Predicting HIV Disease Progression in Children Using Measures of Neuropsychological and Neurological Functioning

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ABSTRACT. Background. Neuropsychological testing and 2 measures of neurological status, cortical atrophy, and motor dysfunction were assessed for their usefulness in predicting human immunodeficiency virus (HIV) disease progression in infants, children, and adolescents who participated in Pediatric AIDS Clinical Trials Group Protocol 152 (PACTG 152).

Methods. A cohort of 722 antiretroviral therapy-naïve children with symptomatic HIV infection were assessed at study entry and at later intervals. Assessments included neurodevelopmental testing, neuroradiologic imaging, and neurological examination of motor function. CD4 cell count and plasma RNA viral load also were measured.

Results. Children with the lowest neuropsychological functioning (IQ < 70) at baseline had the highest risk for later HIV disease progression (56%), compared with those with borderline/low (IQ = 70–89) functioning (26%), or with average or above (IQ > 90) functioning (18%). This was also true of week 48 neuropsychological functioning. Motor dysfunction (especially reduced muscle mass) at entry also predicted disease progression. Furthermore, motor dysfunction and week 48 neuropsychological functioning provided predictive information beyond that obtainable from surrogate markers of HIV disease status (eg, CD4 count, HIV RNA level). Children with cortical atrophy also were at higher risk for later disease progression, but when CD4 count and RNA viral load were known, cortical atrophy information provided no additional predictive information.

Conclusions. Measures of neuropsychological and motor function status provide unique information regarding pediatric HIV disease progression. As such, these findings have important implications for predicting long-term outcomes (eg, longevity) in pediatric patients. Pediatrics 2000;106(6). URL: http://www.pediatrics.org/cgi/content/full/106/6/e76; human immunodeficiency virus, children, neuropsychology, cognitive, development, cortical atrophy, motor function.

ABSTRACTIONS. HIV, human immunodeficiency virus; PACTG 152, Pediatric AIDS Clinical Trial Group Trial 152; WISC-R, Wechsler Intelligence Scale for Children-Revised; WAIS-R, Wechsler Adult Intelligence Scale-Revised; MDI, Mental Developmental Index; SD, standard deviation; GCI, general cognitive index; IQR, intelligence quotient ratio; CT, computed tomography; MRI, magnetic resonance imaging.

Developmental decline is closely associated with central nervous system deterioration caused by human immunodeficiency virus (HIV) type 1 infection in infants, children, and adolescents. Neuropsychological performance in these pediatric patients has been directly linked to degree of encephalopathy. Poor neurocognitive functioning has been related to surrogate markers of HIV disease, such as low CD4+ lymphocyte count percentages. In turn, markers such as a low CD4+ count and a high HIV RNA level are associated with diffuse cortical atrophy, disease progression, and a higher risk of death. Thus, neuropsychological and neurological variables are closely linked with measures of HIV disease progression in infants, children, and adolescents.

Although multiple factors, such as prematurity, age at which HIV infection occurs, prenatal exposure to toxic substances, poor nutrition, socioeconomic status, and treatment compliance also affect development in children with HIV infection, certain patterns of development have been specifically linked to pediatric HIV infection. One prominent pattern seen in decline in both fine and gross motor skills. This pattern of deterioration can be either a failure to acquire new motor skills or a loss of previously acquired milestones. In the infant, motor dysfunction may be expressed as hypotonia, whereas in the older child it might be expressed as a change in gait or refusal to walk.

Cognitive delay or deterioration is another central characteristic of HIV infection in children. However, Cohen et al did not find significant differences between HIV-infected and noninfected children in global intellectual ability, even 3 years after onset, and others have noted that neuropsychological profiles in HIV-infected and

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Received for publication Feb 14, 2000; accepted Jun 20, 2000.

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PEDIATRICS (ISSN 0031-4005). Copyright © 2000 by the American Academy of Pediatrics.
noninfected hemophiliacs did not differ. Thus, infants and children infected with HIV infection have, sometimes, but not always, been found to have deficits in global intellectual functioning.

In addition to these global estimates of functioning, more specific areas may be associated with clinical deterioration. These areas include speed of information processing, attention, and verbal (and, in some cases, nonverbal) memory skills. Deficits have been found on tasks assessing visual scanning, academic achievement, cognitive flexibility, and psychomotor speed in children. Psychomotor slowing also has been reported in adults with HIV infection and has been predictive of dementia, acquired immunodeficiency syndrome, and death. Language deficits have also been commonly reported in children with HIV infection. Language ability is strongly related to academic performance, and these children show declines in academic achievement, especially in mathematics. Findings such as these underscore the importance of examining performance in specific domains (eg, language, psychomotor speed) in addition to administering global measures of neuropsychological functioning (eg, Full-Scale IQ). In fact, global measures of cognitive ability may actually mask subtle patterns of deterioration in specific brain function.

These findings document the relationship between HIV disease progression (eg, encephalopathy or death) and neuropsychological and neurological functioning. Despite the growing literature describing these relationships, as well as immunologic (CD4 counts and vireologic status (HIV RNA load), it remains difficult to predict clinical outcomes in pediatric patients with HIV infection. Because these patients are living longer, it is highly desirable to identify clinical measures that could aid in these predictions. The purpose of this investigation was to evaluate the utility of neuropsychological and neurological variables as predictors of clinical disease progression in infants, children, and adolescents with HIV infection.

We questioned: 1) whether composite neuropsychological scores (at baseline and at week 48) predicted clinical progression, and 2) whether measures of neurological status (cortical atrophy, motor function) predicted clinical disease progression. We hypothesized that poorer neuropsychological functioning at baseline and at week 48 would be associated with a greater risk for HIV-associated disease progression and that cortical atrophy and motor dysfunction also would be predictors. Finally, we examined whether any of these variables would yield independent information regarding clinical outcome, once standard surrogate markers (CD4 counts and plasma HIV RNA load) were taken into account.

METHODS

PACtG 152 Trial Design

PACTG 152 was a randomized, double-blind trial in which the effectiveness of 3 antiretroviral treatment regimens (didanosine monotherapy plus didanosine placebo, didanosine monotherapy plus zidovudine placebo, or combination zidovudine and didanosine) was compared in children 3 months to 18 years old. Participants in this trial were stratified by age (3–30 months and 30 months to 18 years) and randomized to 1 of the 3 treatment regimens. Primary clinical endpoints were time to first HIV disease progression and endpoints were: 1) weight growth failure, 2) decline in 2 or more neurologic parameters (neuropsychological function, age-appropriate neurodevelopmental performance, brain growth), 3) 2 or more serious opportunistic infections, 4) malignancy, or 5) death. Because interim analyses revealed that zidovudine monotherapy was inferior to the other 2 treatments, the zidovudine arm was prematurely unblinded and stopped in the spring of 1995. The other 2 treatment arms continued through the end of the planned data collection phase (August 31, 1995, or 2 years after enrollment of the last patient).

We evaluated the predictive value of neuropsychological and neurological variables for HIV disease progression for children across all 3 treatment arms of the study. The distribution by treatment arm (ie, the effect of each parameter was first estimated within the 3 treatment groups, and then a pooled estimate was calculated based on the 3 specific estimates). Treatment modality was not a factor of interest in this study, ie, neuropsychological and neurological data were analyzed for their predictive value for clinical endpoint across all treatment arms.

Participants

The study participants have been described previously. Briefly, 831 children were enrolled; 92% had never received antiretroviral treatment before entry, and 90% had acquired HIV perinatally. The ethnic origins of the participants were white, non-Hispanic (13.8%), black, non-Hispanic (54%), Hispanic (30%), and other (2%). One half of these children (49.9%) were male. Of these 831 subjects, 722 (87%) had valid baseline cognitive tests scores; 54 (6%) had missing baseline data; and 55 (7%) had invalid test results (eg, because of uncooperative behavior during testing, severe illness that impacted testing, or testing being unavoidably administered after painful medical procedures). Of the 722 participants with valid test scores, 85% had English as their primary language, and 15% had Spanish as their primary language. The institutional boards of each site that participated in the clinical trial reviewed the protocol. Informed consent was obtained from the parent(s) or guardian(s) of all children participating in the study.

The population subsets used for the 3 major analyses (neuropsychological scores, cortical atrophy, motor dysfunction) did not consist of exactly the same children, because some data were missing or invalid. Despite these slight differences in participant numbers, the population characteristics of each group with valid data for the 3 areas of interest were similar to each other and to the overall PACTG 152 cohort.

Neuropsychological Testing

Neuropsychological testing was performed within 14 days before study enrollment and on a specified age-dependent schedule thereafter. For infants 3 to 30.5 months of age, the Bayley Scales of Infant Development were administered every 12 weeks for the first year of follow-up, and then every 24 weeks subsequently. For children 31 months to 6 years of age, the McCarthy Scales of Children’s Abilities were given every 24 weeks. For children 6 years to 13.5 years of age, the Wechsler Intelligence Scale for Children, Revised (WISC-R) was administered every 48 weeks; the same test schedule was used for adolescents >16 years of age, whose cognitive abilities were assessed using the Wechsler Adult Intelligence Scale-Revised (WAIS-R). The cognitive function scores associated with these indices are: for the Bayley, the Mental Developmental Index (MDI; mean = 100; standard deviation [SD] = 16); for the McCarthy, the General Cognitive Index (GCI; mean = 100; SD = 16), Verbal Scale Score (mean = 50; SD = 10), and Perceptual-Performance Score (mean = 50; SD = 10); for the WISC-R and WAIS-R, Full-Scale IQ, Verbal IQ, and Performance IQ (mean for each = 100; SD for each = 15). When a child aged into the age range associated with the next test in subsequent visits, a child enrolled at 24 months became 34 months of age, the next age-appropriate test was administered. However, if a child could not reach basal performance on the chronologically age-appropriate test, the lower level test that would be appropri-
ate to their mental status was administered (eg, a 4-year-old functioning on a 2-year-old level would be tested with a Bayley). It should be noted that 56 of the 422 children (13%) who had the Bayley as their entry test had raw scores that yielded a MDI below the minimum scaled score of 50. For this reason, Bayley IQ ratios (IQR) were used in the analyses. An IQR was calculated by dividing the age equivalent associated with the raw score obtained by the child, by the child’s chronological age, then multiplying the resulting fraction by 100. This procedure has been used in previous PACTG studies.46,51

Brain Growth (Neuroimaging) Assessments

Neuromaging of the head using computed tomography (CT) or magnetic resonance imaging (MRI) without contrast was performed within 30 days of enrollment and every 96 weeks thereafter. A final CT or MRI scan also was obtained before the end of the child’s participation in the study. A radiologist at each participating study site determined the presence and severity of cortical atrophy. Although it was not possible to have one standard imaging procedure for all 78 clinical sites participating in this 4-year study, baseline and follow-up scans were compared for consistency for each child. For the analyses reported in this investigation, we examined the cortical atrophy status at baseline and at week 96.

Motor Function Assessments

Neurological examinations were performed within 14 days before enrollment and every 4 weeks thereafter for children <30 months of age and every 12 weeks for older children. In the primary clinical trial analysis, the neurologic deterioration endpoint was defined as the loss of previously documented motor skills or worsening of reflexes or of behavior.44 Separate evaluations were recorded for left and right upper and lower extremities. However, for this analysis, motor function, which was defined as the presence or absence of abnormalities in muscle tone, muscle strength, and muscle bulk at baseline and week 48, was the sole focus.

Clinical Endpoints

As has been described previously,44 a clinical endpoint, indicating HIV disease progression, was met when significant declines in functioning were documented. Significant neurocognitive deterioration was defined as a decline of 2 SD on the Bayley MDI (because of the greater variability in test performance of infants) or a 1 SD drop on the McCarthy GCI or the WISC-R/WAIS-R Full Scale IQ, since the baseline testing or the most recent testing. Other clinical endpoints included 2 or more serious opportunistic infections, weight-growth failure, failure of brain growth or cortical atrophy, deterioration in motor function, malignancy, or death.

Statistical Methods

Overview

Cox proportional hazards regression models,52 with stratification by study treatment arm (to control for previously described differences in these treatments39,40), were used to assess the prognostic value of neuropsychological and neurological variables, CD4+ lymphocyte counts, plasma HIV-1 RNA levels, and age at time to first clinical endpoint. CD4+ counts and RNA levels were included in the models as continuous variables after log_{10} transformation. Age was analyzed as a continuous variable with a quadratic term to incorporate its nonlinear association with the relative risk (RR) of disease progression. RRs (ratio of progression rates) were estimated to express the effect of a 1-unit increase of a particular variable on progression rates. Clinical follow-up data through study closure (August 31, 1995) were used for the di-

Follow-Up Intervals Used for Analyses

In addition to baseline functioning, we wanted to explore the predictive role of neuropsychological testing after the participants had received a long period of study medication. Because the WISC-R and WAIS-R were only repeated every 48 weeks, week 48 data were used in another set of analyses that examined functional status after treatment for this interval. The follow-up interval for the analyses of cortical atrophy was 96 weeks. The follow-up interval for the analyses of motor dysfunction was 48 weeks.

Verbal and Nonverbal Domain Analyses

Because global measures of neuropsychological functioning may mask declines in specific areas of function, an analysis of the general verbal and nonverbal components of the IQ tests verbal components of the IQ tests was explored. The McCarthy Verbal Scale Index, the WISC-R Verbal IQ, and the WAIS-R Verbal IQ were pooled together as one score representing verbal neuropsychological function. Similarly, to assess nonverbal reasoning, the McCarthy Perceptual-Performance Index, the WISC-R Performance IQ, and the WAIS-R Performance IQ were pooled together. McCarthy scores were transformed so that their underlying distribution was the same as the WISC-R and WAIS-R composite score distributions, ie, mean 100, 15 SD, thus allowing the McCarthy scores to be pooled together with the WISC-R and WAIS-R scores. It was not possible to examine individual subtests because the subtest structure (and scaling) is not comparable across the McCarthy and the WISC-R/WAIS-R. Results were statistically nonsignificant in preliminary analyses examining the predictive ability of WISC-R and WAIS-R subtests on disease progression, which may or may not be caused by insufficient sample size, and, thus, are not reported here.

Subject Attrition

As has been previously reported,44, 9% of the overall PACTG 152 sample died during the course of the study. 9% were lost to follow-up, and 24% discontinued prematurely, resulting in an overall attrition rate of 42%. Another factor contributing to smaller sample sizes in follow-up analyses was the limited availability of variables used in the analyses (eg, RNA viral load, CD4 counts, valid neuropsychological score) for each subject. Sample sizes for all analyses are noted in tables accompanying the text.

RESULTS

Neuropsychological Scores as a Predictor of HIV Disease Progression

Baseline Global Neuropsychological Functioning

Of the 831 study participants, 722 had a valid neuropsychological score at baseline. Of these children, 422 (58%) were tested by the Bayley at baseline, 145 (20%) by the McCarthy, 141 (20%) by the WISC-R, and 14 (2%) by the WAIS-R. Twenty-four percent (173) of the 722 children in this analysis went on to meet an HIV disease progression endpoint. However, our analysis was limited to the 490 children who had complete data (ie, a neuropsychological score, CD4 count, and RNA value) at baseline. Twenty-two percent (109) of these 490 children met a primary endpoint during the study.

Table 1 shows the results of univariate and multivariate analyses of baseline predictors associated with time to progression among this population. Baseline neuropsychological score was a significant
predictor of disease progression ($P < .0001$). As can be seen in Table 1, there was a RR of .98 associated with a 1-point change in neuropsychological score, ie, there was a 2% reduction in the rate of subsequent disease progression associated with a 1-point increase in baseline neuropsychological score. Figure 1 illustrates the univariate relationship between baseline neuropsychological score and subsequent disease progression. As can be seen in this figure, lower scores (ie, poorer neuropsychological functioning at the initial visit) were associated with a higher risk of subsequent disease progression; children whose neurocognitive functioning was in the range of mental retardation (IQ $< 70$) were at particularly high risk for disease progression. By week 48, 56% of these children had reached clinical endpoint, compared with 26% of children who were functioning in the borderline/low average range (IQ $= 70–89$), and only 18% of children in the average/above average range (IQ $= 90+$).

CD4 lymphocyte count and viral RNA load also were significant predictors of disease progression, with lower CD4 counts and higher HIV RNA levels associated with a greater risk of disease progression. However, when all of these factors were entered into a multivariate Cox regression model, baseline neuropsychological functioning had no significant predictive value for disease progression ($P = .75$). To exclude the possibility that this result was an artifact of limited statistical power, these multivariate analyses were repeated using a larger sample of 713 children who were only missing a baseline HIV RNA level. Even in this larger sample, baseline score still did not have significant predictive value ($P = .0935$)

**Table 1.** Baseline Factors Associated With Meeting ACTG 152 Disease Progression Criteria Definition During the Study*

<table>
<thead>
<tr>
<th></th>
<th>Univariate RR</th>
<th>95% CI</th>
<th>P Value</th>
<th>Multivariate† RR</th>
<th>95% CI</th>
<th>P Value</th>
<th>Multivariate†‡ RR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline neuropsychological global score</td>
<td>.98</td>
<td>(.97,.99)</td>
<td>.0001</td>
<td>1.00</td>
<td>(.99,1.01)</td>
<td>.75</td>
<td>1.00</td>
<td>(.99,1.00)</td>
<td>.0935</td>
</tr>
<tr>
<td>Baseline CD4 (log10 count/mm³)</td>
<td>.31</td>
<td>(.24,.41)</td>
<td>.0001</td>
<td>.19</td>
<td>(.13,.28)</td>
<td>.0001</td>
<td>.27</td>
<td>(.22,.33)</td>
<td>.0001</td>
</tr>
<tr>
<td>Baseline RNA (log10 copies)</td>
<td>2.53</td>
<td>(2.03,3.17)</td>
<td>.0001</td>
<td>1.82</td>
<td>(1.35,2.47)</td>
<td>.0001</td>
<td>1.82</td>
<td>(1.35,2.47)</td>
<td>.0001</td>
</tr>
</tbody>
</table>

CI indicates confidence interval.

* $n = 490$.
† Adjusted for age as linear and squared terms.
‡ Without RNA in the model, $n = 713$.

Fig 1. Time to progression by neuropsychological score at baseline.
in a model with baseline CD4 count and age. These analyses confirm that baseline score is a significant univariate predictor of progression but does not provide significant additional information regarding the risk of subsequent disease progression, when age, CD4, and RNA viral levels are also known.

**Week 48 Analysis of Global Neuropsychological Scores**

Of the 490 children whose baseline data were analyzed, 226 also had valid neuropsychological scores, CD4 counts, and HIV RNA levels at week 48. Of these 226 children, 32 (14%) met a primary endpoint after study week 48.

**All Endpoint Types**

As shown in Table 2, week 48 neuropsychological score was a significant predictor of disease progression \((P = .0001)\), for each clinical endpoint: cognitive or neurological decline, weight-growth failure, 2 or more opportunistic infections, malignancy, and death. Unlike baseline neuropsychological scores, week 48 neuropsychological score remained a significant predictor \((P = .0006)\) in a multivariate model that included CD4 count, HIV RNA viral level, and age.

**Endpoint Types Other Than Cognitive Function**

To demonstrate that the predictive effect of week 48 neuropsychological scores on clinical endpoint was not simply a reflection of neuropsychological decline, the predictive value of week 48 neuropsychological scores on endpoints determined by factors other than neuropsychological function was explored. Those who had endpoints determined by their neuropsychological status were censored at the time of their endpoint for this analysis. Table 2 shows that week 48 neuropsychological score still had significant predictive value \((P = .0031)\) in a model with age, CD4 count, and RNA viral load. CD4 count \((P = .0001)\) and HIV RNA viral level \((P = .0018)\) were also significant predictors of non-neuropsychological defined progression beyond week 48. This analysis suggests that week 48 neuropsychological score predicts progression events other than, and as well as, declines in neurocognitive function.

**Baseline Verbal and Nonverbal Scale Analyses**

Because the Bayley does not separate verbal and nonverbal reasoning ability, only children older than 30 months at baseline (ie, who were assessed by a McCarthy, WISC-R or WAIS-R, which do separate these abilities) contributed data to these analyses. Of the 207 children who had CD4 counts, HIV RNA load, and performance scores measured at baseline, 25 (12%) met endpoint criteria during the study. Verbal scores consisted of the Verbal IQ on the WISC-R and WAIS-R, and Verbal Scale Score on the McCarthy. Nonverbal scores consisted of the Performance IQ on the WISC-R or WAIS-R, and Perceptual-Performance Scale score on the McCarthy. Neither baseline verbal scores \((P = .075)\) nor baseline nonverbal scores \((P = .077)\) were significant univariate predictors of disease progression.

**Week 48 Verbal and Nonverbal Scale Analyses**

Only 108 children had baseline and week 48 verbal or nonverbal composite scores, CD4 counts, and HIV RNA levels and had not yet progressed to endpoint by week 48. Of these 108 children, 14 (13%) later met a study endpoint. Week 48 verbal score \((P = .057)\) and week 48 nonverbal score \((P = .35)\) did not predict subsequent disease progression. When week 48 CD4 count, RNA viral load, and verbal and nonverbal scores were used to predict subsequent disease progression in multivariate models, CD4 count emerged as the only significant predictor (CD4 factor in the verbal model: \(P = .002\); CD4 factor in the nonverbal model: \(P = .0003\)).

**Cortical Atrophy as a Predictor of Progression**

Cox proportional hazards models were used to investigate the predictive value of cortical atrophy for disease progression. Cortical atrophy status was assigned by a radiologist as having no atrophy, mild atrophy, or moderate/marked atrophy. The effects of CD4 count, HIV RNA load, and age also were assessed. Of the 797 children with a CT or MRI scan at baseline, the 544 who also had CD4 and HIV RNA load measures at baseline were used in the analyses. Of these 544, 128 (24%) progressed to endpoint during the study.

**Baseline Cortical Atrophy**

As shown in Table 3, univariate analyses of cortical atrophy status as a dichotomous variable (ie, atrophy versus no atrophy) indicated that cortical atrophy at baseline was significantly associated with increased risk of disease progression \((P = .0001)\). However, it

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**TABLE 2. Factors Associated With Meeting ACTG 152 Disease Progression Criteria Beyond Study Week 48***

<table>
<thead>
<tr>
<th>Univariate</th>
<th>Multivariate†</th>
<th>Multivariate‡‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR 95% CI P Value</td>
<td>RR 95% CI P Value</td>
</tr>
<tr>
<td>Week 48 neuropsychological global score</td>
<td>.96 (.94,.97) .0001</td>
<td>.97 (.95,.99) .0016</td>
</tr>
<tr>
<td>Week 48 CD4 ((\log_{10} \text{count/mm}^3))</td>
<td>.19 (.11,.32) .0001</td>
<td>.16 (.08,.31) .0001</td>
</tr>
<tr>
<td>Week 48 RNA ((\log_{10} \text{copies}))</td>
<td>2.68 (1.75,4.11) .0001</td>
<td>2.65 (1.48,4.75) .0011</td>
</tr>
</tbody>
</table>

CI indicates confidence interval.

* \(n = 226\).
† Adjusted for age as linear and squared terms.
‡‡ For non-neuropsychologically defined progression.

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was no longer a significant predictor of disease progression when CD4 count, HIV RNA load, and age were known. A univariate analysis of cortical atrophy status as a categorical variable (ie, none, mild, moderate, marked) indicated that cortical atrophy was associated with an increased risk of disease progression ($P = .0001$), with moderate atrophy having an approximately 1.4 times greater risk than mild cortical atrophy. When CD4 count, age, and HIV RNA viral load were included in the model, cortical atrophy no longer provided any additional predictive information. Table 4 shows the proportion of children who progressed during the study by degree of cortical atrophy at baseline and at week 96. Status of cortical atrophy at week 96 was not a significant predictor of subsequent disease progression.

### Motor Function as a Predictor of Progression

Motor abnormality was assessed by creating an overall “motor abnormality” variable that included any abnormality in muscle strength, tone, or bulk in the right, left, or both extremities. The relationships of CD4 count, HIV RNA level, and age also were assessed for their contribution to disease progression. Of the 817 children who had motor function assessed at baseline, 555 children had a CD4 count, HIV RNA level, and motor function data at baseline and 132 (24%) later met a study endpoint.

#### Baseline Motor Function

As shown in Table 5, when abnormal motor function at baseline was used as a sole predictor of disease progression, it was highly significant ($P = .0001$). However, when age, CD4 count, and HIV RNA level were all known, motor dysfunction provided no significant additional predictive information. When the separate components of motor dysfunction were analyzed for their ability to predict disease progression, poorer muscle tone was significantly associated with increased risk for disease progression ($P = .0001$), as were less muscle bulk ($P = .0009$), and decreased muscle strength ($P = .0018$). Abnormalities in muscle bulk at baseline remained a significant predictor of progression ($P = .035$), even when CD4 count, HIV RNA level, and age were known, whereas muscle tone and strength did not.

#### Week 48 Motor Function

At week 48, there were 360 children in the study who had not yet progressed to endpoint, and who also had motor function data, CD4 count and HIV RNA level data. As shown in Table 6, when motor dysfunction at week 48 was used as a sole predictor of disease progression, it was significant ($P = .0001$). It remained a significant predictor of progression when CD4 count, HIV RNA level, and age were known ($P = .002$), indicating that children with any type of motor dysfunction at week 48 were significantly more likely to develop HIV-associated disease progression.

In addition to the global estimate of motor function at week 48, each of the three components of motor dysfunction were statistically significant predictors of disease progression, even when age, CD4 count and HIV RNA level are known (muscle tone: $P = .009$, muscle strength: $P = .004$; muscle bulk: $P = .003$).

### Table 3

<table>
<thead>
<tr>
<th>Presence of Cortical Atrophy</th>
<th>Univariate RR 95% CI P Value</th>
<th>Multivariate† RR 95% CI P Value</th>
<th>Multivariate‡ RR 95% CI P Value</th>
<th>Multivariate‡ RR 95% CI P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None at baseline</td>
<td>1.0</td>
<td>1.0</td>
<td>.001</td>
<td>.0001</td>
</tr>
<tr>
<td>Mild cortical atrophy</td>
<td>2.86 (1.86,4.39)</td>
<td>.0001</td>
<td>.09 (1.73)</td>
<td>.71</td>
</tr>
<tr>
<td>Moderate/marked cortical atrophy</td>
<td>3.97 (1.83,8.61)</td>
<td>.0005</td>
<td>1.32 (5.92,9.7)</td>
<td>.50</td>
</tr>
<tr>
<td>None at baseline</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline CD4 (log10 count/mm³)</td>
<td>.31 (2.40)</td>
<td>.0001</td>
<td>.21 (1.42)</td>
<td>.001</td>
</tr>
<tr>
<td>Baseline RNA (log10 copies)</td>
<td>2.54 (2.06,3.12)</td>
<td>.0001</td>
<td>1.92 (1.42,2.53)</td>
<td>.001</td>
</tr>
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</table>

CI indicates confidence interval.
† Adjusted for age as linear and squared terms.
‡ Without RNA in the model, $n = 786$. 

### Table 4

<table>
<thead>
<tr>
<th>Degree of Cortical Atrophy</th>
<th>Number of Children at Baseline</th>
<th>Number of Children at Baseline With Subsequent HIV Disease Progression</th>
<th>Percentage of Children at Baseline With Subsequent HIV Disease Progression</th>
<th>Number of Children at Week 96</th>
<th>Number of Children at Week 96 With Subsequent HIV Disease Progression</th>
<th>Percentage of Children at Week 96 With Disease Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>696</td>
<td>149</td>
<td>21</td>
<td>332</td>
<td>21</td>
<td>6</td>
</tr>
<tr>
<td>Mild</td>
<td>79</td>
<td>39</td>
<td>49</td>
<td>17</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>Moderate/marked</td>
<td>22</td>
<td>12</td>
<td>35</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 5. Baseline Motor Function Abnormality as a Predictor of Meeting ACTG 152 Disease Progression Criteria During the Study*

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th>Multivariate†</th>
<th>Multivariate‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR 95% CI</td>
<td>P Value</td>
<td>RR 95% CI</td>
</tr>
<tr>
<td>Any motor function abnormality at baseline</td>
<td>2.76 (1.94,3.93)</td>
<td>.0001</td>
<td>1.43 (0.96,2.13)</td>
</tr>
<tr>
<td>None at baseline</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Abnormal muscle bulk at baseline</td>
<td>2.99 (1.56,5.73)</td>
<td>.0009</td>
<td></td>
</tr>
<tr>
<td>Abnormal muscle strength at baseline</td>
<td>2.22 (1.35,3.66)</td>
<td>.0018</td>
<td></td>
</tr>
<tr>
<td>Abnormal muscle tone at baseline</td>
<td>2.70 (1.89,3.87)</td>
<td>.0001</td>
<td></td>
</tr>
<tr>
<td>Baseline CD4 (log10 count/mm³)</td>
<td>.32 (.25,41)</td>
<td>.0001</td>
<td>.19 (.14,27)</td>
</tr>
<tr>
<td>Baseline RNA (log10 copies)</td>
<td>2.46 (2.01,3.02)</td>
<td>.0001</td>
<td>1.82 (1.39,2.38)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval.
* n = 555.
† Adjusted for age as linear and squared terms.

Table 6. Motor Function Abnormality as a Predictor of Meeting ACTG 152 Disease Progression Criteria Beyond Week 48*

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th>Multivariate†</th>
<th>Multivariate‡</th>
<th>Multivariate§</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR 95% CI</td>
<td>P Value</td>
<td>RR 95% CI</td>
<td>P Value</td>
</tr>
<tr>
<td>Any motor function abnormality at week 48</td>
<td>3.78 (2.14,6.68)</td>
<td>.0001</td>
<td>2.74 (1.45,5.18)</td>
<td>.0002</td>
</tr>
<tr>
<td>None at wk 48</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Abnormal muscle bulk at wk 48</td>
<td>7.18 (2.54,20.36)</td>
<td>.0002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal muscle strength at wk 48</td>
<td>6.32 (3.13,12.74)</td>
<td>.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal muscle tone at wk 48</td>
<td>3.09 (1.70,5.60)</td>
<td>.0002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 wk 48 (log10 count/mm³)</td>
<td>.20 (.14,30)</td>
<td>.0001</td>
<td>.14 (.09,23)</td>
<td>.0001</td>
</tr>
<tr>
<td>RNA wk 48 (log10 copies)</td>
<td>2.31 (1.67,3.20)</td>
<td>.0001</td>
<td>1.54 (1.07,2.14)</td>
<td>.020</td>
</tr>
</tbody>
</table>

CI indicates confidence interval.
* n = 360.
† Adjusted for age as linear and squared terms.
‡ Censoring children who had a motor abnormality defined endpoint at the time of endpoint.
§ Adjusted for baseline abnormality, CD4 and RNA. n = 343.

Table 7. Children With HIV Disease Progression During the Study, According to Baseline and Week 48 Motor Dysfunction

<table>
<thead>
<tr>
<th>Motor Function</th>
<th>Number of Children at Baseline</th>
<th>Number of Children at Baseline With Subsequent HIV Disease Progression</th>
<th>Percentage of Children at Baseline With Subsequent HIV Disease Progression</th>
<th>Number of Children at Week 48</th>
<th>Number of Children at Week 48 With Subsequent HIV Disease Progression</th>
<th>Percentage of Children at Week 48 With Subsequent HIV Disease Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle tone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>648</td>
<td>130</td>
<td>20</td>
<td>543</td>
<td>74</td>
<td>14</td>
</tr>
<tr>
<td>Abnormal</td>
<td>169</td>
<td>75</td>
<td>44</td>
<td>88</td>
<td>27</td>
<td>31</td>
</tr>
<tr>
<td>Muscle strength</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>756</td>
<td>170</td>
<td>22</td>
<td>603</td>
<td>85</td>
<td>14</td>
</tr>
<tr>
<td>Abnormal</td>
<td>58</td>
<td>33</td>
<td>57</td>
<td>27</td>
<td>16</td>
<td>59</td>
</tr>
<tr>
<td>Muscle bulk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>783</td>
<td>184</td>
<td>24</td>
<td>618</td>
<td>94</td>
<td>15</td>
</tr>
<tr>
<td>Abnormal</td>
<td>31</td>
<td>19</td>
<td>61</td>
<td>12</td>
<td>7</td>
<td>58</td>
</tr>
<tr>
<td>All motor functions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>637</td>
<td>124</td>
<td>19</td>
<td>540</td>
<td>71</td>
<td>13</td>
</tr>
<tr>
<td>Abnormal</td>
<td>180</td>
<td>81</td>
<td>45</td>
<td>91</td>
<td>30</td>
<td>33</td>
</tr>
</tbody>
</table>

.03). Table 7 shows the proportion of all children (as opposed to the subset of 360 children who also had CD4 count and RNA viral load data at week 48, and hence were able to contribute to the week 48 multivariate analyses of motor function) who had HIV-associated disease progression during the study according to their motor function status at baseline and week 48. Of the 543 children who had normal motor
Endpoints Other Than Neurologic Endpoints

Finally, to exclude the possibility that the predictive value of motor function for a clinical endpoint was an artifact of motor dysfunction contributing to neurological endpoint criteria, we repeated these analyses to determine whether the motor function variables could predict endpoints other than the neurological endpoints. When the 6 children who met the definition of progression, in part by meeting a neurologic endpoint, were censored at the time of their endpoint, motor dysfunction at week 48 remained a significant predictor of disease progression in a univariate model ($P = .015$). It also remained a significant predictor of progression ($P = .017$) in a multivariate model with CD4 count, HIV RNA level, and age. These findings suggest that children with motor dysfunction at week 48 were significantly more likely to have HIV disease progression events other than neurologic endpoints.

DISCUSSION

We examined the utility of neuropsychological and neurological measures, including cortical atrophy and motor dysfunction, in predicting HIV-related disease progression in children. Our results suggest that these measures are powerful predictors of disease progression and that some provide information beyond traditional surrogate markers of disease progression, such as CD4 counts and HIV RNA levels.

The first hypothesis examined was that poorer performance on standard neuropsychological tests would be associated with a greater risk of HIV disease progression. Neuropsychological performance, both at baseline and after 48 weeks of antiretroviral therapy treatment, was strongly predictive of clinical endpoint. Specifically, children with lower global cognitive functioning were at significantly higher risk for progression. The relationship between week 48 neurocognitive functioning and endpoint was especially strong, such that neuropsychological test information provided predictive power for disease progression beyond that of CD4 count and HIV RNA levels.

Although previous researchers have suggested that estimates of global functioning may be less sensitive to HIV-related disease factors than are measures of more specific skills and abilities, verbal and nonverbal ability were less sensitive measures of disease progression in our patients than were those of global intellectual functioning. Of course, Verbal IQ and Performance IQ are actually composites of more specific skills. For example, the Verbal Scale on the WISC-R taps diverse skills, such as verbal comprehension, associative reasoning, numerical reasoning, long-term memory, social judgment, and freedom from distractibility. It should be noted that our analyses had limited statistical power to find Verbal IQ and Performance IQ scores to be predictive of HIV disease progression, even univariately. As such, this is still a question of interest that should be investigated with a larger dataset.

Our results are similar to those of others who have documented the presence of deficits in neuropsychological functioning in children and adults with HIV infection. However, to our knowledge, our study is the first to demonstrate the usefulness of neuropsychological testing in predicting later disease progression. Interestingly, Sacktor et al found that global estimates of neuropsychological functioning were not predictive of HIV-related illness in adult men, although they did document that a more specific component of neuropsychological functioning (psychomotor speed) was an early indicator of prognosis. Our results suggest that, in children, global neuropsychological measures have predictive value and provide an ongoing measure of progression risk during treatment, even when CD4 counts and HIV RNA viral levels are known.

Our second hypothesis was that children with greater degrees of cortical atrophy would be at greater risk for disease progression. Our findings demonstrate that brain atrophy was a significant predictor of disease progression. The information obtained from CT or MRI scans contributed additional predictive information, regarding disease progression beyond that obtained from HIV RNA level. These findings are consistent with previous findings, demonstrating that MRI and CT scan abnormalities were associated with surrogate markers of more severe HIV disease and with significant neurobehavioral dysfunction. However, our results suggest that when both CD4 count and HIV RNA level are known, cortical atrophy status does not predict which child will experience disease progression. It should be noted that considerable advances in antiretroviral therapy have been made since 1991 when this study was initiated and that these advances have resulted in increased longevity in children with HIV infection. As more of these infants and children live to be adolescents, the relationship between cortical atrophy and long-term disease progression is likely to be more precisely defined.

Finally, we hypothesized that children who experience motor dysfunction would be at greater risk for disease progression. Our data support this hypothesis as well. Children with baseline motor dysfunction, including abnormal muscle tone, less muscle bulk, or less muscle strength, were at significantly greater risk for disease progression. These findings are consistent with those of Hoots et al, who found that muscle atrophy was a highly significant predictor of 5-year mortality in children and adolescents with hemophilia-related HIV infection. Sacktor et al also documented the predictive power of psychomotor functioning for later HIV disease progression. Although baseline motor dysfunction can serve as a significant univariate predictor, it provides little additional information when both CD4 count and HIV RNA level are known. The one exception to this is muscle bulk; muscle wasting at baseline predicted risk for disease progression beyond that expected based on CD4 count and HIV RNA level. This finding underscores the relatively early findings of...
Mitchell et al\textsuperscript{10} who reported that decreases in muscle bulk were associated with diffuse cortical atrophy, which in turn was associated with more severe HIV disease (defined as lower CD4 counts). Mitchell et al\textsuperscript{154} recently noted that decreases in muscle bulk also were associated with systemic factors such as poor nutrition in some patients. Although these findings suggest caution in interpreting decreases in muscle bulk as always being indicative of neurological dysfunction, it seems that muscle bulk is an excellent predictor of subsequent HIV disease progression.

In contrast to the somewhat limited predictive value of baseline motor function, all aspects of week 48 motor function were highly predictive of later disease progression. Children with abnormalities in muscle tone, strength, or bulk at week 48 were at a much higher risk for disease progression. Thus, a child’s current motor functional status was more predictive of future disease progression than was baseline status. As with the neuropsychological test results, the relationship between motor dysfunction and clinical endpoint was not limited to endpoints that were determined by neurological dysfunction. In contrast, motor dysfunction at week 48 was highly predictive of disease progression that was defined by declines in neuropsychological functioning, weight growth failure, serious opportunistic infections, malignancy, or death.

This study provided an important opportunity to investigate the predictive value of neuropsychological and neurological data for subsequent disease progression in pediatric HIV patients. However, because assessment of these data as predictors of progression was only a secondary objective of the original PACTG 152 study, these results should be interpreted with caution. For instance, a large number of significance tests were conducted, but like previous PACTG investigations,\textsuperscript{17,44} $P$ values were not adjusted for multiple comparisons. As such, a few significant $P$ values might be expected by chance alone. Also, plasma HIV-1 RNA measurements were missing for a number of the children in this study. This meant that the baseline and week 48 analyses were based on overlapping but slightly different subsets of children who had complete data. However, inspection of our results suggests that the obtained significance levels for our effects allow the conclusions as formulated.

Our study strongly suggests that measures of neuropsychological and motor functioning are powerful indicators of later disease progression. Intriguingly, the most powerful predictive value of these indices was not found at baseline, but rather after the children had received treatment for 1 year. It may be that the cohort who survived to this time was inherently different from the overall cohort at baseline. However, we did not detect any obvious differences in subject characteristics among children who had not progressed by week 48 and those included in our baseline analyses. Despite our review of subgroup characteristics, this may have introduced cohort differences between subjects in the initial and follow-up samples that we were unable to identify.

Our findings have important clinical implications. To predict risk for later disease progression most accurately, referrals for neuropsychological and motor functioning testing should be considered in the initial evaluation of infants, children, and adolescents with HIV infection, these findings also suggest that these assessments should be repeated during antiretroviral therapy. The predictive value of these 2 measures in the era of highly active antiretroviral therapy regimens will be important to evaluate, particularly because new data suggest that these newer therapies may be less effective than anticipated, when specific pediatric issues such as growth parameters are studied.\textsuperscript{55} The effect of this type of active antiretroviral therapy in the developing central nervous system of young children is not yet clear. Because improved treatment regimens are enhancing longevity in the pediatric population, the predictive utility of measures of neuropsychological and neurological functioning cannot be ignored.

**ACKNOWLEDGMENTS**

This study was supported by the PACTG, the National Institute of Allergy and Infectious Diseases, the National Institute of Child Health and Human Development, Bristol-Myers Squibb, and Glaxo-Wellcome. Additional support for this work was provided by the Hogg Foundation for Mental Health.

We thank the parents and children who participated in this study.

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*Pediatrics* 2000;106;e76
DOI: 10.1542/peds.106.6.e76

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