Strategies for Nevirapine Initiation in HIV-Infected Children Taking Pediatric Fixed-Dose Combination "Baby Pills" in Zambia: A Randomized Controlled Trial

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Background. Fixed-dose combination scored dispersible stavudine, lamivudine, and nevirapine minitablets (Triomune Baby and Junior; Cipla Ltd) are simpler and cheaper than liquid formulations and have correct dose ratios for human immunodeficiency virus–infected children. However, they cannot be used for dose escalation (DE) of nevirapine.

Methods. Children were randomized to initiate antiretroviral therapy with full-dose (FD) nevirapine (Triomune Baby or Junior in the morning and evening) versus DE (half-dose nevirapine for 14 days [Triomune in the morning and stavudine-lamivudine {Lamivir-S} in the evening], then FD), in accordance with World Health Organization weight-band dosing tables. The primary end point was nevirapine-related clinical or laboratory grade 3 or 4 adverse events (AEs).

Results. In total, 211 children (median [interquartile range {IQR}] age, 5 [2–9] years; median [IQR] CD4 cell percentage, 13% [8%–18%]) were enrolled and followed up for a median (IQR) of 92 (68–116) weeks. There were 31 grade 3 or 4 AEs that were definitely/probably or uncertainly related to nevirapine in the FD group (18.0 per 100 child-years), compared with 29 in the DE group (16.5 per 100 child-years) (incidence rate ratio, 1.09; 95% confidence interval, 0.63–1.87; $P = .74$). All were asymptomatic; 11 versus 3 were single grade 3 or 4 elevations in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels, all of which resolved without a change in nevirapine dose or interruption. Thirteen (12%) FD versus 2 (2%) DE children had grade 1 (2 in FD) or grade 2 (11 in FD and 2 in DE) rashes. Three (2 in FD and 1 in DE) substituted efavirenz, 3 (FD) continued FD nevirapine, and 9 (8 in FD and 1 in DE) temporarily interrupted nevirapine, followed by successful DE. Predictors of nevirapine rash were older age ($P = .003$) and higher CD4 cell count for age ($P = .03$). Twenty-two children died (12 in FD and 10 in DE), 1 FD and 5 DE children at <4 weeks; none were considered to be drug related by independent review.

Conclusions. Rash was more frequent with FD nevirapine, but 88% had no clinical toxicity; elevated AST or ALT levels were transient and resolved spontaneously, suggesting that routine laboratory monitoring has limited value. Dual pediatric stavudine-lamivudine minitablets are preferred for safe and simple DE; if unavailable, initiating FD Triomune requires timely review for rash, which could be managed by temporary reduction to half-dose Triomune or efavirenz substitution.

Trial registration. Current Controlled Trials identifier: ISRCTN31084535.

In December 2008, most of the ~2 million children infected with human immunodeficiency virus (HIV) were living in sub-Saharan Africa; only 35% of the 640,000 who needed antiretroviral therapy (ART) there were receiving it [1]. One major challenge to scaling up pediatric ART has been the lack of appropriate antiretroviral drug formulations [2, 3]. Syrups are up to 6 times more expensive than solid formulations, are difficult to transport and store, and have short shelf lives, making them inappropriate for most resource-limited settings [2]. Syrups also cannot easily be coformulated and, with different drugs having different volumes, are complex to measure

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and administer. In contrast, fixed-dose combination (FDC) solid scored tablets, which can be dispersed or crushed and dosed according to weight-band tables, are easier for health workers to prescribe and carers to administer.

Until recently, adult FDC tablets (stavudine, lamivudine, and nevirapine) cut into parts were commonly used to treat HIV-infected children in resource-limited settings [4, 5]. However, lack of scoring, lack of dosing flexibility (as the child grows), and inappropriate ratios of the individual drugs for younger children because of varying drug metabolism with age results in inaccurate dosing—in particular, nevirapine underdosing—with concomitant risks of resistance emergence [5]. Cipla Ltd developed 2 triple-drug FDC tablets with the correct drug ratios for children, Triomune Baby and Triomune Junior (6 and 12 mg of stavudine, respectively; 30 and 60 mg of lamivudine, respectively; and 50 and 100 mg of nevirapine, respectively). These are small scored dispersible tablets providing appropriate pharmacokinetic levels for children when given in accordance with World Health Organization (WHO)–recommended weight-band dosing tables [6]. However, to escalate the nevirapine dose as recommended, common practice in Zambia has been to initiate ART using 3 syrups, changing to triple FDC tablets 2 weeks later.

Nevirapine toxicity has been reported to be relatively uncommon among children, both in the United States [7, 8] and Africa, where a Ugandan study found few problems using full-dose (FD) adult Triomune tablets in children from ART initiation [9]. However, there are few prospective pediatric data on nevirapine toxicity, and no randomized trials have evaluated the safety of starting with FD nevirapine immediately in either adults or children.

METHODS

CHAPAS-1 (Children with HIV in Africa—Pharmacokinetics and Adherence of Simple Antiretroviral Regimens) was an open, randomized trial conducted at the University Teaching Hospital, Lusaka, Zambia (ISRCTN31084535). Children aged 3 months to 14 years with confirmed HIV infection and no history of ART (including for prevention of mother-to-child transmission) who fulfilled WHO 2006 guidelines for ART initiation [10] were enrolled. Children were randomized to initiate ART with FD triple-drug FDC Triomune Baby or Junior twice daily for 2 weeks (the FD group) or to Triomune Baby or Junior once daily for the first 2 weeks, together with once-daily Lamivir-S (dual-drug Baby [6 mg of stavudine and 30 mg of lamivudine] or Junior [twice the dose for Baby] FDC; the dose escalation [DE] group). After 2 weeks, DE children discontinued Lamivir-S and continued with Triomune Baby or Junior twice daily. Lamivir-S Baby and Junior were produced by Cipla for CHAPAS-1.

Randomization was in a 1:1 ratio, stratified by age (3 months to 6 years and 7–14 years). A computer-generated sequential randomization list, constructed using variable block size, was prepared in advance by the trial statistician and incorporated securely into the trial database. The list was fully concealed until allocation, after eligibility had been established and a randomization request made to data management staff.

All children (regardless of randomized group) were seen by a nurse 2 and 4 weeks after randomization (ART initiation) and then every 4 weeks until the last child reached 48 weeks (October 2008). At each visit, children were weighed and measured, any adverse events (AEs) or new WHO events were recorded, and additional ART was prescribed. Children were routinely seen by a doctor at weeks 2, 4, 8, and 12 and then every 12 weeks. Doctors conducted a clinical examination, and blood samples were obtained for hematology, biochemistry, and lymphocyte subsets and plasma storage.

The primary outcome was grade 3 or 4 AEs definitely/probably or uncertainly related to nevirapine. Secondary outcomes were grade 2–4 AEs definitely/probably related to nevirapine; adherence, determined on the basis of questionnaires and pill counts; mortality; disease progression, determined on the basis of new WHO stage 3 or 4 events; viral load, measured retrospectively in stored postbaseline samples by means of the Roche Amplicor 1.5 test (lower limit of detection, 250 copies/mL [because of small volumes requiring dilution]); growth and changes in CD4 cell count and percentage from baseline; and the pharmacokinetic parameters of nevirapine, lamivudine, and stavudine [6]. All WHO 3 or 4 events, deaths, and grade 3 or 4 AEs were reviewed without knowledge of randomized group by the End Point Review Committee, which comprised the United Kingdom principal investigator (D.M.G.) and a clinician from the University Teaching Hospital (C. Kankasa) who was not involved in CHAPAS-1 clinical care.

The sample size of 200 children provided 80% power to detect a 15% absolute increase in nevirapine-related grade 3 or 4 AEs, from 10% in the DE group to 25% in the FD group (1-sided $\alpha = .05$). Fifteen percent was the minimum increase in toxicity judged to be clinically relevant to detect: we could not find any data on expected FD rates in adults or children. When enrollment was nearly complete, few children had been entered into the lowest 3–6-kg dosing band. To enable pharmacokinetic analysis in this subgroup, the sample size was increased to 210 and recruitment was limited to very young children to be followed only to October 2008 [11]. An independent data-monitoring committee reviewed the study twice, in February 2007 and June 2008, and on both occasions recommending continuation.

All analyses were done on an intention-to-treat basis. Comparison of event rates between randomized groups used per-

son-time analysis, comparing rate ratios by exact 2-sided significance tests. Mortality analyses used time-to-event survival methods, comparing hazard ratios (HRs) by log-rank tests. Predictors of nevirapine reactions were investigated by multivariable logistic regression, using backward elimination with Akaike's information criterion. Global comparisons between randomized groups in changes in adherence, CD4 cell count and percentage, viral load, and anthropometric parameters to 96 weeks were analyzed using generalized estimating equations. Weight-for-age and height-for-age *z* scores were determined using the British 1990 reference [12], because it covers the full age range of CHAPAS-1 children. Stata software, version 10 (StataCorp), was used in all analyses.

RESULTS

Between February 2006 and October 2007, 204 children were randomized. An additional 8 children weighing 3–6 kg and <2 years old were randomized to June 2008. One child was randomized in error (mistakenly considered to not meet WHO criteria for ART and not prescribed drugs or followed up) and was excluded from analysis. Thus, the intention-to-treat analyses included 211 children, 105 in the FD group and 106 in the DE group (Figure 1).

Baseline characteristics were reasonably balanced between randomized groups (Table 1). The median age at ART initiation was 5 years (35% were <3 years old). Severe wasting and/or stunting were common, with >50% children having weight-for-age and height-for-age *z* scores below −3 and none having scores above zero. Ninety-nine percent had WHO stage 3 or 4 HIV disease, and 58% had a CD4 cell percentage <15%.

The median duration of follow-up to October 2008 was 92 weeks (interquartile range [IQR], 68–116 weeks). Seventeen children (8%) were not known to have died and were not seen during October 2008 (trial closure); their median duration of follow-up was 25 weeks (IQR, 12–44 weeks), with 2 of 17 not seen after randomization. Changing residence was the most common reason for losses to follow-up.

All children initiated ART within 1 day of randomization. One hundred DE children (94%) completed DE after a median of 14 days (IQR, 14–15 days; range, 12–35 days); the remaining 6 either died (3), were lost to follow-up (1), or substituted efavirenz for nevirapine within 14 days (1 rash and 1 tuberculosis cotreatment). In total, nevirapine was interrupted 32 times in 28 children, 19 (18%) in the FD group and 9 (8%) in the DE group (exact $P = .04$). Thirteen substitutions (8 in FD and 5 in DE) with efavirenz or abacavir were due to tuberculosis cotreatment, 13 changes (11 in FD and 2 in DE) were for AEs (temporary nevirapine interruption [11] or efa-

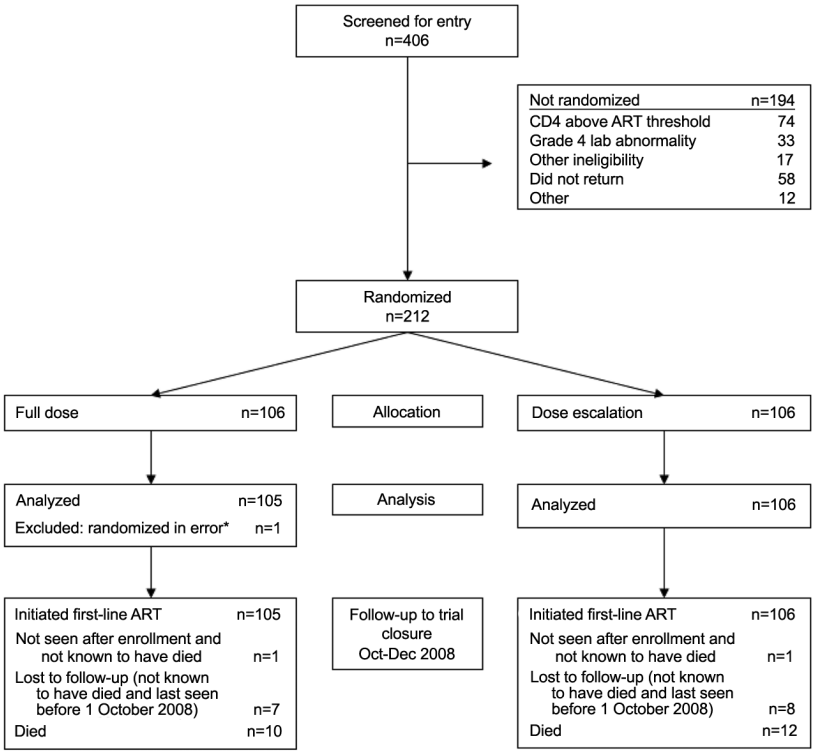

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram. The asterisk (*) indicates that the child was mistakenly considered to not meet World Health Organization criteria for antiretroviral therapy (ART) and was not prescribed drugs or followed up.

Table 1. Baseline Characteristics and Follow-up

Characteristic	FD (n = 105)	DE (n = 106)	All (n = 211)
Male sex	56 (53)	55 (52)	111 (53)
Age			
Median years (IQR)	5.2 (1.6–9.5)	5.7 (2.2–8.7)	5.6 (2.0–9.0)
0–2 years	40 (38)	34 (32)	74 (35)
3–6 years	26 (25)	33 (31)	59 (28)
7–10 years	23 (22)	30 (28)	53 (25)
11–14 years	16 (15)	9 (8)	25 (12)
Median z score (IQR)			
Weight for age[a]	−3.3 (−4.3 to −2.2)	−3.0 (−4.2 to −2.1)	−3.2 (−4.3 to −2.1)
Height for age[a]	−3.1 (−4.2 to −2.4)	−3.1 (−4.1 to −2.0)	−3.1 (−4.1 to −2.2)
WHO HIV stage			
1 or 2	2 (2)	0 (0)	2 (1)
3	68 (65)	68 (64)	136 (64)
4	35 (33)	38 (36)	73 (35)
CD4 cell percentage			
Median percentage (IQR)	13 (9–18)	12 (8–18)	13 (8–18)
0%–4%	16 (15)	9 (9)	25 (12)
5%–14%	43 (41)	54 (51)	97 (46)
15%–24%	37 (35)	34 (32)	71 (34)
⩾25%	9 (9)	8 (8)	17 (8)
CD4 cell count, median cells/μL (IQR)			
All patients	452 (231–824)	437 (245–797)	441 (235–819)
Age 0–2 years	753	882	824
Age 3–6 years	557	422	528
Age 7–10 years	215	306	274
Age 11–14 years	241	246	246
Follow-up			
Median weeks (IQR)	90 (68–113)	96 (68–116)	92 (68–116)
Lost to follow-up	9 (9)	8 (8)	17 (8)

NOTE. Data are no. (%) of patients, unless otherwise indicated. DE, dose escalation; FD, full dose; HIV, human immunodeficiency virus; IQR, interquartile range; WHO, World Health Organization.

[a] British 1990 growth reference [12].

virenz substitution [2]), and 6 were for nonmedical reasons (4 in FD and 2 in DE). No child switched to second-line treatment. Adherence was good: carers reported that their child had not missed medication at 92% of nurse visits (91% in DE and 93% in FD; $P = .28$).

AEs. Sixty (31 in FD and 29 in DE) grade 3 or 4 AEs occurring in 49 children (25 in FD and 24 in DE) were judged to be definitely/probably related to nevirapine ($n = 8$) or to have an uncertain status with respect to their relationship with nevirapine ($n = 52$) by the End Point Review Committee (FD:DE incidence rate ratio [IRR], 1.09; 95% confidence interval [CI], 0.63–1.87; $P = .74$) (Table 2 and Figure 2*A*). All were asymptomatic laboratory AEs, and all children continued nevirapine therapy without interruption or dose change. Most frequent events were elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels (11 in FD and 3 in DE, all single values; 8 [7 in FD and 1 in DE] were judged to be definitely/probably related to nevirapine on the basis of timing) and elevated bilirubin levels ($n = 34$).

Forty (26 in FD and 14 in DE) grade 2–4 AEs occurring in 34 children (22 in FD and 12 in DE) were judged to be definitely/probably related to nevirapine (FD:DE IRR, 1.89; 95% CI, 0.95–3.92; $P = .05$) (Table 2 and Figure 2*B*). These included 14 grade 2 rashes (12 in FD [including 1 repeat rash] and 2 in DE), 25 asymptomatic elevated AST or ALT levels (13 in FD and 12 in DE), and 1 elevated alkaline phosphatase level (FD).

No child developed a grade 3 or 4 rash, but 13 (12%) FD versus 2 (2%) DE children had grade 2 (11 in FD and 2 in DE) or grade 1 (2 in FD) rashes (exact $P = .003$), all judged to be definitely/probably related to nevirapine. Only 1 child (FD) had a second grade 2 rash after rechallenge with half-dose nevirapine. Rashes started a median of 17 days (range, 8–25 days) after ART initiation, with a median duration of 9 days (range, 2–24 days). In 3 FD versus 0 DE children, grade 1

Table 2. Adverse Events (AEs)

Category, parameter	FD (n = 105)	DE (n = 106)	FD:DE rate ratio (95% CI)	P
Grade 3 or 4 AEs with a definite/probable or uncertain relationship with nevirapine (primary end point)				
Children with at least 1 event, no. (%)	25 (24)	24 (23)		
Total events	31	29		
Child-years at risk	173	176		
Rate, events per 100 child-years	18.0	16.5	1.09 (0.63–1.87)	.7
Type of event				
Biochemical	30	29		
Elevated liver enzyme level (AST or ALT)	11	3		
Elevated alkaline phosphatase level	6	4		
Elevated bilirubin level	13	21		
Elevated creatinine level	0	1		
Hematological	1	0		
Thrombocytopenia	1	0		
Grade 2–4 AEs with a definite/probable relationship with nevirapine[a] (secondary end point)				
Children with at least 1 event, no. (%)	22 (21)	12 (11)		
Total events	26	14		
Child-years at risk	173	176		
Rate, events per 100 child-years	14.5	8.0	1.89 (0.95–3.82)	.05
Type of event				
Biochemical	14	12		
Elevation in liver enzyme level (AST or ALT)	13	12		
Elevation in alkaline phosphatase level	1	0		
Clinical	12[b]	2		
Rash	12[b]	2		

NOTE. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; DE, dose escalation; FD, full dose.

[a] Not including events with an uncertain relationship.

[b] Including 2 rashes in 1 child rechallenged with half-dose nevirapine and substituting efavirenz; in total, 11 FD children had grade 2 rashes (and 2 FD children had grade 1 rashes).

(n = 2) or 2 (n = 1) rash was associated with transient grade 3 elevated AST or ALT levels. Of the 15 children who developed rash, 3 (FD) continued FD nevirapine; 9 (8 in FD and 1 in DE) temporarily stopped nevirapine (by substituting Lamivir-S for a median of 8 days [range, 6–8 days]) and then successfully escalated the dose of nevirapine; 1 (FD), in whom rash returned after interruption and DE, substituted efavirenz for nevirapine; and 2 (1 in FD and 1 in DE) substituted efavirenz without retrying half-dose Triomune. All but 2 children (both FD) were managed as outpatients; 2 were admitted for observation (1 early during the trial and 1 during successful continuation of FD nevirapine). In multivariable regression models, nevirapine reactions (either rash alone [15/211; 7%] or rash or definitely/probably nevirapine-related grade 3 or 4 elevated AST or ALT level [21/211; 10%]) were significantly more common both in older children and in those with higher CD4 cell counts for age (Table 3). The risk was also nonsignificantly higher for girls.

HIV-related events. Twenty-two (10%) children died (6.9 and 5.7 deaths per 100 child-years in the FD and DE groups, respectively; FD:DE HR, 1.19; 95% CI, 0.51–2.75; P = .7). No deaths were judged to be drug related, and most occurred soon after randomization: 6 (1 in FD and 5 in DE) during the first 4 weeks and 6 more (4 in FD and 2 in DE) during weeks 4–12. The cause of death was most frequently diarrhoea (n = 7) or serious lung disease (n = 3); most children who died had advanced HIV infection and very low weight-for-age z scores (mean, −4.5) at ART initiation.

Five new or recurrent WHO stage 4 events and 19 stage 3 events occurred in 21 children. WHO stage 3 events were mostly pulmonary tuberculosis (n = 10) or oral candidiasis (n = 8); 3 stage 4 events were extrapulmonary tuberculosis. Overall, 40 children had a WHO stage 3 or 4 event and/or died (19%)—13.9 and 11.1 events per 100 child-years in the FD and DE groups, respectively (FD:DE IRR, 1.26; 95% CI, 0.64–2.49; P = .5).

There were no significant differences between randomized

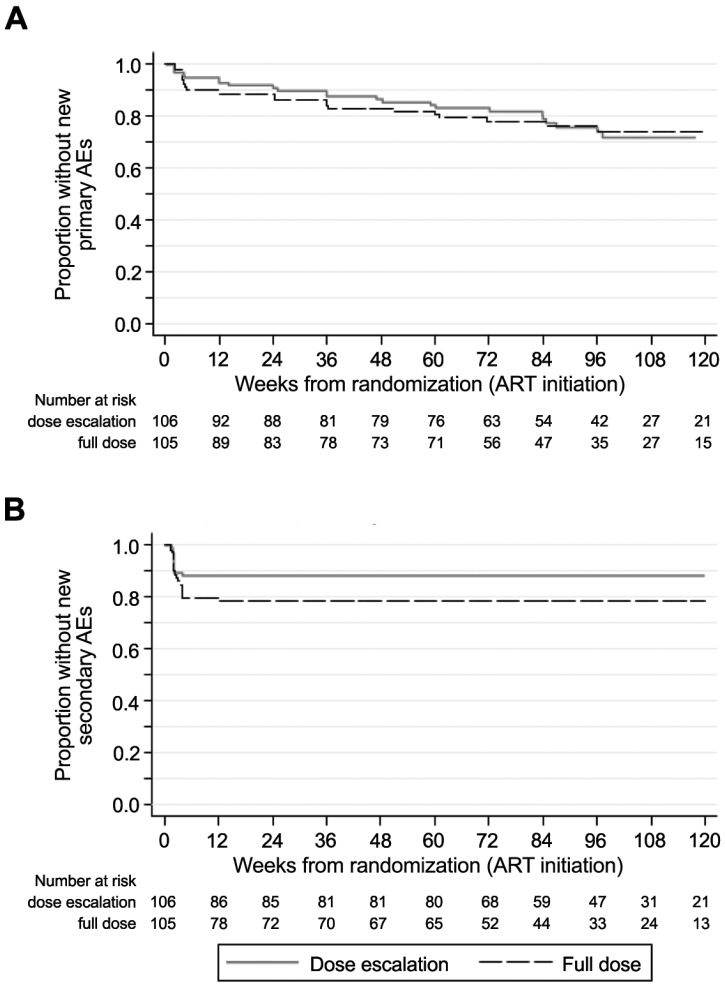

Figure 2. Time to first primary (*A*) and secondary (*B*) adverse event (AE) outcomes. Primary AEs were grade 3 or 4 AEs with a definite/probable or uncertain relationship with nevirapine; secondary AEs were grade 2–4 AEs with a definite/probable relationship with nevirapine.

groups for changes in weight-for-age *z* scores, height-for-age *z* scores, and absolute CD4 cell counts or CD4 cell percentages to 96 weeks ($P = .06$, $P = .66$, $P = .16$, and $P = .99$, respectively). Increases in weight-for-age *z* scores occurred sooner and were larger than increases in height-for-age *z* scores; however, although increases in weight-for-age *z* scores slowed between 48–96 weeks, increases in height-for-age *z* scores continued at a similar rate. At 96 weeks, weight-for-age *z* scores had increased by a mean of +1.7 and +1.4 in the FD and DE groups, respectively; height-for-age *z* scores increased by +0.9 and +0.7, respectively; CD4 cell counts increased by +518 and +554 cells/μL, respectively; and CD4 cell percentage increased by +17.3% and +17.3%, respectively. Viral load was <250 copies/mL in 78% ($n = 116$) at 48 weeks and in 75% ($n = 66$) at 96 weeks, with no differences between groups (74% in FD and 82% in DE at 48 weeks [$P = .2$]; 78% in FD and 73% in DE at 96 weeks [$P = .6$]). Viral load was >1000 copies/mL in 17% ($n = 25$) and 20% ($n = 18$), respectively.

DISCUSSION

The CHAPAS-1 trial was designed to evaluate dosing strategies for the pediatric antiretroviral FDCs Triomune Baby and Junior, which contain different ratios of stavudine, lamivudine, and nevirapine relative to the adult FDC and result in appropriate pharmacokinetic parameters in Zambian children [6, 11]. The US Food and Drug Administration and WHO approved this pediatric FDC across weight bands down to 3 kg in 2007.

Here, we present a comparison of the safety and longer-term clinical and immunological outcomes between starting Triomune Baby/Junior at FD versus the recommended 14-day nevirapine DE, using a combination of dual- and triple-drug FDCs. There are few prospective data documenting adverse reactions to nevirapine in African children, and no randomized trials comparing DE and FD strategies in adults or children have been conducted. The rationale for the trial was that nevirapine DE in children requires additional drug formula-

Table 3. Predictors of Nevirapine Reactions at Antiretroviral Therapy Initiation

	Nevirapine rash or grade 3 or 4 elevated ALT or AST level definitely/probably related to nevirapine				Nevirapine rash alone			
	Univariable[a]		Multivariable[b]		Univariable[a]		Multivariable[b]	
Predictor	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Female sex	1.63 (0.64–4.16)	.31			1.82 (0.61–5.42)	.29		
Age, per year increase	1.07 (0.96–1.19)	.21	1.18 (1.02–1.38)	.03	1.14 (1.00–1.29)	.05	1.35 (1.10–1.64)	.003
CD4 cell count for age, per unit increase	1.08 (0.94–1.25)	.28	1.27 (0.98–1.64)	.08	1.11 (0.91–1.36)	.29	1.51 (1.03–2.20)	.03
Weight for age, per unit increase	1.14 (0.84–1.55)	.41			1.49 (0.98–2.26)	.06	1.50 (0.92–2.45)	.11
Height for age, per unit increase	1.00 (0.73–1.38)	.99			1.39 (0.87–2.20)	.16		
Elevated hemoglobin level, per unit increase	1.12 (0.82–1.54)	.47			1.40 (0.95–2.05)	.09		
Elevated ALT level, per unit increase	1.00 (0.98–1.02)	.97			1.00 (0.98–1.02)	.94		
Elevated AST level, per unit increase	1.00 (0.99–1.01)	.70			1.00 (0.98–1.01)	.70		
FD (vs DE)			7.16 (1.97–26.0)	.003			9.79 (1.97–48.6)	.005

NOTE. Nonlinear associations with continuous variables were investigated using fractional polynomials, but none were found (ie, there was no evidence of any threshold at which risk increased or decreased more quickly). ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; DE, dose escalation; FD, full dose; OR, odds ratio.

[a] Univariable results were also adjusted for FD vs DE (data not shown).

[b] Multivariable models were based on backward selection using Akaike's information criterion.

tions that for syrups are difficult to procure and complex to administer: the dual pediatric lamivudine-stavudine FDC was not available when the trial commenced. Guidelines mandating nevirapine DE may therefore be a significant barrier to ART initiation in children. In addition, early adverse reactions to nevirapine have been reported to be less frequent among children [7, 8] than adults [13, 14], suggesting that DE might be less important in children. Thus, if starting with FD Triomune Baby or Junior resulted in few additional AEs, there could be substantial benefits to program planners from not having to procure extra formulations for nevirapine DE.

The CHAPAS-1 DE strategy was once-daily Triomune Baby or Junior in the morning given with once-daily Lamivir-S Baby or Junior in the evening (lamivudine-stavudine in the same doses as Triomune Baby and Junior), manufactured for the trial by Cipla as scored dispersible tablets. This DE strategy is considerably less costly than separate syrups for each drug in the FDC and is simpler for caregivers and dispensing providers, as well as procurers. One alternative strategy considered was to give a half dose of the whole FDC (ie, half-dose lamivudine-stavudine as well as half-dose nevirapine) for the first 2 weeks. However, the risk of early resistance development from initial lamivudine underdosing was considered greater than the risk of nevirapine toxicity from starting a FD FDC, especially in young children [15]. We found the dual or triple FDC DE approach was very acceptable; the color and shape of the tablets are distinct, and at the 2 week visit nurse questionnaires identified very few wrong doses (data not shown). In addition, at trial exit carers and older children reported by questionnaire that it was easy to initiate ART using these drug formulations.

The CHAPAS-1 primary end point was grade 3 or 4 clinical or laboratory AEs (according to reference toxicity tables) with a definite/probable or uncertain relationship to nevirapine. Similar proportions of children had primary end points in each randomized group, but clinical relevance is limited as most were single grade 3 elevations in liver enzyme or bilirubin levels, which were asymptomatic and resolved spontaneously without stopping nevirapine or changing the dose. The elevated liver enzyme levels generally occurred soon after ART initiation, and there was little overlap with nevirapine-associated rash. Our results add to those of the DART trial, which showed no difference in ART-modifying AEs among African adults receiving routine versus clinically driven biochemistry monitoring, including among those receiving nevirapine [16, 17]. The results of both trials suggest that routine liver function tests are not required after nevirapine initiation in resource-limited settings. The grade 3 elevations in bilirubin levels are unexplained and occurred throughout the trial, if anything more frequently in the DE group; although investigated, laboratory error cannot be excluded.

However, we did observe significantly more grade 1 or 2 rashes in the FD group. Management varied, but most children temporarily interrupted nevirapine and subsequently restarted successfully with DE. Only 3 substituted efavirenz: 1 in the FD group early during the trial, 1 in the DE group, and the only child in the FD group who experienced a recurrent rash on rechallenge with nevirapine DE. Of note, only 1 child was "treated through" the rash, and it is possible that more could have been managed with this approach. Only 2 children with rashes were admitted to the hospital: 1 early during the trial, and the child who was treated though; however, both were admitted for observation, not because of rash severity. Clini-

cians were not masked to randomized group, which introduces the possibility of ascertainment bias; however, a small, nonsignificant increase in nevirapine concentration was observed in children who developed rash (data not shown). We are confident that we did not miss any serious reactions among children early during the trial, when mortality was high; furthermore, only 1 child died during the first month of ART in the FD group, compared with 4 deaths in the DE group.

A nonsignificantly higher risk of nevirapine rash was observed among females, as has been reported in adults [18]. Older children and those with higher CD4 cell counts were also more likely to develop nevirapine rash, in keeping with the more immature immune systems of younger children and with results observed among adults [19, 20]. Although we observed different rates of grade 1 or 2 rashes in the CHAPAS-1 DE and FD groups, our findings broadly agree with previous results showing lower clinical event rates among children than adults [7, 8, 13, 14, 21]. Hepatotoxicity has also been reported more frequently among adults than children in previous studies [7, 8, 20]; in CHAPAS-1, although rates of single elevated liver enzyme levels differed between randomized groups, no child had confirmed (second) elevated levels of liver enzymes.

DE using Lamivir-S does not increase drug costs, compared with FD initiation using Triomune Baby and Junior. However, with DE using syrups the cost of preventing 1 grade 1 or 2 rash is approximately $40. An alternative way to escalate the dose (not evaluated in this trial) is to use cut parts of unscored adult lamivudine-stavudine tablets for the first 2 weeks of ART, when inaccuracies dividing tablets may be less important.

In CHAPAS-1, more than half the deaths occurred during the first 3 months of ART, most commonly due to diarrhoea and pneumonia. Similar findings have been reported in pediatric cohorts in resource-limited settings [22, 23], including Zambia [24]. There were no differences between randomized groups in any measure of HIV disease, including weight or height gains, CD4 cell percentage, and viral load response to ART. As reported elsewhere, CD4 cell response is good in children, and HIV RNA suppression at 48 weeks was comparable to data from previously untreated children in well-resourced [25, 26] and resource-limited [27] countries. These data boost our confidence that triple FDC generic "minipills" for children are appropriate for African children.

In conclusion, we have shown that rash occurred more frequently among children starting nevirapine at FD, although 88% had no clinical toxicity. Elevated AST or ALT values were unconfirmed, transient, and resolved spontaneously, suggesting that routine laboratory monitoring has limited value. Wherever possible, dual pediatric stavudine-lamivudine minitablets should be made available for safe and simple DE, which is more cost-effective than syrups. If dual-drug adult or pediatric solid formulations are not available and FD Triomune Baby or Junior tablets are used, caregivers should be aware of the timing of rash. For children developing rash, the options are to treat through with careful clinical observation or to reduce to half-dose Triomune during reescalation, given that we observed few recurrences of rash with DE after rash following initiation with FD nevirapine.

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