PHARMACOKINETICS OF EFAVIRENZ DOSED ACCORDING TO THE WHO WEIGHT-BANDS IN CHILDREN IN UGANDA

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ABSTRACT

Background: Efavirenz (EFV) is commonly used in children over 3 years worldwide, but there is only limited pharmacokinetic (PK) information available in African children.

Methods: 41 HIV-infected Ugandan children aged 3-12 years on generic EFV plus 3TC+ABC were enrolled in a cross-over PK study of twice to once daily 3TC+ABC 36 weeks after ART initiation in the ARROW trial. Once-daily EFV doses following WHO weight-bands were 200/250/300*/350* mg for children weighing 10-15/15-20/20-25/25-30kg resp., using EFV capsules or *halved 600mg tablets. Intensive plasma PK sampling (t=0,1,2,4,6,8,12h post observed ingestion) was performed on twice-daily ART at steady state (PK1) and repeated 4 weeks later (PK2, including a further 24h sample). EFV daily area under the curve (AUC_{0-24}) and clearance (CL/kg) were estimated using WinNonlin. Predictors of $\log_{10}$AUC and CL were assessed using multivariate mixed models, fitting random effects for each child.

Results: 39&37 children had evaluable EFV profiles at PK1&PK2 respectively. 16/39(41%) children were boys, 18 were aged 3-6 years and 21 7-12 years. 5/16/15/3 were in the 10-15/15-20/20-25/25-30kg weight-bands. The geometric mean (%CV) AUC_{0-24} was 50.4 (91.7%) and 54.0 (80.8%) h.mg/L at PK1 and PK2 respectively, with no significant variation across weight-bands (p=0.51). Between- and within- child %CV were 81% and 28% respectively. 3 sub-populations were identified from normal mixture modeling: 40% children with geometric mean AUC_{0-24} 27.2 h.mg/L, 32% with 49.9 h.mg/L, and 28% with 137 h.mg/L. 6 children at PK1 and 7 at PK2 had sub-therapeutic C8h and/or C12h (<1.0 mg/L); 7/39(18%) at either visit. At PK2, 14/37(38%) children had C24h <1.0 mg/L (median(IQR) [range] 1.1 (0.7-2.5) [0.3-18.4] mg/L). 9 children at PK1 and 10 at PK2 had C8h and/or C12h and/or C24h >4.0 mg/L; 11/39(28%) at either visit. Overall mean(SD) clearance was 6.8(3.9) and 6.2(3.7) L/h at PK1 and PK2 respectively (p=0.04). CL increased by 0.50L/h for every year older (p=0.05), but did not depend on weight (p=0.30), weight-for-age (p=0.56) or height-for-age (p=0.82).

Conclusion: African children aged 3-12 years, on daily EFV using WHO weight-bands, had lower and highly variable EFV PK parameters compared to data from adults. There were no differences across weight-bands, suggesting no major effect of some using half tablets. Increased EFV doses for children should be investigated, but risk increasing the proportion of children with toxic levels further.

Keywords: efavirenz, pharmacokinetics, HIV-1, children, Uganda

INTRODUCTION

- WHO guidelines for the treatment of HIV-1 infected children >3 yrs recommend an NNRTI (EFV/NVP) or PI plus nucleoside reverse transcriptase inhibitor combination therapy for first line therapy[1]
- Until now only little is known about the steady state pharmacokinetics of efavirenz in African children[2,3]
- In this study we determined whether WHO recommended weight-band dosing results in optimal exposure in the target population

METHODS

- 41 HIV-infected Ugandan children aged 3-12 years on generic EFV plus 3TC+ABC were included in the substudy of the ARROW trial (www.arrowtrial.org)
- Children received once daily EFV dosed according to WHO recommendations[1] (Table 1) as 50mg or 200mg capsules or halved 600mg tablets
- At week 32, children were changed to AM intake of EFV if they were taking EFV PM
- At week 36 after starting EFV + twice daily NRTI regimen a 12 hour PK sampling session was done. Samples were taken at t = 0, 1, 2, 4, 6, 8 and 12 hours after observed intake of ART. After PK day children switched to completely once daily regimen
- At week 40 intensive plasma PK sampling was repeated and an extra PK sample was drawn at 24 hours after observed intake

RESULTS - DEMOGRAPHICS

Table 1: Baseline demographics of children in substudy of the ARROW trial

		Total
N with 1 or more evaluable PK*		39
Female, n (%)		23 (59%)
Weight, kg		19.5 (16.5-23.0)
weight-band 10-15 kg, n (%)	200 mg EFV	5 (13%)
weight-band 15-20 kg, n (%)	250 mg EFV	16 (41%)
weight-band 20-25 kg, n (%)	300 mg EFV	15 (38%)
weight-band 25-30 kg, n (%)	350 mg EFV	3 (8%)
Age, years		7.4 (5.5-8.7)
3-6 years, n (%)		18 (46%)
7-12 years, n (%)		21 (54%)
Weight-for-age, z-score		-1.41 (-2.12 to -0.65)
Height-for-age, z score		-1.80 (-2.80 to -1.11)

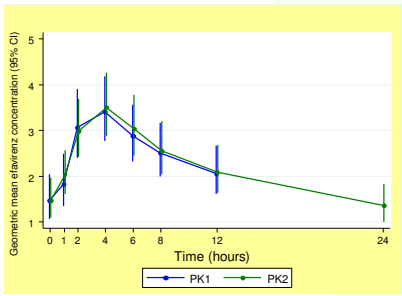
Values are n (%) for categorical variables and median (interquartile range, IQR) for continuous variables

* Two children were excluded from all analyses, because they increased weight band. Two children were excluded from analysis for PK2, because of non-evaluable PK results.

RESULTS - PHARMACOKINETICS - 1

- Mean EFV levels (mg/L) are plotted by PK day in figure 1.

Figure 1: mean EFV levels at week 36 (PK1) and week 40 (PK2)



A large inter- and intra- subject variability was found in EFV PK parameters (eg 81% and 28% for AUC_{0-24})

- 15% (6/39) children at PK1, 19% (7/37) children at PK2 (7 children in total) had a subtherapeutic C_{8h} and/or C_{12h} level (<1.0 mg/L).
- 38% (14/37) had a subtherapeutic C_{24h} level at PK2
- 23% (9/39) children at PK1 and 27% (10/37) children at PK2 (11 children in total) had a toxic C_{8h} and/or C_{12h} level (>4.0 mg/L[5])

RESULTS - PHARMACOKINETICS - 2

- In table 2, pharmacokinetic parameters are compared with data from literature[2]

Table 2: Pharmacokinetic parameters of EFV

EFV	Week 36 (PK1)	Week 40 (PK2)	Lit. data adults[2]
C_{24h} (mg/L)	0.89 [0.62-1.27]	1.36 [1.00-1.85]	1.77 [1.01]
C_{max} (mg/L)	3.41 [2.76-4.20]	3.50 [2.86-4.29]	4.072 [1.16]
AUC_{0-24} (mg/L.h)	50.40 [39.12-64.93]	54.00 [42.63-68.39]	58.08 [23.04]
CL/F (l/h/kg)	5.37 [4.14-6.96]	5.01 [3.93-6.37]	-

Values are geometric mean [95% CI] (arithmetic mean [SD] for adult data). **Target AUC >49-51 mg/L[2,6].**

- EFV C_{24}, C_{max} and AUC were lower than those previously reported in adults
- There were no differences across weight-bands

RESULTS - PREDICTORS

- Three sub-populations were identified from normal mixture modeling: 40% children with geometric mean AUC_{0-24} 27.2 h.mg/L, 32% with 49.9 h.mg/L, and 28% with 137 h.mg/L. Genetic polymorphisms may play a role.
- CL/F increased by 0.50 L/h for every year older (p=0.05)
- After adjusting for age, clearance did not depend on weight (p=0.85), weight-for-age (p=0.52) or height-for-age (p=0.80)

CONCLUSIONS

- EFV exposure was lower than previously reported in adults
- A large inter- and intra- subject variability was found in EFV PK parameters
- There were no differences across weight-bands, which suggests no major effect of using half tablets
- No predictors were found for AUC and CL/F, but CL/F increased with age
- Further analysis of the relationship between EFV concentrations and toxicity is ongoing: viral loads will also be assayed retrospectively in these children
- Increasing the EFV dose for children should be investigated, and has been proposed by WHO. However, higher proportions of children with toxic levels might be expected

1. World Health Organisation. Antiretroviral therapy of HIV infection in infants and children: towards universal access: Recommendations for a public health approach [http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf] **2.** Hirt *et al*; Is the recommended dose of efavirenz optimal in young West African human immunodeficiency virus-infected children? AAC 2009;53(10): 4407-13. **3.** Ren Y, *et al*; High prevalence of subtherapeutic plasma concentrations of efavirenz in children. JAIDS 2007;45:133–136. **4.** EMEA, Stocrin, Summary of Product Characteristics. **5.** Marzolini *et al*; Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. AIDS 2001;15:71-75. **6.** Fletcher *et al*; Pharmacokinetics and pharmaco-dynamics of efavirenz and nelfinavir in HIV-infected children participating in an area-under-the-curve controlled trial. Clin. Pharmacol. Ther. 2008;83:300–6.

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