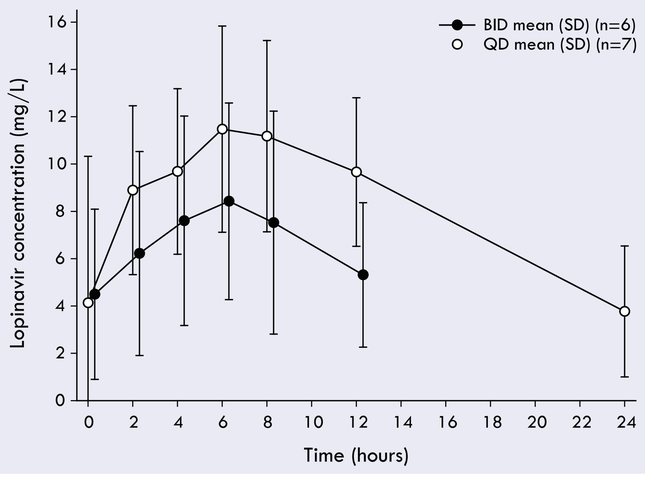


**Figure 3. Lopinavir Cmax and Clast in Box Plots**

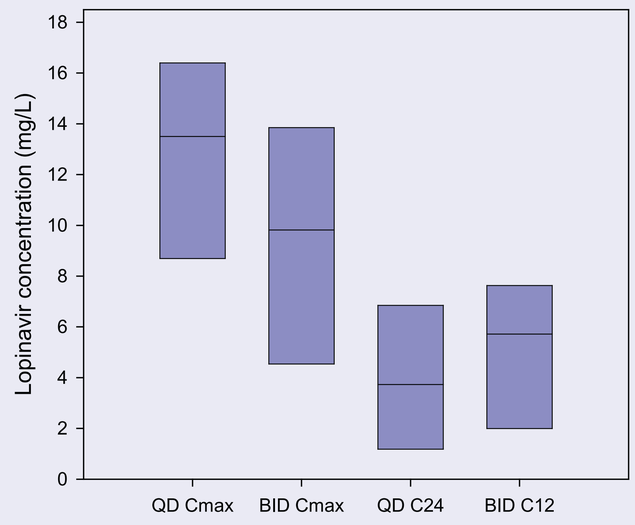


**Table 2. Individual lopinavir pharmacokinetics**

| | # | AUC** (hr*mg/L) | Cmax (mg/L) | Clast** (mg/L) | Tmax (hr) | t1/2 (hr) | Vd/F (L) | CL/F (L/hr) |
|---|---|---|---|---|---|---|---|---|
| QD | 1 | 289.2 | 16.4 | 7.4 | 6.0 | 14.3 | 32.0 | 1.5 |
| | 2 | 169.4 | 9.3 | 3.7 | 4.0 | 12.3 | 74.6 | 4.2 |
| | 3 | 260.6 | 17.5 | 3.1 | 0.0 | 6.8 | 14.9 | 1.5 |
| | 4 | 217.3 | 13.5 | 6.6 | 8.0 | 15.1 | 33.6 | 1.5 |
| | 5* | 116.5 | 8.7 | 6.9 | 8.0 | n/a | n/a | 0.0 |
| | 6 | 114.2 | 8.3 | 0.6 | 4.2 | 4.9 | 22.3 | 3.2 |
| | 7 | 214.6 | 15.5 | 1.2 | 6.0 | n/a | n/a | 0.0 |
| | median | 214.6 | 13.5 | 3.7 | 6.0 | 12.3 | 32.0 | 1.5 |
| BID | 1 | 88.2 | 9.4 | 6.5 | 6.0 | 11.8 | 43.2 | 2.5 |
| | 2 | 130.9 | 13.4 | 7.0 | 4.0 | 7.6 | 29.3 | 2.7 |
| | 3 | 23.3 | 3.4 | 1.7 | 8.0 | n/a | n/a | 0.0 |
| | 4 | 135.9 | 15.2 | 9.7 | 8.0 | n/a | n/a | 0.0 |
| | 5 | 73.6 | 10.2 | 4.9 | 6.0 | 6.3 | 43.2 | 4.7 |
| | 6 | 38.9 | 4.9 | 2.1 | 1.5 | 9.4 | 62.0 | 4.6 |
| | median | 80.9 | 9.8 | 5.7 | 6.0 | 8.5 | 43.2 | 3.6 |

* for patient # 5 AUC is based on the assumption that C24 was 0 mg/L. Clast in this patient was C12.
** AUC is AUC24 for QD and AUC12 for BID, Clast is C24 for QD and C12 for BID

### Safety

Patient # 1 experienced emesis 4 times while on once daily treatment and patient # 7 experienced emesis one time while on twice daily treatment. No other adverse events were related to the study medication.

## Conclusions

In this study the pharmacokinetics of lopinavir and ritonavir in pediatric patients after once daily dosing were comparable to twice daily dosing. In this study short term once daily lopinavir/ritonavir seems generally well tolerated.

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