

LOPINAVIR POPULATION PHARMACOKINETIC MODEL AND DOSE SIMULATION PREDICTS RAPID INCREASE IN EXPOSURE FOR HIV-INFECTED INFANTS INITIATING THERAPY <6 MONTHS OF AGE (IMPAACT/PACTG P1030)

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INTRODUCTION

The incidence of mother to fetal HIV-1 transmission has been dramatically decreasing world-wide with the use of antiretroviral agents. Single-dose nevirapine to mothers and infants is highly effective in preventing transmission in resource limited settings, however infants that do become infected are likely to harbor nevirapine resistant virus. Thus, alternative therapies are needed for young HIV infected infants exposed to nevirapine [1]. Lopinavir (LPV) is an antiretroviral agent which inhibits the HIV protease enzyme required to generate functional viral proteins. Ritonavir (RTV) inhibits LPV metabolism, allowing lower and less frequent dosing of LPV [2, 3]. A combination of LPV and RTV (LPV/r) has been proposed as a primary therapy for HIV-positive infants and has been shown to be safe and effective in infants and children over 6 weeks of age [4]. We have previously shown that LPV/r exposure in infants <6 weeks of age receiving 300 mg/75 mg m² every 12 hours is lower than other pediatric populations receiving recommended doses [5, 6]. However, the exact age at which LPV pharmacokinetics become similar to older populations is poorly understood. In the current study, we have performed a population pharmacokinetic (PK) analysis to characterize maturational changes in LPV pharmacokinetics and assess dosing requirements in infants.

METHODS

Study Design: 31 HIV-infected infants ≥14 days to <6 months of age participated in a prospective Phase I/II, open label, dose finding study. Infants received lopinavir 300 mg/m²/ritonavir 75 mg/m² twice per day and 2 other antiretroviral agents (NRTIs) chosen by the site investigator.

Pharmacokinetics: Intensive PK profiles were determined at Week 2 of the study and when subjects reached 1 year of age. These 12 hour LPV PK profiles consisted of 5 samples each (Pre, 2, 4, 8, and 12 hr). Infants not reaching target LPV exposure at the Week 2 visit (C_{pre}>1 mcg/mL and AUC<170 mcg*hr/mL) had the dose modified and a repeat PK analysis was performed 2 weeks later. Pre-dose levels (sparse data) were drawn every 4-12 weeks throughout study (up to 4 years). LPV and RTV concentrations were determined by LC/MS/MS method with a lower limit of quantitation 0.1 (LPV) and 0.05 (RTV) mcg/mL.

PK analysis: A population pharmacokinetic model was developed using 549 LPV concentrations (intensive and sparse data) using the program NONMEM and allometric weight scaling. Empiric post-hoc LPV PK parameter estimates were generated from visits with multiple samples. The final model was used in Monte Carlo simulations (MC) to assess LPV dosing requirements.

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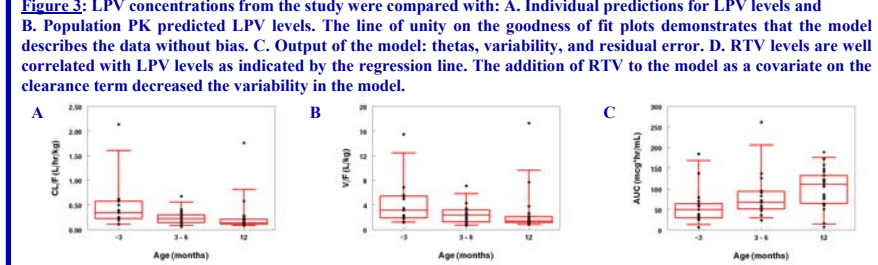
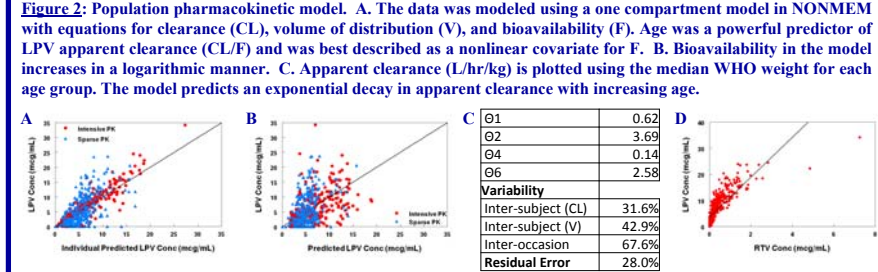
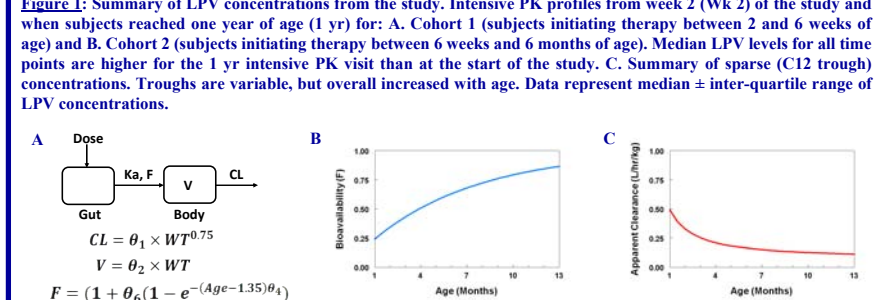
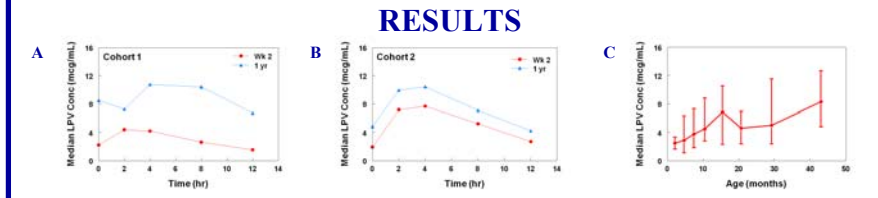


Figure 4: Post-hoc estimates of CL/F, V/F, and AUC by age group (<3 months, 3-6 months, and 1 year of age) for intensive PK data. A. The median clearance (CL/F) decreases with increasing age: 0.34 (<3m), 0.22 (3-6m), 0.13 (~1yr) L/hr/kg. B. Median volume of distribution (V/F) decreases with increasing age: 3.2 (<3m), 2.4 (3-6m), 1.4 (~1yr) L/kg. C. Median AUC increases with increasing age: 49.8 (<3m), 67.1 (3-6m), 111.0 (~1yr) mcg*hr/mL. Thus, LPV AUC in a typical infant reaches the adult value of 80 mcg*hr/mL by 9 months of age.

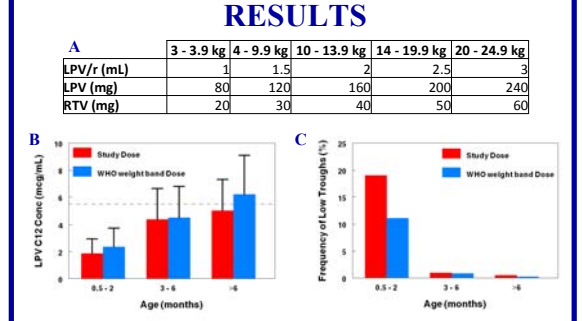


Figure 5: Monte Carlo simulations using the study dose (300 mg/m²) and WHO weight band dosing recommendations. A. Table of WHO weight band dosing. LPV/r (mL) represents a liquid formula of LPV/RTV corresponding to 80 mg LPV and 20 mg RTV. B. LPV trough concentrations (C12) for each age group (0.5-2m, 3-6m, >6m) are similar with either dosing method. Older infants (>3m) appear to have higher LPV trough concentrations than younger infants (<3m). Data represent the mean and standard deviation of LPV trough concentrations. Mean adult trough level is 5.5 mcg/mL (dashed line). C. Predicted frequency of very low LPV troughs (<1 mcg/mL). The frequency of low concentrations with the study dose was 20% in infants <3 months of age, but rare (<1% in older infants. The WHO weight band dosing recommendations predicted a lower frequency (13%) of troughs <1 mcg/mL in the youngest infants.

CONCLUSIONS

- LPV concentration increases during the first year of life are likely due to increased bioavailability.
- A rapid increase in LPV exposure along with sensitive wild-type virus likely accounts for the good virologic suppression seen [7] despite the low LPV concentrations present at the start of therapy in the youngest infants.
- Frequent monitoring of LPV therapy in young infants is warranted due to PK variability and the risk of low LPV exposure.

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