Virologic Response to First-line Efavirenz- or Nevirapine-based Antiretroviral Therapy in HIV-infected African Children

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Background: Poorer virologic response to nevirapine- versus efavirenz-based antiretroviral therapy (ART) has been reported in adult systematic reviews and pediatric studies.

Methods: We compared drug discontinuation and viral load (VL) response in ART-naïve Ugandan/Zimbabwean children ≥3 years of age initiating ART with clinician-chosen nevirapine versus efavirenz in the ARROW trial. Predictors of suppression <80, <400 and <1000 copies/mL at 36, 48 and 144 weeks were identified using multivariable logistic regression with backwards elimination ($P = 0.1$).

Results: A total of 445 (53%) children received efavirenz and 391 (47%) nevirapine. Children receiving efavirenz were older (median age, 8.6 vs. 7.5 years nevirapine, $P < 0.001$) and had higher CD4% (12% vs. 10%, $P = 0.05$), but similar pre-ART VL ($P = 0.17$). The initial non-nucleoside-reverse-transcriptase-inhibitor (NNRTI) was permanently discontinued for adverse events in 7 of 445 (2%) children initiating efavirenz versus 9 of 391 (2%) initiating nevirapine ($P = 0.46$); at switch to second line in 17 versus 23, for tuberculosis in 0 versus 26, for pregnancy in 6 versus 0 and for other reasons in 15 versus 5. Early (36–48 weeks) virologic suppression <80 copies/mL was superior with efavirenz, particularly in children with higher pre-ART VL ($P = 0.0004$); longer-term suppression was superior with nevirapine in older children ($P = 0.05$). Early suppression was poorer in the youngest and oldest children, regardless of NNRTI ($P = 0.02$); longer-term suppression was poorer in those with higher pre-ART VL regardless of NNRTI ($P = 0.05$). Results were broadly similar for <400 and <1000 copies/mL.

Conclusion: Short-term VL suppression favored efavirenz, but long-term relative performance was age dependent, with better suppression in older children with nevirapine, supporting World Health Organization recommendation that nevirapine remains an alternative NNRTI.

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Globally, >3 million children/adolescents are living with HIV, >90% in sub-Saharan Africa.[1] World Health Organization (WHO) guidelines recommend children/adolescents ≥3 years initiate 2 nucleoside-reverse-transcriptase-inhibitors (NRTI) plus 1 non-nucleoside-reverse-transcriptase-inhibitor (NNRTI). The preferred NNRTI is efavirenz (with nevirapine an alternative) based on systematic reviews indicating better viral load (VL) response[2] and short-term toxicity.[3] However, pediatric nevirapine-based fixed-dose combinations are widespread in resource-limited settings[4]; understanding whether nevirapine is associated with poorer virologic response in children initiating antiretroviral therapy (ART) ≥3 years of age has continuing programmatic relevance.

In adults, a 2010 Cochrane review concluded that nevirapine and efavirenz had equivalent efficacy based on 7 randomized controlled trials.[5] A separate examination of 5 observational studies in low- and middle-income countries generally favored efavirenz; 6 studies in high-income countries were more heterogeneous. The 2012 systematic review,[2] on which the WHO guidelines were based, included 26 trials and 7 observational studies with tenofovir + lamivudine or tenofovir + emtricitabine backbones.[6] This review, and a 2013 meta-analysis[7] of 10 trials and 28 studies with no 2 NRTI backbone restriction, concluded efavirenz had superior efficacy. However, a 2012 systematic review[8] restricted to 7 trials in resource-limited settings concluded that nevirapine and efavirenz showed similar efficacy.

In children, observational studies have also generally concluded that efavirenz had superior efficacy. In 804 Batswana children 3–16 years of age initiating ART with nevirapine (median age, 7 years) or efavirenz (8 years) (NNRTI chosen by clinician), 101 of 383 (26%) receiving nevirapine and 57 of 421 (14%) efavirenz experienced virologic failure [lack of suppression to <400 copies/mL by 6 months or confirmed ≥400 copies/mL postsuppression; unadjusted hazard ratio (HR) = 2.0 [95% confidence interval (CI): 1.4–2.7] $P < 0.001$, adjusted HR (aHR) reported as similar].[9] Thai studies have generally reported similar results,[10,11] most recently in 2015[11] where nevirapine was a predictor for virologic failure (≥1000 copies/mL after ≥24-weeks ART) [aHR = 1.63 (1.14–2.32) $P = 0.004$], although a 2011 study[12] reported no significant difference [unadjusted HR = 1.46 (0.66–3.22)]. In 675 children <18 years (84%, ≥3 years) in the United Kingdom/Ireland Collaborative HIV Paediatric Study (CHIPS) initiating 2 NRTI plus nevirapine (median age, 4 years) or efavirenz (10 years), suppression <400 copies/mL within 12 months did not significantly differ [adjusted rate ratio (efavirenz:nevirapine) = 1.16 (0.95–1.41)] but over all follow-up, risk of subsequent virologic failure (confirmed >400 copies/mL) was lower with efavirenz [adjusted rate ratio = 0.54 (0.40–0.72)].[13] Differences were most pronounced in the first 2 years (interaction $P = 0.03$). Two cross-sectional Tanzanian studies reported that risk of virologic failure was lower with efavirenz.[14,15] A study of 250 Ugandan children/adolescents (median age, 9 years, range 0–18) compared

efavirenz predominantly with zidovudine + lamivudine versus nevirapine predominantly with stavudine + lamivudine. Twelve-month virologic failure was higher in nevirapine [adjusted odds ratio (aOR) (nevirapine:efavirenz) = 2.46 (1.23–4.90), $P = 0.01$].[16]

Considering toxicity, a meta-analysis found nevirapine had more adverse events (AEs) resulting in drug substitution or treatment discontinuation [odds ratio (OR) = 2.2 (1.9–2.6) in adults ≥15 years; limited data in infants/children with each study reporting different outcomes].[3] However, with efavirenz, one concern is central nervous system (CNS) events, with a risk ratio (vs. nevirapine) of 1.4 (0.75–2.59) in children/adolescents ≥5 years in 1 Ugandan study.[17] However, in the recent CHIPS study, discontinuation because of toxicity was 27 of 370 (7.3%) with 2 or 3 NRTIs plus nevirapine versus 32 of 424 (7.5%) with efavirenz.[13]

We therefore compared VL response and treatment discontinuation on first-line nevirapine- and efavirenz-based ART initiated in children ≥3 years of age in the ARROW trial.[18]

MATERIALS AND METHODS

Observational analyses included 836 previously untreated Ugandan/Zimbabwean children initiating efavirenz- or nevirapine-based ART, 3–17 years of age in the ARROW trial (ISCRTN24791884).[18] Children were randomized 1:1:1 to open-label lamivudine + abacavir + NNRTI continuously (Arm-A; control, no zidovudine); induction maintenance with 4-drug lamivudine + abacavir + NNRTI + zidovudine for 36 weeks, then lamivudine + abacavir + NNRTI (Arm-B; short-term zidovudine) or lamivudine + abacavir + zidovudine (Arm-C; long-term zidovudine). The NNRTI (nevirapine/efavirenz) was chosen by clinicians; both were available in all centers throughout the trial for initial ART and substitutions. Simultaneously, children were randomized 1:1 in a factorial design to clinically driven monitoring versus laboratory plus clinical monitoring for toxicity (hematology/biochemistry) and efficacy (CD4). After ≥36 weeks, eligible children taking lamivudine + abacavir twice daily were randomized to continue twice daily or move to once daily. Children were recruited from 1 Zimbabwean (University of Zimbabwe, Harare, Zimbabwe) and 3 Ugandan centers (Joint Clinical Research Centre, Kampala, Uganda; Baylor-Uganda, Mulago, Kampala, Uganda; MRC/UVRI Uganda Research Unit on AIDS, Entebbe, Uganda). ARROW was approved by research ethics committees in Uganda, Zimbabwe and the United Kingdom. Caregivers gave written consent.

Postbaseline VL was assayed retrospectively on stored plasma at 4, 24, 36, 48 and 144 weeks in all children <5 years at ART initiation. VL was also assayed at these time points and 24-weekly post-week 48 in a subset of children enrolled post-June 2008 (immunology substudy); and at, and 48 and 96 weeks after, randomization to once- versus twice-daily lamivudine + abacavir (shown to be virologically equivalent).[19] Assays used Abbott RealTime and Roche Amplicor 1.5: because many samples had low volumes and had to be diluted 1:2, the lower limit of detection was 80 copies/mL. Analysis used closest measurements to nominal time points in equally spaced windows [results available for 37% (n = 309), 35% (n = 282), 42% (n = 341), 44% (n = 241) and 49% (n = 265), respectively, of those alive and in follow-up, broadly similar in nevirapine vs. efavirenz]. In 145 Arm-A/B immunology substudy children alive and in follow-up at 24 weeks (with complete VLs), virologic failure was defined as ≥400 copies/mL at week 24 or subsequent confirmed ≥400 copies/mL through 3 years.[9,13,16]

The primary (nonrandomized) exposure was NNRTI received at ART initiation (efavirenz vs. nevirapine) using intention-to-treat. Child characteristics were compared across these groups using χ^2 (categorical factors) and Wilcoxon (continuous factors) tests. Suppression <80, <400 and <1000 copies/mL with efavirenz and nevirapine was compared using generalized estimating equations for global tests over time (binomial distribution, independent working correlation). At 36-, 48- and 144-weeks post-ART initiation, predictors of suppression <80, <400 and <1000 copies/mL were identified using logistic regression, forcing efavirenz versus nevirapine and age at ART initiation into models. Models included children with VL at baseline and the relevant time point (92%, 89% and 83% of those with VLs at 36, 48 and 144 weeks). Other factors considered as potential confounders were pre-ART WHO stage, CD4%, weight/height-for-age,[20] VL, gender, center, ART strategy randomization, monitoring randomization, whether the caregiver/child reported missed doses in the last 4 weeks and percentage of scheduled visits to date with missed doses in the last 4 weeks. For each time point, independent predictors of suppression <80 copies/mL were identified using backward elimination (exit $P \geq 0.1$ to develop an explanatory models; interactions between variables in final models retained where $P < 0.1$). Additional predictors of suppression <400 and <1000 copies/mL were then identified using forward selection (entry $P = 0.1$), forcing in factors included in the <80 copies/mL model. Factors in any of the models were then included in final time-point-specific models for each threshold, allowing the impact of the same factor to be assessed over the different thresholds. Nonlinearity was explored using natural cubic splines[21] (knots at 10th, 50th and 90th centiles), then represented by categorization. Potential confounders of the association between efavirenz/nevirapine and early death (before week 36) and permanent discontinuation of initial NNRTI were identified using logistic [adjusting for CD4% only (low number of events)] and Cox regression (backwards elimination), respectively. Analyses used Stata 14.1 (StataCorp, College Station, TX). *P* values are 2 sided.

RESULTS

A total of 836 previously untreated children 3–17 years of age initiated ART between March 2007 and October 2008. Of the 836 children, 445 (53%) received efavirenz and 391 (47%) nevirapine. Children on efavirenz were more likely to be male and WHO stage 1/2, were older and less underweight/stunted at ART initiation ($P < 0.01$), but had similar VL ($P = 0.17$) (Table 1). Reflecting local availability, center strongly predicted receiving efavirenz versus nevirapine ($P < 0.001$).

Four of 445 (1%) initiating efavirenz and 18 of 391 (5%) initiating nevirapine died before week 36. Although the difference persisted after adjusting for CD4% ($P = 0.01$), causes of death were primarily infection related and similar between efavirenz/nevirapine (septicemia/meningitis 0/7, pneumonia 1/4, chronic diarrhea/wasting/hypokalemia 1/3, stroke/cerebrovascular 1/2 and uncertain 1/2), with similarly low CD4% [median (interquartile range), 8 (5–11) vs. 3 (1–14) respectively]. The initial NNRTI was permanently discontinued before week 36 in 8 (2%) initiating efavirenz [2 AE, 4 voluntary decision and 2 pregnancy-related] and 22 (6%) initiating nevirapine (9 AE and 13 tuberculosis treatment) ($P = 0.001$ Cox regression adjusting for age at ART initiation). At week 36, those randomized to Arm-C (3 NRTI maintenance) discontinued NNRTI [excepting 5/2 previously discontinuing zidovudine (anemia)/abacavir (hypersensitivity), respectively]. Amongst children randomized to 2 NRTI + NNRTI maintenance (Arm-A/B), 13 died after week 36 [6/294 (2%) efavirenz and 7/269 (3%) nevirapine]. After week 36, the initial NNRTI was permanently discontinued in 37/294 (13%) initiating efavirenz (5 AE, 17 switch to second line, 4 pregnancy related, 1 voluntary decision and 10 other) and 41/269 (15%) nevirapine (23 switch to second line, 13 tuberculosis treatment, 1 voluntary decision and 4 other) (Cox $P = 0.31$ unadjusted, 0.009 adjusted for age and CD4% at ART initiation and center). Overall, Arm-A/B children initiating efavirenz or nevirapine spent 94.4% and 88.9% follow-up-time through to their last clinic visit (median, 4-years follow-up) on efavirenz- or nevirapine-containing ART, respectively.

TABLE 1. Characteristics of Children Receiving Efavirenz and Nevirapine at ART Initiation

	Efavirenz (n = 445)	Nevirapine (n = 391)	P*
Male	242 (54%)	176 (45%)	0.007
Age (yrs): median (IQR)	8.6 (6.4–11.0)	7.5 (4.9–10.1)	<0.001
CD4 (cells/μL): median (IQR)	277 (115–436)	261 (102–476)	0.94
CD4%	12 (6–18)	10 (5–17)	0.05
Weight-for-age Z-score: median (IQR)	−1.7 (−2.6 to −1.0)	−2.4 (−3.6 to −1.5)	<0.001
Height-for-age Z-score: median (IQR)	−1.9 (−2.8 to −1.1)	−2.6 (−3.5 to −1.6)	<0.001
VL (copies/mL): median (IQR)	160,000 (52,000–422,000)†	199,000 (67,000–453,000)‡	0.17
WHO stage 3/4	269 (60%)	322 (82%)	<0.001
On tuberculosis treatment	43 (10%)	0 (0%)	<0.001
Randomized treatment strategy			0.61
Arm-A (3TC/ABC/NNRTI throughout)	141 (32%)	135 (35%)	
Arm-B (3TC/ABC/NNRTI throughout, ZDV until week 36)	153 (34%)	134 (34%)	
Arm-C (3TC/ABC/ZDV throughout, NNRTI until week 36)	151 (34%)	122 (31%)	
Allocated monitoring strategy			
Routine CD4 monitoring	225 (51%)	202 (52%)	0.75
No CD4 monitoring	220 (49%)	189 (48%)	
Country/center§			<0.001
Uganda/Entebbe	52 (12%)	94 (24%)	
Uganda/JCRC	205 (46%)	25 (6%)	
Uganda/PIDC	98 (22%)	45 (12%)	
Zimbabwe/Harare	90 (20%)	227 (58%)	

*χ^2 tests for categorical measures and Wilcoxon rank-sum tests for continuous measures unless otherwise indicated.
†n = 260 (185 no baseline VLs).
‡n = 235 (156 no baseline VL).
§36% received efavirenz in Entebbe, 89% in JCRC, 69% in PIDC and 28% in Harare.
JCRC indicates Joint Clinical Research Centre; PIDC, Paediatric Infectious Diseases Clinic; ZDV, zidovudine.

Over total follow-up, the initial NNRTI was permanently discontinued because of an AE in 7 of 445 (2%) initiating efavirenz [3 lipodystrophy (2 Arm-B previously receiving zidovudine), 2 gynecomastia and 2 hypersensitivity reaction] and 9 of 391 (2%) nevirapine (4 hypersensitivity reaction, 1 Stevens-Johnson syndrome, 1 rash, 1 acute febrile episode, 1 lactic acidosis and 1 raised liver enzymes) ($P = 0.46$ Fisher exact test). In nevirapine, all 9 AEs were <10 weeks post-ART initiation (median, 23 days; interquartile range, 15–30) and 8 of 9 substituted with efavirenz; in efavirenz, 2 were <10 weeks, the remaining 5 were a median 3.3 years (3.2–3.8) after ART initiation.

Of the 563 participants, 459 (81.5%) initiating long-term NNRTI (Arm-A/B) had ≥1 postbaseline VL. Over all follow-up, there was a trend to better suppression <80 copies/mL with efavirenz (global unadjusted $P = 0.11$), driven by effects before 36 weeks ($P = 0.007$ ≤36 weeks and $P = 0.83$ ≥48 weeks). There was no evidence of difference for <400 copies/mL ($P = 0.57$) or <1000 copies/mL ($P = 0.33$), with a difference in <1000 copies/mL at week 4 only ($P = 0.02$, ≥24 weeks $P = 0.77$) (Fig. 1). Mean VL reduction from weeks 0–4 was 2.4 $\log_{10}$ with efavirenz and 2.3 $\log_{10}$ with nevirapine ($P = 0.18$, n = 302). At week 36, 160 of 200 (80.0%) efavirenz versus 93 of 141 (66.0%) nevirapine were <80 copies/mL (+14.0% [95% CI: 4.5, 23.6] $P = 0.004$), compared with 181 (90.5%) versus 122 (86.5%), respectively, <400 copies/mL (+4.0% [−3.0,10.9] $P = 0.25$). By week 48, suppression <80, <400 and <1000 copies/mL was similar for efavirenz and nevirapine ($P = 0.97$, $P = 0.78$ and $P = 0.40$, respectively). Despite little switching to second-line ART (similar with both NNRTIs), suppression remained similar at week 144 (106 of 141 (75.2%) vs. 89 of 124 (71.8%) <80 copies/mL, 116 (82.3%) vs. 101 (81.5%) <400 copies/mL and 118 (83.7%) vs. 106 (85.5%) <1000 copies/mL; $P > 0.5$).

However, in adjusted analyses (Table 2), differences in suppression between efavirenz versus nevirapine differed by both baseline VL and age at ART initiation; and these relationships varied over follow-up. At week 36, suppression <80 copies/mL did not depend on pre-ART VL in efavirenz, but declined with increasing pre-ART VL in nevirapine; the net effect was greater suppression with efavirenz in those with pre-ART VL >35,000 copies/mL (overall effect of efavirenz vs. nevirapine $P = 0.0004$; heterogeneity/interaction $P = 0.007$) (Table 2; Fig. A, Supplemental Digital Content 1, http://links.lww.com/INF/C646). Suppression <400 and <1000 copies/mL was broadly similar (Table, Supplemental Digital Content 2, http://links.lww.com/INF/C647). This effect had weakened by week 48 (heterogeneity/interaction $P = 0.15$; Table 2; Fig. B, Supplemental Digital Content 2, http://links.lww.com/INF/C646), and by week 144, suppression <80 copies/mL was lower in those with higher pre-ART VL ($P = 0.05$) in both groups (heterogeneity/interaction $P = 0.8$).

Considering age at ART initiation, at weeks 36 and 48, suppression was poorer in the youngest and older children, irrespective of NNRTI (global $P = 0.02$, $P = 0.003$ and $P = 0.0006$ for <80, <400 and <1000, respectively, at week 36; $P = 0.09$, $P = 0.009$ and $P = 0.03$, respectively, at week 48). However, at week 144, older children/adolescents had poorer suppression <80 copies/mL on efavirenz (aOR per year older = 0.79 [95% CI: 0.69–0.90] $P < 0.001$), but suppression was independent of age on nevirapine (aOR = 0.94 [0.79–1.11] $P = 0.46$) (overall effect of efavirenz vs. nevirapine $P = 0.05$; heterogeneity/interaction $P = 0.09$; Table 2; see Fig. C, Supplemental Digital Content 1, http://links.lww.com/INF/C646). Effect sizes were similar for <400 copies/mL [efavirenz: aOR per year older = 0.74 (0.64–0.87) $P < 0.001$; nevirapine: aOR = 0.88 (0.72–1.08) $P = 0.23$] and <1000 copies/mL [efavirenz: aOR = 0.72 (0.61–0.85) $P < 0.001$; nevirapine: aOR = 0.85 (0.69–1.06) $P = 0.14$], but evidence for heterogeneity was weaker ($P = 0.15$, 0.19, respectively; Table, Supplemental Digital Content 2, http://links.lww.com/INF/C647). The relationship in those on efavirenz increased year-by-year across the age range with no

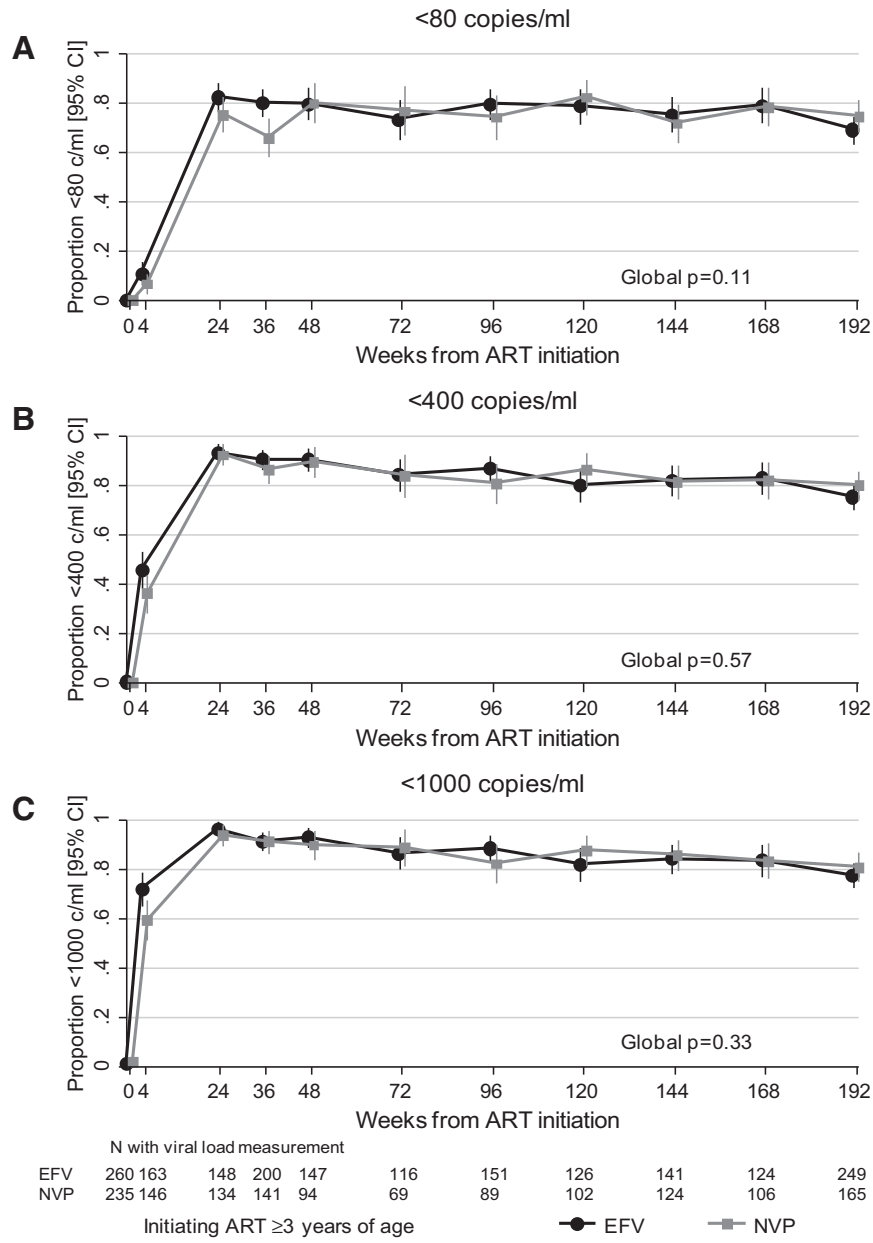

FIGURE 1. Suppression (A) <80 copies/mL over time, (B) <400 copies/mL over time and (C) <1000 copies/mL over time (only including long-term NNRTI (Arm-A/B) from week 48 onwards).

evidence of nonlinearity (noting those 3–4 years of age at ART initiation were 5–9 by week 144).

Effects of other factors did not vary by NNRTI ($P > 0.1$ for all thresholds). Suppression at weeks 48 and 144 was generally poorer in those reporting missing ART doses at a greater percentage of scheduled visits, with larger effects on the higher VL thresholds (<400 and <1000 copies/mL) than <80 copies/mL (Table, Supplemental Digital Content 2, http://links.lww.com/INF/C647). Interestingly, at week 144, suppression was lower in lamivudine + abacavir + NNRTI (Arm-A) versus lamivudine + abacavir + NNRTI + 36 weeks zidovudine (Arm-B) ($P = 0.05$).

In the subset with regular VLs, there was no evidence of a difference in virologic failure (≥400 copies/mL at week 24 or subsequent confirmed ≥400 copies/mL through 3 years) [18 of 93 (19.4%) efavirenz vs. 8 of 52 (15.4%) nevirapine, $P = 0.56$ Cox regression adjusting for age at ART initiation and center).

DISCUSSION

WHO guidelines recommend children/adolescents ≥3 years initiate ART with 2 NRTI + NNRTI, where the NNRTI efavirenz is preferred over nevirapine. Overall, in this nonrandomized comparison in the ARROW trial, short-term suppression favored efavirenz, particularly for <80 copies/mL, but there was little difference from week 24 at <400 and <1000 copies/mL despite the vast majority remaining on the same NNRTI. Longer-term (≥48 weeks) differences were small at all thresholds, although analysis at 144 weeks favored efavirenz ($P = 0.05$). This is broadly consistent with other pediatric studies, which generally found efavirenz associated with better virologic outcome.[9–11,13–16] The United Kingdom/Irish CHIPS study also found the most pronounced differences were shorter term (<2 years).

However, short-term performance of efavirenz versus nevirapine also varied by pre-ART VL, with efavirenz similar at 36 and

TABLE 2. Independent Predictors of VL Suppression <80 Copies/mL at 36, 48 and 144 Weeks After ART Initiation

	36 Weeks (n = 314, Arms A/B/C)		48 Weeks* (n = 213, Arms A/B)		144 Weeks* (n = 221, Arms A/B)	
	aOR (95% CI)	*P*	aOR (95% CI)	*P*	aOR (95% CI)	*P*
VL at ART initiation						
Per $\log_{10}$ higher if taking efavirenz	1.01 (0.58–1.76)	0.96	0.76 (0.39–1.49)	0.42	0.59 (0.35–1.00)	0.05
Per $\log_{10}$ higher if taking nevirapine	0.29 (0.15–0.56)	<0.001	0.33 (0.13–0.86)	0.02		
Heterogeneity		0.003		0.15		
Efavirenz vs. nevirapine if VL 200,000 copies/mL at ART initiation	2.55 (1.29–5.03)	0.007	0.62 (0.27–1.43)	0.27		
Efavirenz vs. nevirapine if 10 yrs of age at ART initiation					1.14 (0.43–3.08)	0.79
Age at ART initiation						
Per year older if taking efavirenz					0.79 (0.69–0.90)	<0.001
Per year older if taking nevirapine					0.94 (0.79–1.11)	0.46
Heterogeneity						0.09
Age at ART initiation vs. 5–9 yrs		0.02		0.09		
3–4	0.73 (0.36–1.46)	0.37	0.47 (0.19–1.15)	0.10		
10+	0.34 (0.16–0.73)	0.006	0.38 (0.14–1.00)	0.05		
3TC/ABC/NNRTI throughout vs. additional 36-weeks ZDV induction*					0.52† (0.27–1.00)	0.05
Missed any doses in last 4 weeks vs. not missed any doses					0.51 (0.17–1.52)	0.23
% visits to date with missed doses in last 4 weeks (per 10% higher)			0.76 (0.57–1.00)	0.05	0.84 (0.59–1.21)	0.36
Center vs. A		0.47‡				
B	1.00 (0.45–2.25)	0.99				
C	0.58 (0.28–1.23)	0.16				
D	0.69 (0.31–1.49)	0.34				
Overall efavirenz vs. nevirapine (incorporating interaction effects above)		0.0004		0.26		0.05

*Only including children receiving long-term NNRTIs (Arm A/B) in analyses from week 48 onwards

†There was no evidence of interaction between NNRTI and allocated ART strategy ($P > 0.1$).

‡Included because significant variation in suppression <400 copies/mL and <1000 copies/mL by center at week 36 (Table, Supplemental Digital Content 2, http://links.lww.com/INF/C647).

n indicates complete cases.

48 weeks regardless of pre-ART VL, but nevirapine better in those with lower VL (Fig. A, Supplemental Digital Content 1, http://links.lww.com/INF/C646). Longer term (144 weeks), this was not apparent: suppression was independently lower in those with higher pre-ART VL regardless of NNRTI received and independently of age, potentially reflecting greater pre-ART reservoir with higher VL, but regardless of cause, highlights the importance of prompt ART initiation. The fact that the initial superiority of efavirenz at high pre-ART VL waned over time raises questions regarding the relevance of short-term suppression as an outcome, because long-term suppression is the goal of treatment.

The other consistent predictor of suppression at every time point was age. Contrasting pre-ART VL, effects of age on early suppression occurred independently of NNRTI, with younger and older children having lower suppression at all thresholds, independently of pre-ART VL and self-reported adherence. Children >10 years were predominantly responsible for their own medication intake, highlighting challenges in preadolescence and adolescent adherence. Most children >3 years were already taking divided tablets, so poorer adherence with syrups is not the cause of lower suppression in the younger children.[22] However, after 3-years ART, in contrast to early suppression, the relative performance of NNRTIs depended on age. Overall, there was at most a modest decline in suppression with age in children on nevirapine, contrasting a marked decline on efavirenz (Fig. C, Supplemental Digital Content 1, http://links.lww.com/INF/C646), the net result being children 10 years of age or older at ART initiation (13 years of age or older at VL measurement) having better long-term suppression with nevirapine, even after adjusting for self-reported adherence. One plausible explanation is the well-documented CNS side effects of efavirenz; preadolescents/adolescents may have taken more unreported treatment interruptions. Certainly, subclinical CNS side effects were commonly reported in adolescents in the weekends-off BREATHER trial[23]: at enrollment, adolescents reported CNS side effects and occasional missed doses, which they found difficult to report to clinic staff (S. Bernays, personal communication, May 7, 2015). Children/adolescents with CNS-related signs/symptoms at ART initiation may have been less likely to receive efavirenz and simultaneously to have lower adherence. If anything, this would tend to favor efavirenz, particularly given necessarily incomplete adjustment for self-reported adherence. It is also unclear whether previous studies investigated varying differences between efavirenz and nevirapine by age (interactions), so these effects may have been missed.

Interestingly, at 144 weeks, children/adolescents who had received an additional NRTI (zidovudine) until week 36 (Arm-B) had marginally better suppression than those who had not (Arm-A) ($P = 0.05$). In contrast in all children,[18] including those <3 years of age, there was no evidence of difference [191 of 259 (73.7%) vs. 169 of 232 (72.8%); $P = 0.82$] (heterogeneity by age <3 vs. ≥3 years at ART initiation $P = 0.08$). Long-term CD4 recovery was also greater in the induction-maintenance Arm-B.[24] Long-term 3 NRTI + NNRTI has been quite widely used (from infancy) in Europe,[13] as this is more palatable than 3-drug lopinavir/ritonavir regimens and potentially more forgiving where persuading children to take medication is problematic.

Our results confirm the generally favorable toxicity profile of both nevirapine and efavirenz, with only 8 nevirapine and 2 efavirenz hypersensitivity reactions, and ~2% permanently discontinuing each NNRTI because of any AE, in a clinical setting where clinicians may not discontinue a drug despite toxicity if the toxicity is not life-threatening. Gynecomastia resulted in permanent discontinuation of efavirenz in 2 children, 1% of those receiving it long term. Permanent discontinuations for non-AE reasons were more frequent with nevirapine, particularly tuberculosis treatment, which is an advantage of efavirenz in children at high risk of tuberculosis shortly after ART initiation.[25] No switches to second-line treatment occurred before 48 weeks with either regimen.

Although children were not randomized to nevirapine or efavirenz, potential confounders were considered for inclusion in models; nonetheless, there is always the possibility of residual confounding. A major limitation of our study is incomplete VL sampling: however, assays were performed to answer questions not depending on receipt of nevirapine or efavirenz, so will not bias this comparison. Although sampling was incomplete, restricting power for interactions particularly, our study is of similar size to others (with 4-year follow-up); the suggestion that older children had better long-term suppression with nevirapine requires further study. All children received the WHO-recommended backbone NRTIs lamivudine + abacavir.[6] Although approximately one-third also received zidovudine until week 36, this did not affect relative performance of efavirenz versus nevirapine; other regimens are unlikely to have altered relative impact of different NNRTIs. We considered 3 thresholds for suppression (<80, <400 and <1000 copies/mL); while <80 copies/mL provides a sensitive investigation of impact of low-level resistant variants, <400 and <1000 copies/mL may be more relevant in clinical practice, particularly resource-limited settings. Results were generally similar over thresholds. We prespecified an exit *P* value of 0.1 for backwards selection to develop an explanatory model; however, this increases the chance of type I error (false positives).

In summary, we confirm results from other pediatric studies that efavirenz is associated with better initial virologic outcome than nevirapine, particularly at higher pre-ART VLs, but longer term, we found they are broadly similar, with nevirapine even having some advantage in older children. This supports the 2013 WHO recommendation that nevirapine should continue as a reasonable alternative to efavirenz, particularly in older children/adolescents. It also suggests there is no particular reason to substitute nevirapine in children doing well on first-line ART. Both nevirapine and efavirenz have generally favorable toxicity profiles, although clinicians need to remain alert to the possibility of hypersensitivity reactions with either.

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