Neurologic, Neurocognitive, and Brain Growth Outcomes in Human Immunodeficiency Virus-Infected Children Receiving Different Nucleoside Antiretroviral Regimens

Claire Raskino, MSc*; Deborah A. Pearson, PhD‡; Carol J. Baker, MD§; Marta H. Lifschitz, MD¶; Karen O’Donnell, PhD¶; Mark Mintz, MD#; Molly Nozyce, PhDb**; Pim Brouwers, PhD§; Ross E. McKinney, MD¶; Eleanor Jimenez, MD‡‡; and Janet A. Englund, MD§§ for the Pediatric AIDS Clinical Trials Group 152 Study Team

ABSTRACT. Objectives. To compare the impact of three different nucleoside reverse transcriptase inhibitor regimens, zidovudine (ZDV) monotherapy, didanosine (ddI) monotherapy, and ZDV plus ddI combination therapy, on central nervous system (CNS) outcomes in symptomatic human immunodeficiency virus (HIV)-infected children.

Methods. Serial neurologic examinations, neurocognitive tests, and brain growth assessments (head circumference measurements and head computed tomography or magnetic resonance imaging studies) were performed in 831 infants and children who participated in a randomized double-blind clinical trial of nucleoside reverse transcriptase inhibitors. The Pediatric AIDS Clinical Trials Group study 152 conducted between 1991 and 1995 enrolled antiretroviral-therapy-naïve children. Subjects were stratified by age (3 to <30 months of age or 30 months to 18 years of age) and randomized in equal proportions to the three treatment groups.

Results. Combination ZDV and ddI therapy was superior to either ZDV or ddI monotherapy for most of the CNS outcomes evaluated. Treatment differences were observed within both age strata. ZDV monotherapy showed a modest statistically significant improvement in cognitive performance compared with ddI monotherapy during the initial 24 weeks, but for subsequent protection against CNS deterioration no clear difference was observed between the two monotherapy arms.

Conclusions. Combination therapy with ZDV and ddI was more effective than either of the two monotherapies against CNS manifestations of human immunodeficiency virus disease. The results of this study did not indicate a long-term beneficial effect for ZDV monotherapy compared with ddI monotherapy. Pediatrics 1999;104(3). URL: http://www.pediatrics.org/cgi/content/full/104/3/e32; zidovudine, didanosine, central nervous system, human immunodeficiency virus, children, head circumference, computed tomography, magnetic resonance imaging, cognitive, motor function.

SERIOUS NEUROLOGIC AND DEVELOPMENTAL ABNORMALITIES ARE IMPORTANT AND FREQUENT COMPLICATIONS OF HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION IN CHILDREN, PARTICULARLY IN YOUNGER PERINATALLY INFECTED CHILDREN. A WIDE RANGE OF CENTRAL NERVOUS SYSTEM MANIFESTATIONS OF HIV DISEASE HAVE BEEN REPORTED. THESE INCLUDE COGNITIVE AND MOTOR DEFICITS, IMPAIRED BRAIN GROWTH, AND LOSS OF DEVELOPMENTAL MILESTONES. IN A RECENT REPORT OF A LARGE NATURAL HISTORY STUDY, HIV ENCEPHALOPATHY, THE MOST SEVERE FORM OF HIV-ASSOCIATED CNS COMPROMISE, WAS DIAGNOSED IN 21% OF INFANTS WITH PERINATALLY ACQUIRED HIV-1 INFECTION.

HIV-1 is known to enter and replicate within the CNS shortly after initial systemic infection and has been found in the CNS of aborted fetuses of HIV-positive mothers as early as 15 weeks of gestation. HIV infection of the CNS seems to be the predominant cause of CNS abnormalities, and the neuropathologic damage seems to be associated with the release of various toxic factors by macrophages and microglia or certain viral proteins rather than through direct infection of neurons by HIV-1.

Therapy with nucleoside reverse transcriptase inhibitors such as zidovudine (ZDV) has been demonstrated to improve CNS function in HIV-infected adults and children. It has been hypothesized that the effectiveness of various antiretroviral drugs...
against HIV-associated CNS manifestations is related in part to their ability to inhibit HIV-1 replication in relevant cells. There are differences in the relevant cells between the CNS, in which the major targets for HIV-1 infection are macrophages and microglia, and the rest of the body.\textsuperscript{20} Thus, penetration of antiviral agents into the CNS is believed to be important.\textsuperscript{21}

Pharmacologic studies have shown that ZDV penetrates the CNS relatively well,\textsuperscript{22} whereas didanosine (ddI) has limited penetration.\textsuperscript{23} Moreover, these agents may be effective in different cell populations.\textsuperscript{24–26} Strategies that are effective against systemic manifestations based on certain clinical, virologic, or immunologic markers may not provide the optimal therapy for CNS manifestations of HIV-1.\textsuperscript{26,27}

Although a number of studies have shown that ZDV is particularly effective against HIV-related CNS disease, the therapeutic effects of ddI may be of a lesser magnitude.\textsuperscript{23,28} However, no randomized studies of CNS effectiveness have been reported in which these two antiretroviral agents are compared directly.

In a randomized clinical trial of nucleoside reverse transcriptase inhibitors conducted in 831 symptomatic HIV-infected infants and children (Pediatric AIDS Clinical Trials Group 152 [PACTG]) treatment with ddI alone or ZDV plus ddI as initial therapy was associated with increased overall clinical benefit compared with ZDV alone.\textsuperscript{29} Clinical benefit was defined by the relative incidence among treatment arms of subjects meeting any protocol-defined disease progression endpoint: CNS deterioration, weight-growth failure, two or more serious opportunistic infections, malignancy, or death.\textsuperscript{29} Thus, although the overall clinical effects in the PACTG 152 trial have been reported, a specific analysis of the CNS-associated variables is warranted. The purpose of this analysis is to assess the impact of different antiretroviral therapies on CNS function. This analysis uses all measurements of neurocognitive performance, motor function, and brain growth over time, regardless of whether or when a patient met a clinical endpoint (CNS deterioration or other) during study follow-up. We compare both the early interventional effects (ie, improvement) of the three treatment regimens and the longer-term prophylactic effects (ie, protection against the development or additional progression of HIV-associated CNS disease). Despite the widespread use of potentially more efficacious antiretroviral therapies (such as combinations using protease inhibitors), a close examination of the PACTG 152 treatments against the CNS effects of HIV is important for the following reasons: 1) for a variety of reasons, some children cannot be treated with newer combinations; 2) potential differences in CNS and systemic effects may exist; and 3) some of the newer regimens include ZDV or ddI in combination with new antiretroviral agents.

\section*{METHODS}

\subsection*{PACTG 152 Study Design}

PACTG 152 was a randomized double-blind clinical trial that enrolled symptomatic, HIV-infected infants and children between 3 months and 18 years of age who had received no or \textlesseq; 6 weeks previous antiretroviral therapy. Entry criteria have been described previously.\textsuperscript{29,30} Study patients were stratified by age (3 to \textlesseq; 30 months of age or 30 months to 18 years of age) and randomized in equal proportions to one of three treatment regimens: ZDV (180 mg/m\textsuperscript{2} every 6 hours) plus ddI placebo; ddI (120 mg/m\textsuperscript{2} every 12 hours) plus ZDV placebo; or a combination of ZDV (120 mg/m\textsuperscript{2} every 6 hours) plus ddI (90 mg/m\textsuperscript{2} every 12 hours). Patients were enrolled from August 19, 1991 through August 31, 1993. The study duration was 2 years for the last enrolled patient.\textsuperscript{29}

The primary study endpoint was time to first clinical HIV disease progression or death, occurring on or off study therapy, and was analyzed according to the initial randomized therapy. Disease progression was defined as weight–growth failure, two or more serious opportunistic infections, malignancy, or CNS deterioration. The CNS endpoint was acquired two or more of the following: neurologic deterioration, a decline in neurocognitive test scores, or impaired brain growth.\textsuperscript{29}

The ZDV monotherapy arm was unblinded early after an interim analysis of data collected through November 16, 1994 that revealed significantly poorer clinical performance in this group for the primary endpoint.\textsuperscript{19} This interim dataset forms the basis of treatment comparisons involving the ZDV arm. The other two treatment arms continued in a blinded manner through August 31, 1995.\textsuperscript{29} This final dataset is analyzed for comparisons between the ddI monotherapy and the ZDV plus ddI combination therapy groups.

\subsection*{Neurocognitive Testing}

Neurocognitive tests were performed within 14 days before enrollment and on an age-appropriate schedule thereafter. For children 3 to 30.5 months of age, the Bayley Scales of Infant Development\textsuperscript{1} were administered every 12 weeks for the first year of follow-up and every 24 weeks thereafter. The McCarthy Scales of Children’s Abilities\textsuperscript{2} for children 31 months to 6 years of age were administered every 24 weeks, and the Wechsler Intelligence Scale for Children-Revised\textsuperscript{3} (WISC-R) for children 6 years to 15 years 11 months of age, or the Wechsler Adult Intelligence Scale-Revised\textsuperscript{4} (WAIS-R), for individuals \textgtr;= 16 years of age were administered every 48 weeks. Cognitive tests were conducted at additional time points if deterioration was suspected. Children were given a new age-appropriate test when they aged into the new categories during follow-up. However, children who were too impaired to reach the minimum scaled score on their age-appropriate test were evaluated with a test suitable for a younger child. Older children whose primary language was Spanish received Spanish versions of the McCarthy, WISC-R, or WAIS-R tests administered by a bilingual examiner or with a translator. The age-scaled cognitive function scores reported were for the Bayley test, the Mental Developmental Index (MDI; range: 50–150); for the McCarthy, the General Cognitive Index (range: 50–150; SD: 16); for the WISC-R, the Full Scale Intelligence Quotient score (FSIQ; range: 40–160; SD: 15); and for the WAIS-R, also the FSIQ (range: 45–150; SD: 15). The mean standard score for each test is 100.

For this report, changes in age-scaled neurocognitive scores from baseline were analyzed. Only valid assessments (determined by a trained examiner or neuropsychologist) were included in the analyses. IQ ratios were used instead of MDI scores for the Bayley test because of the relatively high proportion of children with floor scores, ie, their raw scores could not be scaled to the MDI. In such cases, either a child <30.5 months of age obtained a very low raw score so that the minimum MDI-scaled score of 50 could not be achieved, or a child performed the Bayley test after 30.5 months of age. IQ ratios were defined as age-equivalent score on the test \texttimes; 100/chronologic age, in which the age-equivalent score is the normed population’s mental age for which the child’s raw score corresponds to a value of 100 on the MDI scale.

\subsection*{Motor Function Evaluations}

Neurologic examinations were conducted within 14 days before enrollment and then every 4 weeks for children <30 months of age and every 12 weeks for older children. Motor function abnormalities in muscle bulk, tone, or movement were evaluated separately in the left and right upper and lower extremities. For this report, we compared the proportions of children with motor function abnormalities over time among the three treatment groups.
Brain Growth Assessments

Neuroimaging of the head, using computed tomography (CT) or magnetic resonance imaging (MRI) without contrast, was obtained within 30 days of enrollment and every 96 weeks thereafter or as clinically indicated. The presence and severity of cerebral/cortical atrophy were evaluated locally by the radiologist at each participating clinical site. For children <24 months of age, occipital-frontal head circumferences were measured at entry and every 4 weeks thereafter. Age- and gender-specific head circumference z-scores were calculated using the Fels Research Institute reference values. For this report, we analyzed changes from baseline in cortical atrophy status and head circumference z-scores.

Children who discontinued protocol treatment were continued to be followed and had their study visits scheduled every 12 weeks (instead of 4 weeks) for the remainder of the study. CNS assessments were obtained less frequently during off-treatment weeks (instead of 4 weeks) for the remainder of the study. Children with cerebral atrophy were followed and had their study visits scheduled every 12 weeks thereafter.

RESULTS

Study Population

A total of 831 eligible infants and children participated in the ACTG 152 clinical trial. Baseline characteristics of these subjects have been described previously.29,30 Briefly, the mean and median ages at birth were 3.8 and 2.2 years, respectively; 54% were <30 months of age. Of the children, 50% were male; 54% were black; 30% were Hispanic; and the primary language spoken in the home was English for 82% and Spanish for 16% of patients. Of the children, 90% were known or suspected to have acquired HIV perinatally, and only 8% had received previous antiretroviral therapy (primarily ZDV) for ≤6 weeks.

Neurocognitive Scores

Of the 831 subjects included in the trial, 722 (87%) had a valid baseline cognitive test result (including 74 cognitive tests conducted ≤30 days after starting protocol treatment). Of the subjects, 54 (6%) had missing baseline data; 55 (7%) had invalid results primarily attributable to circumstances such as uncooperative behavior by the child during testing, acute illness that interfered significantly with testing (especially in the infants), and problems associated with testing being unavoidably administered after medical procedures. Overall, 58% of the 722 subjects with valid tests received the Bayley test; 20% the McCarthy; and 22% the WISC-R or WAIS-R as their first test. Test type and primary language were balanced among treatment groups at entry. Among the 422 baseline Bayley tests, 12 subjects were ≥30.5 months of age and contributed to a total of 56 subjects (13%) who had floor scores on the MDI standard scale (ie, below the minimum scaled score of 50). For this reason, Bayley IQ ratios were used in the analyses as described in “Methods”. Only 7 (5%) of the 145 McCarthy scores and 0 of the 155 WISC-R or WAIS-R scores were unscalable at baseline.

No significant differences were seen among treatment groups at baseline for the distribution of scores within each test or when the Bayley IQ ratios were pooled with the McCarthy-, WISC-R-, and WAIS-R-scaled scores. The mean score was significantly higher among subjects old enough for the WISC-R or WAIS-R test (FSIQ mean: 91; SD ± 16) compared with the McCarthy (General Cognitive Index mean: 81; SD ± 16) and Bayley (IQ ratios mean: 80; SD ± 21) test results (P < .001). Among children who were assessed with the McCarthy and WISC-R/WAIS-R tests, English speakers achieved higher scores on average than did those whose primary language was not English (P < .001). The mean ± SD scores among children whose primary language was English were 83 ± 15 for McCarthy tests (n = 118) and were 92 ± 16 for WISC-R/WAIS-R tests (n = 133) compared with 70 ± 14 (n = 27) and 85 ± 14 (n = 22) among children whose primary language was not English.

Figure 1A shows mean changes in cognitive scores for all children from baseline over time. Comparisons of ZDV versus ddI monotherapy and ZDV versus ZDV plus ddI combination therapy groups were limited to data available through week 96 in the November 16, 1994 database, because the ZDV arm was unblinded early. More extensive data that were available in the August 31, 1995 database, because the ZDV arm was unblinded early. More extensive data that were available in the August 31, 1995 database were used from week 72 through week 144 for the ddI monotherapy versus the combination therapy group comparison. The numbers of patients with valid test results were balanced across treatments within the interim and final databases, and there was no indication that patients transitioned to new tests at different rates among the three treatment groups.

Mean changes in cognitive scores were compared among treatment groups by pooling observations during the initial 24 weeks (to compare early improvements) and after week 24 using repeated measures analysis methodology with adjustments for primary language, baseline score, and test transitions. The three treatment groups also were compared...
Fig 1. Mean changes from baseline for Bayley, McCarthy, WISC-R, or WAIS-R cognitive scores: A indicates all children; B, children <30 months of age; C, children ≥30 months of age. The bars represent ± standard error (SE) and the numbers under each figure represent the number of children with data at each time point. The number of children used for comparing the ddl and ZDV plus ddl groups after week 60 were taken from the extended final analysis database after cessation of the ZDV arm. However, the comparison of the ddl-containing arms with the ZDV arm used smaller numbers of children in the ddl-containing arms present in the interim database before cessation of the ZDV arm.
pared at the week 96 time point. During the initial 24 weeks, the ZDV monotherapy (P = .032) and the ZDV plus ddi combination therapy (P = .035) groups showed statistically significant improvement in cognitive function compared with the ddi monotherapy group (Fig 1A). After week 24, the mean changes from baseline were not significantly different between the two monotherapy groups or between the ZDV plus ddi and the ddi groups, but the mean change in the combination arm became significantly higher than in the ZDV monotherapy arm at week 96 (P = .002; Fig 1A). Treatment differences for neurocognitive scores were driven primarily by results from children who were within the <30 months of age stratum (Fig 1B). These children began on the Bayley test and some transitioned to the McCarthy test during follow-up. During the initial 24 weeks, the ZDV-containing arms both showed a modest but statistically significant linear improvement from baseline (P < .001), each reaching a mean increase of five points by week 24 (Fig 1B), and the ddi monotherapy arm did not show a significant change from baseline during this initial period. After week 24, cognitive scores declined in the ZDV-containing arms (more steeply in the ZDV monotherapy arm than in the combination arm), and no significant differences were seen in mean changes from baseline between the two monotherapy arms or between the ddi monotherapy and the combination arms. By week 96, the adjusted mean change from baseline in the ZDV plus ddi combination arm was 11 points higher than in the ZDV monotherapy arm (P = .004) among younger subjects who had a cognitive test result at that time. Figure 1C shows the mean changes from baseline for all types of cognitive test within the ≥30 months of age stratum. No significant differences were seen among the three treatment arms within this older group of children.

A similar analysis was conducted for the initial 24 weeks of follow-up for children of any age who entered the study with a cognitive scaled score <70, −2 SD below the normal population mean, to evaluate early interventive effects (ie, improvements) among the three treatment regimens in those patients with baseline indications of severe cognitive impairment. At entry, 23% of all children had a cognitive score <70 (28% of children in the <30 months of age group and 16% of children in the ≥30 months of age group). During the initial 24 weeks, these cognitive scores increased by a mean of 11 to 13 points from baseline in the three treatment groups with no significant difference observed among treatments. Among children who entered the study with a cognitive score of ≥70 mean changes from baseline seemed to be slightly better in the ZDV-containing arms compared with the ddi arm during the initial 24 weeks. The P values for ZDV and ZDV plus ddi combination versus ddi monotherapy were .071 and .045, respectively.

Motor Function

Motor function assessments at baseline were available for 817 children (98%). Motor function abnormalities at study entry included abnormalities in muscle strength (7%), tone (21%), or bulk (4%). If any of these three categories were abnormal in a patient, then the abnormality often was present in both upper and lower and left and right extremities (59% of subjects with abnormal muscle strength, 71% of subjects with abnormal tone, and 84% of subjects with abnormal bulk). Overall, 22% of subjects had at least one motor function abnormality at baseline. The proportion of subjects with motor dysfunction at baseline decreased with increasing age (P < .001): 44% in infants <12 months of age, 22% in children 12 to <30 months of age, and 8% in children 30 months to 18 years of age. By chance, the percent abnormal at randomization was significantly lower in the ddi monotherapy group compared with the other two treatment groups (P = .015). This was caused primarily by a lower proportion of subjects with abnormal muscle tone falling in the ddi group: 15% in the ddi monotherapy group compared with 25% in the ZDV monotherapy group and 22% in the ZDV plus ddi group (P = .009). We adjusted for these baseline treatment group differences and for age when conducting treatment comparisons of motor dysfunction over time.

Figure 2 shows the proportions of subjects with any motor function abnormality (in muscle strength, tone, or bulk) by treatment group over time in children of all ages. During the initial 24 weeks, a statistically significant decline in the proportion with abnormal motor function from baseline was seen in the ZDV plus ddi arm (P < .001) but not in the ZDV or ddi monotherapy arms (Fig 2). The P values for this initial trend in the ZDV plus ddi combination arm versus the ZDV and the ddi monotherapy arms were .022 and .014, respectively. After week 24, pooling all data from week 36 onward in repeated measures analyses, the ZDV plus ddi combination group experienced significantly less motor dysfunction compared with the ZDV monotherapy group (P < .001) and compared with the ddi monotherapy group (P < .001). For the comparison of the two monotherapy arms after week 24, the proportions of subjects with motor dysfunction were similar for these two treatment groups at all time points (Fig 2). However, after adjusting for the lower percentage with abnormal motor function in the ddi arm at entry the ZDV arm performed significantly better than did the ddi arm after week 24 (P = .012); indicating that the ZDV monotherapy arm experienced a greater reduction from baseline in the proportion with abnormal motor function compared with the ddi monotherapy arm. At week 96, the proportion with any motor dysfunction among children with follow-up data at that time was 6% in the ZDV plus ddi group (reduced from 16% at entry), 12% in the ZDV group (reduced from 21% at entry), and 16% in the ddi group (compared with 16% at entry). The baseline-adjusted P values for the ZDV plus ddi combination group versus the ZDV group and versus the ddi group at week 96 were .025 and .002, respectively; and for the ZDV group versus the ddi group, the P value was .092.

Treatment differences in motor dysfunction during follow-up were caused primarily by abnormali-
ties in muscle tone and muscle strength. After week 24, the combination arm performed significantly better than did the ZDV and ddI monotherapy arms for muscle strength ($P < .005$ and $P < .001$, respectively) and for muscle tone ($P < .001$ vs each monotherapy). The ZDV plus ddI combination arm was also significantly better than was the ddI arm for muscle bulk after week 24 ($P = .046$). In the comparison of the two monotherapy groups after week 24, the ZDV monotherapy arm showed significantly better performance for muscle tone compared with the ddI arm ($P = .038$); but no significant differences were seen for muscle strength or bulk.

Treatment differences for motor dysfunction were similar in the two age strata (data not shown). After week 24, the ZDV plus ddI combination therapy arm performed significantly better than did each monotherapy arm within the <30 months of age stratum ($P < .001$) and significantly better than did the ddI monotherapy arm within the ≥30 months of age stratum ($P = .015$). The $P$ value for the ZDV plus ddI arm versus the ZDV arm in the ≥30 months of age stratum was .081. The ZDV monotherapy arm seemed to perform better than ddI monotherapy in both age groups (after adjusting for baseline motor function), and the difference approached statistical significance within the younger age group ($P = .058$ in the <30 months of age group and $P = .172$ in the ≥30 months of age group).

**Neuroimaging of the Head**

Varying degrees of cerebral cortical atrophy were seen at study entry. A baseline CT or MRI brain scan was obtained for 797 (96%) of the children. Of these subjects, 3% had moderate or marked atrophy, 10% had mild atrophy, whereas the majority (87%) had no atrophy identified at study entry. The proportion of subjects with any cortical atrophy at baseline was higher in children <30 months of age (16%) compared with older children (8%) ($P < .001$).

In the interim analysis database (study visits up to November 16, 1994) used for treatment comparisons involving the ZDV monotherapy arm, a total of 261 subjects among the three treatment groups had brain-imaging results at both study entry and week 96. In the final database (all visits through study closure on August 31, 1995) used for the ddI group versus the ZDV plus ddI group comparison, a total of 283 subjects in these two treatment groups had baseline and week 96 data. No significant differences were seen for baseline cortical atrophy status among treatment arms within the subgroups of patients who had baseline and follow-up data. Figure 3 shows the percentages of patients with progressive cerebral/cortical atrophy at week 96 by treatment arm and age group. Progression was defined as mild or moderate/marked atrophy at week 96 that had progressed from no atrophy at baseline, or moderate/marked atrophy progressed from mild atrophy. These data are shown for the interim analysis database only, but...
additional data from the final database were used for the statistical comparison of the ddI monotherapy versus the ZDV plus ddI combination treatment groups. No significant differences were seen between the ZDV and the ddI treatment groups or between the ZDV plus ddI combination and the ddI treatment groups for treatment comparisons made using all subjects or within age strata (Fig 3). For the comparison of the ZDV group versus the ZDV plus ddI group, the development or increased severity of cortical atrophy by week 96 was significantly worse in the ZDV arm ($P = .010$). By age strata, the ZDV monotherapy versus combination therapy comparison reached statistical significance within the $\geq 30$ months age group ($P = .039$) but not within the $< 30$ months age group ($P = .134$).

The presence and severity of cortical atrophy at baseline were associated with shorter survival times ($P < .001$). Furthermore, of 3 patients who had week 96 neuroimaging studies and died shortly afterward within the week 96 time window (84 to 108 weeks from randomization), all 3 patients had moderate/marked cortical atrophy at week 96 that had progressed from no atrophy or mild atrophy at baseline. Thus, subjects who died before obtaining a week 96 neuroimaging study were more likely to have had severe cortical atrophy. Therefore, we also compared the proportions showing progressive cerebral cortical atrophy or death among the treatment arms. Again, no significant differences were seen for the ddI group compared with the ZDV group or compared with the ZDV plus ddI group, and the combination therapy arm showed a significantly beneficial effect over the ZDV arm ($P = .028$ overall; $P = .042$ within the older age stratum).

**Head Circumferences**

Head circumference measurements were converted to age- and gender-standardized $z$ scores for analysis. No significant differences at study entry were seen among the three treatment arms. Because of the smaller numbers of observations for head circumference compared with other CNS assessments (head circumferences were evaluated only up to 24 months of age during study follow-up); these data were analyzed through week 60 only (Fig 4). The week 60 visit was the minimum follow-up period reached by November 16, 1994; and, therefore, the interim database was appropriate for all treatment comparisons of head circumference growth.

During the initial 24 weeks, the ZDV plus ddI combination therapy group showed a significant linear improvement in mean head circumference $z$ score from baseline (Fig 4; $P < .001$). In the ZDV monotherapy arm, the trend for mean change in $z$ score during this period was nonlinear ($P = .045$) showing an initial increase followed by a plateau and a decline. The ddI monotherapy group did not show a significant improvement from baseline during the initial 24 weeks. Direct treatment comparisons of head circumference growth revealed a statistically significant benefit of combination therapy compared with ddI monotherapy during the initial 24 weeks ($P = .014$), but no significant difference for either of these two treatments compared with the ZDV monotherapy. After week 24, pooling all data through week 60 in one repeated measures analysis model, mean changes in head circumference $z$ score from baseline no longer differed significantly between the ZDV plus ddI and the ddI arms. The combination therapy group seemed to be slightly better than was the ZDV monotherapy group after week 24, but the difference was not statistically significant ($P = .81$).

**DISCUSSION**

This study compared the effects of three different antiretroviral treatment regimens, ZDV monotherapy, ddI monotherapy, and ZDV plus ddI combination therapy, on CNS manifestations of HIV disease in a large cohort of HIV-infected infants and
children. The CNS seems to constitute a relatively independent compartment with respect to both HIV disease manifestations and treatment. Although the focus of the PACTG 152 clinical trial treatment comparison was on overall safety and efficacy, in this study we analyzed specific measures related to the CNS including neurocognitive test scores, motor function, head circumferences, and neuroimaging studies. Both short- and long-term effects were compared among treatment groups. It is likely that subjects who had CNS measurements at later time points in the study were healthier with less HIV-related CNS deterioration than were subjects without data. However, for treatment group comparisons lost-to-follow-up rates were similar among treatment groups within the interim and final databases.

Before the PACTG 152 trial, it was postulated that ZDV would be more effective against HIV-related CNS disease than would ddI, because ZDV, unlike ddI, penetrates the blood–brain barrier well. In this analysis, relatively small linear (or quadratic) improvements from baseline were seen in the ZDV monotherapy arm during the initial 24 weeks for cognitive function, head circumference growth, and motor function (which was not statistically significant). In the ddI monotherapy arm, no change from baseline was seen during the initial 24 weeks of treatment for any of the CNS measurements analyzed, except for a significant improvement in mean cognitive score among the subgroup of children who entered the trial with a baseline cognitive scaled score <70. However, the results of this study did not indicate an overall protective effect of ZDV monotherapy against HIV-related CNS deterioration after week 24. We postulate that a reduction in the systemic effects of HIV in subjects receiving ddI may help to reduce the spread of HIV or associated factors to the CNS.

When ZDV monotherapy (180 mg/m² every 6 hours) was compared with ZDV plus ddI combination therapy (120 mg/m² ZDV every 6 hours plus 90 mg/m² ddI every 12 hours), the combination treatment was superior to that of ZDV monotherapy for the prevention of HIV-associated CNS deterioration. During the initial 24 weeks, treatment with either ZDV plus ddI combination therapy or ZDV monotherapy resulted in statistically significant mean improvements from baseline for cognitive scores and head circumference growth. The combination therapy arm also showed a significant reduction from baseline in the proportion of children with motor dysfunction during the initial 24 weeks. After the initial treatment period the effectiveness of ZDV monotherapy seemed to decline relative to the effectiveness of combination therapy. After week 24, mean cognitive scores declined more steeply in the ZDV arm than in the ZDV plus ddI arm becoming significantly lower in the ZDV group by week 96. A similar trend in favor of combination therapy was seen for head circumference growth after week 24, and neuroimaging studies at week 96 showed significantly less progressive cortical atrophy from baseline in the ZDV plus ddI combination therapy arm compared with the ZDV monotherapy arm. Motor dysfunction remained significantly worse in the ZDV arm compared with the ZDV plus ddI arm during follow-up through 96 weeks. In previous studies in adults and children, the effectiveness of ZDV monotherapy against CNS manifestations of HIV disease has been documented for relatively short periods of time, and some adult studies have suggested a reversal in effectiveness after relatively short intervals. In this study, early improvement was seen with ZDV alone or in combination with ddI, but better long-term protection was seen with the combination therapy. This could be attributable in part to a differential development of resistance on the regimens for ZDV. Another important finding in this study was that CNS improvement was observed with a combination regimen that used less than the usual approved monotherapy dose of ZDV in children. No significant improvement in neurocognitive function was seen over a period of 6 months in a pediatric study in which patients received 60 to 180 mg/m² of ZDV along with 60 to 180 mg/m² of ddI. However, most of the patients in that study were functioning in the normal range at entry, and this may have restricted the ability to detect effects of antiretroviral treatment on CNS function.

When ZDV plus ddI combination therapy was compared with ddI monotherapy, statistically significant benefits from the combination therapy were noted during the initial 24 weeks for neurocognitive test performance, head circumference growth, and motor function. After week 24, cognitive performance and head circumference growth were not significantly different between the two treatment arms, but motor dysfunction remained significantly less prevalent in the ZDV plus ddI combination arm compared with the ddI arm despite having started out with a significantly higher prevalence in the ZDV plus ddI arm at study entry. Progressive cortical atrophy from baseline measured at week 96 seemed to be slightly worse in the ddI arm; but the two treatment arms were not significantly different from one another. Thus, in general, combination therapy seemed to be slightly more effective than was ddI monotherapy against CNS manifestations of HIV disease.

Some of the treatment differences seen for CNS manifestations of HIV disease in this study were in contrast with the trial’s overall clinical efficacy results. In PACTG 152, the ddI monotherapy arm showed an overall efficacy similar to that of the ZDV plus ddI combination therapy arm and superior to the ZDV monotherapy arm, as measured by time to first clinical progression endpoint or death. The differential effects of the three antiretroviral regimens on CNS manifestations compared with systemic manifestations of HIV infection highlight the principle that special attention should be paid to the effects of antiretroviral regimens on CNS disease.

This study included symptomatic HIV-infected infants and children ranging from 3 months to 18 years of age at entry. The majority acquired their HIV infection perinatally. As shown in this and previous PACTG 152 reports, CNS disease manifestations (and other HIV-related abnormalities) were more
common in younger children at study entry. This is likely to have resulted, in part, from a survivor effect in older children. Treatment differences for neurocognitive outcomes were seen primarily among younger children, but for motor function and for cortical atrophy outcomes, treatment differences were demonstrated among older children as well. This important finding indicates that CNS manifestations of HIV disease should be evaluated carefully in children of all ages.

In this study, the effects of antiretroviral treatments on the CNS were evaluated using several types of assessment. Although the conclusions drawn regarding relative treatment effects were primarily similar using different CNS outcome measures, some of the assessments seemed to be more discriminating than were others. For example, the treatment differences for neurocognitive scores in younger children were modest compared with treatment differences for motor function outcomes; and in older children who performed McCarthy, WISC-R, or WAIS-R neurocognitive tests, no significant treatment differences were observed. Head circumference, which is used as an inexpensive and noninvasive measurement of brain growth in infants ≤24 months of age, gave similar trends for treatment differences to those using neuroimaging studies. However, as we reported previously, 30–50% of the infants with cortical atrophy at study entry had a head circumference measurement above the 5th percentile indicating a low sensitivity of the latter measure in these patients. Additional analyses to identify age-specific subsets of neurologic, brain growth, and neurocognitive assessments that might be most useful and cost-effective as predictors of clinical progression will be reported separately.

HIV-related encephalopathy has been found to be associated with high viral loads and early signs and symptoms in infants. In PACTG 152, plasma HIV-1 RNA level and CD4+ lymphocyte count were predictive of clinical progression including CNS deterioration endpoints among infants and children of all ages. Brouwers and colleagues 12,46 reported that the degree of HIV-related CNS compromise is associated with the stage of HIV-1 disease and that CT structural brain lesions are associated with cognitive and social–emotional dysfunction, indicating that HIV-related CNS disease is a continuous rather than a discrete process. The diagnosis of HIV encephalopathy can precede or follow other AIDS-defining conditions in children with perinatally-acquired disease. Cooper and colleagues 8 reported recently that HIV encephalopathy was associated with shortened survival in their study of HIV-infected children. In support of their finding, we noted a significant association between cortical atrophy and shorter survival times in this study.

The impact of encephalopathic conditions on survival and quality of life and the association between HIV encephalopathy and high viral loads suggest that the evaluation of antiretroviral therapies with respect to CNS outcomes is an important issue. In this study, we observed significant differences among three nucleoside reverse transcriptase inhibitor regimens for neurologic, neurocognitive, and brain growth outcomes. In general, ZDV monotherapy was marginally superior to ddI monotherapy initially but showed similar performance to ddI monotherapy after 24 weeks; and combination ZDV plus ddI therapy was superior to both of the two monotherapies overall against CNS manifestations of HIV disease. Newer treatments including protease inhibitors in combination with other antiretroviral agents are demonstrating improved clinical efficacy or viral load reduction in adults and in children. 49,50 It will be important to evaluate the impact of these new therapies on CNS development in HIV-infected children.

ACKNOWLEDGMENTS

This study was supported by the Pediatric AIDS Clinical Trials Group, the National Institute of Allergy and Infectious Diseases, the National Institute of Child Health and Human Development, Bristol-Myers Squibb, and Glaxo-Wellcome. Drs Enghold, Baker, Brouwers, and McKinney have served as ad hoc consultants or as speakers in programs sponsored by Glaxo-Wellcome or Bristol-Myers Squibb, the pharmaceutical firms whose products were studied.

We thank the children and their families who participated in PACTG 152, the complete PACTG 152 study team, and all participating centers and investigators.

REFERENCES

Neurologic, Neurocognitive, and Brain Growth Outcomes in Human Immunodeficiency Virus-Infected Children Receiving Different Nucleoside Antiretroviral Regimens
Claire Raskino, Deborah A. Pearson, Carol J. Baker, Marta H. Lifschitz, Karen O'Donnell, Mark Mintz, Molly Nozyce, Pim Brouwers, Ross E. McKinney, Eleanor Jimenez, Janet A. Englund and for the Pediatric AIDS Clinical Trials Group 152 Study Team

Pediatrics 1999;104;e32

Updated Information & Services
including high resolution figures, can be found at:
http://pediatrics.aappublications.org/content/104/3/e32

References
This article cites 40 articles, 7 of which you can access for free at:
http://pediatrics.aappublications.org/content/104/3/e32.full#ref-list-1

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Infectious Disease
http://classic.pediatrics.aappublications.org/cgi/collection/infectious_diseases_sub
HIV/AIDS
http://classic.pediatrics.aappublications.org/cgi/collection/hiv:aids_sub
Neurologic Disorders
http://classic.pediatrics.aappublications.org/cgi/collection/neurologic_disorders_sub

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
https://shop.aap.org/licensing-permissions/

Reprints
Information about ordering reprints can be found online:
http://classic.pediatrics.aappublications.org/content/reprints

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, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 1999 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005.
Neurologic, Neurocognitive, and Brain Growth Outcomes in Human Immunodeficiency Virus-Infected Children Receiving Different Nucleoside Antiretroviral Regimens

Claire Raskino, Deborah A. Pearson, Carol J. Baker, Marta H. Lifschitz, Karen O'Donnell, Mark Mintz, Molly Nozyce, Pim Brouwers, Ross E. McKinney, Eleanor Jimenez, Janet A. Englund and for the Pediatric AIDS Clinical Trials Group 152 Study Team

Pediatrics 1999;104:e32

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/104/3/e32