Population Pharmacokinetic Modeling of Fosamprenavir in Pediatric HIV- Infected Patients

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BACKGROUND

Fosamprenavir (FPV) is a prodrug of amprenavir (APV), an inhibitor of the human immunodeficiency virus (HIV) protease [1]. FPV is indicated in combination with other antiretroviral agents for the treatment of HIV infection [1,2]. Adult FPV dosing regimens are dependent on prior antiretroviral therapy (ART) status. For ART-naïve adult patients, FPV may be administered as 1400 mg bid (without ritonavir (RTV)), FPV/RTV 1400/100mg qd, FPV/RTV 1400/200mg qd, or FPV/RTV 700/100mg bid. For protease inhibitor-experienced patients, the FPV/RTV 700/100mg bid regimen is approved.

The oral suspension of FPV provides improved delivery of APV for pediatric patients. APV, delivered as Agenerase® oral solution, requires large dosing volumes and is only approved for use in children at least 4 years of age due to large amounts of propylene glycol and Vitamin E. The high propylene glycol content in APV oral solution and the high ethanol content of RTV oral solution, contraindicate co-administration of these two medicines. In contrast, FPV contains significantly lower concentrations of propylene glycol (10.2mg/mL compared with 550mg/mL), which provides the option of FPV treatment to children of all ages and allows co-administration with RTV oral solution. In addition, FPV oral suspension contains no Vitamin E (compared with 46 IU/mL for amprenavir) and is more concentrated (50mg/mL compared with 15mg/mL), thereby reducing the dosing volumes.

Pediatric studies with FPV and FPV/RTV were initiated in children 4 weeks to 18 years old. Data from those studies were included in a population PK analysis as described in this poster.

OBJECTIVES

Characterize the PK of FPV with or without RTV in pediatric patients infected with HIV and describe factors that may influence APV PK in order to simulate FPV and FPV/RTV dosing regimens that deliver target plasma APV exposures in this population.

PHARMACOKINETICS

- FPV is rapidly converted to APV by cellular phosphatases in vivo.
- APV is metabolized in the liver by the cytochrome P450 3A4 (CYP3A4) [3] which can be further glucuronidated.
- Excretion of unchanged APV in urine and feces is minimal.
- APV is approximately 90% bound to plasma proteins, primarily to α1-acid glycoprotein (AAG).
- APV is an inhibitor and inducer of CYP3A4 but does not inhibit other major CYPs or uridine glucuronosyltransferase.
- RTV is a protease and CYP3A4 inhibitor. Co-administration of APV and FPV results in greater APV exposure at a lower dose than observed with APV alone.
- In adults, noncompartmental estimates of clearance values were 84.8 L/hr for a 1400mg bid dose of FPV and 20.2 L/hr for a 1400mg qd dose of FPV + 200mg qd RTV.
- The plasma elimination half-life of APV is approximately 7.7 hours; co-administration of RTV increases half-life 2 to 3 fold.
- A linear two-compartment model with first-order absorption described the steady-state adult APV data using a population PK approach [4].
- Previous simulations suggested that 100 mg or 300 mg BID RTV doses would nearly saturate APV inhibition in adults [5].

METHODS

Three clinical studies contributed to the pediatric population PK dataset:

PROTOCOL APV20002

A 48 Week Phase II, Open-label, 2-cohort, Multi-center Study to Evaluate the PK, Safety, Tolerability and Antiviral Activity of FPV and FPV/RTV When Administered to HIV-1 Infected PI-Naïve and PI-Experienced Pediatric Subjects aged 4 weeks to <2 years

PROTOCOL APV20003

A 48 Week, Phase II, Open-label, Multi-Cohort, Multi-center Study to Evaluate the Safety, Tolerability, PK and Antiviral Activity of FPV/RTV QD and FPV/RTV BID when Administered to HIV 1 Infected, ART Naive and Experienced, Pediatric Subjects 2 to 18 Years Old.

PROTOCOL APV29005

A 48 Week, Phase II, Open-label, Multi-Cohort, Multi-center Study to Evaluate the Safety, Tolerability, PK and Antiviral Activity of FPV/RTV BID when Administered to HIV-1 infected, PI-Naïve and Experienced, Pediatric Subjects, 2 to 18 Years Old and of FPV BID Administered to PI-Naïve, Pediatric Subjects 2 to <6 Years Old.

Data from each study included a single extensive PK sampling day following at least 10 days of multiple-dose therapy and up to 9 days where a single trough (Ct) sample was collected, for up to 10 PK sampling occasions spanning the study interval of up to 18 months.

Population PK data were assembled and formatted for analyses using the R software (version 2.32; R Development Core Team; www.rproject.org).

Model and Modeling Assumptions

- Data were analyzed using nonlinear mixed-effects modeling with the NONMEM software, Version V, Level 1.1 (ICON Development Solutions, Ellicott City, MD).
- First-order conditional estimation with INTERACTION option (FOCEI) method in NONMEM was used.
- Parameter estimates are reported with measures of estimation uncertainty.
- Covariate modeling was conducted using a full model approach emphasizing parameter estimation rather than stepwise hypothesis testing.
- R software was used for all simulations and the creation of all plots and summary tables.
- Parametric distributions were assumed for all random effects. A block covariance matrix for the inter-individual random effects (Ω) for CL/F and V2/F was included as was a term for inter-occasion variability in CL/F.
- Inter-individual error terms were described by an exponential error model.
- Maximal inhibition of FPV CL/F was assumed at the RTV doses included in the model.
- An allometric model was assumed to describe the relationship between body weight and all clearance and volume parameters using a normalized reference weight of 70 kg and fixed allometric power values of 0.75 (CL and Q) and 1 (V2/F and V3).
- Other continuous covariate effects were generally modeled using a normalized power model while the effects of categorical covariates were similarly described.
- Parameter precision was investigated via non-parametric bootstrap (1000 replicates with replacement using the individual as the sampling unit and stratifying by age, race, and RTV co-administration).
- The final model was evaluated using a predictive check [6] (100 Monte Carlo simulation replicates of the original data).

Simulations

- Specific APV exposure targets [AUC(0-τ),ss] were identified, representing geometric mean values observed in adults, for the FPV and FPV/RTV simulations:
  - FPV BID 16.5h*µg/mL;
  - FPV/RTV BID 37.0h*µg/mL;
  - FPV/RTV QD 67.1h*mg/mL.
- The 95th percentiles of APV AUC(0-τ),ss observed in adults following FPV/RTV BID (64.0h*µg/mL) and FPV/RTV QD (107h*µg/mL) were considered upper thresholds in these simulations.

NOTE: Only children ages approximately 2-6 yrs received the FPV BID dose without RTV in the clinical study. It was assumed that the covariate relationships described in the full model were applicable across the entire age range for both boosted and unboosted FPV doses.

- Additional constraints:
  - Suspension formulation used up to the following maximal adult tablet doses: 700mg FPV/RTV BID, 1400mg FPV/RTV QD and 1400mg FPV BID;
  - Doses were administered under fed conditions;
  - FPV/RTV QD dose twice that of the FPV/RTV BID dose;
  - Per-kilogram dosing based on weight stratified by the age group (≤2 yrs, >2 – ≤6 yrs, >6 – ≤12 yrs and >12 yrs). Age groups selected based on the relationship between weight-adjusted CL/F and age in the final model, protocol-defined age groups, and distribution of patients across age in the population dataset.
- Demographic data of 10,000 simulated patients were randomly sampled from the population sample collected by the National Center for Heath Statistics (http://www.cdc.gov/nchs/about/major/nhanes/nh3data.htm).
- Race and AAG were fixed to 1 (Caucasian) and 0.77 g/L (population median) values, respectively.

RESULTS

- The dataset included 137 patients and 1322 plasma APV concentrations.
- Nine subjects were <2 years old; whereas, 128 subjects were between 2 and 18 years of age.
- The majority of patients (119) received FPV with RTV while 18 patients (all 2 to 6 years old) received FPV alone.

Table 1. Summary of Continuous Covariates for PK Analysis

Covariate (units)	Mean	SD	Median (Range)
RTV(mg)	109.47	63.61	100 (0-200)
Baseline Age (years)	9.33	5.14	10 (0.72-18)
Baseline Weight (kg)	34.96	20.47	32.9 (5.9-102.8)
Baseline Height (cm)	129.61	30.91	134.5 (65-180.3)
Baseline AAG (g/L)	0.87	0.34	0.8 (0.41-2.69)

RESULTS

Table 2. Summary of Categorical Covariates

Covariate	Level	Description	Number (Percent)
Food Intake	-1	Missing	N=43 (31.4%)
	0	Administered without food	N=20 (14.6%)
	1	Administered with food	N=74 (54%)
Formulation	1	Suspension	N=89 (65%)
	2	Tablets	N=48 (35%)
Study	20002	Study 20002	N=9 (6.6%)
	20003	Study 20003	N=59 (43.1%)
	290005	Study 290005	N=69 (50.4%)
Sex	0	Males	N=62 (45.3%)
	1	Females	N=75 (54.7%)
Race	1	White	N=79 (57.7%)
	2	Black	N=37 (27%)
	3	Asian	N=2 (1.5%)
	4	Hispanic	N=7 (5.1%)
	5	American Indian	N=8 (5.8%)
	6	Other	N=4 (2.9%)
RTV	0	Administered without ritonavir	N=18 (13.1%)
	1	Administered with ritonavir	N=119 (86.9%)

For time-dependent covariates, median (by patient over all occasions) value was used in this summary

Model

- Two-compartment model with first-order absorption and elimination.
- Relative bioavailability estimated separately for the suspension formulation under fasted conditions ($F_{food,sus}$) and for the tablet formulation (F_{tab}) using the suspension formulation under fed conditions as the reference (F).
- Age described some variability in CL/F not explained by weight (Figure 1) and was therefore entered into the model as described below.

For AGEi ≤ 2*AG50:

$$CL_i = \theta_{TVCL} \bullet \left(\frac{WT_i}{70}\right)^{0.75} \bullet [1 + AMAX \bullet (1 - \frac{0.5 \bullet AGE_i}{AG50})] \bullet \exp^{\eta^{CLi}}$$

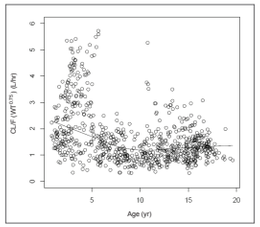
And for AGEi > 2*AG50:

$$CL_i = \theta_{TVCL} \bullet \left(\frac{WT_i}{70}\right)^{0.75} \bullet \exp^{\eta^{CLi}}$$

AMAX: maximum age effect at birth. AG50: age with half of the maximal effect.

- Sex, AAG, and race, were also included in the final model

Figure 1. Individual CL/F Estimates Divided by Weight$^{0.75}$ Versus Age: Base Model



Scatter plot of individual CL/F estimates from the base model normalized to body weight$^{0.75}$ versus age. A solid black lowess (local regression smoother) trend line is included.

- Full model results are provided in the Table 3.
- Improved goodness-of-fit criteria, lower objective function value, and reduced unexplained random variability (30% CV) with full model, compared to the base model (38% CV). No systematic bias was evident and the model adequately described the data.
- When allometrically scaled to a typical adult weight of 70kg, FPV/RTV CL/F (34.1 L/hr) in this pediatric dataset was greater than previously reported in adults (21.5 L/hr), while the FPV CL/F (84.4 L/hr) was similar to adults (91.8 L/hr).
- The youngest children (1.09 years in this population) are expected to have a CL/F which is approximately 1.4-times (upper 95%CI: 2.5-fold) greater than children >4 years.
- This age effect is consistent with that previously reported for RTV and may be due to developmental changes in CYP3A4 [7,8].

Table 3: Final Model Population Pharmacokinetic Parameter Estimates

Population parameter point-estimates and percent standard errors (%SE) for the full two-compartment model and 95% Confidence Intervals (CI) from a non-parametric bootstrap are presented.

Parameter	Notation	Population Estimate	%SE	95%CI
CL/F[1]	θ_1	34.1 (L/hr)	7%	(28.9, 39.7)
V2/F	θ_2	288 (L)	23%	(160, 421)
Q	θ_3	63.5 (L/hr)	15%	(41.3, 91.2)
V3	θ_4	1630 (L)	28%	(882, 3110)
KA	θ_5	1.13 (hr-1)	30%	(0.759, 1.74)
CL/F[2]	θ_6	84.4 (L/hr)	11%	(59.1, 109)
F_{tab}	θ_7	1.09	8%	(0.906, 1.28)
$F_{food,sus}$	θ_8	0.87	8%	(0.699, 1.1)
AMAX	θ_{10}	0.789	65%	(0.521, 2.4)
AG50	θ_{11}	2.05	26%	(1.41, 2.99)
SEX	θ_{12}	0.846	7%	(0.744, 0.971)
$RACE_{black}$	θ_{13}	0.940	8%	(0.782, 1.12)
$RACE_{other}$	θ_{14}	1.06	13%	(0.863, 1.25)
AAG_{CL}	θ_{15}	-0.626	9%	(-0.787, -0.489)
AAG_{V2}	θ_{16}	-0.369	92%	(-0.845, 0.199)
Intersubject variabilities				
η_{CL} variance	Ω_{11}	0.0901 (30% CV)	17%	(0.0391, 0.145)
$\eta_{CL} - \eta_{V2}$ correlation	Ω_{12}	0.0945	40%	(-0.0374, 0.218)
η_{V2} variance	Ω_{22}	0.438 (66% CV)	27%	(0.0276, 0.968)
$\eta_{IOV,CL}$ variance	θ_9	0.114 (34%)		(0.0679, 0.153)
η_Q variance	Ω_{33}	0.536 (73%)	36%	(0.222, 1.02)
Residual Errors				
Prop error	σ_1^2	0.0828	7%	(0.0528, 0.125)
Additive error	σ_2^2	0.0760	12%	(0.035, 0.119)

[1]CL/F when ritonavir dose > 0
[2]CL/F when ritonavir dose = 0

CL/F, V2/F, Q, and V3 estimates are for a typical 70 kg individual; KA = absorption rate constant; Ftab=bioavailability of tablet formulation relative to suspension; Ffood,sus= bioavailability of fasted suspension dose relative to fed suspension dose; AMAX=maximal age effect on CL/F – see methods section for AGE model; AG50=age at half-maximal age effect on CL/F; SEX = fraction of CL/F for females relative to males; RACEblack = fraction of CL/F for Black patients relative to Caucasians; RACEother=fraction of CL/F for patients of non-Black ethnic origin relative to Caucasians; AAG_{CL} =exponential effect of AAG values on CL/F; AAG_{V2}= exponential effect of AAG on V2/F. Body weight was included in the final model using fixed allometric relationships on clearance and volume parameters.

Figure 2: Full Model Diagnostic Plots

A solid line at y = 0 or a line of unity is included as a reference.

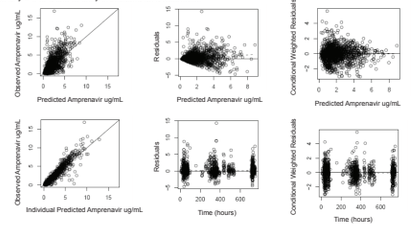
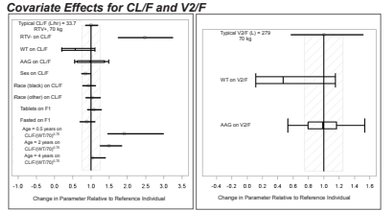


Figure 3: Covariate Effects for CL/F and V2/F



Typical CL/F for reference patient (WT=70Kg, Age>4 yr, White, Male, AAG=0.77 g/L, Suspension formulation under fed conditions, +RTV). Solid vertical line is CL/F point estimate and horizontal black line represents 95% CI. For categorical covariates point estimate represented by open circle with 95% CI represented by horizontal bar. For continuous covariates, box and whisker plots represent the magnitude of the covariate effect on the PK parameter across the observed covariate range, plotted at the covariate effect point estimate (box) and over the 95% CI of the point estimate (whiskers).

Simulations

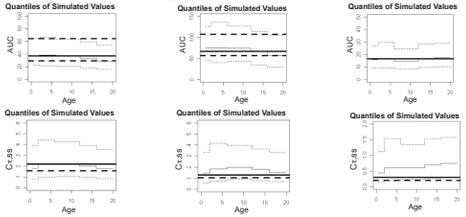
- Based on simulations, dosing by the following age groups and regimens is predicted to minimize variability in exposure and allow plasma APV exposure in pediatric patients to consistently match historical adult (i.e. target) exposure, as determined by mean AUC(0-τ) according to the pre-specified dosing constraints:
  - FPV/RTV BID: AGE ≤2yr 36mg/kg; >2- ≤6yr 23mg/kg; >6yr 18mg/kg; Max 700mg
  - FPV/RTV QD: AGE ≤2yr 72mg/kg; >2 - ≤6yr 46mg/kg; >6yr 36mg/kg; Max 1400mg
  - FPV BID: AGE ≤2yr 38mg/kg; 2 - ≤6yr 25mg/kg; >6yr 17mg/kg; Max 1400mg
- Summaries of the steady-state PK parameters (AUC(0-τ) and C_τ,ss) according to these regimens are shown graphically in Figure 4

Figure 4: Simulation of Dosing Regimens Targeting Mean Adult AUC(0-τ).

BID RTV+; AGE<2: 36mg; AGE 2-6: 23mg/kg; AGE> 6: 18mg/kg; Max 700 mg

QD RTV+; AGE <2: 72mg/kg; AGE 2-6: 46 mg/kg; AGE >6: 36 mg/kg; Max 1400 mg

BID RTV-; AGE <2: 38 mg/kg; AGE 2-6: 25 mg/kg; AGE >6: 17 mg/kg; Max 1400 mg



The thin solid line indicates geometric mean (by age group) of the simulated PK values while thin dashed lines show 5th and 95th percentiles of the simulated values. The bold lines indicate targets: geometric mean (bold solid), 25th percentile and 95th percentiles (bold dashed lines) of the AUC values observed in the adult population. Top row: AUC. Bottom row: C_τ,ss.

CONCLUSIONS

- The population PK of orally administered FPV in pediatric patients was described by a two-compartment model with first-order absorption and elimination.

The main predictors of plasma APV CL/F were:

- The presence or absence of RTV, where co-administration of RTV was estimated to decrease plasma APV CL/F by approximately 60%.
- Age, where weight adjusted CL/F was estimated to be 1.4-fold greater in the youngest children (1.09 years) as compared to children >4 years of age.
- Body weight, with a range of typical population CL/F estimates of 6.6 to 46.2L/hr across the weight range in the dataset.
- AAG, with a range of typical population CL/F estimates of 22.5 to 51.4 L/hr across the AAG range of 0.4 to 1.5g/L.

The main predictors of plasma APV V2/F were:

- Body weight, with a range of typical population V2/F estimates of 32.1 to 432L across the weight range in the dataset.
- AAG, with a range of typical population V2/F estimates of 189 to 367L across the AAG range of 0.4 to 1.5g/L.
- The population PK model and simulations were used to support the approval of FPV dosing recommendations for HIV-1 infected children 2 to 18 years of age and FPV/RTV dosing recommendations for HIV-1 infected children 6 to 18 years of age. In addition, the population PK model and simulations were used to support the on-going evaluation of FPV/RTV dosing in children 4 weeks to 6 years of age.

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