Published in final edited form as:

Antivir Ther. 2010 ; 15(3): 343–350. doi:10.3851/IMP1544.

Steady-state nevirapine, lamivudine and stavudine levels in Malawian HIV-infected children on antiretroviral therapy using split Triomune 30® tablets

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Abstract

Background—Children remain under-represented in national antiretroviral treatment (ART) programmes in settings with limited resources and high HIV prevalence. In Malawi, an increasing number of HIV-infected children have been started on ART with split tablets of an adult fixed-dose combination drug in the past few years. In 2006, the national paediatric ART regime was changed from Triomune 40® (T40) to Triomune 30® (T30).

Methods—This was a cross-sectional study conducted at the paediatric ART clinic in Blantyre (Malawi) from September 2006 to July 2007. Children taking T30 for >6 weeks from each dosing weight band (<5, 5–<8, 8–<12, 12–<14, 14–<19, 19–<26, 26–<30 and ≥30 kg) were recruited. Plasma drug concentration, CD4⁺ T-cell count and HIV viral load were measured.

Results—A total of 74 children were analysed. The median nevirapine (NVP) concentration was 7.35 mg/l. A therapeutic NVP plasma level >3 mg/l was found in 62 (87.8%) children. A subtherapeutic NVP level (<3 mg/l) occurred significantly more often in children treated with T30 doses between one-quarter tablet once daily and one-half tablet twice daily ($p=0.035$). Median prescribed NVP dose was 342 mg/m²/day, but 13 (17.6%) children received a dose below the recommended dose of 300 mg/m²/day. Compared with a historical control, the median prescribed NVP dose was increased (from 243 to 342 mg/m²/day).

Conclusions—Our findings indicate that with the Malawian T30-based ART regime, the majority (87.8%) of children in the study group achieved a therapeutic NVP level. However, treatment remains suboptimal especially for young children receiving T30 dosages less than or equal to one-half tablets twice daily and child appropriate formulations are warranted.

Introduction

Despite the progress in scaling up antiretroviral treatment (ART) programmes in regions with high HIV prevalence, such as sub-Saharan Africa, the percentage of HIV-infected children needing but not accessing therapy is still high.

In Malawi, of the estimated 12,000–16,000 children in need of treatment, only 2,700 (17–22%) were receiving ART in 2006 [1]. Pragmatic approaches such as using split tablets of adult fixed-dose combination (FDC) drugs are applied to increase access to ART for children [2,3].

Although FDC tablets specifically designed for children are now available, many countries with limited resources have not yet incorporated these formulations into national programmes or ‘roll-out’ of the new formulations has begun but is progressing slowly. The use of divided adult FDC tablets in children therefore continues in many settings.

Dosing of ART in children can be based on either weight or surface area. The World Health Organization (WHO) HIV working group has produced standardized dosing tables for the use of fractions of FDC in children [3]. The first Malawian national ART guidelines for children were based on these standardized tables but adapted to allow dosing of children <10 kg and to maximize the dose of nevirapine (NVP). The FDC tablet Triomune® (Cipla Pharmaceuticals, Mumbai, India) was introduced as a first-line national ART drug for adults and children in Malawi in 2003 [4]. It is produced in two different formulations: Triomune 30® (T30; containing 30 mg stavudine [d4T], 200 mg NVP and 150 mg lamivudine [3TC]) and Triomune 40® (T40; containing 40 mg d4T coformulated with the same NVP and 3TC concentrations as in T30). Uniformity of drug distribution within the tablet was demonstrated and studies conducted in children using fractions of the adult FDC showed good tolerability and a satisfactory clinical response [5–7].

There is evidence that a Triomune®-based regimen using divided tablets leads to low NVP drug concentrations, particularly in young children. In a combined Malawian/Zambian study in HIV-infected children, 38% (6/16) of the patients <3 years of age on a T40-based regimen had subtherapeutic NVP plasma levels [8]. These results are supported by findings from a pharmacokinetic study in weH and malnourished Malawian children, where children below the 14 kg weight band had an increased risk of having low NVP concentrations [9].

Because of concerns regarding underdosing of NVP, the paediatric dose regimen in Malawi was changed from T40 to T30 in 2005. The lower d4T content of the T30 tablet allowed adjustment of weight-based dosage tables with an increase in NVP dose while reducing risk of d4T toxicity. In addition, a greater number of children could be prescribed larger fractions of FDC tablets, leading to a reduction in administration problems associated with dividing unscored tablets.

Despite this attempt to optimize the use of adult FDC, concerns remained that the proportions of drugs in these formulations were not appropriate for younger children, with potential overdosing leading to drug toxicity or underdosing with poor efficacy and development of viral resistance.

This study assessed NVP plasma concentrations in Malawian children after the national scheme was switched from a T40- to a T30-based drug regimen, and aimed to collect data on drug concentrations alongside information on immunological and virological response.

Methods

Study population

This cross-sectional study was carried out at the paediatric ART Clinic of Queen Elizabeth Central Hospital (QECH; Blantyre, Malawi). Ethical approval was granted by the Malawi National Health Science Research Committee. We aimed to recruit 10 children in each dosing weight band (<5, 5-<8, 8-<12, 12-<14, 14-<19, 19-<26, 26-<30 and ≥30 kg), which were chosen according to the Malawian paediatric national ART guidelines (Table 1) [4]. T30 was prescribed as either whole, three-quarters, one-half or one-quarter tablets. T30 tablets were not scored and a pill cutter was provided. Tablets were administered at the patient's home by the guardian. Adherence was assessed through self-report and by pill count.

Children <16 years of age on a T30-containing regimen for ≥6 weeks (by which time steady-state was achieved) were eligible. Exclusion criteria were concomitant treatment with drugs known to interact with one of the three T30 drug components, known or suspected malabsorption and evidence of poor adherence within the past 2 months.

Written informed consent was provided. Samples for NVP steady-state and for 3TC and d4T plasma drug concentrations (taken within a window of 5–9 h post-dose), viral load (Roche Amplicator; Roche, Basel, Switzerland) and CD4⁺ T-cell count (Fiori-care™ PLG CD4 reagent; Beckman-Coulter, Brea, CA, USA) were taken. Plasma was stored at –40°C prior to being shipped to the Department of Pharmacology at Liverpool University (Liverpool, UK) and to the Radboud University Medical Centre (Nijmegen, the Netherlands) for drug analyses.

Clinical data was collected from the patients' file. Overall, response to treatment was assessed by a combination of clinical signs of treatment failure, CD4⁺ T-cell count and percentage, as well as viral load. Treatment response was classified as complete response if the viral load was undetectable (<400 cells/μl), absence of clinical signs of treatment failure and none or moderate immunosuppression; as partial response when the patients were clinically well and had no or moderate immunosuppression but had a detectable viral load; and as treatment failure in case of a detectable viral load, advanced or severe immunosuppression (assessed by CD4⁺ T-cell count) and presence of clinical signs, such as poor weight gain, weight loss or down-grading in clinical WHO stage [10].

Drug analyses

Plasma NVP concentration was measured using a validated high-performance liquid chromatography with ultraviolet detection (HPLC-UV) [11]. Intraassay and interassay variability (percentage coefficient of variation) was <5% at low (0.79 mg/l), medium (3.193 mg/l) and high (8.197 mg/l) quality controls with a lower limit of quantification of 0.101 mg/l. The therapeutic range for NVP was defined as 3–8 mg/l [12].

3TC and d4T concentrations were analysed at the Radboud University Medical Centre (Nijmegen, the Netherlands) using a validated HPLC-UV method. The lower and upper limits of quantification were 0.015 and 4.84 mg/l for d4T and 0.05 and 4.94 mg/l for 3TC, respectively. Both laboratories participate in an external quality assurance programme (KKGt, Den Haag, the Netherlands) [13].

Data analyses

Demographic, clinical and drug concentration data were analysed with χ^2 analysis using Fisher's exact test for categorical variables and univariate regression analysis for continuous

variables. Odds ratio (OR) was used for the estimated risk and a multivariate regression model using backwards elimination was utilized to examine the effects of covariates on NVP plasma concentration (SPSS version 15.0; SPSS, Inc., Chicago, IL, USA).

Results

Study population

A total of 78 children were enrolled between September 2006 and July 2007 and 74 were eligible for drug data analysis (4 children were excluded: 2 for non-adherence and 2 were aged >16 years). Of the 74, 40 (54.1 %) patients had been started on a T40-based regime and were switched to T30 tablets between February 2006 and May 2006. Data indicating whether a child had received post-exposure prophylaxis in the past was unavailable. Post-exposure prophylaxis uptake in Malawi was estimated to be 5–10% in 2005 and 10–15% in 2006; therefore, only very few children from the study cohort might have been exposed to NVP previously [14]. Patients were otherwise treatment-naïve for ART drugs.

A total of 64 patients were on treatment for 4 months or longer and 58 of them were eligible for analysis of immunological outcome and viral load. Exclusions included five patients for reported poor adherence in 2005 and one for treatment interruption for financial reasons in 2004. Only one infant receiving a dose of one-quarter T30 tablet once daily could be recruited. Most children receiving a dose of one-quarter tablets once or twice daily were on ART for <4 months and had to be excluded from CD4⁺ T-cell count and viral load analyses.

Patient characteristics for drug level analysis

A total of 74 patients were included and 24.3% ($n=18$) were female. Gender did not influence NVP concentration and was not associated with demographic or clinical characteristics, immunological state and viral load. The main clinical problems at start of ART were failure to thrive (that is, weight for age z-score <-2 standard deviations; 64.9%), tuberculosis (28.4%), chronic lung disease (27.1 %) and oral candidiasis (24.4%). This was similar to the presentation of all children receiving ART at the paediatric ART Clinic (GP, data not shown).

Clinical WHO stage III or IV or a presumptive diagnosis of advanced HIV disease for infants <18 months of age was the reason for commencing ART in 75.6% ($n=56$) of the children; 9 children were started on the basis of low CD4⁺ T-cell count or CD4⁺ T-cell percentage [4]. The median time on ART was 14 months (1.3–55.4 months). There were 32 (42.2%) children in the first four weight bands for T30 dosing and 20 (27%) were <3 years of age. Severe stunting (height for age z-score <-3 standard deviations) was present in 36 (48.6%) patients. Median weight for age z-score was -1.8 (range -4.74–0.78). All children had a weight for height >85%, with the exception of two who had moderate malnutrition (weight for height 80–85%). Baseline demographics for the two analysed patient groups in this study are shown in Table 2.

Pharmacological data

The median (range) NVP concentration of the 74 eligible patients was 7.35 mg/l (0.25–58.6). A therapeutic drug level (defined as >3 mg/l) was measured in 63 (87.8%) patients. The drug concentration was <3 mg/l in 9 (12.2%) patients. A subtherapeutic NVP level was found in 4 of 10 (40%) patients in the three lowest weight bands, but in none of the patients receiving whole T30 tablets.

The median NVP dose was 342 mg/m²/day ($n=73$, data unavailable for one patient). In 13 (17.8%) cases, children received a dose below the recommended 300 mg/m²/day [4]. Of

these 13 children, 10 (76.9%) were in the first three weight bands. The other three received a dose of one tablet twice daily (weight range 44.4–55.6 kg). Table 1 displays median dosages of the FDC drug components and plasma concentrations within each weight band. The average NVP dose of the group of children with a subtherapeutic NVP level was 313 mg/m²/day (range 258–359).

Children treated with T30 doses between one-quarter tablet once daily and one-half tablet twice daily were significantly more likely to have an NVP concentration <3 mg/l ($p=0.035$). In univariate regression analyses, the daily NVP dose in mg/m²/day showed a trend of being a determinant for subtherapeutic NVP level ($p=0.063$). When the three children receiving daily NVP doses <300 mg/m²/day, who were taking whole tablets of T30 twice a day and with weights >44 kg were excluded from analysis, this trend became significant ($p=0.037$). Dosage group and age were related and, consequently, the risk of having an NVP concentration <3 mg/l was increased for children <3 years of age ($p=0.054$; OR 4.1). Figure 1A and 1B show the NVP plasma concentration in relation to age for the different dosage groups. Table 3 compares NVP concentration and the NVP, 3TC and d4T dosages that children received in our cohort with the historical control group of Malawian children on T40.

Four children had minor non-adherence events documented in their records (reported missed drug doses 1–2× per month and higher than expected pill count) and three had stopped the drug because of financial reasons in the past. NVP concentrations of all seven children were within the therapeutic range. Univariate regression analysis showed no significant results for other potential risk factors for low NVP concentration, such as duration of treatment ($p=0.15$), uneven morning and evening T30 dose ($p=0.72$) or severe stunting ($p=0.7$).

A plasma NVP level >8 mg/l was found in 29 (39.2%) children. Three of them had NVP levels >20 mg/l (55.2, 58.6 and 21.4 mg/l), their prescribed daily NVP doses were 294, 353 and 365 mg/m²/day, respectively. Having a plasma NVP level >8 mg/l was not associated with receiving an uneven morning and evening T30 dose or taking quartered tablets ($p=0.078$ and $p=0.32$, respectively), but was more frequent in children >5 years of age ($p=0.042$). Clinical signs of toxicity, such as rash or jaundice, were not observed in any of the study patients. Other indicators for toxicity, such as liver function tests, were unavailable as were data on HBV or HCV coinfection.

Receiving a T30 dose between one-quarter tablet once daily and one-half tablet twice daily remained a significant predictor ($p=0.027$) for NVP concentration <3 mg/l in multivariate regression analysis (ANOVA) when combined with the variables height for age z-score, age, length of time on ART and NVP dose/m²/day.

d4T and 3TC dosages and plasma drug concentrations are shown in Table 3. These plasma levels were comparable with findings from a pharmacokinetic study in children taking Triomune Baby® (containing 6 mg d4T, 30 mg 3TC and 50 mg NVP; Cipla Pharmaceuticals) and Triomune Junior® (containing 12 mg d4T, 60 mg 3TC and 100 mg NVP; Cipla Pharmaceuticals) [15].

Immune status, viral load and clinical data

The demographic characteristics for the 58 patients eligible for viral load and immune status analysis are summarized in Table 2. At 2 years after completion of sample collection) 24 (41.4%) children were regularly seen as in-patients, 22 (37.9%) were transferred to a local treatment centre and 11 (19%) had defaulted from clinic visits (or from the ART clinic; data unavailable for one patient), 6 (10.3%) children had reported clinical problems and 2 (3.4%) of them were started on second-line ART. Two other children presented with static weight;

Kaposi's sarcoma was suspected in one and diagnosed in a second child prior to start of ART.

A total of 39 (67.2%) children had a viral load <400 copies/μl and 19 (32.8%) patients had a detectable viral load with a mean (range) of 37,552 copies/μl (400–669,433). No or mild immunosuppression was present in 46 (83.7%) children and 9 (16.3%) patients were found with advanced or severe immunosuppression according to age-related WHO criteria [15]. Median (range) CD4⁺ T-cell count was 988 cells/μl (9–3,250) and median (range) CD4⁺ T-cell percentage was 24.4% (1–53.9; data unavailable for three patients). Detectable viral load (>500 copies/μl) and advanced or severe immunosuppression correlated significantly ($p<0.0001$).

Young age was not a risk factor for detectable viral load or advanced or severe immunosuppression when dividing the group at 3 years and at 5 years of age ($p=1.0$ and $P=0.47$, respectively). Prior tuberculosis treatment was not associated with virological failure or immunosuppression ($P=0.86$ and $P=1.0$, respectively). A subtherapeutic NVP level was not significantly associated with virological failure ($p=0.4$) or immunosuppression ($p=1.0$).

Data on clinical response was combined with data on viral load and CD4⁺ T-cell count to assess the overall treatment response. Five patients were excluded from analysis as available data was incomplete. Of the remaining 53 children, 35 (66%) had a complete response, 8 (15.1 %) were classified as having a partial response, 8 (15.1%) as partial failure and 2 (3.8%) children as complete failure. The overall treatment response showed no significant association with age <3 years ($p=1.0$), subtherapeutic NVP level ($p=1.0$), drug dose <300 mg/m²/day ($p=1.0$), length of time on treatment ($p=1.0$) and having started on T40 and switched to a T30-containing ART regime ($p=1.0$).

Discussion

Despite the introduction of paediatric FDC formulations, use of divided adult FDC continues in many settings. This study was designed to evaluate NVP plasma concentrations at steady-state in HIV-infected children taking split tablets of a T30 according to the paediatric ART regime in Malawi. The free provision of ART drugs through the Malawian national health system in 2003 was a great achievement, but concessions, especially for paediatric patients, were made because of the lack of appropriate paediatric formulations at that time. The initial regime using T40 avoided overdosing of d4T and accepted the risk of underdosing of NVP especially in children <8 years of age [1,4,8]. Once T30 was reliably available, children were switched to the T30-based scheme, which allowed higher NVP doses with similar d4T doses because of the lower d4T content in the FDC to be administered.

The recommended daily NVP dose for children is 300–400 mg/m²/day [3]. The median prescribed NVP dose in this study was 342 mg/m²/day showing an expected rise compared with a group of Malawian children on a T40-based ART regime (median NVP dose 243 mg/m²/day) [8]. Underdosing still occurred and was found mainly in the first three weight bands.

The long half-life of NVP (median [range] 25.5 [12.1–105.2]) for children [16] makes the difference between NVP peak and trough concentrations minimal at steady-state. No paediatric efficacy cutoffs are defined but a trough concentration of 3.0 mg/l for adults has been proposed [12]. Sampling was not done at trough, but the narrow concentration profile of NVP over the dosing interval allowed us to make a conservative estimate of the proportion of children with suboptimal exposure and concentrations <3 mg/l. Similarly no

effect of post-dose timing of the sampling (median 8.9 h post-dose) was found in the study conducted by Ellis *et al.* [8].

The dosages for 3TC and d4T were comparable to findings of a study in children taking Triomune Baby® and Triomune Junior® tablets [15]. The short half-life of both drugs and the uncertainty of how well plasma levels reflect intracellular drug concentrations make the interpretation of this data difficult and further data is needed on this subject [17].

The children from this study group and the patients enrolled in the study conducted by Ellis *et al.* [8] were recruited from the same paediatric ART clinic at QECH. The decision to start ART was based on clinical grounds in the majority of patients in both groups because of limited availability of CD4⁺ T-cell count in Malawi at the time of the studies. The median age was lower in the study group (96 versus 64.5 months) because in this study, a preset number of patients were enrolled in each weight band. This was to ensure even distribution and adequate evaluation of drug levels in younger children. The median time on ART in the study group was longer (14 versus 5.9 months) than that of children in the study by Ellis *et al.* [8] and consequently there was more time for study patients to gain weight. These factors make the two groups somewhat different at baseline. Adherence to therapy was evaluated in a similar way although pill count was added to this study.

The fact that the percentage of children with a subtherapeutic NVP concentration was smaller ($n=9$ [12.2%] versus $n=19$ [27%]) in our group than in the group of children taking T40 could be related to higher prescribed NVP doses with the T30-based regime (Table 3). This is supported by the finding that the prescribed NVP dose was the strongest predictor for achieving sufficient NVP concentrations in the combined study in Malawian and Zambian HIV-infected children [8].

Only one child taking a dose of one-quarter tablet once daily could be recruited. Unavailability of virological confirmation of HIV infection in infants <18 months of age at the time of the study resulted in low numbers of infants started on ART. Of all children at the paediatric ART clinic at QECH in November 2006 ($n=512$), only 8 (1.56%) children were commenced on a dose of one-quarter tablet once daily.

The recommended therapeutic range for NVP is 3–8 mg/l [12]. More than one-third of the patients displayed concentrations above the upper cutoff. This was more common in older children who were less likely to receive an NVP dose <300 mg/m² and were less frequently found with subtherapeutic NVP concentrations. It is known that genetic factors influence NVP pharmacokinetics. The CYP2B6 516T/T genotype is more often present in African-Americans and was found to be associated with higher NVP plasma concentrations [18,19]. No overt clinical signs of drug toxicity were observed. As drug intake was unobserved, a shorter post-dose interval than communicated by the patient's guardian could explain the higher level to some extent, but the effect would not be so pronounced at steady-state.

In patients on an appropriate drug dose, possible causes for low NVP levels are malabsorption, drug interactions or non-adherence. Patients with possible drug interactions or with clinical signs of malabsorption were excluded from this study. Tablets were given unobserved at home and adherence was measured by pill count and self-report of adherence. These methods have limited sensitivity and poor adherence might be underestimated in this study. The effect of crushing the tablets or of being unequally divided when cutting unscored tablets might have an additional effect on the administered dose. Additional tools such as a Medication Event Monitoring System caps or home visits might have identified other reasons for low concentration apart from underdosing. However, two other studies in African children have consistently observed that the major driver of NVP exposure in very

young children receiving fractions of adult Triomune® formulations is the drug dose [8,9], suggesting that splitting of adult formulations results in underdosing of NVP relative to the nucleoside reverse transcriptase inhibitors in this group of patients.

Data regarding long-term clinical, immunological and virological response is urgently needed to guide decisions on changes in national regimens for countries where divided FDC of adult combinations are used. In a small study conducted in Indian children >3 years of age, all patients apart from one had therapeutic NVP level and a suppressed viral load after 6 months on ART using divided T30 tablets [6]. Clinical response was satisfactory. Data on immunological and virological parameters from this study need to be interpreted with caution. Applying strict exclusion criteria for analysis of response to ART reduced the size of the subgroups and prevented us from drawing further conclusions with regards to the effect of low NVP plasma concentration (or other factors) on the outcome. Combined analysis of clinical data, CD4⁺ T-cell count and viral load ($n=53$) indicated that 19 (18.9%) patients had partial or complete treatment failure of which 4 (7.6%) were clinically well. The relatively shorter time on ART in the study from Lodha *et al.* [6] could have contributed to their higher NVP plasma drug level results. Similar to the Indian study, our data does not provide information on long term outcome. CD4⁺ T-cell count measurements and viral load data at start of ART were not available and would be required to draw more definite conclusions. We considered it unlikely that the median observation time on ART (13.4 months) led to a positive selection of children who did not develop NVP resistance. An observational study at the paediatric ART clinic at QECH conducted in 2004 over 12 months showed that most deaths occurred in the first weeks of treatment (median 1.2 weeks) [20]. It can be assumed that development of drug resistance was not related to these deaths after such a short period on treatment.

Paediatric FDC tablets, including two paediatric Triomune® formulations (Triomune Baby® and Triomune Junior®) are now available. A preliminary pharmacokinetic study performed in 71 Zambian children receiving Triomune Baby® or Triomune Junior® suggest ratios are appropriate in children weighing >6 kg [15]; however, recent pharmacokinetic data indicate that levels might be lower in infants weighing 3–6 kg [21].

Our data strongly supports the use of child appropriate formulations for younger and lighter children; however, we recognize that prescribing divided tablets of an adult FDC is a compromise to increase access to ART under difficult circumstances. Clinical short-term results support this approach in view of the otherwise poor prognosis for this group of children [20,22]. Using the same drug formulation for most people in an ART programme facilitates access and drug supplies, but has to be balanced against inadequate therapy with the risk of development of resistance.

Despite limitations to evaluate the causes for lower NVP levels, this study gives important data on the use of divided adult FDC in children and might inform those countries still using this approach. Children <3 years of age were previously identified to be at risk for subtherapeutic NVP plasma concentrations [8,9]. This finding was confirmed in our study and further underlines that the use of divided adult FDC, particularly one-quarter tablets, places younger children at risk of subtherapeutic levels. Results from a study in South African infants support an early start of ART regardless of their immune state [23]. The WHO recommendations have changed accordingly [24] leading to a marked increase in numbers of very young children commencing ART and enhancing the importance of adequate treatment options.

Few children (7%) in weight bands >14 kg had a subtherapeutic NVP concentration and this was not related to underdosing. These findings were comparable to results from Zambian

children taking Triomune Baby® or Triomune Junior® [15]. The new Malawian National Guidelines reflect these considerations, with the introduction of Triomune Baby® for infants <10 kg but continuing the use of divided adult FDC in heavier children [25]. Further information on this new regime and other paediatric regimes being introduced in resource-limited settings worldwide is required to ensure appropriate and effective treatment of all HIV-infected children.

Acknowledgments

The authors would like to thank the patients, their guardians and the staff of the paediatric ART clinic at QECH, JF Tjia for bioanalytical support and the UK National Institute of Health Research (Department of Health) and the Northwest Development Agency for infrastructural and project support. A grant from UNICEF funded CD4⁺ T-cell count and viral load analyses.

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Figure 1.

Nevirapine plasma concentrations in relation to age in individual patients and in groups of patients <3 and ≥3 year of age

(A) Nevirapine (NVP) plasma concentration plotted against age for each Triomune 30® dosage group (NVP dose in mg/day). Data not shown for two patients with NVP concentrations >50 mg/l (B) Therapeutic and subtherapeutic NVP concentrations in children <3 and ≥3 years of age ($p=0.054$ for NVP<3 mg/l for children aged <3 years).

Table 1

Triomune 30® dosages and weight bands

Am/pm tablet dose and weight bands	Prescribed daily dose			Drug plasma concentration		
	NVP dose, mg/ml ^a	3TC dose, mg/kg	d4T dose, mg/kg	NVP, mg/l	3TC, mg/l	d4T, mg/l
All patients (<i>n</i> =74)	342 (176–428)	10.6 (1.6–5.4)	2.1 (1.1–2.6)	7.35 (0.25–58.6)	0.34(0–1.69)	0.025 (0–0.52)
One-quarter/none <5 kg (<i>n</i> =1)	177	8	1.6	5.4	0.16	0.11
One-quarter/one-quarter 5–<8 kg (<i>n</i> =9)	289 (258–301)	11.3(9.9–12.5)	2.3 (2–2.5)	3.3 (0.25–7.7)	0.12 (0–0.28)	0.001 (0–0.02)
One-half/one-quarter 8–<12 kg (<i>n</i> =10)	313 (274–375)	10.5 (9.6–13.1)	2.1 (1.9–2.6)	7.7 (2.1–55.2)	0.33 (0.03–1.06)	0.01 (0–0.05)
One-half/one-half 12–<14 kg (<i>n</i> =12)	359 (329–400)	11.6 (10.9–12.3)	2.3 (2.2–2.5)	7.2 (1.3–21.4)	0.24 (0–0.99)	0.01 (0–0.08)
Three-quarters/one-half 14–19 kg (<i>n</i> =11)	381 (310–429)	11.2 (10.6–13.2)	2.2 (2.1–2.6)	8.3 (4.6–58.6)	0.34 (0–1.31)	0.03 (0–0.18)
Three-quarters/three-quarters 19–<26 kg (<i>n</i> =11)	356 (316–387)	10.9 (9–11.4)	2(1.8–2.3)	7.3 (2.9–12)	0.33 (0–0.86)	0.01 (0–0.04)
One/three-quarters 26–<30 kg (<i>n</i> =10)	354 (329–384)	9.7 (8.8–10.9)	1.9 (1.8–2.2)	8.5 (1.6–18.6)	0.57 (0.17–1.69)	0.08 (0–0.52)
One/one 30 kg (<i>n</i> =10)	329 (272–370)	8 (5.4–9.9)	1.6 (1.1–2)	8 (3.9–18.9)	0.36 (0.04–0.99)	0.02 (0–0.1)

Values are given as median (range) for all prescribed doses and for nevirapine (NVP) concentration, and as mean (range) for lamivudine (3TC) and stavudine (d4T) concentrations.

^a *n*=73 (1 patient with missing height).

Table 2

Baseline demographics of the study cohort group included for drug data analysis and analysis of clinical data

	Study group on Triomune 30®	
	Drug data analysis (n=74)	CD4⁺ T-cell count and viral load analysis (n=58)
Female gender	18 (24.3)	15 (25.9)
Age, years	64.5 (7.1–191)	74.3 (19.8–191)
Weight, kg	16.2 (4.7–55.6)	17.2 (6.9–55.6)
Height, cm	99 (57.6–151)	106 (69.8–151)
Weight for age z-score	−1.8 (−4.7–0.8)	−1.7 (−3.9–0.8)
Height for age z-score	−2.9 (−7.3–1.4)	−2.75 (−6.4–1.4)
Age at ART start, months	51.8 (4.5–179)	65.8 (8.4–183.5)
Time on ART, months	12 (1.3–55.4)	13.4 (4.2–55.4)
CD4 ⁺ T-cell count, cells/μl	1,093 (9–3,528)	988 (9–3,250)
CD4 ⁺ T-cell percentage	24(1–53.9)	24.4 (1–53.9)

Values are given as *n* (%) for categorical variables and as median (range) for continuous variables. ART, antiretroviral therapy.

Table 3

Comparison of nevirapine, lamivudine and stavudine dosages and plasma drug concentrations for study group and historical control

	Study group on Triomune 30® (n=74)	Historical control group on Triomune 40® (n=71)
Prescribed daily dose		
NVP dose, mg/m ² ^a	342 (176–428)	243 (217–270)
3TC dose, mg/kg	10.6 (1.6–5.4)	7.3 (6.9–7.9)
d4T dose, mg/kg	2.1 (1.1–2.6)	2.0 (1.8–2.1)
Drug plasma concentration		
NVP, mg/l	7.35 (0.25–58.5)	4.8 (2.8–6.5)
3TC, mg/l	0.34 (0–1.69)	NA
d4T, mg/l	0.025 (0–0.52)	NA
Children with nevirapine plasma concentration <3 mg/l, n (%)	9 (12.2)	19 (27) ^b

Values are given as median (range) for all prescribed doses and nevirapine (MVP) concentration and as mean (range) for lamivudine (3TC) and stavudine (d4T) concentration unless indicated otherwise.

^a n=73 (1 patient with missing height).

^b P=0.034. NA, not available.