Nelfinavir Pharmacokinetics in Stable Human Immunodeficiency Virus-Positive Children: Pediatric AIDS Clinical Trials Group Protocol 377

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ABSTRACT. *Objective.* **Pharmacokinetic data obtained from children who have human immunodeficiency virus (HIV) infection are essential for the safe and effective use of antiretroviral agents in pediatric populations. The objective of this study was to assess the impact of body weight on the pharmacokinetic disposition of nelfinavir (NFV) in the absence and presence of nevirapine (NVP) and compare the pharmacokinetic profiles of twice-daily (BID) and three-times-daily (TID) NFV regimens.**

Methods. **This was an intensive pharmacokinetic substudy nested in a phase II, multicenter, randomized, open-label trial. Forty-five HIV-infected children receiving NFV 30 mg/kg TID and 6 HIV-infected children receiving NFV 55 mg/kg BID were enrolled in this study and assigned to 1 of 4 stavudine-containing regimens, 3 containing NFV and 2 containing NVP. Area under the plasma concentration-time curves from 0 to 8 hours ($AUC_{0-8\ hours}$) and from 0 to 12 hours ($AUC_{0-12\ hours}$) for the TID and BID regimens, respectively, were determined. For comparative purposes, the $AUC_{0-24\ hours}$ was also calculated for each regimen.**

Results. **NFV exposure in the absence of NVP was decreased in children who were <25 kg compared with those who were >25 kg (a 2.6-fold difference in median $AUC_{0-8\ hours}$). NFV pharmacokinetics in the presence of NVP did not differ between the <25 kg and >25 kg groups. The $AUC_{0-24\ hours}$ for children who were <30 kg and on NFV BID was comparable to the $AUC_{0-24\ hours}$ for children who were >25 kg and on NFV TID but was 2.7-fold greater than $AUC_{0-24\ hours}$ for children who were <25 kg and on NFV TID.**

Conclusions. **NFV in the absence of NVP resulted in less than half the drug exposure in children who were <25 kg compared with children who were >25 kg. NFV dosed at 55 mg/kg BID in children who are <30 kg provides comparable exposure to that measured in children who are >25 kg and receiving NFV 30 mg/kg TID.** *Pediatrics* **2003;112:e220–e227. URL: http://www.pediatrics.org/cgi/content/full/112/3/e220;** ***pharmacokinetics, nelfinavir, children, HIV, protease inhibitor, nevirapine.***

ABBREVIATIONS. PI, protease inhibitor; HIV, human immunodeficiency virus; NFV, nelfinavir; TID, three times daily; NNRTI, nonnucleoside reverse transcriptase inhibitor; NVP, nevirapine; BID, twice daily; NRTI, nucleoside reverse transcriptase inhibitor; PACTG, Pediatric AIDS Clinical Trials Group; d4T, stavudine; 3TC, lamivudine; AUC, area under the plasma concentration-time curve; CL/F, apparent clearance; C_{min}, minimum plasma concentration.

Protease inhibitors (PIs) for human immunodeficiency virus (HIV-1) have become an important and commonly used component of highly active antiretroviral therapy to treat HIV infection in adults and children.[1] To date, data regarding the disposition and drug interactions of nelfinavir (NFV) and other PIs in the pediatric population are limited.[2–7] We report the unique pharmacokinetic parameters of NFV dosed at a target of 27 to 33 mg/kg orally three times daily (TID), in the absence and presence of the nonnucleoside reverse transcriptase inhibitor (NNRTI) nevirapine (NVP), and dosed at a target of 55 mg/kg twice daily (BID) in clinically stable, antiretroviral-experienced patients who were aged 8 months to 16 years and enrolled in a large Pediatric AIDS Clinical Trials Group Protocol (PACTG) 377. PACTG 377 was designed to evaluate new combinations of potent antiretroviral agents. As most enrollees had already had extensive exposure to nucleoside analog reverse transcriptase inhibitors, we designed a trial involving both of the available HIV PIs and sought to examine the benefits of using a nonnucleoside inhibitor of the viral reverse transcriptase. The pharmacokinetics of the NVP in younger infants were well known, and the drug was available as a liquid formulation. However, its potential effects on NFV metabolism in children had not been evaluated previously.

NFV is an orally active aspartyl PI licensed for use, in combination with other highly active antiretroviral agents, in the treatment of HIV-1 infection. In adults, NFV given in combination with 2 nucleoside reverse transcriptase inhibitors (NRTIs) has suppressed viral replication to levels below the level of

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detection and has limited disease progression.[8,9] Although the availability of a pediatric-specific NFV drug formulation and a Food and Drug Administration indication for use in HIV-infected children 2 to 13 years of age has led to wide use of this agent, there are minimal data describing NFV pharmacokinetics across different ages and sizes in children. It has been reported that children 2 to 13 years of age demonstrate a 2- to 3-fold increase in apparent oral clearance of NFV when compared with adult values.[4]

Because body composition and metabolic pathways are rapidly evolving during the transition from infancy through puberty, learning the disposition of NFV in pediatric patients across different age groups and developmental stages is necessary to produce optimal dosing guidelines, limit toxicity, and enhance the sustainability of an effective NFV-containing antiretroviral regimen. In addition, suboptimal dosing may facilitate the selection of mutations associated with drug resistance to a specific agent[10] and cross-resistance with other therapies in a treatment group.[11]

Complicated antiviral regimens, large pill burdens, and frequent dosing may cause adherence to diminish over time.[12–14] In adults, a BID regimen has replaced TID dosing as the standard of care as NFV pharmacokinetic parameters and therapeutic efficacy between BID and TID regimens has been shown to be comparable.[15] Therefore, it was expected that administration of NFV as a BID regimen could improve antiretroviral therapy adherence and produce the sustained level of drug exposure to maximally suppress viral replication in HIV-1-infected children. The objectives of this pharmacokinetic study were to 1) define the disposition of NFV in antiretroviral experienced HIV-1-infected children, 2) assess the impact of childhood maturation on the apparent oral clearance of NFV in the absence and presence of the NNRTI NVP, and 3) compare the pharmacokinetic profiles of BID and TID NFV regimens in prepubertal children.

METHODS

The Pediatric AIDS Clinical Trials Protocol 377 (PACTG 377) is a phase II, multicenter, randomized, open-label, clinical trial comparing novel treatment regimens in PI-naïve, HIV-infected children. A total of 193 HIV-1-positive children ranging in age from 4 months to 17 years were enrolled in PACTG 377, 51 of whom have undergone intensive pharmacokinetic analysis (substudy participants ranging in age from 8 months to 16 years). The Institutional Review Board at each participating site approved the study protocol and consent forms, and the study was conducted according to the Declaration of Helsinki and its amendments following the principles of Good Clinical Practice. Informed consent was obtained from the child's parent or legal guardian before performing any study-related procedures.

All children had HIV-1 infection, were receiving the same continuous antiretroviral therapy for the 16 weeks before enrollment, and were clinically and immunologically stable. All were naïve to stavudine (d4T), lamivudine (3TC), PIs, and NNRTIs. Age, weight, and height were recorded at entry as well as at each pharmacokinetic study visit. Each patient had a general physical examination and laboratory evaluation including hematology and chemistry every 4 weeks throughout the study to screen for adverse effects. General subject demographics are given in Table 1.

Children were randomly assigned to 1 of 4 d4T-containing regimens, 3 of which contained NFV: 1) d4T plus NVP plus ritonavir, 2) d4T plus 3TC plus NFV, 3) d4T plus NVP plus NFV, or 4) d4T plus 3TC plus NVP plus NFV. Standard doses were used for concomitantly administered drugs, including d4T (1 mg/kg BID if <30 kg, 30 mg BID if >30 to <60 kg, 40 mg BID if >60 kg), 3TC (4 mg/kg BID with a maximum dose of 150 mg BID) ± NVP 120 mg/m^2 daily for 14 days, then 120 mg/m^2 BID. NFV was dosed at a target of 30 mg/kg/dose given 3 times daily if <30 kg or 27 to 33 mg/kg if >30 kg (as per dosing chart) with a maximum dose of 1250 mg TID. NFV was administered as tablets to children >25 kg (except for patient 15, who received tablets and powder, and patient 33, who received only powder) and as a tablet, powder, or a combination of the 2 dosage forms to children <25 kg. Specifically, all children <25 kg received the study dose as a powder formulation except for patients 6, 9, 27, 30, and 32, who received the tablet formulation, and patient 2, who received the dose as a combination. Because on pharmacokinetic study days doses were witnessed, the entire dose was administered regardless of which dosage form was used. The study dose was observed and administered with food as specified by the manufacturer. NFV results are presented to compare pharmacokinetic results for NFV-containing regimens without NVP with results for NFV-containing regimens with NVP.

Children who weighed <30 kg and were able to swallow tablets were permitted to enroll directly into a small substudy to investigate the pharmacokinetics and efficacy of a BID regimen of NFV given at a target dose of 55 mg/kg BID with a maximum of 1500 mg/dose. These children did not receive NVP.

After 4 weeks of NFV treatment, serial plasma samples were collected into ethylenediaminetetraacetate tubes before and 0.5, 1.0, 2.0, 4.0, 6.0, and 8.0 hours after an observed NFV administration in the outpatient setting for pharmacokinetic analysis. The 0 hour measurement was used as the 12-hour time point for patients who were dosed on the NFV BID regimen. Administration times for the previous 2 NFV doses, pharmacokinetic sampling times, and concomitant medications were recorded. Plasma samples were analyzed simultaneously for NFV and its active M8 metabolite (AG-1402) by a validated high-performance liquid chromatography method using ultraviolet detection. The method used is a modification of a method developed by Agouron Pharmaceuticals[16] Briefly, the procedure is an isocratic reverse-phase method using solid-phase extraction. After extraction, final methanol extracts were evaporated to dryness with nitrogen and reconstituted with fresh mobile phase. Prepared samples were subsequently analyzed on a butyl (C-4) reverse-phase high-performance liquid chromatography column and eluted isocratically with a phosphate buffer and acetonitrile-containing mobile phase. The internal standard used was saquinavir. All analytical methods were validated, and samples were analyzed according to Good Laboratory Practice. The assay was linear from 50 to 10 000 μg/L, with $r^2 > 0.99$. The interassay mean coefficient of variation was 7.8% and 10.6% for drug and metabolite, respectively. The intra-assay mean coefficient of variation was 7.6% for NFV and 9.3% for M8. The recovery of drug and metabolite was 83% and 72%, respectively. Interference tests were completed, and there was no cross-reactiv-

TABLE 1. Patient Demographics

Drug Regimen	Weight Group (kg)	No. of Children	Median Weight (kg; Range)	Median Age (Years; Range)	Median BSA (m^2; Range)
NFV (TID) Group 1	<25	9	14.5 (8.8–21.6)	4.2 (0.6–7.0)	0.62 (0.41–0.82)
NFV (TID) Group 2	>25	11	33.7 (25.5–55.2)	9.8 (7.2–16.0)	1.15 (0.92–1.52)
NFV (BID) Group 3	<30	6	23.3 (15.6–29.0)	8.5 (3.4–11.0)	0.91 (0.66–1.00)
NFV (TID) + NVP Group 4	<25	6	20.3 (12.3–22.9)	4.9 (1.6–8.1)	0.80 (0.53–0.88)
NFV (TID) + NVP Group 5	>25	19	33.0 (25.2–60.9)	10.0 (6.3–14.7)	1.12 (0.92–1.66)

BSA indicates body surface area.

ity with other HIV PIs, including ritonavir, indinavir, and saquinavir.

Noncompartmental pharmacokinetic analysis was performed using Winnonlin Pro Version 3.0 software (Pharsight Corp, Mountain View, CA) to determine the disposition of NFV and M8. Individual area under the plasma concentration-time curves from 0 to 8 hours ($AUC_{0-8\ hours}$) were calculated by using the linear trapezoidal rule for increasing plasma concentrations and the log trapezoidal rule for decreasing plasma concentrations. Apparent clearance (CL/F) was calculated as Dose/$AUC_{0-8\ hours}$ for those receiving drug TID and as Dose/$AUC_{0-12\ hours}$ for those receiving drug BID. The terminal disposition coefficient, λ_z, was determined by the logarithmic regression of the last 3 data points that were judged to be in the terminal elimination phase. Dose-corrected AUCs for children who were taking NFV TID were determined by standardizing the dose to 30 mg/kg. For children who were taking the NFV BID regimen, $AUC_{0-12\ hours}$ were calculated where the plasma concentration measured at 0 hours was substituted for the 12-hour time point. For comparing pharmacokinetic exposure for the TID and BID regimens, $AUC_{0-24\ hours}$ were estimated as 3 times the actual $AUC_{0-8\ hours}$ for children who were taking NFV TID and as 2 times the actual $AUC_{0-12\ hours}$ for children who were taking NFV BID. The correlation between age and weight with CL/F was evaluated using linear regression analysis.

Patient groups were compared using the exact Mann-Whitney statistical test (StatXact, Version 4.0.1, Cytel Software Co, Cambridge, MA). All *P* values are 2-sided and are unadjusted for multiple comparisons. Because 45 group comparisons are conducted in this analysis, caution should be exercised in the interpretation of the *P* values. A conservative solution to the multiple comparisons problem is the Bonferroni method, which multiplies the nominal *P* value by the overall number of statistical tests. If the result is still <.05, then the comparison is clearly statistically significant. Using the Bonferroni approach for this study, a *P* value between .001 and .05 should be interpreted as suggestive but not necessarily definitive. $P < .001$ should be considered clear evidence of statistical significance.

RESULTS

NFV pharmacokinetic parameter estimates in the absence and presence of NVP, separated by weight, are summarized in Tables 2 and 3, respectively. No subject <10 kg was randomized to the NVP treatment arm.

As shown in Table 2 and Fig 1, pharmacokinetic analysis of NFV administered TID and in the absence of NVP revealed statistically significant differences between the values from smaller children (<25 kg, ages 0.6–7.0 years) and the larger children (>25 kg, ages 7.2–16.0 years). Exposure to NFV and its metabolite, M8, was approximately half as high in smaller and younger children compared with larger and older children as shown by the NFV $AUC_{0-8\ hours}$ (median: 11 409 vs 29 807 μg*h/L; $P = .0005$), dose-corrected $AUC_{0-8\ hours}$ (to a dose of 30 mg/kg; 12 459 vs 32 835 μg*h/L; $P = .0016$), peak plasma concentration (3323 vs 4845 μg/L; $P = .0023$), minimum plasma concentration (C_{min}; 299 vs 2837 μg/L; $P < .0001$), and M8 $AUC_{0-8\ hours}$ (4251 vs 10 240 μg*h/L; $P = .018$), whereas corresponding NFV CL/F was, as expected, reduced by nearly half (2.4 vs 0.9 L/h/kg; $P = .002$).

Children who <25 kg and on the NFV TID regimen had statistically significant differences for most measures of NFV exposure when compared with children who were <30 kg and treated with NFV BID (Fig 2). For the NFV BID regimen, the $AUC_{0-24\ hours}$ was nearly 3-fold higher than estimates in children who were <25 kg and receiving the drug TID (92 006 vs 34 227 μg*h/L; $P = .012$). In contrast, children who were >25 kg and receiving the drug TID exhibited comparable exposure to BID values.

Unlike the comparison by weight (<25 kg vs >25 kg) for patients who were taking NFV alone, the weight-based comparison of children who were taking the combination therapy of NFV and NVP revealed no significant differences (all $P > .20$) in any of the NFV pharmacokinetic parameters (Table 3). Analysis of NFV pharmacokinetics in children who were <25 kg and >25 kg revealed no clearly significant differences (all $P \geq .026$) between those on NFV compared with NFV and NVP. Although not significant, for children who were <25 kg, there was a doubling of NFV $AUC_{0-8\ hours}$ when administered with NVP as compared with when administered alone. In contrast, M8 exposure was reduced slightly with NVP co-administration. The predictive value of weight or age on CL/F was determined by linear regression analysis. No statistically significant correlation was detected.

DISCUSSION

There is a growing body of data demonstrating the efficacy of complex combinations of antiretroviral drugs in large cohorts of antiretroviral-experienced children that support this therapeutic approach as standard of care.[17–19] Despite these advances, there is a marked lack of published pharmacokinetic data supporting recommended dosing schedules for HIV-infected children. This finding is even more striking given the observation that for children on PIs, developmental differences influence drug disposition between infants, prepubertal children, adolescents, and adults.[20] Furthermore, uncertainty regarding the effects of maturation and growth on antiretroviral pharmacokinetics only complicates questions as to how best to optimize and balance therapeutic efficacy, adherence, and short- and long-term safety of anti-HIV treatment in children. PACTG 377 characterized the pharmacokinetics of NFV, with or without NVP, across the developmental spectrum in children.

PACTG 377 demonstrated that children require a much higher dose of NFV, based on body weight, than adults to maintain drug exposure comparable to those accepted for HIV-infected adults. Therefore, the correct dose for a large portion of the pediatric HIV-infected population exceeds the daily maximum recommended dose for adults and is not adequately addressed in the Food and Drug Administration approved package insert. Administering 30 mg/kg TID resulted in median AUCs of 11 409 and 29 807 μg*h/L for children <25 kg and >25 kg, respectively. This compares to adults receiving 750 mg TID (approximately 10 mg/kg TID) exhibiting AUCs ranging from 15 407 to 21 600 μg*h/L.[21] In addition, NFV disposition is highly variable and changes as children grow and mature. NFV given TID in the absence of NVP resulted in a halving of NFV and M8 exposure and significantly lower trough values in smaller and younger (<25 kg) children when compared with larger and older children (>25 kg). Furthermore, trough concentrations of NFV given at the TID recommended dose, without NVP, were mark-

TABLE 2. Estimated Pharmacokinetic Parameters of NFV in the Absence of NVP

Drug Regimen	Weight Group	Patient ID	$AUC_{0-8\ hours}$ (μg*h/L)*	Dose-Corrected $AUC_{0-8\ hours}$ (μg*h/L)	$AUC_{0-24\ hours}$ (μg*h/L)†	C_{peak} (μg/L)	C_{min} (μg/L)	t_{peak} (Hours)	CL/F (L/h/kg)	$AUC_{0-8\ hours}$ (μg*h/L)	M8:NFV
NFV (TID)	<25 kg	1	16 618	22 684	49 854	3481	202	4.0	1.3	3401	0.20
		2	7167	8170	21 501	1171	59	4.0	3.7	897	0.13
		3	15 965	21 074	47 895	3983	394	8.0	1.4	4853	0.30
Group 1		4	20 503	25 342	61 509	3379	1107	2.0	1.2	ND	ND
		5	19 421	24 138	58 263	3982	309	8.0	1.2	6963	0.36
		6	11 409	12 459	34 227	3323	911	1.0	2.4	8122	0.71
		7	8294	10 838	24 882	2417	blq	2.0	2.8	ND	ND
		8	9217	11 945	27 651	2622	299	6.0	2.5	4251	0.46
		9	6913	7881	20 739	1241	50	2.0	3.8	1136	0.16
		Median	11 409	12 459	34 227	3323	299	4.0	2.4	4251	0.30
NFV (TID)	>25 kg	10	45 105	46 007	135 315	9543	3077	8.0	0.7	16 013	0.36
		11	25 068	25 344	75 204	4342	1129	4.1	1.2	10 240	0.41
		12	31 426	33 940	94 278	5275	2837	3.9	0.9	12 475	0.40
Group 2		13	8261	7534	24 783	1661	1021	2.0	4.0	3341	0.40
		14	34 218	37 366	102 654	5261	3616	1.0	0.8	6981	0.20
		15	26 035	28 639	78 105	4054	1971	4.0	1.0	28 639	0.20
		16	24 785	24 760	74 355	3885	1918	0.5	1.2	ND	ND
		17	37 559	41 826	112 677	6264	4413	4.1	0.7	8817	0.23
		18	24 314	32 211	72 942	3817	1424	0.8	0.9	ND	ND
		19	29 947	35 433	89 841	4851	4172	8.0	0.8	ND	ND
		20	29 807	32 835	89 421	4845	3740	1.0	0.9	ND	ND
		Median	29 807	32 835	89 421	4845	2837	3.9	0.9	10 240	0.36
		(*P* value 1/2)	(.0005)	(.0016)	(.0005)	(.0023)	(<.0001)	(.51)	(.002)	(.018)	(.73)
NFV (BID)	<30 kg	21	39 080	ND	78 160	5896	1256	8.0	1.2	ND	ND
		22	52 926	ND	105 852	7658	2275	8.0	1.1	ND	ND
		23	61 143	ND	122 286	9493	5895	1.9	0.9	ND	ND
Group 3		24	100 616	ND	201 232	15 095	1706	6.2	0.5	ND	ND
		25	26 333	ND	52 666	4663	2014	2.3	2.0	ND	ND
		26	22 461	ND	44 922	2386	blq	2.0	2.3	ND	ND
		Median	46 003		92 006	6777	1860	4.3	1.2		
		(*P* value 2/3)	(.12)		(.73)	(.22)	(.52)	(.36)	(.36)		
		(*P* value 1/3)	(.0004)		(.012)	(.018)	(.026)	(.71)	(.036)		

ND indicates no data available; blq, below limit of quantitation.
* $AUC_{0-12\ hours}$, calculated for NFV and M8 for NFV BID dosing.
† $AUC_{0-24\ hours}$, were estimated as 3 times $AUC_{0-8\ hours}$, for NFV TID and 2 times $AUC_{0-12\ hours}$ for NFV BID.

TABLE 3. Estimated Pharmacokinetic Parameters of NFV in the Presence of NVP

Drug Regimen	Weight Group	Patient ID	$AUC_{0–8\ hours}$ (μg*h/L)	Dose-Corrected $AUC_{0–8\ hours}$ (μg*h/L)	C_{peak} (μg/L)	C_{min} (μg/L)	t_{peak} (Hours)	CL/F (L/h/kg)	M8 $AUC_{0–8\ hours}$ (μg*h/L)	M8:NFV
NFV (TID) + NVP	<25 kg	27	11 570	17 077	2542	491	2.3	1.8	4664	0.40
		28	66 146	69 233	9635	4610	6.0	0.4	15 813	0.24
		29	14 868	20 072	5011	587	8.0	1.5	2472	0.17
Group 4		30	17 960	21 337	3814	979	4.0	1.4	ND	ND
		31	42 103	52 545	7193	1502	4.0	0.6	2188	0.05
		32	29 123	40 015	6727	blq	2.0	0.7	ND	ND
		Median	23 542	30 676	5869	783	4.0	1.1	3568	0.21
		(*P* value 1/4)	(.0496)	(.07)	(.026)	(.12)	(.69)	(.07)	(.93)	(.53)
NFV (TID) + NVP	>25 kg	33	25 188	28 211	4525	4525	0.0	1.1	11 323	0.45
		34	14 253	14 367	2370	152	6.1	2.1	ND	ND
		35	26 052	28 866	4086	2389	4.0	1.0	3509	0.13
Group 5		36	22 289	24 072	4389	1524	2.0	1.3	ND	ND
		37	17 189	20 352	3102	1042	4.0	1.5	ND	ND
		38	25 203	25 934	5000	312	6.0	1.2	3024	0.12
		39	7490	7909	2064	800	2.0	3.8	9822	1.31
		40	42 663	50 513	7411	5113	1.0	0.6	ND	ND
		41	35 009	41 871	6005	4342	2.1	0.7	12 798	0.37
		42	12 595	12 280	2921	1442	2.0	2.4	7607	0.60
		43	28 621	32 199	5080	1800	8.0	0.9	11 366	0.40
		44	18 346	21 443	3676	996	8.0	1.4	6404	0.35
		45	34 111	31 027	5730	3487	4.0	1.0	7995	0.23
		46	23 515	26 807	5143	162	2.2	1.1	ND	ND
		47	14 134	19 912	3315	906	2.1	1.5	2045	0.14
		48	36 631	49 760	5695	4180	4.0	0.6	8233	0.22
		49	19 830	28 984	3393	blq	4.0	1.0	ND	ND
		50	14 928	14 779	3132	blq	4.0	2.0	2700	0.18
		51	41 142	41 224	5990	2501	6.0	0.7	ND	ND
		Median	23 515	26 807	4389	1442	4.0	1.1	7801	0.29
		(*P* value 4/5)	(.78)	(.51)	(.22)	(.51)	(.56)	(.48)	(.52)	(.46)
		(*P* value 2/5)	(.19)	(.20)	(.52)	(.13)	(.59)	(.19)	(.14)	(.73)

ND indicates no data available; blq, below limit of quantitation.

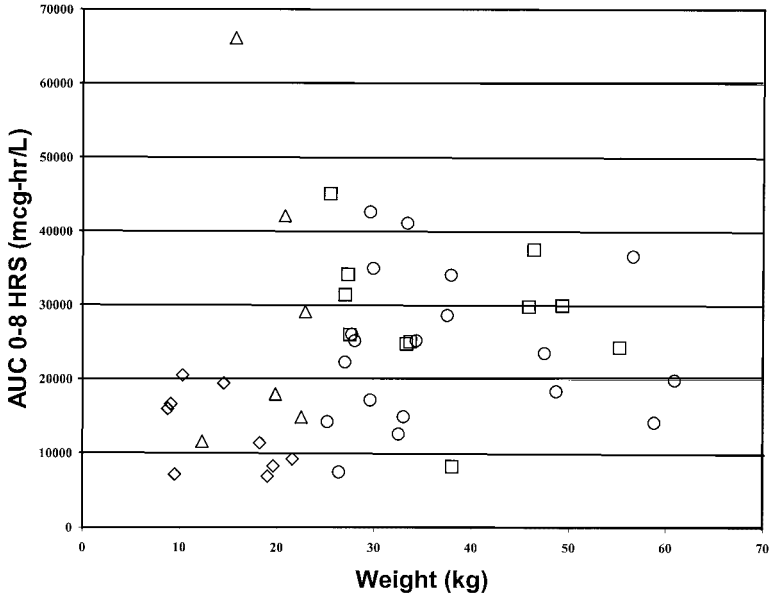

Fig 1. A statistically significant difference in NFV $AUC_{0-8\ hours}$ ($\mu g*h/L$) for children <25 kg (◇) compared with those >25 kg (□) is observed (P = .0005). NFV AUC for children also on NVP <25 kg (△) and >25 kg (○) is also presented. Although not significant, a trend toward greater NFV exposure in smaller children <25 kg with NVP compared with NFV alone is observed (P = .0496).

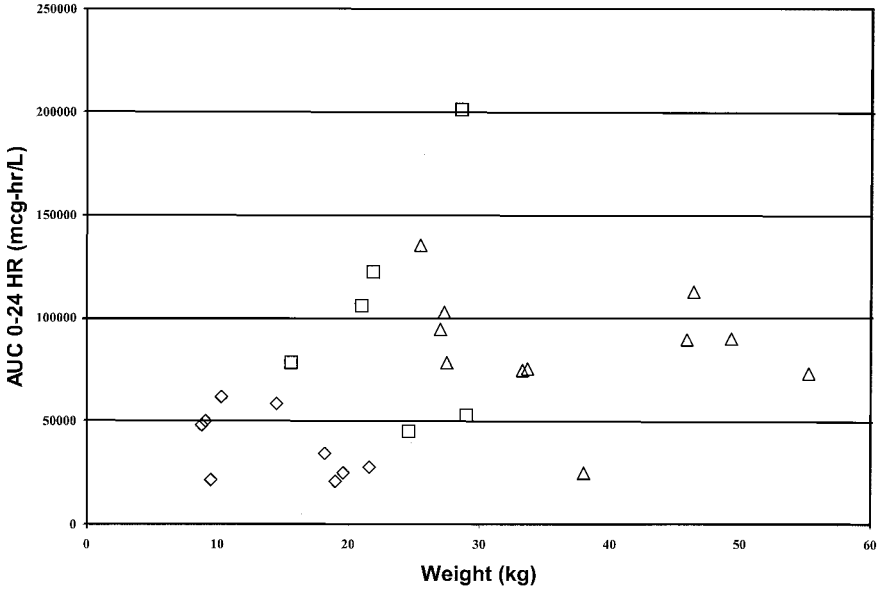

Fig 2. NFV administered BID to children <30 kg (□) yields a greater $AUC_{0-24\ hours}$ ($\mu g*h/L$) compared with the drug administered TID to children <25 kg (△).

edly lower in children who were <25 kg compared with values in larger children and adults (range: 1100–2045 ng/mL[21]). Contributing to these low trough levels is that, when prescribed TID, the median time interval between the nighttime and morning NFV dose was 12.8 hours for children <25 kg. This highlights the importance of considering real-world sleep patterns and food requirements when developing pediatric dosing recommendations, especially in younger children. The impact of low plasma C_{min} on clinical effectiveness of PI-containing regimens is uncertain, although a correlation has been observed between viral load after 12 weeks of therapy and C_{min}.[22] It was observed that children who were >25 kg and treated TID (with or without NVP) had mean C_{min} values exceeding adult values, although 8 of 30 patients (27%) did not have trough values >1000 $\mu g/L$.

We observed a 106% increase in NFV $AUC_{0-8\ hours}$ for children who were <25 kg and receiving NVP compared with those who were receiving NFV alone. The lack of significance may be attributed to insufficient sample size. M8 exposure was slightly less with NVP. Although not statistically significant, these findings suggest inhibition of metabolism in contrast to a previous study indicating no interaction.[23] This warrants additional study and underscores the need for complete pediatric pharmacokinetic evaluations.

In this study, smaller children who were <25 kg generally received the study dose as a powder formulation, whereas larger children who were >25 kg generally received the study dose in tablet form. Concern may be raised that inadequate dosing of the powder formulation or a lower bioavailability could explain the lower exposure in smaller children compared with larger children. However, in this study, all study doses were observed and dose administration was complete regardless of which formulation

was used. In addition, there was no apparent difference in NFV exposure for smaller children who received the powder versus those who received the tablet formulation. Furthermore, bioequivalence of the 2 dosage forms has been previously established.[4]

The pharmacokinetic results for BID dosing of NFV suggest that an NFV dosing schedule can be used to coincide with most other antiretrovirals. Simplification of dosage regimens will undoubtedly enhance adherence with regard to dose and timing.[24] In this study, a dose of 50 to 55 mg/kg BID, to a maximum of 1500 mg/dose, in children who were <30 kg resulted in equivalent or superior drug exposure compared with children who received NFV TID. Furthermore, week 24 data indicate, at a minimum, similar virologic success with the BID NFV dose when compared with any of the 4 main study arms in PACTG 377 (64% vs 39%–67% with RNA values <400 copies/mL).[18] It should be noted that children who received the drug BID (<30 kg) were older and larger than children who received the drug TID (<25 kg); therefore, both age and weight may have confounded this comparison.

In PACTG 377, 51 children, ranging in age from 8 months to 16 years, had extensive NFV pharmacokinetic evaluations. There are numerous confounding variables inherent in pharmacokinetic analyses in infants and adolescents that may warrant careful interpretation of pharmacokinetic findings. Partial doses may be administered when using powdered drug, or absorption may be impaired as a result of variable meal times relative to medication administration. In addition, NFV can exhibit diurnal pharmacokinetic variation that may complicate the comparison of results for TID and BID regimens. In this study, children who were included in intensive pharmacokinetic evaluations had observed doses, the entire dose was administered regardless of the dosage form, and a meal was given as per manufacturer recommendations.

Furthermore, physiologic variability has an impact on the interpretation of pharmacokinetic findings. Maturational effects on absorption contribute to variability, such as the rapid change in gastrointestinal activity during the first 2 years of life.[25] Maturation of metabolic pathways occurs at various rates, with phase I oxidative enzymes reaching adult-level activity sometime between 5 months and 5 years of age, depending on the enzyme. In addition, hepatic enzymatic activity can exceed adult values for a short period of time (between 2 and 5 years of age).[25] Furthermore, the impact of pubertal changes on NFV disposition remains unknown. Children may benefit the most when therapeutic drug monitoring is used for HIV, considering the complexity of maturational effects on drug disposition.

These results underscore the need for careful and thorough pharmacokinetic investigations in children to determine proper dosing strategies. Proper treatment of children requires that pediatric pharmacokinetic parameters be described early in drug development to enhance efficacious use, minimize potential toxicity, and prevent cross-resistance with other therapeutic agents within the same class of drugs, such as PIs.

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