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Case Report

Stable neurological function in subjects treated with 2′3′-dideoxyinosine

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AIDS Dementia Complex (ADC) is a frequent and devastating complication of HIV infection. There is evidence that zidovudine (ZDV) has an effect in alleviating the symptoms of ADC, and may have a role in its prevention. It is therefore important that new antiretroviral therapies be evaluated not only for the risk of neurologic side effects, but also for their relative efficacy to ZDV in the prevention of ADC. The present study reports the effects of 2′3′-dideoxyinosine (DDI, didanosine, Videx) therapy on neuropsychological performance in the context of several large clinical trials targeting advanced systemic HIV-1 infection. Subjects treated with DDI had stable neurologic performance in quantitative tests over a 1 year period and were similar to zidovudine treated subjects.

Keywords: DDI; didanosine; zidovudine; acquired immunodeficiency syndrome; AIDS dementia; HIV

Introduction

In addition to compromised immune function, 15–20% of individuals infected with the human immunodeficiency virus type 1 (HIV-1) are also affected by a progressive neurological disease commonly referred to as the AIDS Dementia Complex (ADC) (Price *et al*, 1988). ADC has been classified as a subcortical dementia because it typically consists of generalized cognitive slowing, diminished motor control, and behavioral changes. The neuropathogenesis of ADC is not fully understood, but it likely involves a temporally evolving, dynamic, interaction among three components: the virus, the central nervous system, and the immune system (Spencer and Price, 1992). Unlike the opportunistic infections and neoplasms that accompany HIV-1 infection, ADC is viewed as a more direct consequence of HIV-1 infection of the nervous system. Successful anti-retroviral therapy, therefore, has the potential for preventing, arresting, or even improving the changes seen in ADC.

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A number of observations have suggested that zidovudine (ZDV, 3′-azido-3′-deoxythymidine, ZDV) has some beneficial effect in the treatment of established ADC. Three of four subjects in a phase-1 study of ZDV experienced improved neurological function (Yarchoan *et al*, 1987). Children with AIDS and progressive encephalopathy that parallels ADC in adults improved with ZDV treatment (Pizzo *et al*, 1988). In the initial controlled trial of ZDV in subjects with AIDS and AIDS related complex (ARC), selected to exclude overt ADC, the treatment group improved on neuropsychological tests while the placebo group deteriorated (Schmitt *et al*, 1988). The efficacy of two doses of ZDV (2000 mg *versus* 1000 mg daily) in the treatment of ADC were studied in the only randomized, double-blinded, placebo-controlled trial (Sidtis *et al*, 1993). After 16 weeks, neuropsychological test performance improved significantly in the treatment group compared to the placebo group. While these studies indicate that ZDV may partially reverse some of the cognitive deficits in established ADC, a second important issue is the potential neuroprotective role of antiretroviral therapy. Several reports contain evidence suggestive of a protective value for early ZDV therapy (Hamilton *et al*, 1992; Nordic Medical

Research Councils HIV Therapy Group, 1992). In a retrospective study, Portegies *et al*, 1989, 1993) demonstrated that the incidence of ADC decreased in the Netherlands in 1987 coincident with the introduction of ZDV.

Didanosine (2′3′-dideoxyinosine, DDI, Videx), like ZDV, is a nucleoside analog that inhibits HIV-1 reverse transcriptase. Didanosine appears to delay the progression of HIV-1 disease in subjects previously treated with ZDV (Kahn *et al*, 1992; Spruance *et al*, 1994). The side effects of DDI are predominantly pancreatitis and peripheral neuropathy (Yarchoan and Broder, 1989) in contrast to the hematological side effects of ZDV, suggesting complementary therapeutic anti-retroviral roles for the two drugs.

Because of lower reported CSF penetration of DDI, there was a concern that DDI would not be as effective as ZDV in neuroprotection, reinforced by early experience in use of DDI (Portegies *et al*, 1994). This study was designed to evaluate the neurologic implications of DDI treatment for HIV-1 infection and compare its efficacy to that of ZDV. Neurological evaluations constituted a 'piggy-back' study (Price and Sidtis, 1990) attached to three parent AIDS Clinical Trial Group (ACTG) protocols.

Results

Since the comparisons of interest in this study were between ZDV and DDI, subjects were grouped according to their treatment rather than according to their parent protocol.

Baseline characteristics

Table 1 presents the characteristics of the study subjects; 107 subjects were recruited to this study. The subjects were predominantly male (93%) and caucasian (82%). Twenty-nine subjects were in the ZDV group, 36 in the DDI/500 group, and 42 in the DDI/750 group. When the ZDV group was compared to a combined DDI group, ages were not significantly different. However, when the three groups were compared, they were statistically different both by age (Kruskal-Wallis P=0.02) and by education (Kruskal-Wallis P=0.002). The subjects in the DDI/750 group were younger and the subjects in the DDI/500 group had more education. A comparison of the Karnofsky performance status scores revealed that ZDV group was functioning at a higher level than either of the DDI groups (Kruskal-Wallis P=0.02). CD4 cell counts also differed significantly across groups (Kruskal-Wallis P=0.007), with the highest counts in the ZDV group. Distribution of stages of HIV infection (asymptomatic, AIDS related complex, or AIDS) differed in a manner consistent with the CD4 cell counts (Kruskal-Wallis P=0.01). Baseline performance by the NPZ score also differed across groups, with the highest performance demonstrated by the ZDV group (Kruskal-Wallis P=0.03). Prior experience with ZDV was varied: 20 subjects were ZDV intolerant, 27 had no prior ZDV exposure, 36 had >16 weeks of prior treatment, with the remaining subjects having <16 weeks experience. The subjects generally had intact neurological function, with only one subject rated as ADC Stage 1 at baseline (DDI/750 group).

Table 1 Subject characteristics of the three treatment groups

Characteristic	*Treatment group* ZDV	DDI/500	DDI/750
Age (years)			
N	29	35	42
Median	37.0	36.0	31.0
Mean	36.0	37.3	32.4
Standard Deviation	8.9	10.0	6.2
Education (years)			
N	28	35	39
Median	13.0	16.0	13.0
Mean	13.9	15.5	13.4
Standard Deviation	2.3	2.5	2.5
Karnofsky performance score (numbers of subjects)			
N	29	36	42
60	0	1	0
70	1	1	2
80	0	7	12
90	27	24	25
100	1	3	3
CD4 cell count			
N	29	36	42
Median	155.0	45.5	78.5
Mean	154.7	99.7	92.8
Standard Deviation	83.7	95.9	78.4
Diagnostic category (numbers of subjects)			
N	29	36	42
AIDS	3	13	16
ARC	22	23	23
Asymptomatic	4	0	3
NPZ score			
N	29	32	40
Median	0.10	−0.26	−0.28
Mean	0.09	−0.28	−0.35
Standard Deviation	0.79	0.59	0.71

Performance at 3 months

At the 3 month evaluation, 71 subjects underwent neuropsychological assessment (20 receiving ZDV, 21 receiving DDI/500 and 30 receiving DDI/750). With respect to changes in NPZ scores compared to baseline, 70% of the subjects in the ZDV group showed either no change or an improvement, 53% of the DDI/500 group, and 77% of the DDI/750 group fell into this category. Small declines (less than 0.25 in the NPZ score) were observed in 20% of the ZDV group, 29% of the DDI/500 group, and 17% of the DDI/750 group. These differences were not significant by the Fisher's Exact test. When the groups were subdivided into subjects with $\leqslant 100$ CD4 cells (ZDV n=6; DDI/500 n=13; DDI/750 n=17) and those with >100 CD4 cells (ZDV n=14; DDI/500 n=8; DDI/750 n=13), there was a greater number of large NPZ declines ($\geqslant 0.50$) in the DDI/500 group

with ⩽100 CD4 cells. The difference between the three treatment groups with respect to changes in NPZ scores was statistically significant for the subgroup of subjects with ⩽100 CD4 cells (Fisher's Exact P=0.009).

Table 2 Median change from baseline in NPZ scores for three treatment groups

	Treatment group *Change* (n)		
Evaluation	*ZDV*	*DDI/500*	*DDI/750*
3 months			
⩽100 CD4[a]	0.05 (6)	−0.07 (13)	0.33 (17)
>100 CD4	0.29 (14)	0.21 (8)	0.18 (13)
Combined	0.15 (20)	0.01 (21)	0.19 (30)
6 months			
⩽100 CD4	0.30 (5)	−0.12 (12)	−0.08 (14)
>100 CD4	0.42 (11)	0.17 (9)	0.18 (11)
Combined[b]	0.37 (16)	0.08 (21)	0.05 (25)
12 months			
⩽100 CD4	0.26 (3)	−0.38 (1)	−0.06 (9)
>100 CD4	0.40 (7)	0.57 (6)	−0.12 (8)
Combined[c]	0.38 (10)	0.53 (7)	−0.08 (17)

[a] Kruskall Wallis P=0.02.
[b] Kruskall Wallis P=0.04.
[c] Kruskall Wallis P=0.02.

When NPZ change scores were examined as a continuous variable a similar pattern was observed. Median NPZ score changes from baseline are presented in Table 2. There were no significant differences across groups when all subjects were considered. In the ⩽100 CD4 cell group, the DDI/500 group performed most poorly, showing a slight decline in NPZ score. In this CD4 subgroup, the difference between the three treatment groups was statistically significant (Kruskal-Wallis P=0.02). No other comparisons had significant differences.

Performance at 6 months

At the 6 month evaluation, 62 subjects underwent neuropsychological assessment. Sixteen of the subjects were receiving ZDV, and 46 DDI (21 on DDI/500 and 25 on DDI/750). Whereas 88% of the subjects in the ZDV group showed either no change or an improvement in NPZ score, 57% of the DDI/500 group and 52% of the DDI/750 group fell into this category. Small declines (less than 0.25 in the NPZ score) were observed in 6% of the ZDV group, 14% of the DDI/500 group, and 28% of the DDI/750 group. These differences were not significant by the Fisher's Exact test. There were no differences when the groups were subdivided on the basis of CD4 cell count.

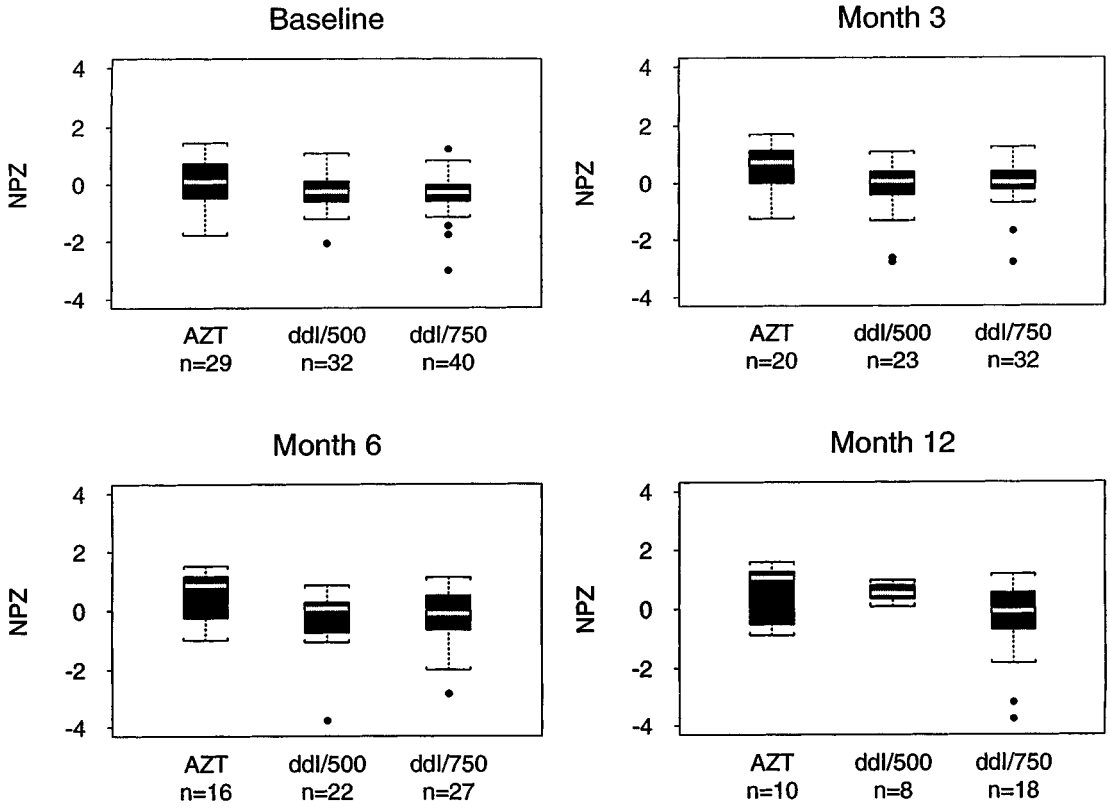

Figure 1 Standardized neuropsychological test (NPZ) scores in the three treatment groups at baseline and months 3, 6 and 12. The figure, a box plot, shows group medians as horizontal lines, boxes which represent the range in which 50% of the data points fall, the standard range, and outliers plotted as individual lines.

When NPZ change scores were examined as a continuous variable, NPZ performance was best for the ZDV group when all subjects were considered. The difference in NPZ change from baseline was significant when comparing the three treatment groups (Kruskal-Wallis P=0.04). As with the examination of the NPZ change by category at 6 months, there were no differences when the groups were subdivided on the basis of CD4 cell count.

Most of the subjects with missing NPZ assessment at the 6 month evaluation had low NPZ scores at the previous evaluation. When using the carry-forward approach and when we consider all subjects, the NPZ change remains significantly different between the groups (Kruskal-Wallis P=0.04). For the subgroup with $\leqslant$100 CD4 cells the value for the median NPZ change improves to -0.01 and 0.12 for the DDI/500 and DDI/750 respectively. No statistically significant differences were detected with the carry-forward approach, when the groups were subdivided on the basis of CD4 cell count.

Performance at 12 months

At the 12 month evaluation, 34 subjects underwent neuropsychological assessment (ten on ZDV, seven on DDI/500, 17 on DDI/750). At this evaluation, 90% of the ZDV group showed either no change or an improvement in NPZ score, 86% of the DDI/500 group and 30% of the DDI/750 group fell into this category. Small declines (<0.25 in the NPZ score) were observed in 40% of the DDI/750 group while larger declines (>0.25 in NPZ score) were observed in an additional 30% of this group. The NPZ change was significantly different between the groups (Fisher's Exact P=0.02). There were no differences when the groups were subdivided on the basis of CD4 cell count. This could be due to the small sample size (n=13) in the $<$100 CD4 group at this point.

When NPZ change scores were examined as a continuous variable, NPZ performance was again poorest for the DDI/750 group when all subjects were considered. (Kruskal-Wallis P=0.015). There were no differences when the groups were subdivided on the basis of CD4 cell count.

Neuropathy

The standardized neurological evaluation addressed several issues related to neuropathy. Data from 88 subjects was available at baseline (24 on ZDV, 31 on DDI/500, 33 on DDI/750). There were no significant differences in the severity of sensory loss or in the change in sensory function over time across the three groups at baseline, 3 months or 6 months. When investigators classified neuropathy as 'none' *versus* identifying a type of neuropathy present at the time of the exam such as 'sensory', 'motor', 'mixed sensorimotor' there was no difference at baseline or month 3. However, by month 6 presence of neuropathy of some sort was recognized in only 14% of ZDV subjects while 32% of DDI/500 and 53% of DDI/750 subjects had identifiable neuropathy (Fisher's Exact P=0.068). By month 12 this difference was significant with 25% of ZDV subjects having neuropathy while 17% (1/6) of DDI/500 subjects and 73% (8/11) of DDI/750 subjects had neuropathy (Fisher's Exact P=0.049).

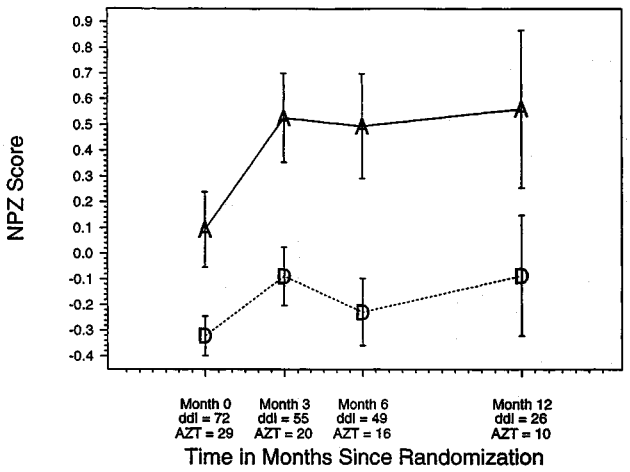

Figure 2 Plot of neuropsychological test (NPZ) mean scores for subjects treated with zidovudine and didanosine over the course of 12 months.

Discussion

Quantitative neuropsychometric performance measures applied cross-sectionally to HIV-infected subjects at different stages of disease have indicated a decline in performance in subjects with advanced immunodeficiency, as measured by declining CD4 counts. The NPZ has proved a sensitive measure revealing slight decreases in neurologic performance associated with advancing immunodeficiency. The NPZ correlates with advancing levels of clinically evident dementia, with NPZ declines of approximately one unit present at the onset of clinically evident AIDS dementia complex. The experience from the Multicenter AIDS Cohort Study (MACS) is that after reaching AIDS, dementia develops in 7% of the population for each year of continued survival (McArthur *et al*, 1993). There is evidence that ZDV may have efficacy in both preventing neuropathologic consequences (Gray *et al*, 1994) and reversing neurologic performance deficits associated with advanced HIV (Schmitt *et al*, 1988). Further, ZDV is known to penetrate the blood brain barrier, with a CSF to plasma ratio reported from 15 to 135% (Balis *et al*, 1989; Klecker *et al*, 1987).

As other antiretroviral agents become available, a critical issue confronted for each of them is the early evaluation of the drugs for neurotoxicity as well as for their efficacy in prevention and treatment of

neurologic complications. Frequently the central nervous system concentrations of systemically administered drugs will only be a fraction of that achieved in the serum. New agents which prove highly efficient in treating systemic disease might fail to effect neurologic disease because they do not cross the blood brain barrier (BBB), and therefore do not reach effective concentrations in the nervous system.

DDI was the second antiretroviral approved for treatment of HIV, and there is limited evidence of reasonable penetration of the CNS; one study of adult subjects indicated CSF levels of 21% of the simultaneous serum level, 1 h after a 90 min infusion of DDI (Hartman *et al*, 1990). However, its effect on the nervous system has not been adequately evaluated. Butler *et al* (1991) report improvements in IQ scores in children treated with DDI, while Portegies report excess dementia in DDI treated subjects (Portegies *et al*, 1994). We present a report of quantitative neurologic performance measures from a group of AIDS subjects treated with DDI. The testing tools chosen have previously proved to be well tolerated, inexpensive, brief, sensitive to change in AIDS dementia and resistant to practice effect.

This study provides quantitative evidence that serially tested AIDS subjects (mean CD4 $<$ 100 for the DDI population) treated with DDI over a 12 month interval respond in a comparable fashion to a ZDV treated population with respect to neurologic function. In both the ZDV and DDI groups the neurologic performance remained rather stable over the duration of the trial (Figure 2). Subjects in all three groups exhibited improved performance on a battery of psychomotor tests after three months of treatment. Some of this improvement could be a practice effect. However, continued improvement was not seen and the tests selected were chosen because they tend to have minimal practice effect changes. We believe it is more likely that much of this improvement represents a response to initiation of therapy.

A limiting factor of the study is the clear difference in stage of HIV between the treatment groups. It could be predicted that subjects with more advanced disease stage might be more difficult to treat. The DDI groups had poorer baseline neurologic performance, lower CD4 counts and more advanced disease stage than the ZDV group. This could be predicted as subjects in the ZDV group were more often naive to therapy or had experienced limited duration therapy, while the DDI treated group included ZDV intolerant subjects and those in whom ZDV had failed. Stratification of the population by CD4 cell count as well as by the initial neurologic performance did not reveal any consistent differences over time in the performance of the two drugs, again supporting the relative similarity of DDI when compared to ZDV in this setting.

In current neurologic practice, high doses of ZDV are recommended for subjects who have developed AIDS dementia. This is based on the concern that reduction in systemic concentrations of drug will result in ineffective CNS levels. In an AIDS Clinical Trials Group study of the effects of ZDV on dementia, 2000 mg per day was relatively more effective than 1000 mg per day in the treatment of ADC (Sidtis *et al*, 1993). It is therefore of note that in the current study there was slight decline in the performance of advanced subjects in the DDI/500 group after 3 months of therapy, while the higher dose DDI and the ZDV treated groups showed improvement. As this dose effect was not consistently demonstrated throughout the study, and since the combined high dose DDI group showed less improvement at 6 and 12 months than the other groups, high dose therapy cannot be recommended based on these observations.

This study was not designed to answer the question of whether either ZDV or DDI protects individuals from development of the full AIDS dementia complex. A much larger population and greater follow-up period would be required. However, it is of interest that Kahn reported that only three of 913 subjects on ACTG Protocol 116B/117 (from which many of the current subjects were drawn) developed dementia. This study compared maintenance of ZDV therapy with changing to DDI, with an average duration on trial of 55 weeks. One of the demented subjects was in the ZDV group, two in the DDI/500 group and none in DDI/750 group. If this incidence of ADC is accurate, it represents a figure considerably below the anticipated 7% per year in such a population and suggests efficacy of both ZDV and DDI in prevention of AIDS dementia. Caution must be used however since this study did not include active neurologic surveillance.

Peripheral neuropathy is a complication that has been associated with the nucleoside antiretrovirals with the exception of ZDV. Reports linking neuropathy with DDI (Connolly *et al*, 1991; Kieburtz *et al*, 1992; Rathbun and Martin, 1992; Moyle *et al*, 1993) suggest that this drug is associated with neurotoxicity which may be dose limiting. While the high dose DDI in ACTG Protocol 118 (personal communication, J Davis Allan, MD) and in the European/Australian Alpha study (Darbyshire and Aboulker, 1992) was associated with development of neuropathy, it was surprising that the report of Kahn *et al* (1992) showed no significant difference in development of neuropathy in the treatment groups including DDI, all having 13–14% incidence per year. Because the diagnosis of neuropathic syndromes may not be well reflected when reporting is achieved without the evaluaton of neurologists, it was important to re-examine this issue in the present study. All subjects were evaluated serially in a blinded

fashion by neurologists expert in the diagnosis and management of HIV associated neurologic problems. The experience from this subset confirms that in this population, there was no significant increase in symptomatic peripheral neuropathy when judged by complaints of subjects in distal extremities. It is probable that the absence of clinical neuropathic symptoms resulted from very conservative management of the therapy dictated by the protocol. If minimal neuropathic symptoms were experienced, the DDI was stopped until improvement occurred, then restarted with dose reduction. However, when a neurological exam including testing of reflexes and gradients of sensory loss by vibration and sharp sensation are included, in the group followed up to 12 months it appears that detectable peripheral neuropathy on examination is significantly more frequent in the high dose DDI group, consistent with clearcut dose dependent neurotoxicity of DDI.

In summary, DDI has proved an important additional drug in the armamentarium for treating HIV. The parent studies established that the DDI is an effective therapy, providing a better outlook particularly for those subjects who had already accumulated an experience with ZDV (Kahn *et al*, 1992; Dolin *et al*, 1995). Recent reports of ACTG 175 (personal communication) and the Delta study (Choo, 1995) suggest that combination therapy including DDI or DDI alone in ZDV experienced subjects improves survival and may become widespread therapy for HIV. The nested studies described here showed DDI to have response characteristic comparable with ZDV in preservation of quantitative neurologic performance measures. While the evidence presented here is less convincing than the evidence demonstrating efficacy for zidovudine in HIV neurologic disease, we believe this evaluation suggests that DDI may be used as an alternate therapy for HIV associated neurologic disease in subjects who have developed their disease on ZDV, or in whom ZDV is not tolerated. Continued comparison of new antiretroviral agents as they are introduced may suggest other drugs which will be more specifically effective in the central nervous system.

Materials and methods

Parent protocols

Subjects were recruited from three parent AIDS Clinical Trial Group (ACTG) Protocols: ACTG 116, ACTG 117, and ACTG 118. ACTG Protocol 116 compared two doses of DDI (500 mg and 750 mg) with ZDV 600 mg in subjects with limited prior ZDV therapy. ACTG Protocol 117 compared these two doses of DDI with ZDV 600 mg in subjects with long-term prior ZDV therapy. ACTG Protocol 118 evaluated 200, 500, and 750 mg per day doses of DDI in ZDV intolerant subjects. Subjects from the latter two dose levels were included in this evaluation. In all cases, DDI doses were reduced for subjects weighing less than 60 kg, and were reduced during the study for signs of peripheral nerve toxicity.

Patient selection

The only inclusion criterion added to those of the parent protocol was that subjects could be evaluated for ADC. This excluded subjects with neurologic, psychiatric, or medical conditions that would confound the interpretation of the neuropsychological test results with respect to ADC. Subjects with potentially confounding developmental disorders, substance abuse, or current psychotropic medication use were excluded.

The study subjects were recruited from five AIDS Clinical Trial Units sponsored by the National Institute of Allergy and Infectious Disease. The study was approved by institutional review boards at each unit. Informed consent was obtained from each patient, and when indicated by any question of impaired judgment, by next of kin or legal guardian.

Evaluations

Standardized clinical and quantitative neurological examinations (Sidtis *et al*, 1993; Price and Sidtis, 1990) were administered at baseline and repeated at 3 month intervals. The standardized clinical neurological evaluation, including both history and physical, was used to establish a diagnosis and ADC Stage (Price *et al*, 1988) when appropriate, and to exclude the presence of confounding neurologic problems.

A quantitative neurological examination (neuropsychological testing) similar to that used in a placebo-controlled study of ZDV treatment for ADC provided the primary measures of treatment efficacy in this study (Sidtis *et al*, 1993; Sidtis, 1994). The examination consisted of the following timed tests: timed gait (a test of walking speed which required subjects to walk 10 yards, turn, and return to the start point); Trail Making A and B (tests of sequential problem solving); Digit Symbol (a test of symbolic transcription speed); grooved pegboard for the dominant and non-dominant hands (tests of rapid fine motor control) and finger tapping for the dominant and non-dominant hands (tests of digit speed in a repetitive task). The raw-score for an individual's performance on a particular test was converted to a z-score by subtracting the reference group mean, and dividing the resulting difference by the reference group's standard deviation. The reference population consisted of 90 HIV-1 seropositive individuals who were classified as ADC Stage 0. Separate reference means and standard deviations were determined for subjects under 30 years of age, subjects from 30 to 40 years of age, and subjects above 40 years of age. For an individual patient, the same reference values were used throughout the

study. A summary measure, the Neuropsychological z-score (NPZ), was derived by taking an average of the individual z-scores.

Statistical analysis
The NPZ was used as the primary scale for assessing outcome in this study. Changes from the baseline NPZ score at 3 months, 6 months, and 12 months were compared for the ZDV arm and each of the DDI arms (500 mg and 750 mg). Additional analyses combined the two different doses of DDI to one arm to compare with ZDV arm. NPZ changes were analyzed both as a continuous and a discrete variable. The NPZ was categorized by creating six discrete variables at increments of 0.25 points (ranging from $\leqslant -0.5$ to >0.5). Subgroup analyses were also performed based on the CD4 counts at baseline (CD4 >100 and CD4 $\leqslant 100$). Another analysis focused on subjects with low baseline NPZ (less than or equal to -0.25).

We stratified by CD4 count to address the confounding of treatment with baseline CD4 count. Kruskal-Wallis tests were used for the three arm comparisons and Wilcoxon Rank Sum tests for the two arm comparisons. All reported *P* values are for two-sided tests and are based on stratified tests.

The data were analyzed in parallel with other methods to check for consistency of results. We used the nonparametric method for incomplete two sample longitudinal data introduced by Wei and Johnson (1985) for the two arm comparison of NPZ and NPZ change from baseline. Random effects models including different combinations of baseline variables were applied to the data. In the analysis with random effects models we included as covariates age, education level, T4 count stratum, diagnosis, Karnofsky Score, month of follow-up visit, baseline NPZ score and the interaction of treatment by month. The baseline NPZ score was found to be highly significant while all other covariates were not significant. Thus, we proceeded in looking at NPZ changes from baseline. Finally, we modeled the data using linear regression models for each subject and compared the fitted intercepts (baseline) and slopes (change rate) among the treatment arms. These analyses were repeated using the carry-forward approach to substitute for missing NPZ values. All these analytic approaches produce consistent results and yield the same conclusions. Analyses were performed with a SAS statistical package (SAS Institute, Inc. SAS/STAT User's Guide, Release 6.03 edition, Cary, NC:SAS Institute, 1988).

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