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Single-Dose and Steady-State Pharmacokinetics of Tenofovir Disoproxil Fumarate in Human Immunodeficiency Virus-Infected Children

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Tenofovir disoproxil fumarate (DF) is a potent nucleotide analog reverse transcriptase inhibitor approved for the treatment of human immunodeficiency virus (HIV)-infected adults. The single-dose and steady-state pharmacokinetics of tenofovir were evaluated following administration of tenofovir DF in treatment-experienced HIV-infected children requiring a change in antiretroviral therapy. Using increments of tenofovir DF 75-mg tablets, the target dose was 175 mg/m^2; the median administered dose was 208 mg/m^2. Single-dose pharmacokinetics were evaluated in 18 subjects, and the geometric mean area under the concentration-time curve from 0 h to ∞ ($AUC_{0-\infty}$) was 2,150 ng · h/ml and the geometric mean maximum concentration (C_{max}) was 266 ng/ml. Subsequently, other antiretrovirals were added to each patient's regimen based upon treatment history and baseline viral resistance results. Steady-state pharmacokinetics were evaluated in 16 subjects at week 4. The steady-state, geometric mean AUC for the 24-h dosing interval was 2,920 ng · h/ml and was significantly higher than the $AUC_{0-\infty}$ after the first dose ($P = 0.0004$). The geometric mean C_{max} at steady state was 302 ng/ml. Tenofovir DF was generally very well tolerated. Steady-state tenofovir exposures in children receiving tenofovir DF-containing combination antiretroviral therapy approached values seen in HIV-infected adults (AUC, ~3,000 ng · h/ml; C_{max}, ~300 ng/ml) treated with tenofovir DF at 300 mg.

Highly active antiretroviral therapy (HAART) has altered the clinical course of human immunodeficiency virus (HIV) infection in children (6), but the virologic response rates of HAART are lower in children than in adults (12). The diminished efficacy of HAART in HIV-infected children and the need for simpler, more accessible antiretrovirals to prevent mother-to-child transmission (MTCT) of HIV present compelling reasons to develop new antiretroviral agents for use in infants and children. Separate clinical trials and pharmacological studies are conducted in the pediatric patient population to determine whether new agents pose any special risks for pediatric patients and whether drug metabolism is affected by the many developmental changes that occur during the newborn period, infancy, childhood, and adolescence (5). In previous studies of the nucleoside reverse transcriptase inhibitors and the nucleotide reverse transcriptase inhibitor adefovir, differences in absorption, metabolism, safety, and efficacy between pediatric patients and adults were demonstrated (1, 7–10). These age-related differences in drug disposition are most often reflected in an increased apparent clearance of the drug and/or lower bioavailability in children, necessitating higher doses per body weight or body surface area (BSA).

Tenofovir disoproxil fumarate {tenofovir DF; formerly known as PMPA prodrug, 9-[(*R*)-2-[[bis[[(isopropoxycarbonyl)oxy] methoxy]phosphinyl] methoxy] propyl]adenine fumarate} is an orally bioavailable prodrug of tenofovir, an acyclic nucleotide analog of AMP with activity in vitro against HIV type 1 (HIV-1) and HIV-2 (2). Tenofovir DF is converted to tenofovir by serum and tissue esterases. Intracellular phosphorylation yields the active metabolite, tenofovir diphosphate, which is a competitive inhibitor of HIV-1 reverse transcriptase and causes chain termination of the nascent viral cDNA. The pharmacokinetic profile of tenofovir following oral administration of 300 mg of tenofovir DF has been well characterized in HIV-infected and healthy adult subjects (3). After oral administration, tenofovir concentrations increase over 1 to 3 h with a maximum concentration (C_{max}) of approximately 300 ng/ml. Absorption is enhanced by approximately 40% when tenofovir DF is administered with a high-fat meal. In HIV-infected and healthy adults given tenofovir DF 300 mg once daily, a mean area under the serum concentration-time curve (AUC) at steady state of approximately 3,000 ng · h/ml is observed. Tenofovir is primarily eliminated unchanged in the urine by the processes of glomerular filtration and active tubular secretion (4; B. P. Kearney, D. F. Coakley, J. Sayre, J. J. Wolf, and J. F. Flaherty, submitted for publication). Its serum elimination half-life of 17 h, following single dose administration, and the long half-life of the intracellular metabolite tenofovir diphosphate support a once-daily dosing schedule.

Given the need for new antiretroviral agents in pediatrics and tenofovir DF's safety, tolerability, activity, resistance pro-

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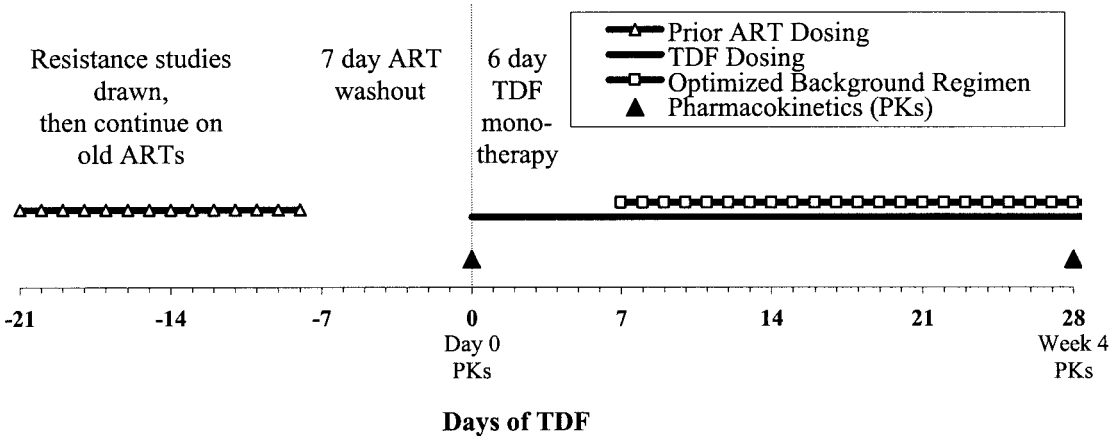

FIG. 1. Diagram outlining the study schema.

files in adults (11, 13; S. Staszewski, J. Gallant, A. L. Pozniak, J. M. A. H. Suleiman, E. DeJesus, B. Lu, J. Sayre, and A. Cheng, Abstr. 10th Conf. Retrovir. Opportunistic Infect., abstr. 564b, 2003), and its demonstrated effects in primate postexposure prophylaxis and MTCT models (14, 15), tenofovir DF could prove to be a beneficial agent in pediatric HIV disease. The present phase I study was undertaken at the HIV and AIDS Malignancy Branch of the National Cancer Institute (NCI) to evaluate the pharmacokinetics, safety, and tolerability of tenofovir DF in HIV-infected children when administered alone and in combination with other antiretroviral agents.

MATERIALS AND METHODS

Study population. Eligible subjects included children ≥4 and <18 years old, with a BSA of ≥0.50 m^2, documented HIV-1 infection, plasma HIV RNA level of ≥10,000 copies/ml, a history of having failed at least two prior antiretroviral regimens, and an ability to swallow tablets. At the time of screening, subjects were required to have a total leukocyte count of >1,500/mm^3, absolute neutrophil count (ANC) of >750/mm^3, hemoglobin level of >8.0 gm/dl, platelet count of >75,000/mm^3, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels ≤3 times the upper limit of normal, creatine phosphokinase <2.5 times the upper limit of normal, and a normal serum creatinine for age (≤0.8 mg/dl for <5 years, ≤1.0 mg/dl for age 5 to 10 years, ≤1.2 mg/dl for age 10 to 15 years, and ≤1.5 mg/dl for >15 years). A negative pregnancy test was required at the time of enrollment for females with childbearing potential. Subjects were excluded if they were receiving ongoing therapy with agents considered to have nephrotoxic potential, if they were receiving cancer chemotherapy, if they had received immunomodulating agents within the previous 30 days (with the exception of granulocyte colony-stimulating factor, erythropoietin, corticosteroids, or immunoglobulin therapy), if they had received any investigational agent within the previous 28 days, or if they had a severe systemic illness.

The Institutional Review Board of the NCI approved the study protocol and the informed consent. Parents or guardians of the subjects agreed to and signed the informed consent. Children capable of understanding the protocol provided their assent.

Study design. Tenofovir DF was administered in an open-label fashion once daily at an initial target dose of 175 mg/m^2. This dose was chosen to match most closely in children the approved 300-mg fixed dose in adults. A schema outlining the study design is shown in Fig. 1. Upon enrollment, subjects had a sample sent for viral resistance testing. They continued on their current antiretroviral regimen for two additional weeks and then stopped all antiretrovirals for 1 week. After that 7-day washout period, they received a single dose of the study drug on day 0, after consuming a standardized breakfast. They received a second dose 48 h after the first dose and daily doses after that point. At day 7 an optimized background regimen of other antiretrovirals, based upon their viral resistance results and clinical and treatment histories, was added to the tenofovir DF. During the first 9 days all antiretrovirals were administered as directly observed therapy.

Safety evaluations. Clinical assessments were performed, and blood and urine for safety monitoring were obtained regularly during the first 9 days and at week 4. Safety laboratory testing included serum chemistry and electrolyte panels, hematology, coagulation parameters, and urinalyses. The NCI's Common Toxicity Criteria version 2.0 (http://ctep.info.nih.gov/reporting/ctc.html) were used for grading laboratory and clinical parameters with the following exceptions: (i) partial thromboplastin time elevations secondary to hemophilia or heparin administration were not graded; (ii) CD4 count and total leukocyte count were not graded; and (iii) ANC of <500 cells/mm^3 was considered a grade 3 toxicity, and ANC of <250/mm^3 was considered a grade 4 toxicity (since HIV-infected children often experience disease-related neutropenia but have less morbidity associated with neutropenia than do children with neutropenia secondary to cytotoxic chemotherapy).

Study drug. Each subject received tenofovir DF as multiples of 75-mg tablets. Study medication was provided by Gilead Sciences, Inc. Patients were not permitted to crush or subdivide the study medication. Given the constraints of the 75-mg formulation, the target dose was 175 mg/m^2, but the dose administered could range from 173 to 300 mg/m^2, depending upon BSA. Tenofovir DF target dose was as follows: BSA of 0.50 to 0.84 m^2, 150 mg; BSA of 0.85 to 1.29 m^2, 225 mg; BSA of ≥1.30 m^2, 300 mg. Adherence was monitored by counting the returned study drug at week 4 and by questioning the parent or guardian (and child if appropriate). The National Institutes of Health Clinical Center Research Pharmacy dispensed the drugs, and the pharmacy's prescription fill and dispensing records were reviewed.

Pharmacokinetic analyses. Pharmacokinetic monitoring was performed after the first dose of tenofovir DF and again at steady state (week 4) when patients were receiving tenofovir DF in combination with an optimized background regimen. Prior to both pharmacokinetic sampling periods, subjects were given a patient-selected moderate-fat breakfast containing 10 cal per kilogram of body weight (42% carbohydrate, 41% fat, and 17% protein). After consumption, breakfast trays were checked for unconsumed food to determine actual calories consumed and caloric distribution. Study drug was administered within 5 min following completion of the morning meal. Blood samples were drawn at 0 h (predose) and at 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, 36, and 48 h after the first dose of tenofovir DF for determination of serum tenofovir pharmacokinetic parameters. Urine was collected at 0 h and within 15 min of the following intervals after administration of the first dose of drug: 0 to 4 h, 4 to 8 h, 8 to 12 h, 12 to 24 h, 24 to 36 h, and 36 to 48 h. At week 4, blood was collected at 0, 1, 2, 4, 8, and 12 h, and urine was collected over the 0-to-4-h, 4-to-8-h, and 8-to-12-h intervals following drug administration.

Blood samples were allowed to clot at room temperature (~30 min) and were centrifuged to separate the serum, which was stored at −20°C until analyzed. Analysis of tenofovir concentrations in serum was performed using a validated liquid chromatography-tandem mass spectrometry assay by MDS Pharma Services, Inc. (Montreal, Canada). The liquid chromatography-tandem mass spectrometry assay is highly sensitive and specific for tenofovir, and no interferences with drugs have been found to date, including drugs that are part of these subjects' HAART regimens. An internal standard (750 μl) was added to 150 μl

of serum that was processed using weak anion exchange solid-phase extraction cartridges (PSA; 100 mg, 1 ml; Varian, Palo Alto, Calif.). Fifteen microliters of eluant was then injected onto a 50- by 2.1-mm, 3.5-μm Symmetry C_{18} analytical column (Waters Corporation, Milford, Mass.) with a 6-to-94% MeOH–25 mM ammonium acetate mobile phase at a flow rate of 0.2 ml/min over 4.2 min. Mass spectrographic conditions were multiple reaction mode (positive ion) monitoring of *m/z* transitions of 288.1→176.1 for tenofovir and 274.4→162.1 for the internal standard with 200-ms dwell and 5-ms pause times. During sample analysis, a predose sample from each subject at each period was extracted with internal standard to detect potential interference from contaminants or endogenous compounds at the mass transition and the retention time of tenofovir. No interference was observed. The validated standard curve was linear over the range of 3.00 to 600 ng/ml with between-batch precision (coefficient of variation) and accuracy (percent nominal) metrics for the lower limit of quantification (3.01 ng/ml) of 9.2 and 98.0%, respectively. The coefficient of determination (R^2) was >0.996 for all analytical runs. Urine samples were analyzed under the same conditions following dilution (9:1) with 10 mM potassium hydroxide solution and addition of internal standard.

Tenofovir pharmacokinetic parameters were determined by noncompartmental methods using the linear-log trapezoidal rule using WinNonlin (standard edition; Pharsight Corporation, Mountain View, Calif.). Key pharmacokinetic parameters determined included AUC, C_{max}, time of maximum observed concentration (T_{max}), and elimination half-life. Half-life ($t_{1/2}$) was calculated by the equation $t_{1/2} = \ln 2/\lambda_z$, where λ_z is the elimination rate constant derived from the slope of the log-linear phase of the observed concentration-time data. Calculation of $AUC_{0-\infty}$ was by the equation $AUC_{0-\infty} = AUC_{0-\tau} + (C_{last}/\lambda_z)$. The tenofovir steady-state AUC for the 24-h dosing interval ($AUC_{0-\tau}$) was determined using the predose concentration as a surrogate for the trough concentration at the end of the observed dosing interval. For the calculations of urinary pharmacokinetics, the amount and percentage of a tenofovir dose recovered was calculated by summation of drug excretion (concentration times urine volume) and comparison to the administered dose. Renal clearance (CL_{renal}) was calculated by the matched X_u/AUC ratio, where X_u is the amount of drug excreted in the urine.

Statistical analyses. All comparisons of pharmacokinetic parameters were done in a pair-wise fashion using the Wilcoxon signed rank test, while correlations of clearance parameters with age were performed using the Spearman correlation. Correlation coefficients (r) were interpreted as follows: $|r| > 0.7$ as strong, $0.3 < |r| < 0.7$ as moderate, and $|r| < 0.3$ as weak. The comparison of clearance in males versus females was done using the Wilcoxon rank sum test. All P values are two-sided and have not been adjusted for multiple comparisons reported.

RESULTS

Study subjects. Nineteen children were enrolled on the study. One subject who developed elevated serum transaminases during the 1-week washout period prior to initiation of tenofovir DF never received study drug and was therefore not included in the analysis. The 18 subjects who received at least one dose of study drug were enrolled between 5 November 2001 and 8 July 2002. Selected baseline characteristics of the subjects (7 females and 11 males) were as follows (means ± standard deviations): 12 ± 2.5 years of age (median age was 11.9 years and the range was 6.2 to 16.2 years); weight of 40 ± 15.6 kg (median, 37.4 kg; range, 22.4 to 80.2 kg) (the weight Z score was −0.59 ± 1.46). All children had acquired HIV infection by MTCT.

Of the 18 patients who received the first dose of tenofovir DF, 8 received 300 mg and 10 received 225 mg. By week 4, 16 patients were still receiving study drug; 8 received 300 mg and 8 received 225 mg, in combination with other antiretrovirals. The median number of antiretrovirals added to the tenofovir DF, on day 7, was four agents (range, three to five). The combination regimens for all the children included low-dose ritonavir with at least one other protease inhibitor: 13 received lopinavir-ritonavir, 1 received lopinavir-ritonavir and saquinavir, 1 received amprenavir, and 1 received indinavir.

Pharmacokinetics. Pharmacokinetic parameters after the first dose and at week 4 are summarized in Table 1. The median day 0 dose normalized to BSA was 208 mg/m^2 (range, 161 to 256). Oral tenofovir DF was rapidly absorbed with a median T_{max} of 1.3 h (range, 0.5 to 3) on day 0. The geometric mean C_{max} on day 0 was 266 ng/ml (range, 78 to 556) and was similar for patients taking 225 mg (270 ng/ml) or 300 mg (262 ng/ml). Total drug exposure after the first dose (geometric mean $AUC_{0-\infty}$) was 2,150 ng · h/ml (range, 1,060 to 3,630). At 48 h after drug administration, the mean concentration of tenofovir in serum was 9.87 ng/ml, and 16 of 17 patients with samples collected at that time point had detectable levels of tenofovir. By week 4, total drug exposure (geometric mean $AUC_{0-\tau}$) was 2,920 ng · h/ml (range, 1,800 to 5,590) and was significantly higher than the $AUC_{0-\infty}$ measured in the same patients after the first dose ($P = 0.0004$). Median half-life at week 4 was 12.5 h (range, 8 to 18). The mean concentration-time curves after the first dose and at week 4 are shown in Fig. 2.

With the first dose in the fed state (median calories consumed prior to dosing was 270, with a median 39% of calories consumed as fat), median tenofovir urinary recovery over 48 h was 20% of the administered dose. Tenofovir renal clearance was similar after the first dose and at week 4 ($P = 0.46$). In contrast, apparent oral clearance adjusted for BSA and for weight was higher after the first dose versus week 4 ($P = 0.0006$ for each). When normalized to BSA or body weight, there was no significant association with age on apparent clearance. However, if apparent clearance was not normalized to BSA or weight, clearance increased with age, and the correlation between the two appeared to be moderate ($r = 0.58$; $P = 0.02$). Apparent clearance was similar in male and female children ($P = 0.87$).

Acute safety and tolerability. The study drug was generally very well tolerated. Prior to week 4 only two subjects experienced grade 3 or 4 toxicity possibly or probably related to the study drug. In both instances, the subjects developed grade 3 transaminase elevation (one with grade 3 AST elevation, and the other with grade 3 ALT and AST elevations) at day 2, during the monotherapy phase of the study, and permanently discontinued tenofovir DF. The latter subject had grade 1 ALT and grade 2 AST elevations at baseline. In both cases the abnormalities subsequently resolved and were judged possibly related to tenofovir DF. No other patient experienced clinically significant changes in laboratory or physical findings during the first 4 weeks.

DISCUSSION

This study was designed to evaluate the pharmacokinetics and safety of tenofovir DF in HIV-infected children. Age-related differences in drug disposition have been seen with many antiretrovirals (1, 7–10). Often these differences consist of higher clearance of the drug or lower bioavailability in children, necessitating higher doses per body weight or BSA. The present study was limited to a narrow age range of HIV-infected children, given the requirement that the children be able to swallow pills. The target dose, 175 mg/m^2, was chosen

TABLE 1. Single-dose and steady-state tenofovir pharmacokinetic parameters for the subjects in the study

Age (yrs)	Gender	Wt (kg)	BSA (m^2)	Tanner stage	Time point	Dose[a] (mg)	C_{max} (ng/ml)	T_{max} (h)	AUC[b] (ng · h/ml)	Half-life (h)	Apparent clearance (ml/min/m^2)	Renal clearance (ml/min/m^2)
10.4	M	29.6	1.03	I	Day 0	225	485	0.5	3,630	12.7	454	92
					Week 4	225	485	2	5,590	17.8	286	59
11.2	M	51.3	1.47	III	Day 0	300	556	1	3,530	14.1	436	152
					Week 4	300	472	1	4,420	10.5	343	72
16.2	F	80.2	1.87	IV	Day 0	300	348	1	3,290	18.5	367	60
					Week 4	300	396	2	4,280	14	278	90
13.9	M	30.3	1.08	I	Day 0	225	78	1	1,060	12.9	1,485	
					Week 4	225	280	1	1,800	12.7	882	
13.7	F	40.9	1.31	III	Day 0	300	144	1.5	1,320	14.6	1,311	142
					Week 4	300	278	1	2,620	17.3	655	144
10.3	M	29.2	1.07	I	Day 0	225	31.7	2	2,510	16.3	631	129
					Week 4	225	295	1	2,020	12	776	154
11.3	M	24.9	0.95	I	Day 0	225	246	1	1,630	13.5	1,096	174
					Week 4	225	290	1	1,960	12.2	912	76
8.3	M	23.1	0.89	I	Day 0	225	476	1	3,310	15.4	575	117
					Week 4	225	395	2	3,800	17.8		
13.2	F	33.8	1.16	II	Day 0	225	134	2	1,150	9.4	1,270	167
					Week 4	225	219	1	1,810	11.4	822	104
6.2	M	24.6	0.90	I	Day 0	225	269	1	2,000	14.7	939	260
14.6	F	59.5	1.69	III	Day 0	300	259	2	2,140	16.8	625	219
					Week 4	300	229	2	2,510	11.9	529	131
14	M	44.1	1.42	II	Day 0	300	265	1	1,950	9.9	816	100
					Week 4	300	204	4	2,030	8	797	108
16.5	F	46.9	1.46	III	Day 0	300	160	1.5	1,910	14.5	809	246
					Week 4	300	187	2	2,840	14	541	136
10.8	M	43	1.29	I	Day 0	225	373	3	2,000	11.9	657	144
					Week 4	300	434	2	4,160	10	421	141
12.5	F	51.1	1.50	III	Day 0	300	271	2	2,610	20.6	577	159
					Week 4	300	258	2	2,720	13.8	550	197
10.4	M	28.8	1.08	I	Day 0	225	314	1	2,220	14.6	708	66
					Week 4	225	231	4	3,290		472	134
10.7	M	22.4	0.88	I	Day 0	225	344	2	2,670	11.4	722	134
					Week 4	225	410	I	3,780		498	145
13.3	F	55.7	1.55	IV	Day 0	300	268	1.5				
Median					Day 0		266[c]	1.3	2,150[c]	14.5	708	143
					Week 4		302[c]	2	2,920[c]	12.5	541	132
Range					Day 0		78–556	0.5–3	1,060–3,630	9.4–21	367–1,485	60–260
					Week 4		187–485	1–4	1,800–5,590	8–18	278–912	59–197

[a] Median (range) dose on day 0 was 208 (161 to 256) mg/m^2 or 7.1 (3.7 to 10) mg/kg, and the median (range) dose on week 4 was 209 (158 to 253) mg/m^2 or 7.1 (3.6 to 9.8) mg/kg.
[b] AUC on day 0 is $AUC_{0-\infty}$; AUC on week 4 is $AUC_{0-\tau}$.
[c] Geometric mean value.

to match most closely in children the exposure associated with the approved 300-mg fixed dose in adults. The median dose administered, 208 mg/m^2, was higher than the target because of the constraints of the 75-mg tablet.

Pharmacokinetic analyses in HIV-infected adults who received 300 mg of tenofovir DF alone revealed a mean single-dose AUC of 3,265 ng · h/ml (range, 2,033 to 4,323), a mean steady-state AUC of 3,371 ng · h/ml (range, 2,097 to 6,050), a mean single-dose C_{max} of 362 ng/ml (range, 169 to 463), a mean steady-state C_{max} of 326 ng/ml (range, 155 to 532), and a median T_{max} of 2 h after single dose and 3 h at steady state (3). Even though the first dose administered to the children in the present study was higher than the targeted adult-equivalent dose, the mean AUC and C_{max} were 34 and 27% lower, respectively, compared to the values reported in adults. The possible explanations for these findings include lower oral bioavailability and/or higher renal clearance in children relative to adults. With the first dose the median urinary recovery of tenofovir was 20% of the administered dose. These data are similar to results observed in adults, where 17 and 24% of the tenofovir dose was recovered in the urine over 48 h in the fasted and fed states, respectively (Kearney et al., submitted), and suggest that the oral bioavailability of tenofovir is comparable in children and adults. However, the renal clearance of tenofovir was approximately 1.5-fold higher in children relative to published data for HIV-infected adults and likely explains the lower exposures observed with the first dose of tenofovir DF in the present study. Urine collections were carried out carefully. However, if the collections were incomplete, both renal clearance and bioavailability would be underestimated.

Other antiretrovirals were added to the tenofovir DF monotherapy on day 7 to optimize the regimen in these children, and tenofovir pharmacokinetics were evaluated again at week 4. By this time, at steady state, the pharmacokinetic profile of tenofovir more closely resembled that seen in adults. Despite similar median renal clearance values at the two pharmacokinetic sampling periods, median apparent clearance in these children was approximately 25% lower at week 4 in comparison to the

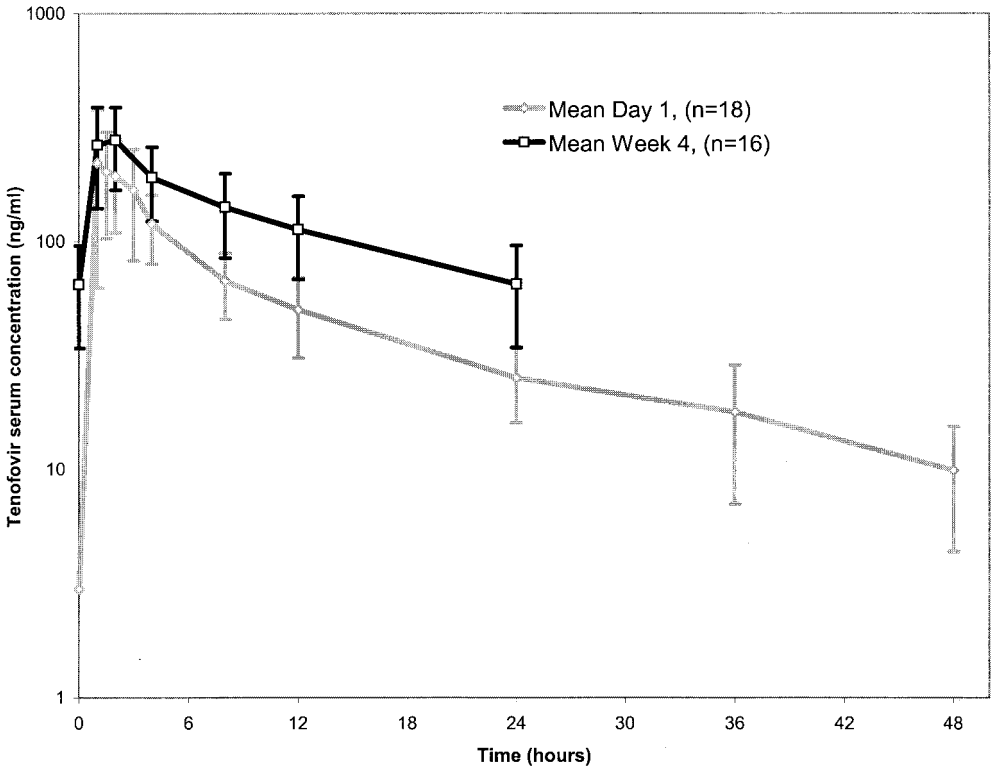

FIG. 2. Concentrations of tenofovir in serum after the first dose and at steady state. Data are the mean ± standard deviation for the subjects in the study.

first dose. The reduced apparent clearance may be attributable to an effect of the additional antiretroviral agents and increased oral bioavailability of tenofovir at steady state. The addition of other antiretrovirals precluded a comparison of results from first dose and steady state to characterize the possibility of accumulation or nonlinear elimination. However, data in adults treated with tenofovir DF monotherapy for 4 weeks did not demonstrate unexpected drug accumulation or an effect of time on the pharmacokinetic parameters (3).

It is important that the first-dose and steady-state pharmacokinetic profiles that have been reported for adults were measured in patients who received 28 days of tenofovir DF monotherapy (3). In that study, a similar increase in the oral bioavailability of tenofovir DF was seen when the drug was taken with food compared to when it was taken in the fasted state. However, a food effect cannot be the explanation in the present study, since the drug was taken after breakfast at both pharmacokinetic time points.

Notably, due to their advanced disease, prior antiretroviral histories, and viral resistance profiles, all of the children evaluated at week 4 were receiving a protease inhibitor plus low-dose ritonavir as a pharmacokinetic boosting agent, most as the combination lopinavir-ritonavir. Pharmacokinetic drug interaction data in adults have shown that concomitant administration of tenofovir DF with lopinavir-ritonavir is associated with increased tenofovir exposures of approximately 34%, presumably via enhanced oral bioavailability, as tenofovir DF is eliminated as unchanged drug in the urine (J. F. Flaherty, B. P. Kearney, J. J. Wolf, J. R. Sayre, D. F. Coakley, Abstr. 1st IAS Conf. HIV Pathogenesis Treat., abstr. 336, 2001). A difference in bioavailability with and without low-dose ritonavir may explain the observed differences seen between first-dose and steady-state pharmacokinetics at week 4 in the present study.

Another study of tenofovir DF in HIV-infected children also revealed higher tenofovir exposures at steady state (day 7) compared to values observed in a separate group of subjects who received a single dose of tenofovir DF as monotherapy on day 1 (S. Blanche and J. Bresson, unpublished data). All of the subjects at steady state in that study were receiving tenofovir DF as part of a combination regimen that included lopinavir-ritonavir, and the results observed served to confirm the consistency of tenofovir DF pharmacokinetics in children.

Further elucidation of a possible mechanism for an interaction between low-dose ritonavir and tenofovir DF is necessary. In particular, studies in children receiving unboosted or protease inhibitor-sparing regimens are necessary to determine if higher tenofovir DF doses are warranted to achieve the desired drug exposure.

Tenofovir DF was well tolerated by HIV-infected children. Only 2 of 18 children in the present study experienced an event that required protocol-mandated permanent discontinuation of the study drug during the first 4 weeks. In both instances, the children developed asymptomatic grade 3 transaminase elevation during the monotherapy phase of the study, which resolved without sequelae. Longer-term toxicity and the efficacy of the combination regimens are being assessed as the study progresses.

Based upon its tolerability, safety, resistance profile, and

pharmacokinetic properties in children, tenofovir DF could prove to be a beneficial agent for inclusion in pediatric HIV combination therapy regimens, particularly for those children who have failed prior antiretroviral therapy regimens. Because this study was limited to older children able to swallow pills, the pharmacokinetics, safety, and tolerability of the drug, including a liquid formulation, will need to be studied in younger children and infants. Steady-state absorption, elimination, and variability of tenofovir pharmacokinetics in children treated with tenofovir DF-containing combination regimens approached those seen in HIV-infected adults treated with 300 mg once daily.

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