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Tenofovir Disoproxil Fumarate and an Optimized Background Regimen of Antiretroviral Agents as Salvage Therapy for Pediatric HIV Infection

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ABSTRACT. *Objectives.* Highly active antiretroviral therapy has altered the course of HIV infection among children, but new antiretroviral agents are needed for treatment-experienced children with drug-resistant virus. Tenofovir disoproxil fumarate (DF) is a promising agent for use in pediatric salvage therapy, because of its tolerability, efficacy, and resistance profile. We designed this study to provide preliminary pediatric safety and dosing information on tenofovir DF, while also providing potentially efficacious salvage therapy for heavily treatment-experienced, HIV-infected children.

Methods. Tenofovir DF, alone and in combination with optimized background antiretroviral regimens, was studied among 18 HIV-infected children (age range: 8.3–16.2 years) who had progressive disease with ≥ 2 prior antiretroviral regimens, in a single-center, open-label trial. Tenofovir DF monotherapy for 6 days was followed by the addition of individualized antiretroviral regimens. Subjects were monitored with HIV RNA reverse transcription-polymerase chain reaction, flow cytometry, and routine laboratory studies; monitoring for bone toxicity included measurement of lumbar spine bone mineral density (BMD) with dual-energy x-ray absorptiometry. Subjects were monitored through 48 weeks.

Results. Two subjects developed grade 3 elevated hepatic transaminase levels during monotherapy and were removed from the study. The remaining 16 subjects had a median of 4 antiretroviral agents (range: 3–5 agents) added to tenofovir DF. HIV plasma RNA levels decreased from a median pretreatment level of 5.4 \log_{10} copies per mL (range: 4.1–5.9 \log_{10} copies per mL) to 4.21 \log_{10} copies per mL at week 48 ($n = 15$), with 6 subjects having < 400 copies per mL, including 4 with < 50 copies per mL. The overall median increases in CD4⁺ T cell counts were 58 cells per mm^3 (range: -64 to 589 cells per mm^3) at week 24 and 0 cells per mm^3 (range: -274 to 768 cells per mm^3) at week 48. The CD4⁺ cell responses among the virologic responders were high and sustained.

The major toxicity attributed to tenofovir DF was a $> 6\%$ decrease in BMD for 5 of 15 subjects evaluated at week 48, necessitating the discontinuation of tenofovir DF therapy for 2; all 5 subjects experienced $> 2 \log_{10}$ copies per mL decreases in HIV plasma RNA levels.

Conclusions. Tenofovir DF-containing, individualized, highly active antiretroviral therapy regimens were well tolerated and effective among heavily treatment-experienced, HIV-infected children. Loss of BMD may limit tenofovir DF use among prepubertal patients. *Pediatrics* 2005;116:e846–e854. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2005-0975; *tenofovir, HIV, children, multidrug resistance, bone toxicity.*

ABBREVIATIONS. HAART, highly active antiretroviral therapy; DF, disoproxil fumarate; BMD, bone mineral density; TAM, thymidine analog mutation; DTH, delayed-type hypersensitivity.

Highly active antiretroviral therapy (HAART) has reduced dramatically the morbidity and mortality rates for HIV infection among children.¹ However, drug-resistant virus emerges eventually for most children, and better salvage regimens that include non-cross-resistant antiretroviral agents are needed.

Tenofovir disoproxil fumarate (DF) is an orally bioavailable prodrug of tenofovir, which is a nucleotide HIV reverse transcriptase inhibitor. Tenofovir has shown potent antiviral activity in a number of animal models. Most pertinent to the pediatric setting are its demonstrated effects in primate post-exposure prophylaxis and mother-to-infant transmission models^{2,3} and its favorable resistance profile. Studies demonstrating its safety and efficacy among both treatment-naive and treatment-experienced, HIV-infected adults led to its approval as part of combination antiretroviral therapy for HIV-infected adults in 2001.^{4–6}

We performed a phase I trial of a 6-day course of tenofovir DF monotherapy, followed by an individualized combination regimen that included tenofovir DF, for treatment-experienced, HIV-infected children. The toxicity and immunologic, virologic, and clinical effects of tenofovir DF as a salvage agent are reported here.

METHODS

Study Design

The National Cancer Institute institutional review board approved the protocol. Parents or guardians of the subjects agreed to

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Conflict of interest: Dr Flaherty, Ms Yale, and Dr Kearney are employees of Gilead Sciences, the manufacturer of tenofovir.

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and signed the informed consent form. This single-center, open-label, phase I trial opened for enrollment in November 2001 and closed in July 2002. At the time of enrollment, HIV drug resistance testing was performed, and subjects continued to receive their prior antiretroviral regimen. After 2 weeks, all antiretroviral therapy was stopped for 1 week. Subsequently, subjects received a single dose of tenofovir DF, a second dose 48 hours later, and daily doses thereafter. At day 7, an optimized background regimen of other antiretroviral agents was selected on the basis of drug resistance profiles and treatment histories. During the first 9 days, morning doses were observed directly by health care personnel.

Study Population

Inclusion criteria included age of >4 years and <18 years, body surface area of ≥ 0.50 m², plasma HIV RNA levels of ≥ 10 000 copies per mL, aspartate aminotransferase and alanine aminotransferase levels ≤ 3 times the upper limit of the normal range, normal serum creatinine levels for age, history of treatment failure of ≥ 2 antiretroviral regimens, and ability to swallow tablets. Exclusion criteria included current treatment with nephrotoxic agents, cancer chemotherapy, or treatment with other investigational agents.

Assessments

Clinical assessments, determination of plasma HIV RNA levels (Amplicor monitor 1.5; Roche Diagnostics, Alameda, CA), enumeration of lymphocytes and lymphocyte subsets, and routine laboratory monitoring were performed during the 9-day initiation of therapy and at weeks 4, 8, 12, 16, 24, 36, and 48. The Tanner stage was evaluated as part of the general physical examination, but the assessment did not include orchimetry. CD4⁺ naive cells and CD4⁺ memory lymphocytes were identified on the basis of positivity for CD45RA and CD62L and for CD4 and CD45RO, respectively. Estimates of glomerular filtration rate were made with the Schwartz formula.⁷ Drug resistance profiles were generated by using HIV reverse transcriptase and protease genotypes with inferred phenotypes (VirtualPhenotype; Virco, Raritan, NJ). Virologic responses were defined as declines of >0.5 log₁₀ HIV copies per mL. Delayed-type hypersensitivity (DTH) responses were assessed by administering intradermal injections (0.1 mL) of *Candida albicans* skin test antigen (1:100; Allered, San Diego, CA), mumps skin test antigen (Aventis, Bridgewater, NJ), and a saline control sample to each subject at baseline and weeks 24 and 48. Responses were assessed 48 hours after placement and were considered positive if the diameter of induration was >5 mm.

Monitoring for bone toxicity included measurement of lumbar spine bone mineral density (BMD) with dual-energy x-ray absorptiometry at baseline and 24 and 48 weeks (QDR 4500; Hologic, Bedford, MA). BMD z scores were calculated by using available databases.^{8,9} The original protocol required discontinuation of tenofovir DF in the event of confirmed decreases of $>6\%$ in the BMD of the lumbar spine. After the first subject experienced such a decrease in the presence of virologic and immunologic benefits, the protocol was amended so that subjects experiencing $>6\%$ decreases in lumbar spine BMD could continue provided that they had not experienced minimal-trauma fractures, had BMD z scores greater than -2.5 , and had experienced ≥ 0.5 log₁₀ decreases in HIV plasma RNA levels or $\geq 25\%$ increases in absolute CD4⁺ cell counts. Subjects who did not meet these conditions discontinued tenofovir DF treatment but remained in the study for follow-up monitoring.

The National Cancer Institute Common Toxicity Criteria (version 2.0) were used to grade laboratory and clinical events, except that CD4⁺ cell counts and total leukocyte counts were not graded, absolute neutrophil counts of <500 cells per mm³ were considered grade 3 toxicity, and absolute neutrophil counts of <250 cells per mm³ were considered grade 4 toxicity. Subjects and their families were reminded verbally to bring back their tenofovir DF medication bottles. Adherence was monitored by counting returned tenofovir DF pills at each visit and by performing interviews. Unreturned pills were assumed to have been consumed. Adherence to other antiretroviral regimens was not assessed formally.

Study Drug

Each subject received tenofovir DF as multiples of 75-mg tablets (provided by Gilead Sciences, Foster City, CA). Given the con-

straints of the 75-mg formulation, the target dose was 175 mg/m², but the dose administered could range from 173 to 300 mg/m². Tenofovir pharmacokinetic characteristics were reported previously.¹⁰

Statistical Analyses

The significance of differences between baseline and treatment values was determined with Wilcoxon signed rank tests. Comparisons of parameters between the virologic responders (sustained >0.5 log₁₀ decline) and nonresponders were performed with exact Wilcoxon rank sum tests for continuously measured parameters and with Fisher's exact tests for binary parameters. A Spearman correlation matrix was constructed to examine the strength of relationships between variables. In view of the number of comparisons performed, we required $P < .01$ to declare results significant, with $.01 < P < .05$ indicating strong trends. All P values are 2-sided and are presented without formal adjustment for multiple comparisons.

RESULTS

Study Subjects

Table 1 shows the baseline characteristics of the 18 children who received ≥ 1 dose of tenofovir DF. An additional subject was removed from the study because of elevated hepatic transaminase levels that developed before tenofovir DF administration; the subject was excluded from this and other analyses. Subjects had extensive treatment experience. Nine patients had previous treatment with lopinavir/ritonavir, and 16 patients had a history of treatment with a nonnucleoside reverse transcriptase inhibitor. Drug resistance mutations are listed in Table 2. The median number of thymidine analog mutations (TAMs) associated with reduced susceptibility to tenofovir DF (M41L, D67N, K70R, L210W, T215F/Y, and K219Q/E/N) was 4 (range: 0–5 TAMs). Thirteen genotypes carried the M41L mutation; all 13 carried ≥ 3 of these TAMs, including 8 that carried L210W

TABLE 1. Baseline Characteristics of the 18 Subjects Who Received ≥ 1 Dose of Tenofovir DF

Female, no. (%)	7 (39)
Race or ethnic group, no. (%)	
Non-Hispanic white	6 (33.3)
Non-Hispanic black	10 (55.5)
Hispanic (all races)	1 (5.5)
Other	1 (5.5)
Maternal transmission, no. (%)	18 (100)
CDC class, no. (%)	
Class A3	1 (5.5)
Class B2	1 (5.5)
Class B3	5 (28)
Class C2	2 (11)
Class C3	9 (50)
Age, y, mean \pm SD	12 \pm 2.5
Prior antiretroviral agents, no., median (range)	10 (4–13)
Duration of prior antiretroviral therapy, y, median (range)	9.7 (4.8–13.5)
Weight z score, mean \pm SD	-0.59 ± 1.46
CD4 ⁺ cell count, cells per mm ³ , median (range)	206 (0–766)
Log ₁₀ HIV RNA copies per mL, median (range)	5.4 (4.1–5.9)
Major reverse transcriptase mutations, no., median (range)	7 (3–9)
Major protease mutations, no., median (range)	8 (1–10)

CDC indicates Centers for Disease Control and Prevention.

TABLE 2. Major Reverse Transcriptase and Protease Mutations at Baseline, and Optimized Background HAART Regimens Added to Tenofovir DF on Day 7

Patient No.	Major Reverse Transcriptase Mutations*	Major Protease Mutations†	Optimized Background Regimen
1	41L, 67N, 74I, 184V, 210L/F, 215C/F, 219Q	10V, 24I, 33F, 46I, 54V, 63P, 82A	ZDV, 3TC, LPV/RTV/SQV
2	41L, 44D, 67N, 69D, 118I, 184V, 210W, 215Y	10V, 46I, 63P, 71T, 82T/A, 90M	d4T, EFV, LPV/RTV
3	67N, 69D, 70R, 74I, 184V, 215F, 219Q	10I, 33F, 46L, 54V, 63P, 71T, 82A, 90M	ddI, EFV, LPV/RTV
4	62V, 69 insertion, 75T, 118I, 181C, 184I, 215Y	10I, 20R, 33F, 46I, 54V, 63P, 71V, 73S, 82A, 90M	ZDV, 3TC, APV, RTV
5	41L, 67N, 74I, 118I, 184V, 210W, 215Y, 219N	10I, 20R, 54V, 63P, 71I, 73S, 82A, 90M	d4T, 3TC, LPV/RTV
6	62V, 67N, 75I, 116Y, 151M, 181I, 219Q	10L/I, 54V/I, 63P, 71V, 82A, 90M	ZDV, 3TC, LPV/RTV
7	41L, 67G, 69D, 70R, 74V/I, 75T, 184V, 210W, 215Y	10I, 20R, 33F, 54V, 63P, 82A, 84V, 90M	ZDV, 3TC, LPV/RTV
8	41L, 44D, 67N, 69D, 118I, 184V, 210W, 215Y	10F, 30N, 46I, 63P, 90L/M	ddI, EFV, LPV/RTV
9	69A, 118V/I, 215T/S	54V/I	ZDV, 3TC, EFV, LPV/RTV
11	41L, 44D, 67N, 69D, 74V, 118I, 184V, 210S, 215Y	10I, 46I, 54V, 63P, 71V, 82N	ddI, LPV/RTV
12	41L, 44D/E, 67G, 69 insertion, 70A, 74V, 184V, 210W, 215Y	10I, 20I, 46I, 47V, 54V, 63P, 71V, 73S, 84V, 90M	d4T, 3TC, IDV, RTV
13	41L, 74V, 210W, 215Y	10I, 20R, 46I, 54V, 63P, 71V, 82A, 90M	ZDV, 3TC, ABC, LPV/RTV
15	67N, 69G, 116Y, 151M, 215V, 219E	10F, 33F, 46I, 54V, 63P, 71V, 82A, 90M	ZDV, 3TC, ABC, LPV/RTV
16	41L, 67N, 74V, 118I, 184V, 210W, 215Y, 219N	10I/V, 33F, 46L, 53L, 54V, 63P, 71V, 82S, 90M	ZDV, 3TC, ABC, LPV/RTV
17	41L, 69D, 74I, 184V, 210W, 215Y	10I, 20R, 54V, 63P, 71V/T/I, 82A, 90M	d4T, 3TC, LPV/RTV
18	41L, 67N, 69D, 70R, 74I, 75S, 118I, 215F, 219Q	10I, 20R, 33F, 46L, 54V/A, 63P, 71V, 73S, 84V, 90M	d4T, ABC, LPV/RTV

ABC indicates abacavir; APV, amprenavir; ddI, didanosine; d4T, stavudine; EFV, efavirenz; IDV, indinavir; LPV, lopinavir; RTV, ritonavir; SQV, saquinavir; ZDV, zidovudine; 3TC, lamivudine.

* Mutations at reverse transcriptase codons 41, 44, 62, 65, 67, 69, 70, 74, 75, 77, 115, 116, 118, 151, 184, 210, 215, and 219.

† Mutations at protease codons 10, 20, 24, 30, 32, 33, 46, 47, 50, 53, 54, 63, 71, 73, 82, 84, and 90.

and T215Y. No subject's viral genotype demonstrated the reverse transcriptase mutation K65R, although prior results for 1 subject did demonstrate the presence of K65R. All of the subjects' viral phenotypes at baseline demonstrated susceptibility to tenofovir DF, except for 2 subjects with the 69 insertion complex.

Adverse Events and Toxicity

During tenofovir DF monotherapy, 2 subjects developed grade 3 hepatic transaminase elevations and were removed from the study (Table 3). On day 7, the remaining 16 subjects had a median of 4 antiretroviral agents (range: 3–5 agents) added to tenofovir DF. One subject with grade 3 transaminase elevation

TABLE 3. Grade 3 or Higher Adverse Events Possibly or Probably Related to Antiretroviral Therapy or Requiring Discontinuation of Antiretroviral Therapy

Subject No.	Toxicity	Grade	Study Time Point	Tenofovir DF Action	Comment
10	Elevated transaminase levels	3	Tenofovir DF monotherapy	Discontinued	Probably related to tenofovir DF
19	Elevated transaminase levels	3	Tenofovir DF monotherapy	Discontinued	Possibly related to tenofovir DF
9	Confusion	2	Week 2	No change	Resolved with discontinuation of efavirenz
8	Rash	3	Week 2	No change	Possibly related to efavirenz or viral illness; resolved without discontinuation of efavirenz
12	Hematuria	2	Week 12	Regimen interrupted	Resolved with discontinuation of indinavir
6	Anemia (2 episodes)	3	After week 16	No change	Resolved with substitution of zidovudine with stavudine
13	Elevated transaminase levels	3	Week 18	Discontinued	Grade 4 elevation, probably related to oral contraceptives, after tenofovir DF discontinuation
7	Intracranial hemorrhage	5	Week 34	Death	Unrelated to tenofovir DF
4	Disease progression	NA	Week 43	Discontinued	Decrease in CD4 ⁺ cell count
8	BMD decrease	3	Week 48	Discontinued	Possibly related to tenofovir DF
17	BMD decrease	3	Week 48	Discontinued	Possibly related to tenofovir DF

NA indicates not applicable.

at week 18 experienced similar elevations, including a grade 4 event, after discontinuation of tenofovir DF; the elevations were attributed to oral contraceptive use. The only other grade 3 or higher toxicities possibly or probably related to tenofovir DF were grade 3 BMD decreases for 2 subjects at 48 weeks. The other toxicities that necessitated discontinuation of other antiretroviral agents were grade 3 anemia (zidovudine), grade 2 confusion (efavirenz), and grade 2 hematuria (indinavir). One death occurred at week 34 as a result of intracranial hemorrhage unrelated to tenofovir DF; 1 child discontinued study medications at week 43 because of disease progression (decreased CD4⁺ cell count).

The maximal increase in serum creatinine levels at 48 weeks was 0.3 mg/dL. The median estimated glomerular filtration rate at baseline was 186 mL/minute per 1.73 m² (range: 119–279 mL/minute per 1.73 m²), and the median decrease by week 48 was –27 mL/minute per 1.73 m² (range: –114 to 12 mL/minute per 1.73 m²; *P* = .02). No subject developed evidence of proximal renal tubular damage (grade 2 or higher hypophosphatemia, hypokalemia, acidemia, proteinuria, or glycosuria).

At baseline, the median lumbar spine BMD z score was –1.18. At week 24, the median decrease in BMD z score was –0.38 (range: –1.19 to 0.52; *P* = .007); 10 subjects had decreases in BMD from baseline, 7 of whom were virologic responders (decrease in log₁₀ HIV RNA of –1.57 to –4.0). At week 48, the median decrease in BMD z score from baseline was –0.30 (range: –2.9 to 0.21; *P* = .02); 5 subjects of the 15 evaluated at that time point had decreases in BMD from baseline, and all 5 had virologic responses (decrease in log₁₀ HIV RNA of –2.15 to –4.0). The median Tanner scores were 1 (range: 1–3) for the 5 subjects who experienced decreases in BMD at week 48 and 2.5 (range: 1–4) for the 10 subjects who did not experience decreases. Despite the BMD decreases, no subject experienced an orthopedic fracture during the 48 weeks. As shown in Fig 1, there was a moderately strong correlation (*r* = 0.67, *P* = .007) between decreases in BMD z scores at week 48 and the age of the subjects. Decreases in BMD z

scores at week 48 were not correlated with tenofovir pharmacokinetic parameters or tenofovir DF doses. Height z scores did not change significantly over the 48 weeks.

Virologic Responses

The median change in viral load during the 6 days of tenofovir DF monotherapy was not statistically significant (*P* = .12), with only 2 subjects having a >0.5 log₁₀ decrease in viral load. On day 7, subjects had optimized HAART regimens (Table 2) added to tenofovir DF. All subjects received ritonavir-boosted protease inhibitor-containing regimens and were treated with a median of 5 antiretroviral agents (range: 4–6 agents). By day 9, an additional 5 subjects experienced >0.5 log₁₀ decreases in viral load (Fig 2). By day 28, 3 more subjects experienced a >0.5 log₁₀ decline, for a total of 10 virologic responders at this time point. Seven of the 10 children with virologic responses by day 28 maintained their responses at weeks 24 and 48. Viral load responses by day 6 and day 28 were not correlated significantly with tenofovir pharmacokinetic parameters. As shown in Fig 3, the median viral load had decreased to 4.96 log₁₀ copies per mL at week 24 (*P* = .01 for the change from baseline) and to 4.21 log₁₀ copies per mL at week 48 (*P* = .01 for the change from baseline). At weeks 24 and 48, HIV RNA levels were <400 copies per mL in 6 subjects, including 4 subjects who had HIV RNA levels of <50 copies per mL.

Development of Drug Resistance

We compared the genotypic resistance results at 48 weeks with those obtained at baseline for the 8 subjects who did not have virologic responses at week 48 and who had data available at that time point (Table 4). The genotypic resistance assay for subject 15 revealed development of the K65R reverse transcriptase mutation. This likely represented reemergence of K65R, because previous genotypic results for this patient, obtained before enrollment in this study, demonstrated the presence of this mutation. This subject's genotype was positive for the Q151M mutation at baseline and, along with the reemer-

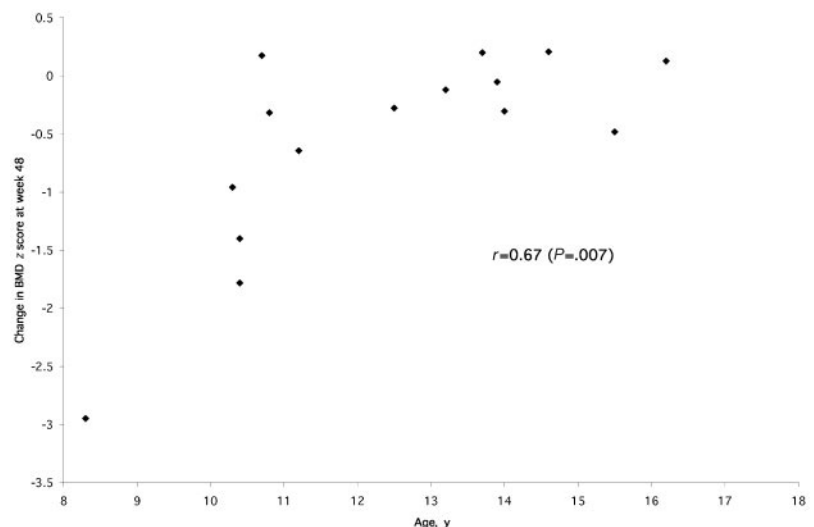


Fig 1. Changes in BMD z scores at week 48 and ages at baseline.

Fig 2. Individual and median viral loads through 28 days.

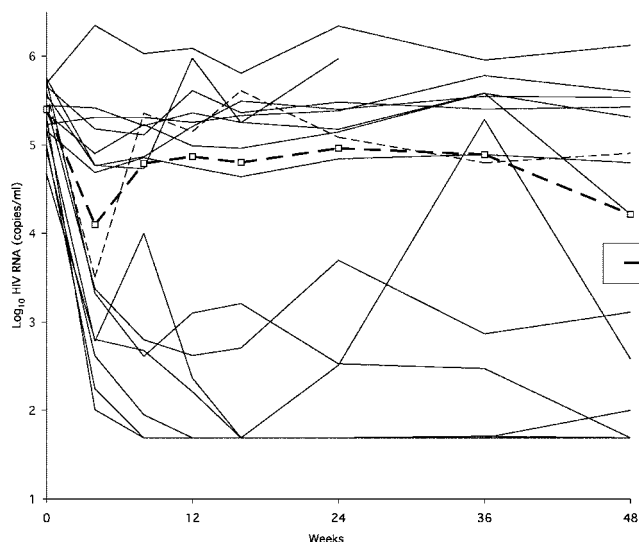
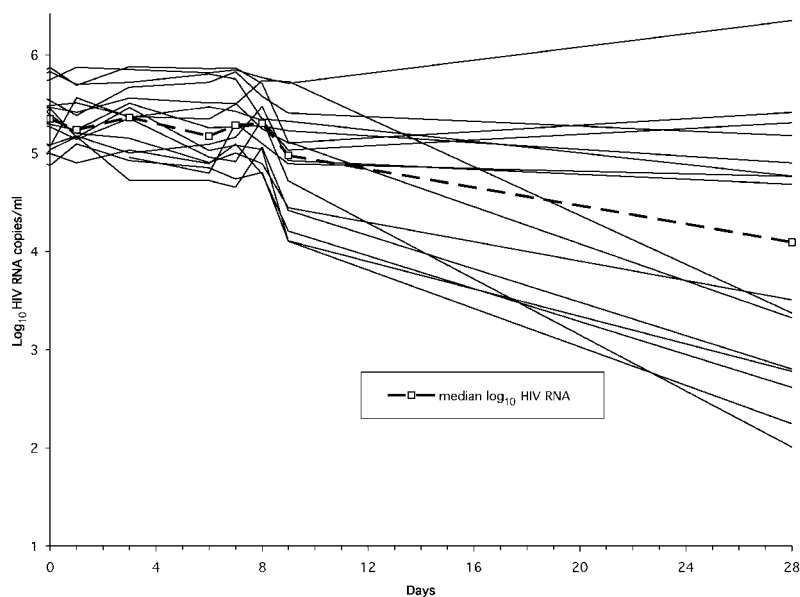


Fig 3. Individual and median viral loads through 48 weeks.

gence of K65R and K70R, the subject developed V75I and F77L mutations during the course of the study. Subject 9 had an essentially wild-type genotype at baseline but had discontinued receiving all antiretroviral agents for >5 months. By 48 weeks, her genotype demonstrated many reverse transcriptase and protease mutations but, given her treatment history, these probably represented reemergence of archived mutations. Two subjects developed major protease mutations (I84V for one and M46I and A71V for the other). Otherwise, lack of virologic response was not associated with the development of significant mutations.

Immunologic Responses

The overall median increase in CD4⁺ T cell counts at week 24 was 58 cells per mm³ (range: -64 to 589 cells per mm³; $P = .01$ for change from baseline) (Fig 4). At week 48, the median CD4⁺ T cell increase was 0 cells per mm³ (range: -274 to 768 cells per

mm³; $P = .43$ for change from baseline). The CD4⁺ cell response among the virologic responders was high and sustained. Immunophenotypic analysis of circulating CD4⁺ lymphocytes showed a median baseline naive CD4⁺ cell count of 148 cells per mm³ (range: 2-369 cells per mm³), which increased to 248 cells per mm³ (range: 46-501 cells per mm³ for change from baseline) by week 24 ($P = .02$ for change from baseline) and was 256 cells per mm³ (range: 68-501 cells per mm³) by week 48 ($P = .58$ for change from baseline). The median baseline memory CD4⁺ cell count was 55 cells per mm³ (range: 2-181 cells per mm³), which increased to 119 cells per mm³ (range: 21-240 cells per mm³) by week 24 ($P = .005$ for change from baseline) and was 115 cells per mm³ (range: 18-196 cells per mm³) by week 48 ($P = .17$ for change from baseline).

All except 1 subject was anergic in response to both *Candida* and mumps at baseline. Over the course of 48 weeks, 1 subject who was a virologic

TABLE 4. Major Reverse Transcriptase and Protease Mutations at Baseline and at 48 Weeks Among Subjects Who Did Not Have a Virologic Response

Patient No.	Major Reverse Transcriptase Mutations*	Major Protease Mutations†
4		
Baseline	62V, 69 insertion, 75T, 118I, 181C, 184I, 215Y	10I, 20R, 33F, 46I, 54V, 63P, 71V, 73S, 82A, 90M
Week 48	62V, 69 insertion, 75T, 118I, 181C, 184I, 215Y	10I, 20R, 33F, 46L/I, ‡ 54L, ‡ 63P, 71V, 73S, 82A, 84V/I, ‡ 90M
5		
Baseline	41L, 67N, 74I, 118I, 184V, 210W, 215Y, 219N	10I, 20R, 54V, 63P, 71I, 73S, 82A, 90M
Week 48	41L, 67N, 74I, 118I, 184V, 210W, 215Y, 219N	10F, ‡ 20R, 46I, ‡ 54V, 63P, 71V/I, ‡ 73G/S, ‡ 82A, 90M
9		
Baseline	69A, 118V/I, 215T/S	54V/I
Week 48	41L, ‡ 67N, ‡ 69D, ‡ 118I, 184V, ‡ 210W, ‡ 215Y, ‡	10F, ‡ 20T, ‡ 32V/I, ‡ 46I, ‡ 47V, ‡ 54V, 63P, ‡ 71V, ‡ 90M, ‡
11		
Baseline	41L, 44D, 67N, 69D, 74V, 118I, 184V, 210S, 215Y	10I, 46I, 54V, 63P, 71V, 82N
Week 48	41L, 44D, 67N, 69D, 74V, 118I, 184M/V, 210S, 215Y	10I, 46I, 54V, 63P, 71V, 82N
12		
Baseline	41L, 44D/E, ‡ 67G, 69 insertion, 70A, 74V, 184V, 210W, 215Y	10I, 20I, 46I, 47V, 54V, 63P, 71V, 73S, 84V, 90M
Week 48	41L, 67G, 69 insertion, 70A/T, ‡ 74V, 184V, 210W, 215Y	10I, 20I, 46I, 47V, 54V, 63P, 71V, 73S, 84V, 90M
15		
Baseline	67N, 69G, 116Y, 151M, 215V, 219E	10F, 33F, 46I, 54V, 63P, 71V, 82A, 90M
Week 48	65R, ‡ 67N, 69G, 70R, ‡ 75I, ‡ 77L, ‡ 115F, ‡ 116Y, 151M, 215V, 219E	10F, 33F, 46I, 54V, 63P, 71V, 82A, 90M
16		
Baseline	41L, 67N, 74V, 118I, 184V, 210W, 215Y, 219N	10I/V, 33F, 46L, 53L, 54V, 63P, 71V, 82S, 90M
Week 48	41L, 44A/E, ‡ 67N, 74V, 118I, 184V, 210W, 215Y, 219N	10I, 33F, 46L, 53L, 54V, 63P, 71V, 82S, 90M
18		
Baseline	41L, 67N, 69D, 70R, 74I, 75S, 118I, 215F, 219Q	10I, 20R, 33F, 46L, 54V/A, 63P, 71V, 73S, 84V, 90M
Week 48	41L, 67N, 69D, 70R, 74I, 75S, 118I, 215F, 219Q	10I, 20R, 33F, 46L, 54V, 63P, 71V, 73A/T, ‡ 84V, 90M

* Mutations at reverse transcriptase codons 41, 44, 62, 65, 67, 69, 70, 74, 75, 77, 115, 116, 118, 151, 184, 210, 215, and 219.

† Mutations at protease codons 10, 20, 24, 30, 32, 33, 46, 47, 50, 53, 54, 63, 71, 73, 82, 84, and 90.

‡ Differences.

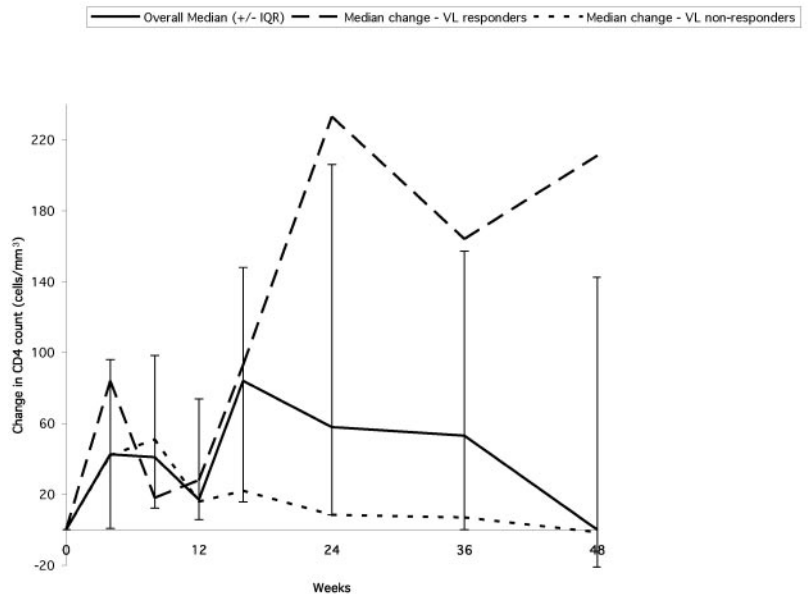


Fig 4. Median changes in CD4⁺ T cell counts for the overall group and for the virologic responders and nonresponders through 48 weeks. IQR indicates interquartile range; VL, viral load.

nonresponder developed a positive DTH response to both antigens and 2 virologic responders developed positive responses to mumps.

Analysis of Virologic Responders Versus Nonresponders

Tenofovir exposure, measured as the area under the concentration-time curve, exhibited a strong

trend for being higher after the first dose ($P = .02$) and at week 4 ($P = .03$) for the 7 virologic responders versus the 9 nonresponders (Table 5). Adherence to tenofovir DF therapy did not differ between the groups. Baseline BMD z scores also exhibited a strong trend for being higher for the virologic responders ($P = .01$); children in this group were more likely to have experienced a decrease in BMD at

TABLE 5. Analysis of Virologic Responders Versus Nonresponders

	Responders* (n = 7)	Nonresponders (n = 9)	P Value
Prior antiretroviral drugs, no., median (range)	9 (4-13)	12 (8-13)	.063
Median baseline weight z score	-0.784	-0.961	.14
Median baseline BMD z score	-0.427	-1.467	.012
Median baseline height z score	-0.354	-1.649	.25
Age, y, median (range)	10.4 (8.3-16.2)	13.2 (10.7-14.6)	.24
Baseline log ₁₀ HIV RNA, median (range)	5.31 (4.61-5.69)	5.46 (4.6-6.44)	.47
Baseline CD4 ⁺ cell count, cells per mm ³ , median (range)	269 (2-605)	59 (0-649)	.20
Major reverse transcriptase mutations, no., median (range)	7 (4-8)	8 (3-9)	.27
Major protease mutations, no., median (range)	7 (5-8)	8 (1-10)	.08
Presence of 69 insertion, no.	0/7	2/9	.48
Tenofovir DF dose, mg/m ² , median (range)	208 (161-254)	207 (174-256)	1.00
Single-dose tenofovir DF AUC, ng-h/mL, median (range)	3290 (1910-3630)	1950 (1060-2670)	.0164
Steady-state tenofovir DF AUC, ng-h/mL, median (range)	3800 (2020-5590)	2510 (1800-4160)	.031
Antiretroviral drugs, no., median (range)	5 (5-6)	5 (4-6)	1.00
Treatment with efavirenz, no.	3/7	0/9†	.0625
Treatment with lamivudine, no.	4/7	7/9	.60
Treatment with lopinavir, no.	7/7	7/9	.48
BMD decrease at week 24, no.	7/7	3/9	.011
BMD decrease at week 48, no.	5/7	0/8	.007

* Virologic response was defined as >0.5 log₁₀ HIV copies per milliliter decline.

† One subject received efavirenz for a short time, but it was discontinued because of central nervous system toxicity.

week 48 ($P = .007$). The virologic responders had received a smaller median number of previous antiretroviral agents, had a higher median baseline weight z score, were younger, had a higher median CD4⁺ cell count, had a smaller median number of drug resistance mutations (but all 7 responders had ≥ 3 TAMs at baseline), and were more likely to be treated with efavirenz, compared with the nonresponders. None of these differences was statistically significant.

DISCUSSION

Our study was designed to provide preliminary pediatric safety and dosing information on tenofovir DF, while also providing potentially efficacious salvage therapy for heavily treatment-experienced, HIV-infected children. Tenofovir's high genetic barrier to resistance allows for short-term monotherapy studies to evaluate acute safety and potency with minimal risk of resistance development.^{11,12} The 6-day monotherapy phase allowed for single-dose pharmacokinetic studies and for an assessment of acute toxicity and tolerability. Two children developed grade 3 hepatic transaminase elevations during monotherapy and were removed from the study, and there was no evidence that resistance mutations emerged during this short monotherapy period. The remaining 16 children had an optimized background regimen added to their tenofovir DF therapy.

The multidrug regimens were generally well tolerated. The major concerns regarding potential adverse events among children treated with tenofovir DF were renal and bone toxicity. Although proximal renal tubular dysfunction was reported in a few small case series of HIV-infected adults treated with tenofovir DF,¹³⁻¹⁵ no subject developed clinically significant renal toxicity during the first 48 weeks of the current study.

Significant bone toxicity was seen in young animals treated with high doses of tenofovir.^{16,17} In a study of HIV-infected adults comparing stavudine

and tenofovir DF with a background of lamivudine and efavirenz, subjects who received tenofovir DF demonstrated significantly greater decreases in lumbar spine BMD than did those who received stavudine, but the magnitude of the decreases was small and did not result in pathologic fractures in the tenofovir DF group.⁶ Similar to our baseline findings, decreased BMD or bone mineral content was reported in several studies of HIV-infected children.¹⁸⁻²⁰ A 1-year longitudinal study of BMD among 32 HIV-infected children treated with HAART (but not tenofovir DF) demonstrated low BMD, but the HIV-infected children experienced increases in BMD comparable to those experienced by healthy, non-HIV-infected, control subjects.²¹ In contrast, we found that 5 of 15 HIV-infected children who received tenofovir DF-containing HAART experienced absolute decreases in BMD at week 48; all were virologic responders. These decreases were not attributable to poor growth, because height z scores were unchanged. Additional study is necessary to determine the cause and appropriate management of the decreased BMD associated with tenofovir DF.

Despite extensive treatment experience and evidence of multidrug-resistant virus at baseline, 7 of the 16 children in our study experienced potent and sustained virologic responses. These responses were associated with increases in CD4⁺ T cell counts and clinical improvement. Despite the increases in the absolute and naive CD4⁺ T cell counts, only 1 of the 17 subjects who were anergic at baseline developed a positive DTH response to *Candida*. The development of responses to *Candida* was more frequent with HAART in previous studies by our group, but in those studies children were naive to protease inhibitors and development of positive DTH responses was seen with the first HAART regimen.^{22,23}

As stated previously, this study was designed to provide pediatric safety and dosing information on tenofovir DF, in the context of providing potentially efficacious salvage therapy for heavily treatment-

experienced, HIV-infected children. The study was not designed to investigate effective approaches to salvage therapy, and the limitations of the small sample size, the lack of a control population, and the inability to perform multivariate analyses preclude firm conclusions in this regard, but the excellent rate of virologic response raises important issues. Adherence is a major determinant of antiretroviral therapeutic success.²⁴ Administration of morning doses during the first 9 days of therapy was observed directly by health care personnel; therefore, it is unlikely that the explanation for the initial virologic responses was simply better adherence. Subsequently, we assessed adherence by counting the number of tenofovir DF pills that were returned at each visit. With this method, adherence did not differ between virologic responders and nonresponders. This was an imperfect measure, however, because many families did not bring back all of their medication bottles, and we did not formally assess adherence to the other agents in the regimen. The determinants, measurements, and interventions to improve HAART adherence are poorly understood, and more research on this critical topic is needed.

Another important determinant of antiretroviral therapeutic success is antiretroviral pharmacokinetics.^{25,26} The large interpatient variability in blood concentrations of antiretroviral agents results primarily from differences in drug absorption and clearance.²⁷ We measured only tenofovir serum concentrations and not tenofovir intracellular concentrations or levels of the other antiretroviral agents in the regimens. Serum exposure of tenofovir exhibited a strong trend for being higher among the virologic responders, compared with the nonresponders, despite similar doses of tenofovir DF. Higher exposures may reflect increased absorption among the responders. These patients might have experienced increased absorption of other antiretroviral agents also, thus increasing viral suppression.

A third important determinant of antiretroviral therapeutic success is drug resistance. Tenofovir DF was not associated with a significant viral load decrease during the monotherapy phase of our study, but its effects might have been hampered by the presence of TAMs associated with decreased susceptibility to tenofovir, suboptimal drug concentrations,¹⁰ and administration of a single dose in the first 48 hours. The added, optimized, background regimens might have acted synergistically with tenofovir DF to increase its effect. The presence of the reverse transcriptase mutation M184V, which confers high-level lamivudine resistance, is associated with increased susceptibility to tenofovir, zidovudine, and stavudine.²⁸⁻³¹ Combining zidovudine with tenofovir DF may prevent development of K65R, tenofovir's signature reverse transcriptase mutation.³²

The availability of combination formulations of zidovudine and lamivudine (with or without abacavir) allowed us to exploit these favorable resistance interactions, to maximize the number of antiretroviral agents, and to maintain reasonable pill burdens, even when resistance testing did not support their use. The rationale for maximizing the number of

antiretroviral agents is that countless viral variants emerge during incomplete suppression, each with its own resistance genotype,³³ and administering as many drugs as possible may increase the chance that all strains will be suppressed.^{34,35} Children in this study received a median of 5 antiretroviral agents. Two retrospective studies of ≥ 4 antiretroviral agents for treatment-experienced, HIV-infected children demonstrated good tolerability and toxicity profiles and virologic responses.^{36,37} The data from our prospective study support the idea that such regimens may be of benefit.

If this approach is used for heavily treatment-experienced, HIV-infected children, our experience suggests that the utility of viral resistance testing is modest. In some studies among adults, resistance testing was shown to provide short-term benefits, especially after initial HAART failure.³⁸⁻⁴⁰ However, a large randomized study showed no benefit of resistance testing.⁴¹ Although resistance testing has been adopted widely, other factors (such as toxicity, tolerability, pill burden, and drug-drug pharmacokinetic and resistance interactions), many of which affect adherence greatly, may be more important than viral resistance results alone in designing salvage regimens involving ≥ 5 drugs to treat highly resistant virus. In our study, only 1 of the 7 virologic responders had resistance testing results that aided in the selection of a protease inhibitor; that patient's genotype lacked the protease mutation 90M, and the inferred phenotype demonstrated susceptibility to saquinavir.

Optimizing tenofovir DF use in pediatrics will require additional study. Although the drug was well tolerated, the potential for bone toxicity, especially during the second decade of life, when peak bone mass is achieved, is concerning. This potential toxicity must be weighed against the ease of daily dosing, a favorable resistance profile, and the lack of other options. This study demonstrates that tenofovir DF may be an effective component of HAART for heavily treatment-experienced, HIV-infected children and that such patients can be treated safely with multidrug salvage therapy within the context of a phase I study. This approach resulted in durable virologic responses for 7 of 16 children. Additional efforts are necessary to define strategies to achieve higher rates of durable virologic responses among heavily treatment-experienced, HIV-infected children.

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Tenofovir Disoproxil Fumarate and an Optimized Background Regimen of Antiretroviral Agents as Salvage Therapy for Pediatric HIV Infection
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