

Combination Therapy With Stavudine (d4T) Plus Didanosine (ddI) in Children With Human Immunodeficiency Virus Infection

Mark W. Kline, MD*; Russell B. Van Dyke, MD†; Jane C. Lindsey, ScDS; Margaret Gwynne, BA||; Mary Culnane, MS, CRNP¶; Clemente Diaz, MD#; Ram Yogev, MD**; Ross E. McKinney, Jr, MD‡‡; Elaine J. Abrams, MD§§; Lynne M. Mofenson, MD|||; and the Pediatric AIDS Clinical Trials Group 327 Team^{a,b}

ABSTRACT. *Objectives.* To evaluate the safety, tolerance, and antiviral activity of combination therapy with stavudine (d4T) plus didanosine (ddI) in symptomatic human immunodeficiency virus (HIV)-infected children.

Methods. The study enrolled HIV-infected children who successfully completed Pediatric AIDS Clinical Trials Group (PACTG) protocol 240 (d4T versus zidovudine [ZDV] monotherapy) without disease progression or who had received ZDV monotherapy by prescription for at least the preceding 6 months. Children who had received d4T monotherapy in PACTG 240 were assigned to treatment with d4T plus ddI (arm 1). Children who had received ZDV monotherapy in PACTG 240 or by prescription were randomized in a double-blind manner to treatment with either d4T alone (arm 2) or d4T plus ddI (arm 3). Patients were followed for 48 weeks each.

Results. A total of 108 children were enrolled. The mean age was 5.0 years (range, 1.6 to 11.5 years), with mean baseline plasma HIV RNA concentration and CD4⁺ lymphocyte count of 4.6 log₁₀ copies/mL (range, 2.6 to 5.9 log₁₀ copies/mL) and 819 cells/μL (range, 8 to 3431 cells/μL), respectively. Both d4T monotherapy and d4T plus

ddI combination therapy were well-tolerated, with 96 (89%) patients completing 48 weeks of study treatment. Plasma HIV RNA concentrations showed larger average declines in arm 3 compared with arm 2 at study week 12 (0.49 vs 0.18 log₁₀ copies/mL, respectively); these average declines were maintained through week 48 (0.51 vs 0.17 log₁₀ copies/mL, respectively). Fewer than 8% of the patients in any of the treatment arms had plasma HIV RNA concentrations below the limit of quantification (200 copies/mL) at any time point.

Conclusions. Combination therapy with d4T plus ddI is safe and well-tolerated in HIV-infected children, producing durable, but incomplete, suppression of virus replication. This combination of nucleoside antiretroviral agents may provide a valuable backbone to protease inhibitor-containing treatment regimens for HIV-infected children. *Pediatrics* 1999;103(5). URL: <http://www.pediatrics.org/cgi/content/full/103/5/e62>; *stavudine, didanosine, HIV infection, infant or child.*

ABBREVIATIONS. HIV, human immunodeficiency virus; ZDV, zidovudine; 3TC, lamivudine; ddI, didanosine; d4T, stavudine; PACTG, Pediatric AIDS Clinical Trials Group; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

From the *Department of Pediatrics, Baylor College of Medicine and Texas Children's Hospital, Houston, Texas; †Department of Pediatrics, Tulane University Medical School, New Orleans, Louisiana; ‡Center for Biostatistics in AIDS Research, Harvard School of Public Health, Boston, Massachusetts; §Pediatric ACTG Operations Center, Rockville, Maryland; ¶Division of AIDS, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland; #Department of Pediatrics, University of Puerto Rico, San Juan, Puerto Rico; **Department of Pediatrics, Children's Memorial Hospital and Northwestern University Medical School, Chicago, Illinois; ††Department of Pediatrics, Duke University Medical Center, Durham, North Carolina; ‡‡Department of Pediatrics, Harlem Hospital Center, Harlem, New York; and †††Pediatric, Adolescent and Maternal AIDS Branch, National Institute of Child Health and Human Development, Rockville, Maryland.

^aOther Protocol PACTG 327 Team Members include the following (in alphabetical order): James Balsley, MD, PhD, National Institutes of Health, Bethesda, MD; Marilyn Crain, MPH, MD, University of Alabama School of Medicine, Birmingham, AL; Lisa Dunkle, MD, Bristol-Myers Squibb Co, Wallingford, CT; Marianne E. Federici, Bristol-Myers Squibb Co, Wallingford, CT; Courtney V. Fletcher, PharmD, University of Minnesota, Minneapolis, MN; Alice T. Harris, MS, CPNP, RN, Baylor College of Medicine, Houston, TX; Katherine Luzuriaga, MD, University of Massachusetts Medical School, Worcester, MA; Wendy G. Mitchell, MD, Children's Hospital of Los Angeles, Los Angeles, CA; Sharon Nichols, PhD, University of California, San Diego, San Diego, CA; Barbara Nowak, BA, Frontier Science and Technology Research Foundation, Amherst, NY; Lynette Purdue, PharmD, National Institutes of Health, Bethesda, MD; John Sever, MD, PhD, Children's National Medical Center, Washington, DC.

^bOther participating investigators and institutions are listed in the Appendix. Received for publication Oct 13, 1998; accepted Dec 22, 1998.

Address correspondence to Mark W. Kline, MD, Department of Pediatrics, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030.

PEDIATRICS (ISSN 0031 4005). Copyright © 1999 by the American Academy of Pediatrics.

Antiretroviral therapy of human immunodeficiency virus (HIV)-infected children results in a variety of virologic, immunologic, and clinical benefits.¹⁻³ Recently published pediatric antiretroviral treatment guidelines recommend treatment of most HIV-infected children with a combination of two nucleoside antiretroviral agents plus one HIV protease inhibitor.⁴ The guidelines note that more data exist on the use of zidovudine (ZDV) plus lamivudine (3TC) or ZDV plus didanosine (ddI) than for stavudine (d4T) plus ddI or other combinations of nucleoside antiretroviral agents. To date, only one small pilot study has examined the use of combination therapy with d4T plus ddI for HIV-infected children.⁵ Additional initial and alternative nucleoside antiretroviral treatment options are needed for children. The purpose of this phase II clinical trial was to evaluate the safety, tolerance, and antiviral activity of combination therapy with d4T plus ddI in children with symptomatic HIV infection.

METHODS

Patients and Study Design

This was a partially randomized, partially double-blind, phase II clinical trial. The study population included HIV-infected chil-

dren 6 months to 10 years of age who successfully completed Pediatric AIDS Clinical Trials Group (PACTG) protocol 240 (d4T versus ZDV monotherapy)⁶ without disease progression or who had received ZDV monotherapy by prescription for at least the preceding 6 months. The following baseline laboratory values were required: a hemoglobin concentration ≥ 7 g/dL; a polymorphonuclear leukocyte count $\geq 400/\mu\text{L}$; a platelet count $\geq 50\,000/\mu\text{L}$; aspartate aminotransferase (AST) and alanine aminotransferase (ALT) less than 10 times the upper limit of normal; bilirubin less than 3 times the upper limit of normal; and a serum creatinine concentration < 1.2 (age 3 months to 2 years) or 1.7 mg/dL (age 2 to 10 years). Children were excluded from study participation if they had intractable diarrhea or vomiting, an acute opportunistic infection requiring treatment, or active malignancy requiring chemotherapy. Children who were receiving ZDV at the time of study enrollment were excluded if they previously had received > 6 weeks of therapy with either d4T or ddI. The study was approved by the review boards for Human Subject Research at each participating institution. Informed consent was obtained from each subject's parent or legal guardian.

Children who had received d4T monotherapy in PACTG 240 were assigned to oral treatment with d4T (1 mg/kg/dose twice daily; maximum, 40 mg twice daily) plus ddI (90 mg/m²/dose twice daily; maximum, 150 mg twice daily) (arm 1). Children who had received ZDV monotherapy in PACTG 240 or by prescription were randomized in a double-blind manner to oral therapy with either d4T (same dose as arm 1) plus ddI placebo (arm 2) or d4T (same dose as arm 1) plus ddI (same dose as arm 1) (arm 3). Randomization was stratified by previous participation in PACTG 240.

Patients received prophylaxis for *Pneumocystis carinii* pneumonia according to established guidelines,⁷ and nutritional support and antibiotic therapy were prescribed as needed. Use of immunomodulators (excluding corticosteroids and intravenous immunoglobulin) or antiretroviral agents other than the study drugs was prohibited.

Toxicities were graded according to the Division of AIDS Toxicity Grading Table for Pediatric Adverse Experiences. In brief, this Table grades a variety of potential study drug-associated clinical and laboratory adverse events on a 4-point scale from grade 1 (least severe) to grade 4 (most severe). Laboratory values constituting grade 3 or greater abnormalities include the following: hemoglobin concentration < 7 g/dL; absolute neutrophil count $< 400/\mu\text{L}$; ALT, at least 10 times the upper limit of normal; bilirubin, at least 3 times the upper limit of normal; and serum creatinine > 1.1 (age 3 months to 2 years) or 1.6 mg/dL (age 2 years or older).

Grade 3 or greater instances of presumed study drug-associated toxicity or intolerance were managed according to a dose-modification scheme that mandated interruption of study drug therapy for up to 28 days. If the toxicity improved during that time to less than grade 3, study drug therapy was resumed at a reduced dose. If the toxicity did not worsen to grade 3 or greater, therapy ultimately was resumed at full dose.

For purposes of the trial, primary study endpoints and response variables were defined as follows: 1) the occurrence of any grade 3 or greater toxicity or intolerance during, or up to 60 days after discontinuation of, study treatment (all arms); and 2) short- and long-term changes in plasma HIV RNA concentrations between baseline and study weeks 12 and 48 in the two randomized arms (arms 2 and 3). Secondary endpoints and response variables included disease progression, survival, and changes in CD4⁺ lymphocyte counts.

If a primary toxicity or intolerance endpoint, or disease progression, was suspected, the investigator was asked to contact the protocol chair before discontinuing study treatment. All study endpoints were reviewed by the protocol chair, and only those that satisfied protocol definitions were included in the analysis.

Drug Administration

d4T was supplied as a pediatric powder blend that yielded a concentration of 1 mg/mL after reconstitution with water, and in capsule sizes of 5, 10, and 20 mg. d4T capsules were administered either intact or by sprinkling the contents onto soft food (eg, applesauce or pudding) at room temperature or below. ddI was supplied as a dry powder, which was constituted with water to a concentration of 20 mg/mL and mixed immediately with antacid

to a final concentration of 10 mg/mL, as well as in chewable and dispersible buffered tablets of 25, 50, and 100 mg. Children were asked to fast for 2 hours before and 1 hour after each ddI dose. d4T and ddI were administered simultaneously, twice daily.

Weight and body surface area were determined every 4 weeks, and the drug dose was changed when there was an increase or decrease of $\geq 10\%$. Compliance was monitored by measuring or counting returned medication and by questioning the parent at each scheduled clinic visit.

Clinical and Laboratory Monitoring

Subjects were evaluated clinically and with complete blood counts and routine blood chemistries (creatinine, ALT, bilirubin, and amylase) at preentry and entry, and at study weeks 4, 8, 12, 16, 24, 32, 40, and 48. Lymphocyte monoclonal antibody phenotyping was performed at preentry and entry, and at study weeks 4, 12, 24, and 48. Phenotyping was performed by standard methods at local flow cytometry laboratories certified by the AIDS Clinical Trials Group flow cytometry quality assurance program.⁸

Blood specimens were drawn into tubes containing ACD anti-coagulant at preentry and entry, and at study weeks 4, 8, 12, 24, 36, and 48. Plasma was separated from whole blood specimens within 6 hours of collection and stored at -70°C . After completion of the study, stored plasma specimens were used for determination of HIV RNA concentrations (Roche Molecular Systems, Branchburg, NJ). All specimens from each child were assayed in batch manner. All plasma HIV RNA measurements were performed at a single laboratory certified by the AIDS Clinical Trials Group virology quality assurance program.⁹

Statistical Methods

The study was designed to have 80% power to detect a 0.5 log₁₀ copies/mL difference between arms 2 and 3 with respect to changes in plasma HIV RNA concentration between baseline and weeks 12 and 48. Allowing for loss-to-follow-up and subjects with unevaluable plasma HIV RNA measurements at baseline or weeks 12 or 48, this required 40 patients per arm. The study was not powered to detect other than very large differences in toxicity or disease progression rates. When accrual to arms 2 and 3 was halted prematurely because of low enrollment rates (59 of 80 patients had been enrolled), it compromised power to detect even these large differences.

The intent-to-treat rule was used for all virologic, immunologic, and clinical endpoint analyses, with patients analyzed according to their initial randomized treatment, regardless of treatment discontinuation or poor compliance. The censoring time for these analyses was the date of the last visit. Only on-treatment analyses of toxicity were possible. The censoring time for these analyses was the final on-treatment date plus 60 days. All longitudinal outcomes and times-to-events were measured from the date of randomization, with the exception of toxicities, which were measured from the time the first dose of study drug was administered. Baseline plasma HIV RNA and immunologic measurements were taken as the average of the results of assays performed on preentry and entry specimens.

Formal treatment comparisons were made between arms 2 and 3 for all parameters. Treatment comparisons in toxicity rates also were made between the combination treatment arms (arms 1 and 3) to assess the possibility that previous treatment might impact toxicity rates. Randomization to arms 2 and 3 was stratified by previous enrollment in PACTG 240 to ensure balance in the two treatment arms. Because of the small numbers in the randomized arms and the necessity of using nonparametric tests on some of the response variables, correct adjustment for previous participation in PACTG 240 was not always possible. In analyses where it was possible to account for the stratification, it did not affect any of the treatment comparisons. Rather than use a mixture of approaches, primary results in this report are from analyses that do not account for the stratification.

Comparisons at the primary time points of interest for plasma HIV RNA concentrations (changes from baseline to weeks 12 and 48) were performed using *t* tests after exploratory analyses of covariance showed no need to adjust for age, baseline plasma HIV RNA concentration, or previous participation in PACTG 240. Treatment comparisons for time-to-event toxicity data were performed using log-rank tests. Secondary analyses on changes from baseline to weeks 12 and 48 in immunologic parameters were

performed using nonparametric Wilcoxon tests.¹⁰ Additional analyses for treatment differences in the continuous measures collected repeatedly during the study (plasma HIV RNA and immunologic measurements, growth) were performed using repeated-measures ANCOVA for the normally distributed data and were confirmed with the nonparametric Wei-Johnson test.¹¹

RESULTS

Baseline Patient Characteristics

A total of 108 children were enrolled in the study between August 1996, and March 1997, at 31 separate institutions in the United States. Because of slow accrual into arms 2 and 3, enrollment was halted before the target of 40 children per study arm was reached. Forty-nine children who had received d4T monotherapy in ACTG 240 were assigned to treatment with d4T plus ddI (arm 1). Twenty-five children who had received ZDV monotherapy in ACTG 240 and 34 children who had received ZDV monotherapy by prescription were randomized to treatment with either d4T alone (arm 2, $n = 30$) or d4T plus ddI (arm 3, $n = 29$).

Selected characteristics of study subjects are shown in Table 1. In the two randomized study arms, there were slightly fewer males, higher baseline plasma HIV RNA concentration, and lower baseline CD4⁺ lymphocyte count in arm 2 than in arm 3, but these differences were not statistically significant.

At least 105 (97%) of the children enrolled in the study had vertical HIV infection. The treatment arms were well-balanced with regard to baseline weight-for-age-and-gender z scores (data not shown). Only five (5%) mothers of study subjects had received antiretroviral or immunomodulator therapy during pregnancy. Ten of the patients assigned to arm 1 had received up to 6 weeks of ZDV therapy before enrollment in ACTG 240. Patients in arms 2 and 3 had received a median of 28.7 and 28.9 months of ZDV therapy, respectively, before enrollment in the present study. Two patients had received some treatment with 3TC before study enrollment.

Safety

Both d4T monotherapy and d4T plus ddI combination therapy were well-tolerated, with 96 (89%) patients completing 48 weeks of study treatment. Table 2 summarizes all the grade 3 or greater laboratory toxicities and clinical signs and symptoms that were observed during the course of the trial. Patients assigned to arm 2 experienced hematologic events, clinical signs and symptoms, and any grade 3 or greater event at a higher rate than did children assigned to the other treatment arms, but the difference in rates between arms 2 and 3 was not statistically significant using a time-to-event analysis on any events ($P = .124$), and was only marginally significant for hematologic events ($P = .052$). Only 1 of the 78 children receiving d4T plus ddI combination therapy (arms 1 and 3) experienced a grade 3 or greater laboratory toxicity. With so few events, there was little power to detect treatment differences if they did exist. One patient (from arm 2) discontinued study treatment at week 14 because of pancreatitis. No other patients were removed from treatment because of toxicity.

Clinical Observations

Ten (20%) patients in arm 1, 3 (10%) in arm 2, and 5 (17%) in arm 3 had weight or weight-for-height measurements below the 25th percentile and 6-month weight growth velocities below the 3rd percentile, after at least 24 weeks on study. Examination of changes from baseline in weight-for-age-and-gender z scores revealed no differences between study arms 2 and 3. Only 1 child (arm 2) developed a new AIDS-defining condition during the course of the study (recurrent bacteremia). No deaths were reported on study.

Virologic and Immunologic Observations

Mean changes from baseline in plasma HIV RNA concentration by treatment arm and week on study are shown in Figure 1. Plasma HIV RNA concentra-

TABLE 1. Baseline Characteristics of Study Participants

Characteristic	Total ($N = 108$)	Arm 1 ($N = 49$)	Arm 2 ($N = 30$)	Arm 3 ($N = 29$)
Age, y				
Mean	5.0	4.3	5.3	5.8
SE	0.2	0.2	0.4	0.5
Sex				
Male	52 (48)	25 (51)	11 (37)	16 (55)
Female	56 (52)	24 (49)	19 (63)	13 (45)
Race/ethnicity				
White/not Hispanic	9 (8)	5 (10)	2 (7)	2 (7)
Black/not Hispanic	76 (70)	36 (74)	21 (70)	19 (66)
Hispanic	23 (21)	8 (16)	7 (23)	8 (28)
Plasma HIV RNA concentration, log ₁₀ copies/mL				
Mean	4.55	4.48	4.69	4.53
SE	0.07	0.10	0.14	0.13
CD4 ⁺ count, cells/ μ L				
Median	730	742	688	773
Mean	819	904	687	810
SE	53.1	91.9	97.1	66.5

Arm 1: d4T plus ddI, previous d4T; arm 2: d4T, previous ZDV; arm 3: d4T plus ddI, previous ZDV. Numbers in parentheses indicate percent.

$P = NS$ for all comparisons between treatment arms 2 and 3.

TABLE 2. Incidence of Grade 3 or Greater Toxicities

Abnormal Finding	Total (N = 108)	Arm 1 (N = 49)	Arm 2 (N = 30)	Arm 3 (N = 29)
Any hematologic abnormality	4 (4)	0	4 (13)	0
Anemia	1 (1)	0	1 (3)	0
Neutropenia	2 (2)	0	2 (7)	0
Thrombocytopenia	1 (1)	0	1 (3)	0
Any chemistry abnormality	2 (2)	1 (2)	1 (3)	0
Creatine phosphokinase	1 (1)	1 (2)	0	0
Amylase/lipase	1 (1)	0	1 (3)	0
Any clinical sign or symptom	15 (14)	4 (8)	7 (23)	4 (14)

Arm 1: d4T plus ddI, previous d4T; arm 2: d4T, previous ZDV; arm 3: d4T plus ddI, previous ZDV. Numbers in parentheses indicate percent of patients assigned to that treatment.

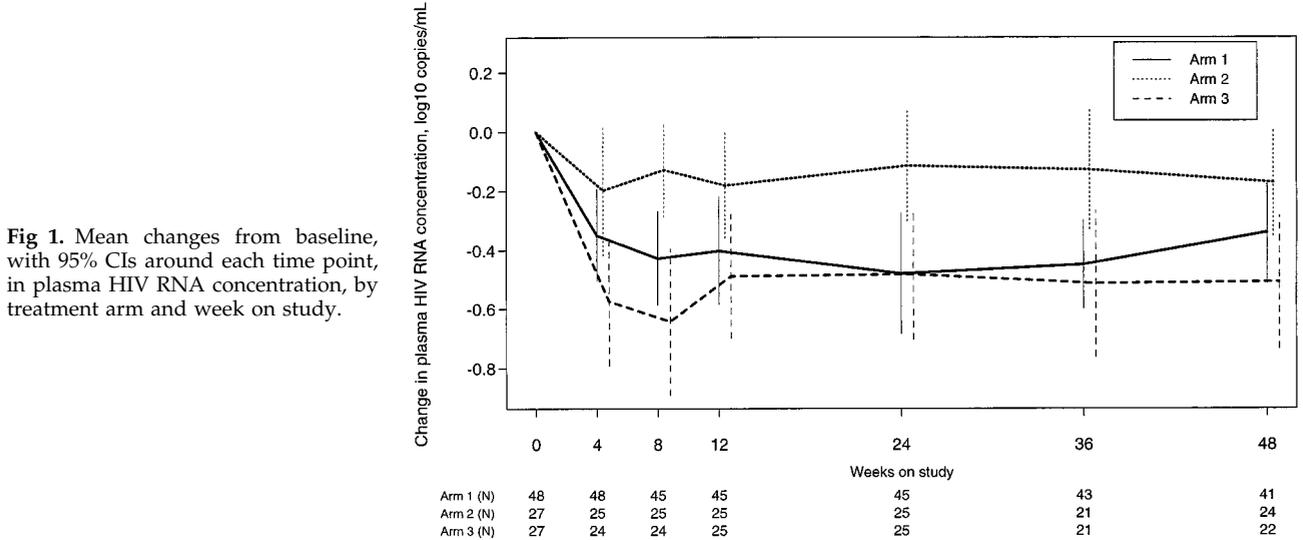


Fig 1. Mean changes from baseline, with 95% CIs around each time point, in plasma HIV RNA concentration, by treatment arm and week on study.

tions showed larger average declines in arm 3 compared with arm 2 at study weeks 12 (0.49 vs 0.18 log₁₀ copies/mL, respectively; *P* = .033) and 48 (0.51 vs 0.17 log₁₀ copies/mL, respectively; *P* = .026). Although no formal comparisons were made between arms 1 (d4t plus ddI, previous d4T) and 3 (d4T plus ddI, previous ZDV), the declines in plasma HIV RNA concentrations between baseline and study weeks 12 and 48 were smaller in the group of patients that received only one new drug (arm 1). Fewer than 8% of the patients in any of the treatment arms had plasma HIV RNA concentrations below the limit of quantification (200 copies/mL) at any time point.

Median changes from baseline in CD4⁺ lymphocyte count by treatment arm and week on study are shown in Figure 2. Examination of changes from baseline in CD4⁺ lymphocyte count and percentage revealed no differences between study arms 2 and 3.

DISCUSSION

Both d4T and ddI have been used widely in the single-agent therapy of HIV infection in children.^{6,12-14} Peripheral neuropathy is a dose-limiting toxicity of d4T and ddI therapy in HIV-infected adults, but this adverse effect has been observed infrequently in children, and both drugs generally are well-tolerated.

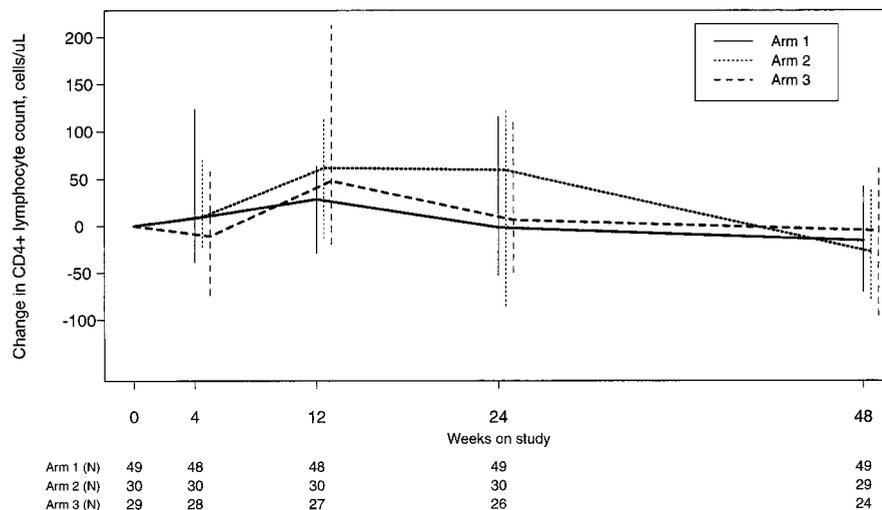
Although both d4T and ddI are inhibitors of HIV reverse transcriptase, the enzymatic pathways by

which the drugs are activated, and their respective activities in resting or proliferating cells, are different,¹⁵ suggesting that their anti-HIV effects may be complementary. In vitro, the drugs act synergistically to inhibit clinical isolates of HIV.¹⁶ Furthermore, a pilot study of combination therapy with d4T plus ddI revealed no clinical pharmacokinetic interaction between the drugs, excellent tolerance and safety, and preliminary evidence of virologic and immunologic benefit in a small number of children with advanced HIV disease and previous d4T monotherapy.⁵ For these reasons, and because additional antiretroviral treatment options are needed for children, we undertook this study to evaluate the safety, tolerance, and antiviral activity of combination therapy with d4T plus ddI in children with symptomatic HIV infection.

Combination therapy with d4T plus ddI was remarkably well-tolerated by the children we studied. Only one grade 3 or greater laboratory adverse event of any kind was reported among the 78 children who received combination therapy for up to 48 weeks each, and adverse clinical signs or symptoms of any kind attributable to study treatment were reported in only ~10% of patients. There were no cases of pancreatitis or peripheral neuropathy among recipients of combination therapy, and no patients discontinued treatment because of toxicity.

In the present study, average declines in plasma HIV RNA concentration between baseline and study

Fig 2. Median changes from baseline, with 95% CIs around each time point, in CD4⁺ lymphocyte count, by treatment arm and week on study.



weeks 12 and 48 were significantly greater among children who discontinued ZDV and began therapy with d4T plus ddI (0.49 and 0.51 log₁₀ copies/mL, respectively) than among those who discontinued ZDV and began therapy with d4T alone. This finding is consistent with current recommendations that at least two new drugs should be given when antiretroviral therapy is changed.⁴ Although the magnitude of these changes in plasma HIV RNA concentration is modest in comparison to that which has been observed in some studies of HIV protease inhibitor-containing combination treatment regimens, the durability of the antiviral response is encouraging and suggests that d4T plus ddI combination therapy may have particular utility when used with newer, more potent antiretroviral agents.

Based on our findings from this study of d4T plus ddI combination therapy, which demonstrate excellent safety and tolerance and durable antiviral effect, we believe that this combination of nucleoside antiretroviral agents may provide a valuable backbone to HIV protease inhibitor-containing treatment regimens for HIV-infected children. In a preliminary phase I pilot study of HIV-infected children, combination therapy with d4T, ddI, and the HIV protease inhibitor indinavir has shown excellent safety and tolerance and potent antiviral activity.¹⁷

APPENDIX

Other participating investigators and institutions include Cara Simon, MSN, RN, CPNP; Nancy R. Calles, BSN, RN, ACRN; Celine G. Hanson, MD; William T. Shearer, MD, PhD (Baylor College of Medicine and Texas Children's Hospital); Ellen Chadwick, MD; Deborah Fonken, BSN, RN (Children's Memorial Hospital, Chicago); Daniel Johnson, MD (University of Chicago Children's Hospital); Lisette Lugo, MD; Irma Febo, MD; Carmen Rivera, RN, MPH (University of Puerto Rico); Megan Valentine, PA-C; Lori Ferguson, RN; Jean Hurwitz, RPh (Duke University Medical Center); Delia Calo, Susan E. Champion, MD, MPH; Maxine Frere, RN (Harlem Hospital); Senih Fikrig, MD; Hamid Moallem, MD; Savina Wiltshire, RN; Denise Swindell (Children's Hospital of Brooklyn); Savita Pahwa, MD; Saroj Bakshi, MD; Aida Matias (North Shore University Hospital); Mobeen H. Rathore, MD; Samir Midani, MD; L. Michelle Eagle, PA-C; Erin Buckley, RN (University of Florida Health Science Center, Jacksonville); Peter Vink, MD; Susan Lovelace, CPNP (Johns Hopkins University); Sunanda Gaur, MD; Patricia Whitley-Williams, MD; Robin Scudder, CPNP; Karen Stralkus, RN (University of Medicine and

Dentistry of New Jersey-Robert Wood Johnson Medical School); Hermann Mendez, MD; Edward Handelsman, MD; Helen Winthrop, PNP (Kings County Hospital Center); Nancy Karthas, MS, RN, CPNP; Dawn Jacobs, RN; Robert Bishop, MS; Kenneth McIntosh, MD (Children's Hospital of Boston); Steve Nicholas, MD; Leslie Nielsen, RN; Marie Donahue, RN, PNP; Anne Gershon, MD (Columbia Presbyterian Medical Center); Vincent R. Bonagura, MD; Susan J. Schuval, MD; Steven J. Weiss, MD, PhD; Constance Colter, MS, CPNP (Schneider Children's Hospital); Andrew Wiznia, MD; Joanna Dobroszycki, MD; Wanda Biernick, RN; Jorge Sansary, MPH (Bronx Lebanon Hospital Center); John L. Sever, MD, PhD; Tamara A. Rakusan, MD, PhD; Brett J. Loecheit, MD; Susan Zamer, BSN, RN (Children's National Medical Center); Duane Harrison, MD; Charnell Cromer, MSN, RN, Mary Moss, RN (Children's Hospital of Michigan); Ellen C. Moore, MD (Wayne State University); Myron J. Levin, MD; Elizabeth J. McFarland, MD; Carol Salbenblatt, MSN, RN; Janie Eddy, RN, CPNP (Children's Hospital, Denver); Francis Gigliotti, MD; Geoffrey A. Weinberg, MD; Barbra Murante, MS, RNC, PNP; Susan Laverty, RN (University of Rochester Medical Center); Margarita Sileo, MD; Kimberly Anglin, BS; Troylynn Maupin, BN (Tulane University and Charity Hospital).

ACKNOWLEDGMENTS

This work was supported in part by the Pediatric AIDS Clinical Trials Group of the National Institute of Allergy and Infectious Diseases, the Pediatric/Perinatal HIV Clinical Trials Network of the National Institute of Child Health and Human Development, the General Clinical Research Center Units of the National Center for Research Resources, and Bristol-Myers Squibb Company.

REFERENCES

- McKinney RE Jr, Pizzo PA, Scott GB, et al. Safety and tolerance of intermittent intravenous and oral zidovudine therapy in human immunodeficiency virus-infected pediatric patients. *J Pediatr.* 1990;116: 640-647
- McKinney RE Jr, Maha MA, Connor EM, et al. A multicenter trial of oral zidovudine in children with advanced human immunodeficiency virus disease. *N Engl J Med.* 1991;324:1018-1025
- Mueller BU, Butler KM, Stocker VL, et al. Clinical and pharmacokinetic evaluation of long-term therapy with didanosine in children with HIV infection. *Pediatrics.* 1994;94:724-731
- Centers for Disease Control and Prevention. Guidelines for the use of antiretroviral agents in pediatric HIV infection. *MMWR.* 1998;47:1-43
- Kline MW, Fletcher CV, Federici ME, et al. Combination therapy with stavudine and didanosine in children with advanced human immunodeficiency virus infection: pharmacokinetic properties, safety, and immunologic and virologic effects. *Pediatrics.* 1996;97:886-890
- Kline MW, Van Dyke RB, Lindsey JC, et al. A randomized comparative trial of stavudine (d4T) versus zidovudine (ZDV, AZT) in children with human immunodeficiency virus infection. *Pediatrics.* 1998;101: 214-220
- Centers for Disease Control and Prevention. 1995 Revised guidelines for

- prophylaxis against *Pneumocystis carinii* pneumonia for children infected with or perinatally exposed to human immunodeficiency virus. *MMWR*. 1995;44:1–11
8. Calvelli T, Denny TN, Paxton H, Gelman R, Kagan J. Guidelines for flow cytometric immunophenotyping: a report from the National Institute of Allergy and Infectious Diseases, Division of AIDS. *Cytometry*. 1993;14:702–715
 9. Hollinger FB, Bremer JW, Myers LE, Gold JWM, McQuay L. Standardization of sensitive human immunodeficiency virus coculture procedures and establishment of a multicenter quality assurance program for the AIDS Clinical Trials Group. *J Clin Microbiol*. 1992;30:1787–1794
 10. Pagano M, Gauvreau K. *Principles of Biostatistics*. Wadsworth, CA: Duxbury Press; 1993
 11. Wei LJ, Johnson WE. Combining dependent tests with incomplete repeated measurements. *Biometrika*. 1985;72:359–364
 12. Kline MW, Dunkle LM, Church JA, et al. A phase I/II evaluation of stavudine (d4T) in children with human immunodeficiency virus infection. *Pediatrics*. 1995;96:247–252
 13. Mueller BU, Butler KM, Stocker VL, et al. Clinical and pharmacokinetic evaluation of long-term therapy with didanosine in children with HIV infection. *Pediatrics*. 1994;94:724–731
 14. Englund JA, Baker CJ, Raskino C, et al. Zidovudine, didanosine, or both as the initial treatment for symptomatic HIV-infected children. *N Engl J Med*. 1997;336:1704–1712
 15. Sommadossi J-P. Comparison of metabolism and in vitro antiviral activity of stavudine versus other 2',3'-dideoxynucleoside analogues. *J Infect Dis*. 1995;171(suppl 2):S88–S92
 16. Merrill DP, Moonis M, Chou T-C, Hirsch MS. Lamivudine or stavudine in two- and three-drug combinations against human immunodeficiency virus type 1 replication in vitro. *J Infect Dis*. 1996;173:355–364
 17. Kline MW, Fletcher CV, Harris AT, et al. A pilot study of combination therapy with indinavir, stavudine (d4T), and didanosine (ddl) in children infected with the human immunodeficiency virus. *J Pediatr*. 1998;132:543–546

Combination Therapy With Stavudine (d4T) Plus Didanosine (ddI) in Children With Human Immunodeficiency Virus Infection

Mark W. Kline, Russell B. Van Dyke, Jane C. Lindsey, Margaret Gwynne, Mary Culnane, Clemente Diaz, Ram Yogeve, Ross E. McKinney Jr, Elaine J. Abrams, Lynne M. Mofenson and the Pediatric AIDS Clinical Trials Group 327 Team

Pediatrics 1999;103:e62

DOI: 10.1542/peds.103.5.e62

Updated Information & Services	including high resolution figures, can be found at: http://pediatrics.aappublications.org/content/103/5/e62
References	This article cites 16 articles, 6 of which you can access for free at: http://pediatrics.aappublications.org/content/103/5/e62#BIBL
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): Infectious Disease http://www.aappublications.org/cgi/collection/infectious_diseases_sub HIV/AIDS http://www.aappublications.org/cgi/collection/hiv/aids_sub
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.aappublications.org/site/misc/Permissions.xhtml
Reprints	Information about ordering reprints can be found online: http://www.aappublications.org/site/misc/reprints.xhtml

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®



PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Combination Therapy With Stavudine (d4T) Plus Didanosine (ddI) in Children With Human Immunodeficiency Virus Infection

Mark W. Kline, Russell B. Van Dyke, Jane C. Lindsey, Margaret Gwynne, Mary Culnane, Clemente Diaz, Ram Yogev, Ross E. McKinney Jr, Elaine J. Abrams, Lynne M. Mofenson and the Pediatric AIDS Clinical Trials Group 327 Team

Pediatrics 1999;103:e62

DOI: 10.1542/peds.103.5.e62

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/103/5/e62>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 345 Park Avenue, Itasca, Illinois, 60143. Copyright © 1999 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®

