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

POSTER NO. 878

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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) |

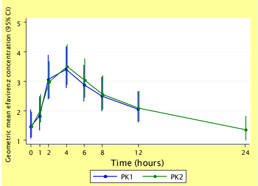
Values are n (%) for categorical variables and median (interquartile range, IQR) for continuous variables

* 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 pharmacodynamics of efavirenz and nelfinavir in HIV-infected children participating in an area-under-the-curve controlled trial. Clin. Pharmacol. Ther. 2008;83:300–6.

**We thank all the patients and staff from all the centres participating in the ARROW trial.**
Joint Clinical Research Centre, Kampala, Uganda: P Mugyenyi, V Musiime, VD Afayo, E Bagurukira, J Bwomezi, J Byaruhanga, P Erimu, C Karungi, H Kizito, M Mutumba, WS Namala, J Namusanje, R Nandugwa, TK Najjuko, E Natukunda, M Ndigendawani, SO Nsiyona, F Odongo, K Robinah, M Ssenyonga, D Sseremba, J Tezikyabbiri, CS Tumusiime; MRC/UVRI Uganda Research Unit on AIDS, Entebbe, Uganda: P Munderi, P Nahirya-Ntege, M Aber, FN Kaggwa, P Kaleebu,R Katuramu, JH Kyalimpa, J Lutaakome, L Matama, M Musinguzi, G Nabulime, A Ruberantwari, R Sebukyu, IM Ssekamatte, G Tushabe, D Wangi. Baylor-Uganda, Paediatric Infectious Disease Centre, Mulago Hospital, Uganda: A Kekitiinwa, P Musoke, S Bakeera-Kitaka, R Namuddu, P Kasirye, JK Balungi, A Babirye, J Asello, S Nakalanzi, NC Ssemambo, J Nakafeero, JN Kairu, EK George, G Musoba, J Ssanyu, S Ssenyonjo. University of Zimbabwe, Harare, Zimbabwe: KJ Nathoo, MF Bwakura-Dangarembizi, F Mapinge, T Mhute, T Vhembo, R Mandidewa, D Nyoni, C Katanda, GC Tinago, J Bhiri, D Muchabaiwa, S Mudzingwa, MM Chipiti, M Phiri, J Steamer, CC Marozva, SJ Maturure, L Matanhike, S Tsikirayi, L Munetsi. Medical Research Council Clinical Trials Unit, London, UK: DM Gibb, MJ Thomason, AD Cook, JM Crawley, AA Ferrier, B Naidoo, MJ Spyer, AS Walker, LK Kendall. Independent DART Trial Monitors: R Nanfuka. Trial Steering Committee: I Weller (Chair), E Luyirika, H Lyall, E Malianga, C Mwansambo, M Nyathi, A Wapakhabulo, DM Gibb, A Kekitiinwa, P Mugyenyi, P Munderi, KJ Nathoo: Observers S Kinn, M MacNeil, M Roberts, W Snowden. Data and Safety Monitoring Committee: A Breckenridge (Chair), C Giaquinto, C Hill, J Matenga, J Tumwine. Endpoint Review Committee: G Tudor-Williams (Chair), H Barigye, HA Mujuru, G Ndeezi. Funding: ARROW is funded by the UK Medical Research Council and the UK Department for International Development (DfID). Drugs are provided by GlaxoSmithKline.