



Age Related Pharmacokinetics (PK) of Efavirenz (EFV) Solution (IMPAACT/PACTG P1021)

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Abstract

Background: Use of once daily EFV based HAART therapy in HIV infected infants is limited by formulation availability and a lack of EFV PK and dosing information. We evaluated the pharmacokinetics of EFV solution in patients less than 3 yrs of age (Group 1) and compared them to PK seen in older pediatric patients (Groups 2&3).

Methods: EFV PK data were analyzed from a prospective study, IMPAACT /PACTG P1021, that enrolled 43 HIV infected subjects ages 90 days to 21 years. In the 6 subjects < 3 yrs, an initial dose of 390mg (<10kg) or 600 mg (>10kg) EFV solution was given split with FTC and ddI. Older subjects received EFV, 250-600mg, solution or capsules based on weight. An intensive 24-hour PK evaluation was performed after 2 weeks of therapy. Dose modifications were performed for subjects with AUC outside the range of 35-120 mcg·h/mL. Repeat intensive PK evaluations were performed for subjects with dose or formulation modifications. EFV pharmacokinetics were assessed by non-compartmental methods.

Results: The median ages in the three groups were 0.5, 6.3 and 18 years. Two (33%) of the Group 1 subjects had dose modifications, one due to high (AUC=269) and other low (AUC=28.8) EFV exposure. Three Group 1 subjects had dose increases to 600 at weight > 10kg with repeat AUCs that ranged from 80 to 150. EFV apparent clearance (CL/F) was greater (P< 0.003) in Group 1 than Groups 2&3. The median EFV PK parameters with the solution formulation were:

	Group 1 Age <3y (n=6)	Group 2 Age 3-12y (n=17)	Group 3 Age 13-21 (n=13)
EFV dose	390	600	600
EFV dose (mg/kg)	47	17.5	8.8
Half-life (h)	11.4	17	23.5
CL/F (L/h/m ²)	14.4	8.4	4.7
AUC (mcg·h/mL)	66.2	55.6	61.2
Cmin (mcg/mL)	1.1	1.3	2.0

Intermittent pre-dose trough concentrations collected during up to 2 years of treatment were consistent with the intensive PK study results. The dose-normalized EFV AUC and Cmax for the solution formulation were approximately 80% of the values obtained with the capsule formulation.

Conclusion: EFV PK demonstrates pronounced age effects with apparent clearance much greater in young infants than older children. High EFV dose requirements and PK variability in infants will require additional studies to determine appropriate EFV dosing strategies.

Background

Recent trials indicate benefit from early initiation of highly active antiretroviral therapy (HAART) in HIV infected infants. However it is critical to maintain therapeutic drug concentrations to prevent emergence of HIV resistance. Therefore detailed understanding infant PK is essential for infant therapy.

Efavirenz (EFV) is a very effective antiretroviral that is used as a first line agent for treatment of HIV infection in older children and adults. However, EFV pharmacokinetics have not been well described in infants and limited studies in young children suggest low concentrations occur frequently.

Objectives

Characterize the pharmacokinetics of EFV solution in HIV-infected infants, and compare them to older children.

Compare the pharmacokinetics of EFV solution and capsules in older children.

Study Methods

Study Design: Prospective, open-label study, the Pediatric AIDS Clinical Group (PACTG/IMPACT) P1021.

Patient population: 36 HIV-infected subjects receiving EFV as the solution formulation during a PK evaluation, ages 90 days to 21 years, using the treatment-naïve.

Initial Therapy: Once daily administration of EFV, emtricitabine (FTC) and didanosine (ddI)

EFV dosing and dosing adjustments: In the subjects < 3 yrs, an initial dose of 390mg (<10kg) or 600 mg (>10kg). Older subjects received EFV, 250-600mg, solution or capsules based on weight. An intensive 24-hour PK evaluation was performed after 2 weeks of therapy. Optional repeat PK evaluation for change in dosage or formulation. Dose modifications were performed for subjects with AUC outside the range of 35-120 mcg·h/mL.

PK Studies: Intensive 24-hour PK evaluations included samples at:

Pre-dose, 1, 2, 4, 8, 12 and 24 hours post dose (Age ≥ 3y)

Pre-dose, 3, 5, 10 and 24 hours post dose (Age < 3y)

Population samples drawn pre-dose every 4-8 weeks

Pharmacokinetic Analysis: The concentration-time curves for each subject were analyzed non-compartmental methods using WinNonLin. Clearance, half-life, drug exposure (AUC), and trough concentrations were assessed. EFV determined by HPLC method at a PACTG/IMPACT pharmacy laboratory with assay limit of quantitation of 50 ng/mL. Cohort PK difference were assessed using Wilcoxon test performed with program with SAS.

Clinical Characteristics

Table 1	Cohort 1 <3y (n=6)	Cohort 2 3-12y (n=17)	Cohort 3 13-21y (n=13)	All Cohorts (n=36)
Race				
White (non-Hispanic)	0 (0%)	1 (6%)	1 (8%)	2 (5%)
Black (non-Hispanic)	4 (67%)	9 (53%)	10 (77%)	23 (64%)
Hispanic	2 (33%)	7 (41%)	2 (15%)	11 (31%)
Age	0.54 (0.31 - 2.7)	6.0 (4.1 - 12.4)	18.1 (14.8 - 21.3)	7.1 (0.31-21.3)
Sex (M/F)	2/4	8/9	9/4	17/19
Weight (kg)	8.9 (4.6 - 11.2)	19.1 (13.4 - 35.0)	68.5 (45.5 - 111.4)	22.6 (4.6-111.4)
BSA (m²)	0.39 (0.26 - 0.51)	0.75 (0.58 - 1.18)	1.81 (1.47 - 2.34)	0.85 (0.26 - 2.34)
Baseline CD4 (cells/µL)	1405 (225 - 3,576)	365 (41 - 1,893)	270 (2 - 990)	349 (2 - 3576)
Baseline CD4%	33.5 (10 - 50)	18.0 (0.1 - 34.0)	15.0 (2.0 - 31.0)	17.5 (0 - 50)
Baseline Log HIV-RNA (Copies/mL)	5.66 (4.84 - 5.99)	4.40 (3.68 - 6.37)	4.55 (3.56 - 5.79)	4.82 (3.56 - 6.37)

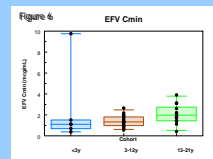
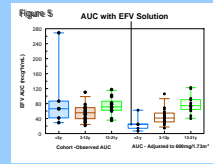
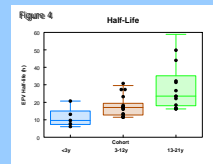
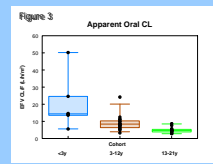
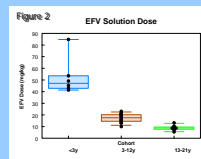
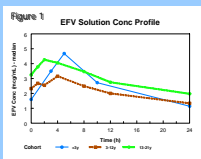
Results

- 36 subjects included in analysis
 - 22 had intensive PK evaluations with both formulations (Cohorts 2 & 3 only)
 - 7 had repeat multiple PK evaluations on solution – first used in analysis
 - 7 subjects in the study never received EFV solution formulation (capsules only) were not included in this analysis
- Subject Characteristics (Table 1)
 - Similar gender, ethnic distribution across cohorts
 - Similar HIV RNA copy number
 - Higher CD4+ and CD4% in youngest cohort – as expected
- Intensive PK Analysis (Table 2 / Figure 1)
 - Higher EFV (mg/kg) dose in youngest cohort by study design (Figure 2)
 - Significantly Higher Clearance in Cohort 1 vs. Cohorts 2 & 3 (Figure 3)
 - Very short half-life in Cohort 1 – less than 1/2 the dose interval (24h) (Figure 4)
 - 3 to 5 times higher EFV dose in Cohort 1 to achieve similar AUC to Cohorts 2 & 3 (Figure 5)
 - Cmin only 1.1 mcg/mL in Cohort 1 despite large dose (Figure 6)
- Solution vs. Capsule Formulation (Figures 7-8)
 - Solution and Capsule similar in AUC (median 69.1 vs. 70.9 mcg·h/mL) and CL/F (median 4.7 vs. 5.2 L/h/m²)

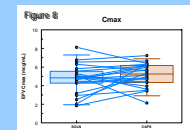
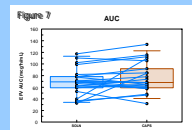
Efavirenz Pharmacokinetics

Table 2	Cohort 1 < 3 y	Cohort 2 3-12 y	Cohort 3 13-21 y	P values 1 vs. 2 & 3
EFV dose (mg)	390	350	600	-
EFV dose (mg/kg)	47	17.5	8.8	-
Half-life (h)	11.4	17.0	23.5	0.09
CL/F (L/h/m ²)	14.4	8.4	4.7	0.003
AUC (mcg·h/mL)	66.2	55.6	71.2	0.88
Cmin (mcg/mL)	1.1	1.3	2.0	0.23

*Median values listed



Capsule Formulation



Conclusions

- EFV apparent clearance in infants is much higher than older pediatric populations.
- The lack of differences between EFV solution and capsules in older children suggest that the low EFV exposure (relative to dose) was not due to the formulation used.
- The short half-life in infants made it difficult to maintain therapeutic Cmin (>1 mcg/mL) with once daily EFV, even with high doses.
- The high EFV dose requirement and variability in PK parameters suggest a role for TDM and additional EFV PK studies in infants.

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