Predictors of Change in the Functional Status of Children With Human Immunodeficiency Virus Infection

Stacey A. Missmer, MSc*; Donna Spiegelman, ScD*‡§; Sherwood L. Gorbach, MD§; and
Tracie L. Miller, MD, SM‖¶#

ABSTRACT. *Objective.* The purpose of this study was to identify important clinical predictors of change in the functional status of children with perinatally acquired human immunodeficiency virus (HIV) infection.

Methods. Children who were perinatally exposed to HIV underwent evaluation of growth, nutritional, and functional status parameters as part of a prospective study of HIV and nutrition in children. The main outcome measures for HIV-infected children were change over time in: 1) Total Health, 2) General Health, and 3) Responsiveness as measured by the Functional Status II(R) (FSII[R]). Candidate predictors included anthropometric measurements, social factors, HIV disease stage, CD4 T lymphocyte count, medications, and other clinical markers of illness.

Results. The parents or legal guardians of 35 perinatally HIV-infected children completed 2 FSII(R) surveys over a mean of 16 months. Functional Status scores were significantly correlated with number of times and days hospitalized in the past 6 months and with illness at the time of baseline evaluation. Functional status declined overtime on all 3 scales; however, only the change in Total Health score was statistically significant. Total, General Health, and Responsiveness scores declined by ≥5 points in 20.0%, 17.1%, and 14.3% of children, respectively. Significant univariate predictors of change in at least 1 component of the functional status survey included race, guardianship, height z score, prescription of antiviral medications other than antiretrovirals, and illness at time of baseline evaluation. In multivariate models, adjusting for baseline score and biologic relationship of guardian completing survey, significant predictors of a decline in Total Health scores included non-white race and lower baseline height z score. The General Health score declined with lower baseline absolute CD4 count and lower baseline height z score. Finally, Responsiveness scores declined in children whose guardian was their biologic parent and in children with lower baseline height z scores.

Conclusion. The FSII(R) questionnaire correlates with other markers of disease severity in children with

HIV infection. Growth parameters, immune status, and social factors are important predictors of functional status in HIV-infected children. *Pediatrics* 2000;106(2). URL: http://www.pediatrics.org/cgi/content/full/106/2/e24; *human immunodeficiency virus, children, functional status.*

ABBREVIATIONS. HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; FSII(R), Functional Status II(R); SD, standard deviation; TSF, triceps skinfold thickness; MAC, midarm circumference; AMC, arm-muscle circumference.

Human immunodeficiency virus (HIV) infection of children continues to be both a national and international problem. In 1997, the Centers for Disease Control and Prevention reported >40 000 HIV-infected children in the United States, 7310 of whom have acquired immunodeficiency syndrome (AIDS), while >1 million children worldwide are afflicted with this disease.[1] Although early prenatal screening, counseling, and administration of antiretroviral therapies have significantly decreased the incidence of HIV in children, they continue to become infected perinatally because of lack of prenatal care and failed prophylactic regimens. Furthermore, with the advent of highly active antiretroviral therapy, children currently infected are living longer, with many perinatally infected children expected to live into adolescence and adulthood.[2,3] HIV disease in children has become a chronic illness.

With increasing access to effective clinical interventions and longer life expectancy, epidemiologic evaluation of disease morbidity must expand from the acute definitions typically used in infectious disease research to an evaluation of functional status and quality of life. In the pediatric population, health status and quality of life are most often measured with surveys of functional status that include physical, behavioral, social, and cognitive development as factors of morbidity.[4] By focusing on quality of life as a medical outcome, clinicians are able to better assess the important effect that services and treatments have on patient populations. For this reason, it is important to understand what factors contribute to changes in the functional status of HIV-infected children so that future care can be directed at improving these factors. Although functional status has been evaluated in chronically ill children with brain tumors, cancer, cystic fibrosis, low birth weight, and asthma,[5–9] limited studies have addressed the func-

tional status or predictors of functional status in HIV-infected children.[10,11]

Many social and clinical factors can affect functional status and quality of life for HIV-infected children. HIV-infected children are exposed to and live with altered family dynamics, living in foster homes or homes with ill parents who may also have poor access to care. Children are often administered medications to control the progress of their disease, with many potential toxicities and side effects. In addition, poor nutritional status and growth are common and can occur in up to 100% of children during the course of the disease.[12–15] Malnutrition alone is an independent predictor of morbidity and mortality in both adults and children with HIV infection, with weight loss and failure to thrive resulting in decreased quality of life and increased medical costs attributable to frequent hospitalizations.[16,17] The goal of this study was to determine which nutritional, anthropometric, clinical, and social factors are predictive of a change in functional status. We hypothesized that markers of poor nutritional status and of advanced HIV disease would predict a decline in functional status over time.

METHODS

Study Cohort

Sixty-five children who were enrolled in a prospective, multidimensional, and longitudinal study of nutrition in HIV-infected children between July 1993 and October 1996 at Children's Hospital in Boston were identified. Children were determined to be HIV-infected by enzyme-linked immunosorbent assay, Western blot analysis, and HIV culture.[18] No children were receiving protease inhibitor or highly active antiretroviral therapy at the time of study. All children were outpatients, being evaluated in the Children's Hospital AIDS Program. Patients with enteral supplementation were excluded from all the analyses because of small numbers (n = 5). HIV-infected patients for whom only 1 survey measurement was available were excluded from the follow-up analyses attributable to the inability to evaluate change over time (n = 25). This study was approved by the Committee on Human Investigation at Children's Hospital.

Outcome Measurements

The main outcome of this study was change in functional status as measured by the long version of the Functional Status II(R) (FSII[R]). This survey was designed to assess the health status of children with chronic physical disorders[19,20] by measuring normal daily, age-appropriate functions (how well the child eats, sleeps, dresses himself, seems happy or moody, plays with other children, etc). This survey did not measure school function. The survey was administered to the parent or legal guardian of each HIV-infected child by a trained interviewer approximately once per year.

Each question has 2 parts; part I asks whether the child performs the specified activity or exhibits a specified behavior "never or rarely," "some of the time," or "almost always." Part II, administered after the completion of the entire list of part I items, probes those part I items that reflect poor functioning to determine whether a given functional impairment was attributable "fully," "partly," or "not at all" to an illness. A score that reflects functional status as impacted by an illness is generated on a scale of 0 to 100. Three outcome measures were evaluated in this analysis: General Health, Responsiveness (children <1 year old)/Activity (children 1 year and older)/Interpersonal Functioning (children >2 years old; referred to hence as Responsiveness for brevity), and Total score (a combination of the other 2 scales), all adjusted for age. Each score is the percent of possible points that the child obtains for that scale and age group. Change in functional status was calculated for each child by subtracting his or her scores at baseline from his or her scores at follow-up.

Although the FSII(R) has been validated in children with other chronic diseases, to our knowledge the survey instrument has never been evaluated in the pediatric HIV population. We correlated the outcome scores among those measured with HIV at baseline, using Spearman correlation with: 1) number of times hospitalized, 2) number of days hospitalized, and 3) number of current non-HIV illness symptoms (vomiting, diarrhea, abdominal pain, fever, and common cold symptoms) as shown in Table 1. Six percent of the HIV-infected children were hospitalized 1 or more times in the past 6 months (range: 0–3 times) with a mean of 1.4 hospital days (range: 0–36 days), and 45% had 1 or more non-HIV illness symptoms (vomiting, diarrhea, abdominal pain, fever, and common cold symptoms). In general, the FSII(R) correlated well with other markers of disease severity, such as hospitalization rates, days, and current illness, although the responsiveness category was least correlated with hospitalization.

Predictor Measurements

A trained nutritionist collected all anthropometric and nutritional variables on the day of FSII(R) survey. Clinical variables were collected from interviews with the nutritionist, family, and medical team who cared for the child on the day of the FSII(R) survey and were confirmed by the study coordinator through a review of the medical record. The purpose of the analysis was to investigate which baseline measurements predicted change in the FSII(R) scores over time.

Anthropometric and Nutritional Variables

Weight and recumbent length (children <2 years old) or standing height (children 2 years or older) were recorded using recommended techniques.[21] Length or height and weight were plotted on the National Center for Health Statistics percentiles to obtain age- and sex-adjusted measurements.[22] To identify children who were 2 standard deviations (SDs) below the mean, z scores were calculated by dividing the difference between the observed datum and the normal predicted value by 1 SD (as established by the National Center for Health Statistics). For the resulting z score, 0 indicates the normal population mean, whereas 2 indicates that the measure is at the 97.5th percentile of the distribution of values in the normal population (eg, 2 SDs above the mean). A negative z score indicates that the value is below the predicted population mean.[23] Triceps skinfold thickness (TSF), a measure of fat mass, was taken with Lange skinfold calipers (Cambridge Scientific Industries, Cambridge, MA) at the midpoint between the acromion and the olecranon on the relaxed right arm. The layer of skin and subcutaneous tissue was moved away from the underlying muscle and held until caliper measurement was complete. Readings were taken to .5 mm, 3 seconds after application of the calipers. Midarm circumference (MAC) was measured with a steel tape midway between the tip of the acromion and olecranon process on the relaxed right arm to the nearest .25 cm. Arm-muscle circumference (AMC), a measure of muscle mass, was calculated using the formula: AMC = MAC − [3.14 × TSF (mm)].[24] Age-adjusted percentiles for TSF and AMC were derived from the Ten-State Nutrition Survey for infants and children.[25]

TABLE 1. Correlation of FSII(R) With Markers of Disease Severity

Parameter	Correlation Coefficient	P Value
Total score		
Number of times hospitalized in past 6 mo	−.33	.04
Number of d hospitalized in past 6 mo	−.32	.05
Current illness	−.55	<.01
General Health score		
Number of times hospitalized in past 6 mo	−.42	<.01
Number of d hospitalized in past 6 mo	−.39	.01
Current illness	−.60	<.01
Responsiveness score		
Number of times hospitalized in past 6 mo	−.28	.08
Number of d hospitalized in past 6 mo	−.26	.11
Current illness	−.46	<.01

Clinical Variables

Each child was classified as having or as not having AIDS as defined by the pediatric-specific criteria of the Centers for Disease Control and Prevention.[18] CD4 T lymphocyte counts were expressed as absolute concentrations (cells/mm³). CD4 T lymphocyte counts were also adjusted for age.[26] For the logistic regression analysis, CD4 T lymphocyte count was divided into categories by increments of 100 cells/mm³. Other variables included gender, race, care taker, current use of prescription medications (antiretroviral, antiviral, prophylactic [anti-*Pneumocystis carinii*, antifungal, and antimycobacterial]), and current symptoms of non-HIV-associated illness (vomiting, diarrhea, abdominal pain, fever, and common cold).

Statistical Analysis

Descriptive statistics, including frequencies and percentages for categorical data and means, standard deviations, and ranges for continuous data, were calculated to characterize the study population. Significance of change in functional status scores from baseline to follow-up was evaluated using the paired t test. Univariate linear regression was used to assess which baseline variables were predictive of change in the functional status outcome scores. Covariates with significance at $P < .20$ were then selected as candidates for inclusion in a backward linear regression model. The robust variance was used to obtain valid inference regardless of the distribution of the residuals.[27] The biologic relationship of the person who completed the survey to the child was included a priori in all multivariate models because of the emotional and social factors involved in perinatal HIV infection. Baseline functional status scores were associated with both change in functional status score and with the predictors of change and were, therefore, included in all models to control for confounding. Three separate linear regressions were performed to determine the association between significant predictor variables and change in: 1) Total score, 2) General Health score, and 3) Responsiveness score. Results were considered significant if the 2-sided P value was $<.05$. Once a final model was selected, all other predictors were tested as confounders. Any variable that had been dropped from the model during backward selection but changed the β-coefficient of any predictor by $>10\%$ was kept in the final model as a confounder.[28] Collinearity of anthropometric measurements was evaluated by including different combinations of potentially collinear variables in the predictor models. In addition to analysis of predictors of change in outcome score, a univariate analysis of predictors of decline of ≥ 5 points was conducted to improve clinical interpretability, since a change of >5 points reflects a decline in functioning attributable to illness in 3 to 5 areas of performance. Tests of statistical power were not performed because they are indirect indicators of precision and require an assumption about the magnitude of the effect. We used confidence intervals to convey essential information by indicating the range of values that are compatible with the observations.[29] Statistical analyses were performed using SAS Statistical Software, Version 6.12 (SAS Institute Inc, Cary, NC).

RESULTS

One hundred three FSII(R) surveys were completed by the parent or legal guardian of 65 perinatally HIV-infected children who received care from the Children's Hospital AIDS Program over the study interval. Five HIV-infected children were excluded from the analyses because of enteral supplementation. The baseline patient characteristics are described in Table 2. Among the HIV-infected children, the mean age at baseline was 5.5 years old, 43% of the children were boys, 32% were white, and 50% were primarily cared for by a biologic parent. In general, these children were relatively healthy at baseline with only 30% diagnosed with AIDS, and a mean absolute CD4 cell count of 740 cells/mm³. The use of prescription drugs was prevalent, with 87% of children taking 1 or more antiretrovirals and 58% taking prophylactic medications. However, these

TABLE 2. Baseline Characteristics of the Study Population

Parameter*	All Children (n = 60)	Children With Follow-Up Measurements (n = 35)
Age, y		
Mean, (SD)	5.5 (3.0)	5.3 (2.5)
(Range)	(.5–12.9)	(.8–10.6)
Male (%)	26 (43)	21 (60)
White (%)	19 (32)	11 (31)
Relationship to guardian who completed questionnaire		
Biologic parent, n (%)	30 (50)	19 (54)
AIDS diagnosis, n (%)	18 (30)	9 (26)
Absolute CD4 cell count, cell/mm³	n = 56	n = 34
Mean, (SD)	740 (668)	724 (781)
(Range)	(0–3785)	(0–3785)
Height z score (SD)		
Mean (SD)	−.9 (1.3)	−.93 (1.2)
(Range)	(−4.6–1.4)	(−3.65–1.3)
Weight z score		
Mean (SD)	−.4 (1.2)	−.43 (1.2)
(Range)	(−2.6–3.6)	(−2.6–3.6)
Weight for height z score	n = 38	n = 35
Mean (SD)	.3 (1.1)	.3 (1.1)
(Range)	(−1.6–4.3)	(−1.37–4.3)
TSF %, (SD)	n = 54	n = 31
Mean (SD)	38 (26)	35 (23)
(Range)	(0–100)	(0–90)
AMC %	n = 54	n = 31
Mean (SD)	56 (28)	56 (28)
(Range)	(0–100)	(10–100)
Current illness symptoms, n (%)		
No symptoms	45 (75)	27 (77)
1 symptom	8 (13)	6 (17)
2 symptoms	3 (5)	1 (3)
3 symptoms	2 (3.5)	0 (0)
Unknown	2 (3.5)	1 (3)
Non-HIV perinatal illness, n (%)		
None	42 (70)	21 (60)
1 or more	18 (30)	14 (40)
Antiretroviral use, n (%)		
No antiretrovirals	8 (13)	6 (17)
1 or more antiretrovirals	52 (87)	29 (83)
Antiviral use, n (%)		
No antivirals	49 (82)	26 (74)
1 or more antivirals	3 (6)	2 (6)
Unknown	8 (13)	7 (20)
Prophylactic use, n (%)		
No prophylactic drugs	22 (37)	14 (40)
1 or more prophylactic drugs	30 (50)	14 (40)
Unknown	8 (13)	7 (20)
FSII(R) score—Total, %		
Mean (SD)	95.2 (8)	97.4 (5)
(Range)	(62.2–100.0)	(82.3–100)
FSII(R) score—General Health, %		
Mean (SD)	94.2 (10)	96.0 (8)
(Range)	(55.0–100.0)	(62.5–100)
FSII(R) score—Responsiveness, %		
Mean (SD)	95.2 (10)	96.9 (7)
(Range)	(56.0–100.0)	(75–100)

* No significant differences were found between children with 1 or serial measurements in any parameter.

children tended to be smaller than the US average by age group with a mean height z score of −.9, mean weight z score of −.4, mean TSF percent of 38%, and mean AMC percent of 56%. We compared baseline characteristics between children with only 1 evaluation and children with a follow-up test. We found no significant differences between the 2 groups of children.

Change in Functional Status

The changes in functional status outcome scores for HIV-infected children from baseline to follow-up measurement are summarized in Table 3. The mean time between measurements was 16 months. Although changes of up to 35.7 percentage points were observed, the overall outcome scores remained skewed to the upper end of the scale, with only a statistically significant change in Total score (P = .04). Total score declined by ≥5 points in 7 children (20%), General Health score declined by ≥5 points in 6 children (17%), and Responsiveness score declined by ≥5 points in 5 children (14%).

Univariate Predictors of Change in Functional Status Score

Univariate predictors of change in Total, General Health, and Responsiveness scores are presented in Table 4. A change in many covariates had a relationship with at least 1 of the 3 functional status outcome scores with a P value of .10. We found that lower height z score (r = .34 Total score; r = .19 General Health; r = .37 Responsiveness) and non-white race (mean change by −3.2 vs .8 points in Total score, −1.8 vs 1.9 points in General Health, and −3.7 vs 1.7 points in Responsiveness) were associated with a change in functional status scores in all scales ($P ≤$ .10). Other significant univariate predictors ($P ≤$ .05). of change in at least 1 category included current clinical symptoms (mean: −4.4-point vs .7-point change in General Health), and antiviral medications (mean: −10.8-point vs −1.9-point change in Total Score). Guardianship was related to change in functional status score on the Responsiveness scale, where parental guardianship showed a mean decrease of −5.6-point versus 1.0-point improvement for children who were not living with their parents (P = .03). Borderline predictors of change in at least 1 category included CD4 T lymphocyte counts, male gender, antiretroviral medications, and non-HIV perinatal chronic illness.

Multivariate Results

Table 5 includes the final multivariate models for change in the 3 functional status outcome scores. Significant predictors of change in Total Health score included race (mean increase of 2.9 more points for white children compared with those of other races; P = .04) and height z score (mean increase of 1.1

points per 1 SD height z score at baseline; $P <$ .01). Children being cared for by a nonbiologic parent had less of a decline in scores, although this did not reach significance (P = .09).

General Health scores improved significantly in children per 1 SD height z score at baseline (mean change in General Health score: 1.2; P = .03). There was also a significant relationship between absolute CD4 count at baseline and General Health score; however, the mean change in score per 100 cells/mm^3 was only .20 point (P = .03). When CD4 counts were adjusted for age, final multivariate results did not differ. Also, although included a priori as a potential confounder, General Health score at baseline was found to predict change in General Health score over time, with children declining a mean of 1.7 points for every 5 points higher at baseline.

In our evaluation of change in scores on the Responsiveness scale, we found that height z score at baseline was a significant positive predictor. For every 1 SD height z score at baseline, children improved an average of 4.1 points in Responsiveness score (P = .01). Also, children whose guardian was not their biologic parent improved their Responsiveness score by an average of 9.6 points (P = .01).

DISCUSSION

Because HIV-infected children live longer and fuller lives, it has become increasingly important that we understand what factors are predictive of future changes in functional status. There have been limited studies that have evaluated functional status in children with HIV infection, with little emphasis on validity of preexisting instruments and important clinical predictors of decline. Although HIV disease and its management are ever-changing, baseline knowledge of important clinical predictors of functional status will enable investigators to determine what factors or interventions can be expected to have a positive or negative effect on future functioning. Our study of 35 HIV-infected children with longitudinal functional status data showed that race, social factors, immune suppression, and linear growth independently influenced a change in at least 1 component of the functional status questionnaire over the study interval.

The FSII(R) questionnaire was developed for children with chronic illness, although to our knowledge, its use in pediatric HIV has been limited. To

TABLE 3. Functional Status Outcome Scores

	Baseline (n = 35)	Follow-Up (n = 35)		Change (n = 35)		% Who Declined ≥5 Points
Total, %			Mean (SE)	−2.0 (.9)		
Mean (deviation)	97.4 (5.0)	95.5 (7.8)	(Range)	(−17.6–+8.3)		
(Range)	(82.4–100)	(70.6–100)	P value*	.04	% (n)	20.0 (7/35)
General Health, %			Mean (SE)	−.6 (1.2)		
Mean (deviation)	96.0 (7.0)	95.4 (7.7)	(Range)	(−22.9–+13.8)		
(Range)	(62.5–100)	(70.8–100)	P value*	.60	% (n)	17.1 (6/35)
Responsiveness, %			Mean (SE)	−2.0 (1.5)		
Mean (deviation)	96.9 (7.0)	94.9 (11.1)	(Range)	(−35.7–+14.3)		
(Range)	(75.0–100)	(57.1–100)	P value*	.20	% (n)	14.3 (5/35)

SE indicates standard error.

* P value is testing the null hypothesis that there is no change in functional status score over time.

TABLE 4. Univariate Predictors of Change in Functional Status Score

Predictor	Total			General Health			Responsiveness		
	Mean Change (SD)	r	P Value	Mean Change (SD)	r	P Value	Mean Change (SD)	r	P Value
Gender									
Male	−3.3 (5.8)		.25	−3.1 (7.4)		.09	−3.6 (7.1)		.37
Female	−1.1 (5.2)			1.0 (6.1)			−1.0 (10.2)		
Race									
White	.8 (3.1)		.01	1.9 (4.1)		.07	1.7 (2.6)		.02
Other	−3.2 (5.9)			−1.8 (7.6)			−3.7 (10.5)		
Guardianship									
Biologic parent	−2.7 (5.5)		.46	−1.3 (5.6)		.59	−5.6 (11.8)		.03
Nonbiologic parent	−1.3 (5.5)			−.1 (7.8)			1.0 (4.4)		
Disease stage									
AIDS	−4.4 (6.2)		.15	−1.0 (6.7)		.84	−6.0 (13.4)		.24
Non-AIDS	−1.1 (5.1)			−.5 (7.0)			−.7 (6.9)		
Current illness symptoms†									
Yes	−5.1 (6.6)		.08	−4.4 (4.5)		.01	−5.4 (14.0)		.33
No	−.7 (4.8)			.7 (7.2)			−.9 (6.8)		
Non-HIV perinatal illness									
Yes	−3.0 (6.2)		.35	−.5 (7.4)		.93	−5.7 (12.9)		.09
No	−1.2 (5.0)			.7 (6.6)			.4 (4.0)		
Antiviral medication*									
Yes	−10.8 (6.9)		.02	−4.2 (2.0)		.08	−17.9 (25.2)		.22
No	−1.9 (5.5)			−1.1 (7.2)			−1.9 (7.4)		
Antiretroviral medication									
Yes	−2.3 (6.0)		.09	−.7 (7.5)		.56	−1.6 (9.3)		.48
No	−.3 (0.8)			.0 (0)			−4.2 (8.6)		
Absolute CD4 count (cells/mm³)		.22	.14		.30	.10		.07	.72
Height z score		.34	.02		.19	.06		.37	.10
Weight z score		.25	.11		.15	.18		.23	.24
TSF percent		.28	.06		.17	.25		.11	.43
AMC percent		.25	.14		.14	.36		.19	.32

* Other than antiretroviral medications.
† Reports 1 or more of vomiting, diarrhea, abdominal pain, fever, common cold.

TABLE 5. Multivariate Model of Predictors of Change in Functional Status Score

Parameter	Parameter Estimate (SE)	P Value
Total score		
White	2.94 (1.36)	.04
Height z score at baseline	1.08 (.61)	<.01
Total score at baseline*	.42 (.79)	.60
Nonbiologic parent completed survey	2.99 (1.72)	.09
General Health score		
CD4 count (cells/mm³) at baseline†	.20 (00)	.03
Height z score at baseline	1.16 (.50)	.03
General health score at baseline*	−1.73 (.70)	.02
Nonbiologic parent completed survey	2.07 (2.06)	.32
Responsiveness score		
Height z score at baseline	4.13 (1.55)	.01
Responsiveness score at baseline*	.08 (.94)	.94
Nonbiologic parent completed survey	9.62 (3.24)	.01

SE indicates standard error.
* Parameter represents the effect over time on Total, General Health, or Responsiveness score per 5-point change in the baseline score.
† Parameter represents the effect over time on General Health score per 100 cell/mm3 change in absolute number of CD4 cells.

ensure that this instrument was appropriate for use in pediatric HIV disease, we correlated results of the questionnaire with other markers of disease severity and impaired function, such as hospital days, hospi-tal rates, and current illness. We found that, in general, the questionnaire correlated well with these parameters. In other studies of HIV-infected adults, the presence, number, and severity of constitutional symptoms in HIV disease are strongly associated with health-related quality of life in symptomatic patients.[30] Disorders or symptoms, such as fatigue, neurologic disease, hypertension, depression, and GI disease are significant, independent predictors of 8-month activity of daily living scores.[31] It is encouraging that this instrument worked well in our study, although our results may be biased toward healthier HIV-infected children. These children were receiving care from a tertiary medical center as outpatients and we have documented that nearly 100% of the children were receiving some form of medical or nutritional intervention at the time of functional status measurement. Hence, the scores for many children were skewed to the upper end of the scale. We have not reported on functional status scores of inpatients, who would likely have worse scores.

A consistent trend in the univariate analysis was the association between nutritional factors and functional status. Other studies of HIV- and non-HIV-infected patients have shown similar associations.[32–34] In the multivariate model, the most consistent predictor of change in functional status among all categories was height z score. Although weights and heights have been consistently reported to be below standard, progressive decreases in height have been noted and have been correlated

with viral factors and disease activity.[35,36] Height, in this situation, may be a surrogate marker for disease severity as well. These findings support the influence of growth and nutrition on functional status of HIV-infected children. A larger sample size is needed to determine the effect of other nutritional factors.

Our study found race to be an independent predictor of change in functional status. Non-white race was associated with a greater likelihood of decline in total scores over time. This finding is consistent with other studies that showed that inner-city children with chronic conditions are more withdrawn, with increased anxiety, depression,[37] and homelessness[38] being independent predictors of poor health. Each of these conditions is more prevalent in black children.[39] McConnochie et al[40] found differences in hospitalizations of young infants relating to socioeconomic status within Rochester. Parental reporting of child health and nutrition is poorer in the Hispanic population than in the general public.[41] For HIV-infected adults, race can also impact on quality of life.[42] Special attention and interventions by clinicians should be directed to all children, with focus on non-white HIV-infected children, because they are at increased risk for decline in functional status over time.

Although not anticipated, we also found that children who were in the care of their biologic parent were also at greater risk for decline in the Responsiveness score. Perinatally acquired HIV disease of childhood is unique because 1 or both of the biologic parents have HIV as well. The families then need to contend with health concerns of child and parent, as well as other potential factors, such as access to medical care, food, shelter, and potential substance abuse. In the above-cited study on homelessness,[38] the mother's emotional distress was independently associated with acute illness symptoms of the child. A study of HIV in adults found that higher baseline support was predictive of improved general health, reduced pain, and fewer disease symptoms.[43] Although we controlled for the biologic relationship of the person who completed the survey to the child in all multivariate analyses, it is possible that there are more subtle differences within the nonbiologic parent category (made up of other biologic relatives and adoptive and foster guardians) that were not appropriately modeled. In addition, all reporting adults were women. Fathers or other male guardians may report differently. We were not able to evaluate how long these children had been in their current guardian's care. Future studies should aim to confirm our findings as well as to define what factors in the biologic family may put children at risk for this decline. Clinicians providing care for HIV-infected children should continue to be sensitive and supportive to the needs of HIV-infected parents.

A diagnosis of AIDS was not significantly predictive of change in functional status on any of the 3 scales. One potential concern about the evaluation of this variable is the way in which it is defined. The Centers for Disease Control and Prevention classification system for HIV infection in children is not only a statement of current health but of medical history as well. Once a child has clinical signs that fall within a certain stage, he or she can never be reassigned to a lower stage. Progression is always toward worsening health, not improving. Given that the FSII(R) is a cross-sectional evaluation of functional status, it may not correlate with past illness such as is marked by HIV stage. The only HIV-specific marker that was predictive of functional status was absolute CD4 T lymphocyte count, although the magnitude of effect on change in functional status score was negligible.

Future evaluation of predictors of a change in the functional status of HIV-infected children would be strengthened by inclusion of a HIV-seroreverted comparison group. These children will have been exposed perinatally to HIV and live in similar environments to our HIV-infected population. We have preliminary baseline results on noninfected children (data not shown) that suggest that factors other than HIV impact on functional status. Parents or guardians may perceive their noninfected children to be different for reasons based solely on exposure to risk. This may confound our ability to measure the relationship between quality of care and functional status and may be difficult to measure and control. A second control group of non-HIV-exposed children matched for age and socioeconomic status may provide greater insights into both HIV-infected and HIV-seroreverted children.

As data collection continues in this population, we anticipate that a longer follow-up and larger sample size will improve our ability to evaluate the relationship between functional status and variables that we found to be marginally predictive on univariate analysis. It is likely that attributable to the sample size our study had insufficient power to ascertain weaker, but significant, associations. In addition, use of the functional status questionnaire in children undergoing other clinical interventions, such as treatment with protease inhibitors, will enable investigators to evaluate another important exposure for the clinical care of the child.[44-46]

REFERENCES

1. Centers for Disease Control and Prevention. Update: perinatally acquired HIV/AIDS—United States, 1997. *MMWR CDC Surveill Summ*. 1997;46:1086–1092
2. Pizzo PA, Wilfert CM, eds. *Pediatric AIDS: The Challenge of HIV Infection in Infants, Children and Adolescents*. 3rd ed. Baltimore, MD: Williams and Wilkins; 1998
3. Auger I, Thomas P, DeGruttola V, et al. Incubation periods for pediatric AIDS patients. *Nature*. 1988;336:575–577
4. Rosenbaum P, Cadman D, Kirpalan H. Pediatrics: assessing quality of life. In: Staquet MJ, Hays RD, Fayers PM. *Quality of Life Assessment in Clinical Trials*. New York, NY: Raven Press; 1990

5. Kun LE, Mulhern RK, Crisco J. Quality of life in children treated for brain tumors. *J Neurosurg*. 1983;58:1–6

6. Lebaron S, Zeltzer PM, Zeltzer LK, Scott S, Marlin AE. Assessment of quality of survival in children with medulloblastoma and cerebellar astrocytoma. *Cancer*. 1988;62:1215–1222

7. Katz JN, Horwitz RI, Dolan TF, Shapiro ED. Clinical features as predictors of functional status in children with cystic fibrosis. *J Pediatr*. 1986; 108:352–358

8. Saigal S, Szatmaari P, Rosenbaum P, Campbell D, King S. Intellectual and functional status at school entry of children who weighed 1000 grams or less at birth: a regional perspective of births in the 1980s. *J Pediatr*. 1990;116:409–416

9. Lewis CC, Pantell RH, Keickhefer GM. Assessment of children's health status. *Med Care*. 1989;27:S54–S65

10. Hirschfeld S, Moss H, Dragisic K, Smith W, Pizzo PA. Pain in pediatric human immunodeficiency virus infection: incidence and characteristics in a singe-institution pilot study. *Pediatrics*. 1996;98:449–452

11. Gahs MC, Waite D, Sesholtz M, et al. Results of the ACSUS for pediatric AIDS patients: utilization of services, functional status, and social severity. *Health Serv Res*. 1994;29:549–568

12. Miller TL, Evans S, Orav EJ, McIntosh K, Winter HS. Growth and body composition in children with human immunodeficiency virus-1 infection. *Am J Clin Nutr*. 1993;57:588–592

13. McKinney RE, Robertson WR, the Duke Pediatric AIDS Clinical Trials Unit. Effect of human immunodeficiency virus infection on the growth of young children. *J Pediatr*. 1993;123:579–582

14. Saavedra JM, Henderson RA, Perman JA, et al. Longitudinal assessment of growth in children born to mothers with human immunodeficiency virus infection. *Arch Pediatr Adolesc Med*. 1995;149:497–502

15. Arpadi SM, Horlick MN, Wang J, et al. Body composition in prebubertal children with human immunodeficiency virus type 1 infection. *Arch Pediatr Adolesc Med*. 1998;152:688–693

16. Guenter P, Muurahainen N, Simons G, et al. Relationships among nutritional status, disease progression, and survival in HIV infection. *J Acquir Immune Defic Syndr*. 1993;6:1130–1138

17. Miller TL, Awnetwant EL, Evans SE, Morris VM, Vazquez IM, McIntosh K. Gastrostomy tube supplementation for HIV-infected children. *Pediatrics*. 1995;96:696–702

18. Centers for Disease Control and Prevention. Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR CDC Surveill Summ*. 1994;43:1–10

19. Stein REK, Jessop DJ. *Manual for the Functional Status II(R) Measure: PACTS Papers*. Bronx, NY: Albert Einstein College of Medicine; 1991

20. Stein REK, Jessop DJ. Functional Status II(R): a measure of child health status. *Med Care*. 1990;28:1041–1055

21. Lohman TG, Roche AF, Marttorell R. *Anthropometric Standardization Manual*. Champaign, IL: Human Kinetics Publishers; 1988

22. Hamill PVV, Drizd TA, Johnson CL, Reed RB, Roche AF, Moore WN. Physical growth: National Center for Health Statistics percentiles. *Am J Clin Nutr*. 1979;32:607–629

23. Zar JH. *Biostatistical Analysis*. Englewood Cliffs, NJ: Prentice Hall; 1984

24. Roberts SLW. *Nutritional Assessment Manual*. Iowa City, IA: University of Iowa Hospital and Clinics; 1987

25. United States Department of Health, Education and Welfare. *Ten-State Nutrition Survey in the United States 1968–1970*. Atlanta, GA: Centers for Disease Control and Prevention; 1972

26. Mofenson LM, Moye J, Cadden C. Effect of IVIG on CD4 cell decline in HIV-infected children in a clinical trial of IVIG prophylaxis. In: *VIII International Conference on AIDS*. Amsterdam, the Netherlands: Congrex Holland BV; 1992. Abstract

27. White H. Maximum likelihood estimation of misspecified models. *Econometrica*. 1982;50:1–26

28. Maldonado G, Greenland S. Simulation study of confounder-selection strategies. *Am J Epidemiol*. 138;923–936

29. Rothman KJ, Greenland S. *Modern Epidemiology*. New York, NY: Lippincott Williams & Wilkins; 1998

30. Cunningham WE, Shapiro ME, Hats RD, et al. Constitutional symptoms and health-related quality of life in patients with symptomatic HIV disease. *Am J Med*. 1998;104:129–136

31. Wilson IB, Cleary PD. Clinical predictors of declines in physical functioning in persons with AIDS: results of a longitudinal study. *J Acquir Immune Defic Synd Hum Retrovirol*. 1997;16:343–349

32. Kim L, Keiserman M, Schmidt JM, et al. Nutritional status and health-related quality of life in patients infected with HIV. *Int Conference AIDS*. 1998;12:841. Abstract 42338

33. Miller K, Corcoran C, Armstrong C, et al. Transdermal testosterone administration in women with acquired immunodeficiency syndrome wasting: a pilot study. *J Clin Endocrinol Metab*. 1998;83:2717–2725

34. Ovesen L, Allinstrup L, Hannibal J, Mortensen EL, Hansen OP. Effect of dietary counseling on food intake body weight, response rate, survival, and quality of life in cancer patients undergoing chemotherapy treatment: a prospective, randomized study. *J Clin Oncol*. 1993;11: 2043–2049

35. Moye J, Rich KC, Kalish LA, et al. Natural history of somatic growth in infants born to women infected by human immunodeficiency virus. Women and Infants Transmission Study Group. *J Pediatr*. 1996;128: 58–69

36. McKinney RE, Wilfert C. Growth as a prognostic indicator in children with human immunodeficiency virus infection treated with zidovudine: AIDS Clinical Trials Group Protocol 043 Study. *J Pediatr*. 1994;125: 728–733

37. Stein REK, Westbrook LE, Sliver EJ. Comparison of adjustment of school age children with and without chronic conditions: results from community-based samples. *J Dev Behav Pediatr*. 1998;19:267–272

38. Weinreb L, Goldberg R, Bassuk E, Perloff J. Determinants of health and service use patterns in homeless and low-income housed families. *Pediatrics*. 1998;102:554–562

39. Macnee CL. Forrest LJ. Factors associated with return visits to a homeless clinic. *J Health Care Poor Underserved*. 1997;8:437–445

40. McConnochie KM, Roghmann KJ, Liptak GS. Socioeconomic variation in discretionary and mandatory hospitalization of infants: an ecologic analysis. *Pediatrics*. 1997;99:774–784

41. Arcia E. Latino parents' perception of their children's health status. *Soc Sci Med*. 1998;46:1271–1274

42. Israelski D, Eversley R, Janjua S, Smith S. Race, HIV symptoms, recovery from drug abuse, and appointment adherence are associated with quality of life among HIV infected women. *Int AIDS Conference*. 1998; 12:1075. Abstract 60408

43. Lubeck D, Fries JF. Social support, social functioning and health status in HIV positive men. *Int Conference AIDS*. 1998;12:253. Abstract 14356

44. Cohen C, Revicki DA, Nabulsi A, Sarocco PW, Jiang P. A randomized trial of the effect of ritonavir in maintaining quality of life in advanced HIV disease. *AIDS*. 1998;12:1495–1502

45. Vergel NR, Salvato P, Mooney M. Anabolic steroids, resistance exercise and protein supplementation effect on lean body mass in HIV+ patients. *Int Conference AIDS*. 1998;12:557. Abstract 32185

Predictors of Change in the Functional Status of Children With Human Immunodeficiency Virus Infection

Stacey A. Missmer, Donna Spiegelman, Sherwood L. Gorbach and Tracie L. Miller

Updated Information & Services	including high resolution figures, can be found at: http://pediatrics.aappublications.org/content/106/2/e24
References	This article cites 35 articles, 7 of which you can access for free at: http://pediatrics.aappublications.org/content/106/2/e24#BIBL
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): **Infectious Disease** http://www.aappublications.org/cgi/collection/infectious_diseases_sub **HIV/AIDS** http://www.aappublications.org/cgi/collection/hiv:aids_sub
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.aappublications.org/site/misc/Permissions.xhtml
Reprints	Information about ordering reprints can be found online: http://www.aappublications.org/site/misc/reprints.xhtml

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Predictors of Change in the Functional Status of Children With Human Immunodeficiency Virus Infection

Stacey A. Missmer, Donna Spiegelman, Sherwood L. Gorbach and Tracie L. Miller

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/106/2/e24

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™