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

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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.

ANTIRETROVIRAL THERAPY OF HUMAN IMMUNEDEFICIENCY VIRUS-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 children...
dren 6 months to 10 years of age who successfully completed Pediatric AIDS Clinical Trials Group (PACTG) protocol 240 (d4T versus ZDV monotherapy) 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 ≥400/µL; a platelet count ≥50,000/µL; alanine aminotransferase (ALT) and aspartate 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 recently off ZDV at the time of study entry were excluded if they 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 placebo (same dose as arm 1) plus ddI (arm 1). Randomization was stratified by previous participation in PACTG 240.

Patients received prophylaxis for Pneumocystis carinii pneumonia according to established guidelines, 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/µL; 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 over).

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 was reinitiated 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 measured 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 ±10%. Compliance was monitored by measuring or counting returned medication and by questioning the patient 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 mononuclear 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.

Blood specimens were drawn into tubes containing ACD anticoagulant 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.

**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 unvaluable 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 premature because of low enrollment rates (59 of 80 patients had been enrolled), it compromized 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 used to control for 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 toxicities. Randomization to arms 2 and 3 ensured a balanced 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 unadjusted data 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. 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.

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 ddl (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 ddl (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 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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N = 108)</th>
<th>Arm 1 (N = 49)</th>
<th>Arm 2 (N = 30)</th>
<th>Arm 3 (N = 29)</th>
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<td>Age, y</td>
<td></td>
<td></td>
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<td>8 (28)</td>
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<td>Plasma HIV RNA concentration, log_{10} copies/mL</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean</td>
<td>4.55</td>
<td>4.48</td>
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<td>CD4+ count, cells/μL</td>
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<td>Median</td>
<td>730</td>
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<tr>
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<td>904</td>
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<td>53.1</td>
<td>91.9</td>
<td>97.1</td>
<td>66.5</td>
</tr>
</tbody>
</table>

Arm 1: d4T plus ddl, previous d4T; arm 2: d4T, previous ZDV; arm 3: d4T plus ddl, previous ZDV.

Numbers in parentheses indicate percent.

P = NS for all comparisons between treatment arms 2 and 3.
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 ddl, previous d4T) and 3 (d4T plus ddl, 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 ddl 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 ddl 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 ddl 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 ddl 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 ddl in children with symptomatic HIV infection.

Combination therapy with d4T plus ddl 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

<table>
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<tr>
<th>Abnormal Finding</th>
<th>Total (N = 108)</th>
<th>Arm 1 (N = 49)</th>
<th>Arm 2 (N = 30)</th>
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<td>Any hematologic abnormality</td>
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<td>0</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Any chemistry abnormality</td>
<td>2 (2)</td>
<td>1 (2)</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Creatine phosphokinase</td>
<td>1 (1)</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Amylase/lipase</td>
<td>1 (1)</td>
<td>0</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Any clinical sign or symptom</td>
<td>15 (14)</td>
<td>4 (8)</td>
<td>7 (23)</td>
<td>4 (14)</td>
</tr>
</tbody>
</table>

Arm 1: d4T plus ddl, previous d4T; arm 2: d4T, previous ZDV; arm 3: d4T plus ddl, 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.](image-url)
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. 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 anti-retroviral 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.\(^\text{17}\)

**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 Michigan); Ellen C. Moore, MD (Wayne State University); Myron J. Levin, MD; Elizabeth J. McFarland, MD; Carol Salbenblatt, BSN, RN; Janie Eddy, RN, CPNP (Children’s Hospital, Denver); Francis Gigliotti, MD; Geoffrey A. Weinberg, MD; Barbra Murante, MSN, RN, PNP; Susan Laverty, RN (University of Rochester Medical Center); Margarita Silio, MD; Kimberly Anglin, BS; Troyllyn Maupin, RN (Tulane University and Charity Hospital).

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**REFERENCES**

7. 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
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