Pharmacokinetics of Efavirenz dosed according to the WHO weight-bands in children in Uganda

Sabrina Bakeera-Kitaka, Lindsay Kendall ,Eva Natukunda , Quirine Fillekes ,Addy R Kekitiinwa, Constance Tumusiime, Peter Mugyenyi, Ann Sarah Walker ,Diana M Gibb,David Burger and the ARROW TRIAL

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The ARROW Trial

- The ARROW Trial is a multi-centered study in Uganda and Zimbabwe

ARROW Study Design

CDM vs. LCM

(Clinically Driven Monitoring vs. Laboratory and Clinical Monitoring)

Meet WHO criteria; ART naïve; age 6 months-17years;
no contra-indications to antiretroviral therapy

CDM
n=600

LCM
n=600

Arm A ABC+3TC+NVP
Arm B ABC+3TC+NVP/EFV+ZDV (at 36 weeks drop ZDV)
Arm C ABC+3TC+NVP/EFV+ZDV (at 36 weeks drop NVP)

Clinical Endpoints - follow-up 3½ to 5 years

Background:

- Efavirenz (EFV) is commonly used in children over 3 years worldwide,
- There is only limited pharmacokinetic (PK) information available in African children.
- This study was aimed at understanding the PK of EFV at different weight bands

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 respectively using EFV capsules or *halved 600mg tablets.

Methods

- 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.

Baseline demographics

		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)

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.
- 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

Results

- 3 sub-populations were identified from normal mixture modeling:
- 40% children with geometric mean $AUC_{0\text{-}24}$ 27.2 h.mg/L,
- 32% with 49.9 h.mg/L,
- and 28% with 137 h.mg/L.

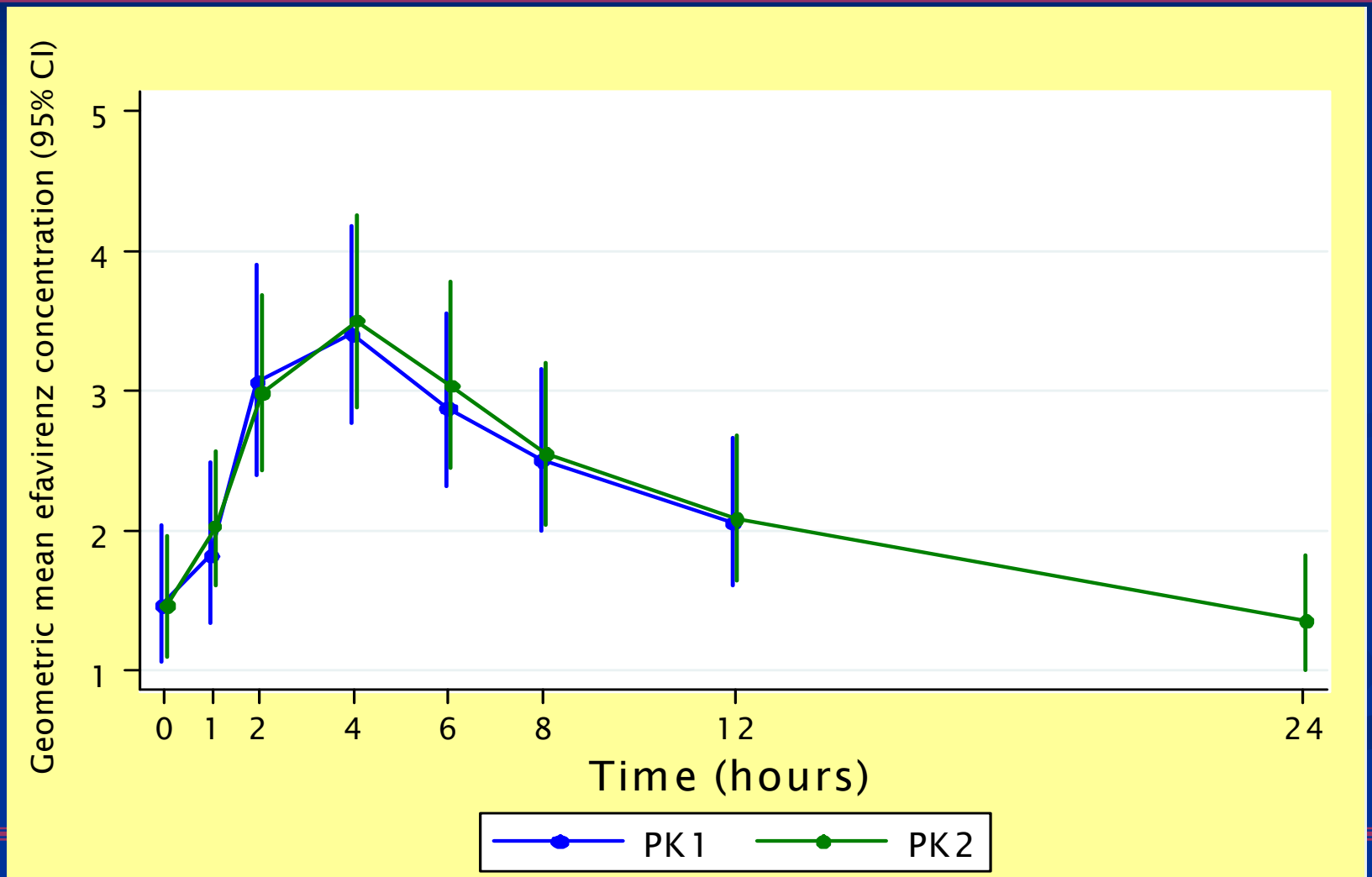
EFV levels

- A large inter- and intra- subject variability was found in EFV PK parameters (eg 81% and 28% for AUC0-24)
- 15% (6/39) children at PK1, 19% (7/37) children at PK2 (7 children in total) had a subtherapeutic C8h and/or C12h level (<1.0 mg/L).

EFV Levels

- 38% (14/37) had a subtherapeutic C24h level at PK2
- 23% (9/39) children at PK1 and 27% (10/37) children at PK2 (11 children in total) had a toxic C8h and/or C12h level (>4.0 mg/L)

Mean EFV levels at week 36 (PK1) and week 40 (PK2)



Clearance

- 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.

Recommendations

- Increased EFV doses for children should be investigated, but risk increasing the proportion of children with toxic levels further.

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