# Simulation and Exposure-Based Assessment of Pediatric Lopinavir Fixed-Dose Combination Product

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## ABSTRACT

**Background:** The development of low-cost, solid fixed-dose combinations of LPV/r with various nucleoside reverse transcriptase inhibitor (NRTI) backbones in modular unit forms (LPV/ABC/3TC and LPV/ZDV/3TC) is greatly needed to improve both management and adherence of children especially in resource-limited settings.

**Methodology:** The pharmacokinetic (PK) analysis combined 25 datasets including therapeutic drug monitoring and published clinical studies from IMPAACT and PENTA. Intensive and sparse PK data totaling 1394 LPV concentrations from 338 subjects, aged 2 days to 24 years old, were analysed. For 3TC, ABC, and ZDV, a total of 927 patients with 3820 concentrations, 188 patients with 1232 concentrations, and 756 patients with 3312 concentrations were used, respectively.

**Results:** The simulations indicated that the WHO dosing recommendations resulted in more than 95% of subjects with LPV Cmin > 1.0 mg/L. However, using the recommended drug ratios, the combination dosage for the 4-6 kg weight band (LPV/ZDV: 120/90mg BID) resulted in high ZDV exposure with more than 20% of subjects at levels associated with high risk of neutropenia ($C_{ave}$>0.8 mg/L). Reducing the LPV/ZDV dosage to 80/60 mg BID significantly decreased frequency of high ZDV concentrations and risk of neutropenia. This dosage reduction retained LPV Cmin >1.0 mg/L in more than 95% of subjects and did not adversely affect reaching the NRTIs therapeutic target levels. Moreover, this proposed dosage fully corresponded to the WHO guidelines for all NRTIs.

**Conclusions:** These simulations suggest that a pediatric fixed-dose LPV/3TC/ZDV or ABC formulation could be developed to achieve targeted therapeutic levels for all ARV components. Each unit would include 40 mg LPV, 10 mg RTV, 15 mg 3TC and 30 mg ABC or ZDV. According to the weight bands, i.e. 4-6 kg, 6-10 kg, 10-14 kg, 14-20 kg, 20-25 kg, therapeutic doses would be 2, 3, 4, 5, or 6 units twice daily of this formulation.

## INTRODUCTION

The 2013 WHO Antiretroviral Guidelines recommend lopinavir/ritonavir (LPV/r) with lamivudine (3TC) and either abacavir (ABC) or zidovudine (ZDV) for all HIV-infected children under three years of age. Current LPV/r liquid formulations are difficult to administer with a high risk of dosing errors; they have poorly-tolerated taste, significant toxicity, severe logistical constraints (short shelf-life, cold chain requirement, large storage volumes) and high price. The development of solid ABC(ZDV) /3TC/LPVr fixed-dose formulations would greatly facilitate adherence and storage/dispensation.

The challenge of defining the dosage strengths for pediatric multidrug combinations is that the metabolic pathway and elimination routes of each component differ, and that the mechanisms involved in absorption, distribution, metabolism and excretion do not mature at the same rate from birth to adolescence.

## METHODS

We executed a meta-analysis of the pediatric PK data available for LPV, ABC, ZDV and 3TC to model the pharmacokinetics of each drug and performed simulations using the original FDA dosing recommendations, the 2010 WHO weight band dosing, and its subsequent modifications. We estimated the proportions of children above efficacy targets and the proportion of children at risk of toxicity for each of the weight bands.

The analysis combined 25 datasets including therapeutic drug monitoring and published clinical studies from IMPAACT and PENTA. The patients characteristics are summarized below.

### Patients

The pharmacokinetic (PK) analysis combined 25 datasets including therapeutic drug monitoring and published clinical studies from IMPAACT and PENTA. The patients' characteristics are summarized below.

| | Patients | Bodyweight (kg) | Age (yrs) | Dose (mg/kg) | DATA (ref) |
|---|---|---|---|---|---|
| | N (obs.) | | Median (IQR) | | |
| **LPV** | 338 (1394) | 21.8 (8.5 - 37.9) | 7 (1 - 12.4) | 24.4 (18.5 - 30.1) | [1–5] |
| **3TC** | 920 (3820) | 18 (10.4 - 26.9) | 5.4 (1.4 - 9.4) | 7.7 (6.8 - 8.3) | [6–9] |
| **ABC** | 187 (1231) | 29.9 (18.6 - 53) | 10.2 (5.5 - 14.7) | 15.7 (12.8 - 16.4) | [10–13] |
| **ZDV** | 755 (3311) | 16.9 (10.7 - 29.2) | 4.7 (1.7 - 9.9) | 12.9 (7.5 - 20.4) | [8,14–16] |

### Modelling strategy and population PK models

Data were analyzed using the nonlinear mixed effect modelling software Monolix version 4 (www.lixoft.eu). Parameters were estimated by computing their maximum likelihood estimator without any approximation of the model (no linearization) using the stochastic approximation expectation maximization (SAEM) algorithm combined with a Markov Chain Monte Carlo procedure.

### Dose simulations

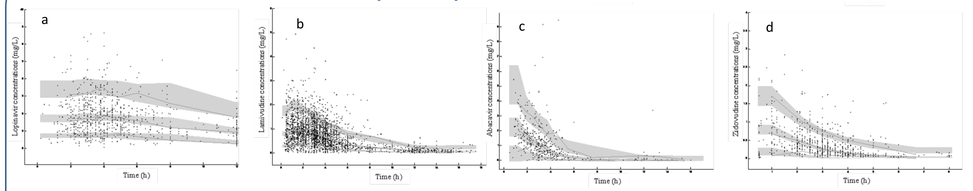
Simulations of current recommendations were performed in order to provide optimal exposure for each drug. For lopinavir, doses evaluated followed the WHO guidelines i.e. 120 mg bid from 4 to 10 kg, 160 mg bid from 10 to 14 kg, 200 mg bid from 14 to 20 kg, and 240 mg bid from 20 to 25 kg and the FDA approved doses i.e. 16 mg/kg bid for children less than 6 months, 12 mg/kg bid for those less than 15 kg, and 10 mg/kg bid from 15 to 40 kg. For NRTIs and following WHO guidelines, dose ratios of 0.375 and 2 were used for 3TC to LPV and AZT-ABC to 3TC, respectively.

The optimal exposure targets were defined as follows:
LPV: >95% subjects with Cmin>1.0 mg/L; >75% subjects with Cmin>3 mg/L;
3TC: >75% of subjects with AUC0-24 > 8 mg.h/L (≈ adult mean- sd)
ABC: >75% of subjects with AUC0-24 > 8 mg.h/L (≈ adult mean- sd)
ZDV: >75% of subjects with AUC0-24 > 2 mg.h/L (≈ adult mean- sd)
<25% of subjects with AUC0-24 > 8.4 mg.h/L (associated with mild anemia)
<5% of subjects with AUC0-24 > 19.2 mg.h/L (associated with neutropenia)

Simulations were made for 4 to 25Kg body weight and > 3 months of age children .

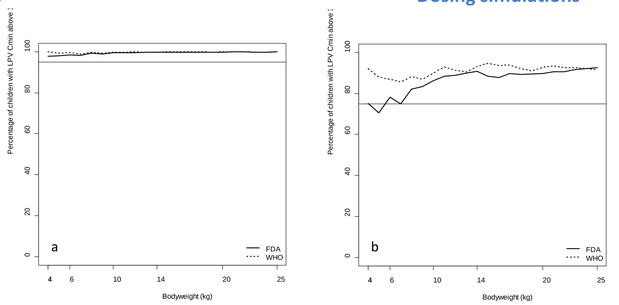
## RESULTS

### Population pharmacokinetic models

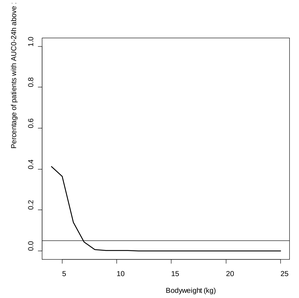



*Prediction-corrected visual predictive check plots for the twice daily regimens : a) lopinavir, b) lamivudine, c) abacavir and d) zidovudine.*

### Dosing simulations

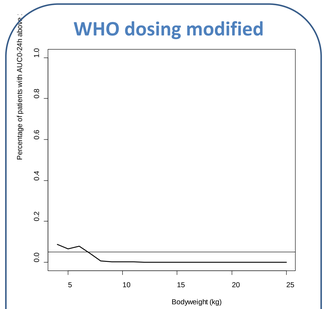



*Percentage of children with LPV Cmin values above 1 mg/L (a) and 3 mg/L (b) as a function of bodyweight. The continuous curve corresponds to the FDA recommended dosing simulations and the dashed curve corresponds to WHO guideline simulations. The horizontal lines represent the targets : 95% and 75% of patients that reach 1mg/L (a) and 3mg/L (b), respectively .*

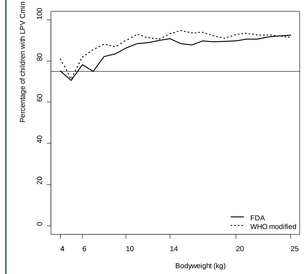



*Percentage of children with $AZT\ AUC_{0\text{-}24h}$ values above 19.2 mg.h/L using the following bid doses: 90mg for 4-10kg, 120mg for 10-14kg, 150mg for 14-20kg and 180mg for 20-25kg.*

### WHO dosing modified




*Percentage of children with $AZT\ AUC_{0\text{-}24h}$ values above 19.2 mg.h/L using the following bid doses: 60mg for 4-6kg, 90mg for 6-10kg, 120mg for 10-14kg, 150mg for 14-20kg and 180mg for 20-25kg.*




*Percentage of children with LPV Cmin values above 3 mg/L following FDA guidelines (continuous curve) and WHO guidelines modified for 4-6 kg (dashed curve).*

## CONCLUSIONS

**A pediatric fixed-dose LPV/3TC/ZDV or ABC formulation can be developed to achieve targeted therapeutic levels for all ARV components with a flexible unit dose through the full range of weight bands. Each unit would contain 40 mg LPV, 10 mg RTV, 15 mg 3TC and 30 mg ABC or ZDV. According to weight bands, i.e. 4-6 kg, 6-10 kg, 10-14 kg, 14-20 kg, 20-25 kg, therapeutic doses would be 2, 3, 4, 5, or 6 units of this formulation twice daily .**

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