Pediatric Underdosing of Efavirenz: A Pharmacokinetic Study in Uganda

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Objectives: To evaluate international pediatric efavirenz dosing recommendations using full pharmacokinetic (PK) information.

Design: Open-label, multicenter, PK study.

Methods: Forty-one HIV-infected Ugandan children (3–12 years) on efavirenz + lamivudine + abacavir were enrolled in a study of twice-daily to once-daily lamivudine + abacavir 36 weeks after antiretroviral therapy initiation in the ARROW trial. Once-daily efavirenz doses were 200, 250, 300, 350 mg for children weighing 10 to <15, 15 to <20, 20 to <25, 25 to <30 kg, respectively, using 200/50 mg capsules or halved 600 mg tablets in case of 300 and 350 mg doses. Intensive plasma PK sampling (t = 0, 1, 2, 4, 6, 8, 12 hours postobserved ingestion) was performed at steady state (PK1) and repeated 4 weeks later (PK2, including a further 24-hour sample).

Results: Forty-one and 39 children had evaluable efavirenz profiles at PK1 and PK2, respectively. Seventeen (41%) were boys. Five, 16, 17, 3 were in the 10 to <15, 15 to <20, 20 to <25, 25 to <30 kg weight bands. The geometric mean (%CV) the area under the concentration–time curve 0–24 hours postdose was 50.8 (90.8%) and 55.5 (82.7%) $h \cdot mg \cdot L^{-1}$ at PK1 and PK2, respectively. Six children at PK1 and 7 at PK2 had subtherapeutic C_{8h} and/or C_{12h} (<1.0 mg/L), 7 of 41 (17%) at either visit. At PK2, 15 of 39 (38%) children had C_{24h} <1.0 mg/L (median (interquartile range) [range] 1.1 (0.7–2.9) [0.3–18.4]). Ten children at PK1 and 11 at PK2 had C_{8h} and/or C_{12h} >4.0 mg/L; 12 of 41 (29%) at either visit.

Conclusions: African children aged 3–12 years, on efavirenz dosed according to 2006 WHO/manufacturer's recommendations, had lower and highly variable efavirenz PK parameters compared with adult data from manufacturer's leaflet. There were no differences across weight bands, suggesting no major effect of using half tablets. Higher pediatric efavirenz doses, as per WHO 2010 recommendations, should be used and investigated further but may risk increasing the proportion of children with potentially toxic levels.

Key Words: children, efavirenz, HIV-1, pharmacokinetics, Uganda

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INTRODUCTION

The revised WHO guidelines of 2010 for the treatment of HIV-1–infected children older than 3 years of age recommend 2 nucleoside reverse transcriptase inhibitors (NRTI) plus a nonnucleoside reverse transcriptase inhibitor for first-line antiretroviral therapy (ART).[1] Efavirenz (EFV), an nonnucleoside reverse transcriptase inhibitor, has potent antiviral activity and a long elimination half-life (40–55 hours), which makes it suitable for once-daily dosing.[2] It is also suitable for coadministration with antituberculosis medications. For these reasons, the drug is therefore one of the most preferred first-line antiretroviral agents and is currently used widely in HIV-infected children. The licensed and recommended pediatric dosages for EFV are based upon weight bands (Table 1), with allometric doses targeting at least 300 mg/m^2 in each. However doses have not been established for children younger than 3 years and/or weighing below 10 kg, due to problems in achieving appropriate drug levels despite giving high doses.[1,4]

Until now, there is limited knowledge about steady state pharmacokinetics (PKs) of EFV in children, particularly in African populations. Studies have reported high proportions of children with subtherapeutic plasma concentrations of EFV[5–8] receiving doses in accordance with current licensed doses[2] and previous 2006 WHO guidelines, which were mainly based on data assessed in adult patients.[9,10]

However, most pediatric studies to date have analyzed sparse PK samples rather than full PK curves, including the only 2 studies that have been reported in African children.[5,7]

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The authors have no conflicts of interest to disclose.

The members of the ARROW Trial team are listed in Appendix I.

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TABLE 1. EFV Pediatric Dosing Guidelines

		Sustiva Leaflet 2004/2008					ARROW Protocol				
		EFV Daily Dose					EFV Daily Dose†				
			mg/kg		mg/m²			mg/kg		mg/m²	
Bodyweight (kg)	Approximate Surface Area (m²)*	mg	Min	Max	Min	Max	mg	Min	Max	Min	Max
10 to <12	0.49 to 0.56	200	16.7	20.0	360	410	200	16.7	20.0	360	410
12 to <14	0.56 to 0.62	200	14.3	16.7	320	360	200	14.3	16.7	320	360
14 to <15	0.62 to 0.65	200	13.3	14.3	310	320	200	13.3	14.3	310	320
15 to <17	0.65 to 0.71	250	14.7	16.7	350	380	250	14.7	16.7	350	380
17 to <20	0.71 to 0.79	250	12.5	14.7	320	350	250	12.5	14.7	320	350
20 to <25	0.79 to 0.92	300	12.0	15.0	330	380	300	12.0	15.0	330	380
25 to <30	0.92 to 1.1	350	11.7	14.0	320	380	350	11.7	14.0	320	380
30 to <32.5	1.1	350	10.8	11.7	320	320	**400**	12.3	13.3	360	360
32.5 to <35	1.1 to 1.2	400	11.4	12.3	330	360	400	11.4	12.3	330	360
35 to <40	1.2 to 1.3	400	10.0	11.4	310	330	400	10.0	11.4	310	330
40	1.3	600	—	15.0	—	460	600	—	15.0	—	460

		WHO Guidelines 2006					WHO Guidelines 2010				
		EFV Daily Dose					EFV Daily Dose				
			mg/kg		mg/m²			mg/kg		mg/m²	
Bodyweight (kg)	Approximate Surface Area (m²)*	mg	Min	Max	Min	Max	mg	Min	Max	Min	Max
10 to <12	0.49 to 0.56	200	16.7	20.0	360	410	200	16.7	20.0	360	410
12 to <14	0.56 to 0.62	200	14.3	16.7	320	360	200	14.3	16.7	320	360
14 to <15	0.62 to 0.65	**250**	16.7	17.9	380	400	**300**	20.0	21.4	460	480
15 to <17	0.65 to 0.71	250	14.7	16.7	350	380	**300**	17.6	20.0	420	460
17 to <20	0.71 to 0.79	250	12.5	14.7	320	350	**300**	15.0	17.6	380	420
20 to <25	0.79 to 0.92	300	12.0	15.0	330	380	300	12.0	15.0	330	380
25 to <30	0.92 to 1.1	350	11.7	14.0	320	380	**400**	13.3	16.0	360	430
30 to <32.5	1.1	400	12.3	13.3	360	360	400	12.3	13.3	360	360
32.5 to <35	1.1 to 1.2	400	11.4	12.3	330	360	400	11.4	12.3	330	360
35 to <40	1.2 to 1.3	400	10.0	11.4	310	330	**600**	15.0	17.1	460	500
40	1.3	600	—	15.0	—	460	600	—	15.0	—	460

*Based on standard from pediatric oncology.[3]
†Using halved 600 mg tablets in those weighing 20–30 kg.
The bold values show increases compared with the dosing recommendation in the previous column.

Ren et al[7] found a high prevalence (40%) of subtherapeutic plasma concentrations of EFV in a small cohort of 15 children, based on 3 samples taken 12–24 hours after observed dose. Hirt et al[5] conducted a population PK study based on 3 samples taken before, 1 and 3 hours after EFV administration in 48 children in Burkina Faso (9 of whom had full PK samples taken) and found an association between estimated the area under the concentration–time curve 0–24 hours postdose (AUC_{0-24}) $>51\ h \cdot mg \cdot L^{-1}$ and virological efficacy. They concluded that younger children should receive higher EFV doses than currently recommended. In both studies,[5,7] doses were derived from the licensed dose (Table 1).[2] Together with earlier studies, these findings suggest that a large proportion of children taking EFV after the pediatric licensed or WHO 2006 dosing guidelines might need a higher dose.

Because there are few studies validating international weight band dosing recommendations for EFV to date, in particular in African HIV-infected children, we conducted a PK substudy to determine whether the 2006 WHO weight band dosing, similar to the manufacturer's recommendations, resulted in optimal exposure in 41 Ugandan children over 3 years old in the AntiRetroviral Research for Watoto (ARROW) trial.

METHODS

Population and Study Design

ARROW is an open-label randomized trial comparing routine laboratory (toxicity, CD4) versus clinically driven monitoring strategies, and also comparing three different NRTI-based ART strategies in 1206 symptomatic HIV-infected infants and children in Uganda and Zimbabwe (www.arrowtrial.org). Forty-one children aged 3–12 years from 2 Ugandan ARROW centers (the Joint Clinical Research Centre, Kampala and the Paediatric Infectious Disease Centre, Mulago Hospital) who had been taking lamivudine + abacavir twice-daily with once-daily EFV for at least 36 weeks in ARROW and were not expected to change weight bands in the next 4 weeks participated in a 2-period, crossover, open-label PK study comparing twice versus

once-daily lamivudine + abacavir.[11] EFV was dosed once-daily according to WHO 2006 pediatric recommendations as 50 mg or 200 mg capsules or halved 600 mg tablets (Table 1), except that children weighing 14 to <15 kg received 200 mg (the licensed dose) rather than 250 mg EFV to harmonize with NRTI weight bands. The 200 mg, 250 mg, 300 mg and 350 mg EFV dose consisted of one 200 mg capsule, one 200 mg plus one 50 mg capsule, one halved 600 mg tablet, and one halved 600 mg tablet plus one 50 mg capsule, respectively. EFV 600 mg tablets were unscored but were cut in the pharmacy before dispensing at 4 weekly visits. Children on any concomitant medication with known interactions to any drug in the antiretroviral regimen or with anemia or illnesses that could influence the PKs of EFV, such as diarrhea, vomiting, renal, or liver disease were not eligible. Children who missed any dose of any antiretroviral drug in the 3 days before the PK evaluation (confirmed by pill count and questionnaire) were excluded. All carers gave fully informed written consent for both the main trial and the PK study, and children provided additional assent as appropriate according to age and knowledge of HIV status. The PK study was approved by the Ethics Committee from each participating centre and by the Uganda National Council of Science and Technology.

EFV Blood Sampling and Analyses

Four weeks before the PK evaluation was undertaken (32 weeks after starting ART), children were changed to efavirenz administration in the morning if they were taking EFV in the evening. At week 36, after starting ART (once-daily EFV plus twice-daily NRTIs), a 12-hour PK sampling session was done. Samples were taken immediately before directly observed medication intake (t = 0) and at 1, 2, 4, 6, 8, and 12 hours later. Breakfast (nonstandardized, but mostly milk/milky tea with samosas/bread/chapati) was provided 2 hours after the morning dose. One and a half milliliter of blood was collected per time point. Plasma was separated and stored at −80°C until transportation on dry ice for analysis of EFV (and NRTI) plasma concentrations. After the PK evaluation at week 36, the children were switched to a completely once-daily regimen (morning administration). At week 40, the intensive plasma PK sampling was repeated, including an extra PK sample at 24 hours after observed intake. Serum biochemistry and hematology were performed at week 36.

Plasma concentrations of EFV were assayed by a validated high-performance liquid chromatography method at the Department of Clinical Pharmacy of Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands, using a validated high-performance liquid chromatography assay with UV detection.[12] The lower limit of quantification was 0.05 mg/L. Three samples had concentrations below the detection limit. They were treated as zero for the determination of PK parameters in WinNonlin and as 0.05 mg/L for estimation of geometric mean concentration.

Statistical Methods

Because WHO growth charts only go up to 10 years of age, weight-for-age and height-for-age *Z* scores were calculated using the 1990 British Growth Charts[13] in STATA statistical software, version 11.1 (STATA Corp, College Station, TX). PK parameters [C_{24h}, C_{max}, $AUC_{0–24h}$, and CL/F] of EFV were calculated by noncompartmental analysis of the plasma concentration data using WinNonlin software version 5.2 (Pharsight Corporation, Mountain View, CA). AUC was calculated using a trapezoidal rule. C_{24h} at week 36 was estimated by extrapolation of the 12-hour PK curve using the exponential equation for first-order PK: $\ln(C_{24h}) = \ln(C_{12h}) - (\Delta t_{0–12h} * k)$ with $k = \ln 2/t_{1/2}$. Elimination half-life was calculated on ≥3 time points after C_{max}. Four children had $R^2 < 0.85$ for the log-linear regression to calculate the elimination rate constant or elimination half-life. C_{24h} was therefore not extrapolated. EFV PK parameters were compared across weight bands, and predictors of $\log_{10}$ $AUC_{0–24}$ and CL/F/kg including sex, age, weight-for-age, height-for-age and dose were assessed using mixed models, fitting random effects for each child. As CYP2B6 516G>T genotype is known to strongly increase plasma EFV exposure[14–16] but was not measured in this study. We used finite normal mixture modeling to estimate the geometric mean EFV exposure in and the size (percentage of the population) of 3 population subgroups to correspond to GG, GT, and TT genotypes.

RESULTS

Forty-one children (24 girls, 17 boys) were included in this ARROW PK substudy. Four children increased weight bands between weeks 36 and 40 (2 from 10 to <15 kg to 15 to <20 kg; 2 from 20 to <25 kg to 25 to <30 kg) and are included in all analyses as the primary goal was to evaluate the weight band based dosing. Two children had implausible time–concentration curves (possible labeling errors) at week 40 which were excluded from analysis. The median (interquartile range [IQR]) age and body weight were 7.6 (5.6–9.1) years and 20.0 (16.6–23.0) kg, respectively, at 36 weeks after starting ART. Eighteen and 23 children were aged 3–6 years and 7–12 years, respectively. The majority were moderately stunted [median (IQR) height-for-age −1.85 (−2.78 to −1.11)] and wasted [median (IQR) weight-for-age −1.56 (−2.15 to −0.82)]. Five (12%), 16 (39%), 17 (41%), and 3 (7%) were in weight bands 10 to <15/15 to <20/20 to <25/25 to <30 kg, receiving 200, 250, 300 and 350 mg EFV, respectively, at the first PK day (Table 1, 300 and 350 mg doses including halved adult 600 mg tablets). Median (IQR) (range) doses per bodyweight were 13.6 mg/kg (12.8–14.6) (11.6–16.7) and 13.9 mg/kg (12.8–14.7) (11.9–16.7) at first and second PK days, respectively; and 345 mg/m^2 (323–360) (291–400) and 352 mg/m^2 (329–367) (296–395) respectively, per unit surface area. Doses in mg/kg received were highest in the 15 to <20 kg weight band (median 14.7) and lowest in the 20 to <25 kg weight band (median 13.0) (Kruskal–Wallis $P = 0.001$). Doses in mg/m^2 were lowest in the 10 to <15 kg weight band (median 315) and were higher in other weight bands (medians between 342 and 363; Kruskal–Wallis $P = 0.0002$).

The geometric mean EFV plasma concentration versus time curves obtained at the PK evaluation days 36 and 40 weeks after starting ART were very similar (Fig. 1). Seven of the 41 (17%) children in total had subtherapeutic (<1.0 mg/L) plasma concentrations at 8 hours (C_{8h}) and/or at 12 hours

(C_{12h}) after observed intake at 1 or both PK days (Fig. 2). Six of the 41 (15%) children had subtherapeutic C_{8h} and/or C_{12h} plasma concentrations at week 36 and 7 of 39 (18%) children at week 40. Twenty-two (59%) of the 37 children in whom C_{24h} could be extrapolated at week 36 had values <1.0 mg/L and 15 of 39 (38%) observed C_{24h} plasma levels at week 40 were <1.0 mg/L. Supratherapeutic and potentially toxic C_{8h} and/or C_{12h} plasma levels (>4.0 mg/L) were found in 12 (29%) children: 10 (24%) children at week 36 and 11 (28%) children at week 40.

The geometric mean PK parameters of EFV are presented in Table 2. In the 35 children who stayed on the same EFV dose and had both PK evaluations, there was no evidence of variation in C_{max}, $AUC_{0–24h}$, and clearance between the 2 PK evaluation days (geometric mean ratio [90% confidence interval (CI)]: 0.99 (0.88 to 1.10) P = 0.83, 0.92 (0.82 to 1.02) P = 0.18, 1.09 (0.98 to 1.21) P = 0.18, respectively). EFV concentrations were mainly lower than those previously reported in adult patients.[2] In particular, 26 of 41 (63%) and 20 of 39 (51%) children had $AUC_{0–24}$ <50 h·mg·L^{-1} at week 36 and 40, respectively, 27 (66%) at either PK visit. A large intersubject, but moderate intrasubject variability, was found in EFV PK parameters: being 57% and 28% for C_{max}, 81% and 28% for $AUC_{0–24}$, 84% and 27% for clearance, and 113% and 39% for C_{min} (estimated not observed in 37 patients at week 36). There was no evidence of significant difference in EFV across the 4 weight bands for C_{max} (P = 0.58), $AUC_{0–24}$ (P = 0.12), clearance (P = 0.22), or C_{min} (P = 0.52). However, with only 41 children power was relatively low. Compared with the 15 to <20 kg weight band (which had the most children), $AUC_{0–24}$ was 29% lower (95% CI: 55% lower to 10% higher) in those weighing 10 to <15 kg and 25% lower (95% CI 53% lower to 20% higher) in those weighing 20 to <25 kg. $AUC_{0–24}$ was more similar in the small number of children weighing 25 to <30 kg (11% higher, 95% CI: 38% lower to 99% higher).

Although pharmacogenetic testing was not performed in this study, we used finite normal mixture modeling to identify the 3 most likely subpopulations for $AUC_{0–24}$. Forty percent

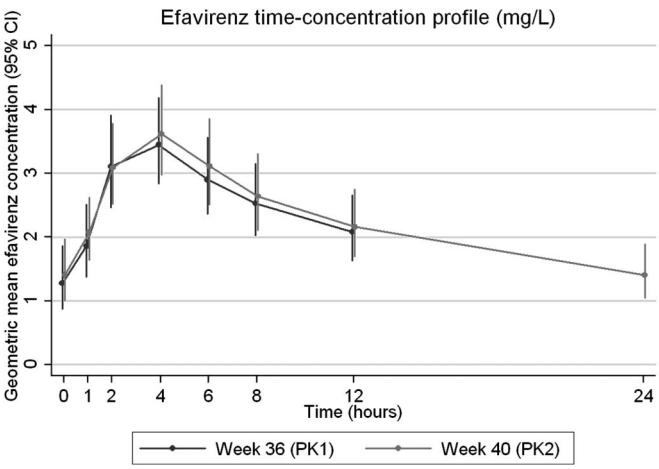

FIGURE 1. Mean efavirenz levels at week 36 (PK1) and week 40 (PK2).

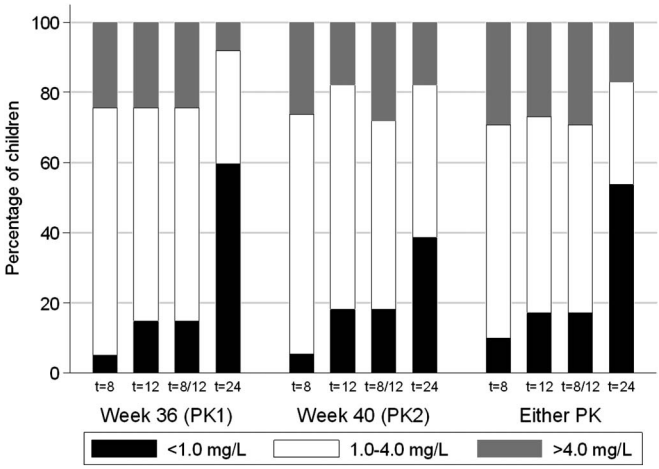

FIGURE 2. Efavirenz concentrations 8, 12, and 24 hours after observed intake. n = 41 and 39 at week 36 and 40, respectively. C_{24} extrapolated at week 36 in 37 children and observed at week 40.

of the children had a geometric mean $AUC_{0–24}$ of 27.2 h·mg·L^{-1}, 32% 49.9 h·mg·L^{-1}, and 28% 137.7 h·mg·L^{-1} (Fig. 3). However, there was no evidence of association between sex, age, weight, receipt of halved tablets, weight-for-age or height-for age with $AUC_{0–24}$ (P > 0.2). There was a marginal trend toward higher $AUC_{0–24}$ with greater doses, [+8.8 per mg/kg higher (95% CI: −1.2 to +18.9); +20.3 per 50 mg/m^2 higher (−3.2 to +43.8); both P = 0.09]. No child substituted EFV for toxicity, and there were no grade 3/4 clinical events considered definitely/probably related to EFV in these children, with the exception of 3 rashes during the first week on ART (children had week 36 $AUC_{0–24}$ 42, 56 and 258 h·mg·L^{-1}).

DISCUSSION

A group of 41 HIV-infected Ugandan children aged between 3 and 12 years, receiving EFV once-daily and using the 2006 WHO weight band dosing recommendations had lower and highly variable PK parameters of EFV compared with historical data from adults. The EFV C_{max}, C_{min}, and $AUC_{0–24}$ in our patients were 15%, 36%, and 10% lower, respectively, than those observed in adult patients receiving once-daily EFV 600 mg (Table 2).[2] If we compare our week 36/40 data to previously reported EFV data in African children, C_{max}, C_{min}, and $AUC_{0–24}$ were similar or even somewhat lower than those of previous studies: 4.10/4.10 mg/L, 0.84/1.40 mg/L, and 50.79/55.41 h·mg·L^{-1}, respectively, in our study compared with 3.71 mg/L,[4] 1.18 to 1.64 mg/L,[5,7] and 65.2 h·mg·L^{-1},[5] respectively.

Based on the study of Marzolini relating EFV to efficacy and toxicity in adults, a minimum target of 1.0 mg/L 8–20 hours postdose and a maximum target of 4.0 mg/L is advocated.[17] Of note, this study did not measure the true trough concentration at 24 hours but was based on samples taken 8–20 hours postdose. Fifteen percent (week 36) and 18% (week 40) of the children in the current study had subtherapeutic plasma concentrations (<1.0 mg/L) 8–12 hours

TABLE 2. PK Parameters of EFV

EFV	Week 36 (PK1) Geometric Mean (95% CI), (Range)	Week 40 (PK2) Geometric Mean (95% CI), (Range)	Lit. Data Adults2 Arithmetic Mean (SD)
C_{max} (mg/L)	4.10 (3.37 to 4.98), (1.45–14.87)	4.10 (3.41 to 4.93), (1.18–21.97)	4.072 (1.16)
AUC_{0-24} ($h \cdot mg \cdot L^{-1}$)	50.79 (39.77 to 64.88), (16.04–258.84)	55.49 (43.91 to 70.11), (18.18–479.91)	58.08 (23.04)
CL/F (L/h)	5.29 (4.12 to 6.80), (0.77–15.99)	4.94 (3.90 to 6.25), (0.52–17.92)	NA
$C_{24\ h}$ (mg/L)	0.84 (0.60 to 1.18)*, (0.17–9.28)	1.40 (1.03 to 1.90), (0.27–18.39)	1.77 (1.01)

*Extrapolated (n = 37).
Note: ranges provided with geometric means to describe the variation across children.

postdose, which is consistent with other PK studies of EFV in African children. The study by Ren et. al, where the 15 children received lower EFV doses[2] than in our study,[1,18] found 40% of the patients had estimated C_{min} extrapolated from samples taken 12–24 hours postdose <1.0 mg/L,[7] compared with 59% extrapolated and 38% observed C_{24h} in our study. Ren et. al also found a higher chance of detectable viral load in children with subtherapeutic plasma concentrations. Another study evaluating EFV exposure in African children demonstrated that 19% had estimated C_{min} <1.0 mg/L,[5] and again, subtherapeutic exposure was linked to suboptimal antiviral efficacy.

In addition to adult and pediatric data showing an association between a C_{min} target of 1.0 mg/L and virological efficacy, 2 recently published studies have found an exposure-efficacy link for EFV AUC in children.[5,19] Both found an EFV AUC_{0-24} above ~50 $h \cdot mg \cdot L^{-1}$ significantly improved virological efficacy. In our study, the geometric mean AUC_{0-24} of EFV is only just above this 50 $h \cdot mg \cdot L^{-1}$ threshold (Table 2). Twenty-six of 41 (63%) children at week 36 and 20 of the 39 (51%) evaluable PK profiles at week 40 had an EFV exposure lower than 50 $h \cdot mg \cdot L^{-1}$.

Taken together, our data, added to the previously reported information, strongly suggests that children should receive EFV doses higher than the WHO 2006 recommendations to increase the percentage of children with C_{min} and/or AUC in the target ranges, leading to maximal antiviral efficacy. The fact that these WHO 2006 recommendations[18] are very similar to the manufacturers leaflet[2] daily dose (50 mg higher only for those children weighing 14 to <15 kg and 30 to 32.5 kg) highlights the importance of our results for children in resource-rich and resource-limited settings. On the other hand, due to the large interpatient variability (81% in our patients), we found a considerable proportion of children (29%) with an EFV C_{max} in the supratherapeutic and potentially toxic range (>4.0 mg/L). Because of the relatively large proportions of children with EFV exposure outside the therapeutic range, it is not difficult to understand that only a small majority of children [22 of the 41 (54%)] was dosed adequately (1.0–4.0 mg/L) 8–12 hours post intake, which is consistent with data from the previous 2 studies in African children: 47% and 66%.[5,7] The latest 2010 WHO dosing guidelines have higher EFV doses than evaluated in our study (and than licenced) for children weighing 14 to <20, 25 to <30, and 35 to <40 kg: of note, these higher doses were chosen not only to reflect concerns about underdosing raised by the 2 previous African studies[5,7] but also to remove the 50 mg capsules from dosing tables, as these were becoming no longer available. Our data suggest that, although these doses should lead to greater exposure and thus greater virological efficacy, the necessary trade-off is that more than one-third of children will be exposed to potentially toxic EFV levels. Although overt grade 3/4 toxicity was not reported and CNS side effects is transient in most adults, CNS side effects associated with EFV in children (colorful dreams, impaired concentration) can be problematic, particularly at school, without ever reaching high toxicity grades or without recognition that their source may be an adverse event and their importance should not be ignored. However, WHO 2010 guidelines retain the same 300 mg dose for children weighing 20 to <25 kg as we evaluated in ARROW: 21 of 31 (68%) AUC_{0-24} in this weight band were below the 50 $h \cdot mg \cdot L^{-1}$ target with this 300 mg dose, suggesting this should be increased. All children in ARROW weighed 14 to 30 kg, so our data cannot inform whether the WHO 2010 doses for the 10 to 14 kg (200 mg) or 30 to <35 kg (400 mg) weight bands are sufficient. However, EFV CNS side effects can be more problematic in adolescents where problems with concentration can have major impacts on schooling, so avoidance of very high levels may be more important in those >30 kg.

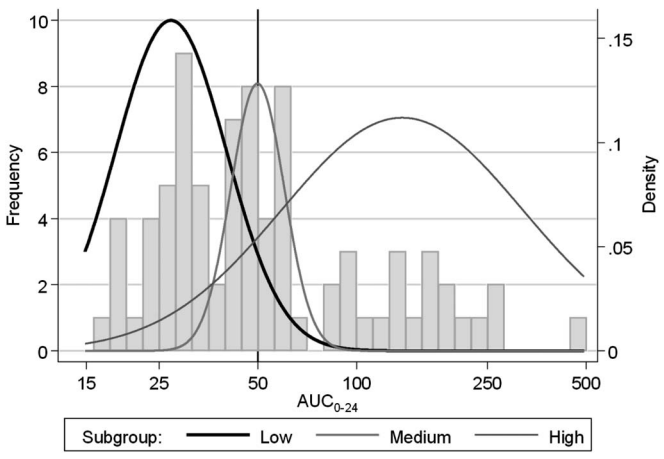

FIGURE 3. Subpopulations of AUC_{0-24} efavirenz within the ARROW PK substudy.

Lower plasma concentrations found for EFV in these African children showed one important distinction compared with adults, namely that the apparent clearance for EFV in our patients is faster than that observed in adult patients.[19] These data support the hypothesis that EFV metabolism is affected

by age and that children are pharmacokinetically different from adults. Another factor that could influence EFV metabolism is genetic polymorphisms in CYP2B6, the enzyme responsible for metabolism of EFV. African patients have been found to have higher frequencies of 516G>T polymorphism for the CYP2B6 enzyme,[20–23] which is associated with much higher and potentially toxic EFV concentrations.[8] Additionally, Leger et al showed that distinct CYP2B6 polymorphisms decreased plasma EFV exposure in patients of African descent.[24] Although we do not have pharmacogenetic data available for our patient population, the trimodal distribution of EFV AUC as shown in Figure 3 suggests a division of patients being either normal metabolizers (homozygote wild-type CYP2B6), intermediate metabolizers (heterozygote CYP2B6 mutants), and slow metabolizers (homozygote CYP2B6 mutants). Our small patient set is roughly divided in 3 equal-sized subpopulations with a gene frequency of 0.44 for the T allele.

One limitation of our study is that it included only Ugandan (East African) children: however, results are broadly compatible with earlier studies in South Africa and Burkina Faso (West Africa),[5,7] and we were able to include a larger number of children than Ren et al. As far as we know, our study is the first using full PK information to evaluate the 2006 WHO weight band dosing table which harmonized the licensed dosing recommendations for EFV with weight bands for other antiretrovirals. This dosing table used split adult 600 mg tablets to provide 300 mg as all or part of another dose in those 20 to <30 kg. Although exposure seemed slightly lower in children receiving these split tablets in the 20 to <25 kg weight band in our study, given the low exposures in all weight bands, it is difficult to attribute all or even much of this to a possible effect of splitting tablets. Using split adult tablets enables a far larger number of children to receiving life-saving ART, and is also recommended in WHO 2010 dosing guidelines: our findings highlight the importance of testing all pediatric dosing recommendations regardless of dosing modality. In terms of methodology, both previous studies used population PK models to determine of PK parameters, with the disadvantage that full EFV exposure can only be estimated by complex models. Here we used a full PK curve for every individual child after observed intake, which is more reliable for the estimation of PK parameters. Although grade 3/4 and ART-modifying toxicity was collected as part of the ARROW trial, lower grade adverse events, which may be important for children, such as poor concentration, were not collected. Thus, while we observed no severe or serious toxicity associated with high EFV levels, we cannot rule out other toxic effects.

The final limitation of the study is the lack of virological data to evaluate the association of PK parameters of EFV with virologic response. However, previous studies have demonstrated a strong concentration-effect relationship, not only in adults (subtherapeutic C_{8-24h}<1mg/L),[17] but also in children (AUC_{0-24} $<\sim 50\ h \cdot mg \cdot L^{-1}$).[5,19] The lack of virological data in this study is thus less important than for drugs where such associations have not been previously described. Hence, we are confident that our EFV exposure data are truly suboptimal and that those treating children with EFV in resource-limited and resource-rich settings should move urgently to the adjusted WHO 2010 dosing recommendations. However, even with these new recommendations, dosing in some weight bands (particularly from 20 to <25 kg but also possibly 10 to <14 kg and 30 to <35 kg) remains relatively low. A new PK substudy within the CHAPAS-3 trial has just started to evaluate increased EFV dosing in African children. Extensive monitoring of EFV-associated toxicity, particularly active solicitation for lower grade side effects and retrospective evaluation of virological efficacy will be performed for this important but difficult to handle antiretroviral agent.

Ugandan children aged between 3 and 12 years, on EFV once daily and using the 2006 WHO weight band dosing recommendations, had lower and highly intersubject variable PK parameters of EFV compared with data from adults. There were no statistically significant differences across weight bands, suggesting no major effect of some using half-tablets. Our findings suggest that children receiving EFV dosed according to 2006 WHO guidelines (or licensed recommendations on which these were based) could be at a higher risk of virological failure, and all pediatricians in resource-limited and resource-rich countries should move to WHO 2010 guideline dosing as a matter of urgency. Nevertheless, doses in some weight bands may need to be increased still further, and this should be investigated promptly. Yet, the higher proportion of children expected to have high and potentially toxic levels remains a concern.

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