Protease Inhibitor Combination Therapy, Severity of Illness, and Quality of Life Among Children With Perinatally Acquired HIV-1 Infection

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ABSTRACT. *Objectives.* **This study examines quality of life (QOL) among school-aged children with perinatally acquired HIV infection and compares QOL outcomes between treatment groups that differ according to the use of protease inhibitor (PI) combination therapy (PI therapy). To gain insights into how PI therapy might influence QOL, associations between severity of illness and QOL were also investigated.**

Methods. **Cross-sectional data for 940 children, 5 to 18 years of age, who were enrolled in Pediatric AIDS Clinical Trials Group Late Outcomes Protocol 219 were used to examine domains of caregiver-reported QOL, as assessed with the General Health Assessment for Children, during 1999. The General Health Assessment for Children is an age-specific, modular, QOL assessment that was developed for the study with previously validated measures. QOL differences between treatment groups were estimated with linear and logistic regressions that controlled for sociodemographic characteristics (age, gender, race/ethnicity, maternal/caregiver education, and respondent) and severity-of-illness indicators related to receipt of PI therapy (AIDS status, $\log_{10}$ CD4$^+$ cell counts, and height-for-age *z* scores).**

Results. **The mean age of participants was 9.7 years. Most children were non-Hispanic black (54%) or Hispanic (31%), and 49% of the participants were female. At the 1999 study visit, ~14% of children had severe immune suppression (<15% CD4$^+$ cells), whereas 62% of children had ≥25% CD4$^+$ cells, ie, no immune suppression. Participants did exhibit some lag in growth, with mean height and weight *z* scores of −0.70 and −0.20, respectively. Twenty-eight percent of the children were reported to have met criteria for AIDS at study entry (1993–1999). When treatment groups were compared, children receiving PI therapy (72%) were older, had lower CD4$^+$ cell percentages, and had lower height and weight *z* scores than did those receiving non-PI therapies. They were also more likely to have met criteria for AIDS at study entry. The most commonly used PIs were ritonavir (46%) and nelfinavir (63%). Health perceptions ratings for most children were at the upper end of the scale, whereas ratings for 25% of the children ranged over the lower 70% of scale scores. Almost one half of the children had at least some limitations in physical functioning, with more frequent limitations in energy-demanding activities (46%) than in basic activities of daily living (32%). The Behavior Problems Index was used to assess psychologic functioning. The mean total Behavior Problems Index score (9.34) and the proportion of children with extreme scores (23%) were consistent with values reported for chronically ill children and those at social and economic risk. One or more limitations in social/school functioning were reported for 58% of children. More than one third of the children (38%) experienced ≥1 physical symptoms that were at least moderately distressing. Health perceptions, physical functioning, psychologic functioning, social/school functioning, and overall HIV symptom scores did not differ between treatment groups. However, receipt of PI therapy was associated with an increased rate of diarrhea (28 vs 13%; adjusted odds ratio: 2.59; 95% confidence interval: 1.74–3.85). Severity of illness was associated with QOL in all domains except psychologic functioning. Higher $\log_{10}$ CD4$^+$ cell counts, higher height-for-age *z* scores, and absence of AIDS at study entry were independently associated with fewer social/school limitations and better HIV symptom scores. Health perceptions and physical functioning scores were associated with $\log_{10}$ CD4$^+$ cell counts and height *z* scores, respectively.**

Conclusions. **QOL among children receiving PI therapy differed little from that among children receiving non-PI therapy, despite clinical indications of more advanced disease. Importantly, the study found no evidence of direct negative effects of PI therapy on QOL outcomes, other than an increased rate of diarrhea. Findings suggest that the effects of PI combination therapies to slow or to prevent disease progression and to increase CD4$^+$ cell counts and height growth have the potential to improve QOL among children with HIV infection. However, many children do experience a constellation of functional impairments indicated by behavioral problems and clinical symptoms, with limitations in activities and in school performance. Comprehensive health services will continue to be required to minimize long-term illness and disability and to maximize children's potential as they move into adolescence and adulthood.** *Pediatrics* **2005;115:e173–e182. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-1693; *children, health status, HIV-1, protease inhibitor, quality of life.***

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ABBREVIATIONS. GHAC, General Health Assessment for Children; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibi-

tor; PACTG, Pediatric AIDS Clinical Trials Group; QOL, quality of life.

Pediatric antiretroviral treatment guidelines recommend early aggressive treatment of HIV infection with a drug regimen that usually includes a protease inhibitor (PI) in combination with 2 nucleoside reverse transcriptase inhibitors (NRTIs).[1,2] Clinical trials have demonstrated the effectiveness of PI combination therapy (PI therapy) in decreasing plasma HIV RNA levels, although the proportion of children with virologic suppression to undetectable levels is generally smaller than the corresponding proportion of adults.[3–6] Antiretroviral regimens including PIs have been shown to increase $CD4^+$ cell counts, even for children with advanced disease,[4–9] and studies are now beginning to document their effects on clinical outcomes. Baseline and treatment-mediated changes in immunologic and virologic markers were independent predictors of survival in a meta-analysis of pediatric antiretroviral clinical trials, and virologic markers predicted weight growth and cognitive failure among children >1 year of age.[10] The use of PI therapy has been found to reduce morbidity and mortality rates among HIV-infected children and adolescents[11,12] and has been shown to increase height and weight growth.[13,14] To date, however, studies have not examined the association of PI therapy with children's health-related quality of life (QOL).

QOL refers to multidimensional indicators of health and functional status and is an important consideration in the clinical management of chronic progressive illnesses, such as HIV infection. Assessment of QOL provides the opportunity to expand understanding of the effects of disease and treatment to include their impact on physical, psychologic, and social functioning, factors that have special relevance in the care of developing children. Information about QOL among children with HIV infection is limited. Studies conducted before the introduction of PIs for treating children found that more advanced disease was associated with worse QOL in at least some areas of functioning and perceived health status.[15,16]

Available data support the idea that PI therapy can maintain or enhance QOL in pediatric HIV infection, through slowed disease progression and improvements in clinical outcomes. However, Gortmaker et al[11] found that children with more advanced disease initiated PI therapy sooner than did those with less severe illness. This selection according to indication also has been observed among adults with HIV infection and complicates evaluation of treatment.[17] Furthermore, regimens containing PIs are complex and raise concerns about both acute and long-term side effects. The regimens are often challenging to administer or take, because of the amount of medication required and problems with the availability and palatability of pediatric formulations of PIs. This study examined QOL among school-aged children with perinatally acquired HIV infection and compared several dimensions of QOL between treatment groups that differed in the use of PI therapy, after adjustment for severity-of-illness indicators associated with receipt of PI therapy. To gain insights into how PIs influence QOL, relationships between clinical indicators of severity of illness and QOL outcomes were also investigated.

METHODS

Study Design

This analysis used cross-sectional data from Pediatric AIDS Clinical Trials Group (PACTG) Late Outcomes Protocol 219, a prospective cohort study. PACTG 219 was designed to assess late outcomes of in utero and neonatal exposure to antiretroviral drugs in clinical trials, as well as the long-term effects of antiretroviral treatment among children with HIV-1 infection, as described previously.[11,13,18] Human-subject research review boards at participating sites in the United States and Puerto Rico approved the research protocol. Before enrollment, written informed consent was obtained from participants' parents or legal guardians or from participants who were above the legal age limit. Written assent was obtained from children when appropriate. Clinical, laboratory, and QOL data were collected at baseline and every 6 months for children <3 years of age and annually for children ≥3 years of age.

The study sample was limited to children with perinatally acquired HIV infection, 5 through 18 years of age, for whom caregiver-reported QOL data were collected during 1999. Of the 1006 participants who met these criteria, 940 children were included in the analysis. Sixty-six children were excluded because of extensive missing data in their QOL questionnaires or because of missing data for other key variables (antiretroviral therapy, $CD4^+$ lymphocyte counts, height, weight, or AIDS status). Demographic characteristics and receipt of PI therapy for excluded participants did not differ significantly from findings for participants included in the analysis.

Antiretroviral Therapy

Data on antiretroviral medications at the 1999 QOL visit were used to create 2 treatment categories. Treatment information reflected all antiretroviral drugs used in the past 12 months (for newly enrolled subjects) or since the last annual PACTG 219 study visit. Precise information about the timing and duration of therapy was not collected, although data on types and dates of antiretroviral therapy used in PACTG clinical trials were available for some children. Participants who received ≥1 PI in combination with NRTIs and/or a nonnucleoside reverse transcriptase inhibitor (NNRTI) were classified as receiving PI therapy. Participants who received only NRTIs and/or NNRTIs were classified as receiving non-PI therapy. Children who received no antiretroviral drugs were classified with the non-PI therapy group, because they represented part of the group of children who did not receive PIs. Major study results were not altered in analyses that excluded the 14 children who did not receive antiretroviral therapy and in analyses that also excluded 25 children who received NRTI monotherapy, another small subset of the non-PI therapy group.

Clinical Indicators of Severity of Illness

Most $CD4^+$ lymphocyte and growth measurements (84% and 92%, respectively) were obtained at the same time as the 1999 QOL assessment, and the remainder were obtained within 6 months of the assessment. Height and weight measurements were converted to age- and gender-adjusted percentiles and z scores with the Centers for Disease Control and Prevention 2000 growth charts.[19] Children at the median (50th percentile) have a z score of 0; positive or negative z scores reflect SD units above or below the median, respectively. Report of AIDS status at study entry was used as the criterion for AIDS in the analysis; study entry dates ranged from 1993 to 1999.

QOL Measurements

QOL was assessed with parent or guardian reports with the General Health Assessment for Children (GHAC), a group of age-specific, modular instruments developed for PACTG 219 by Gortmaker et al,[15] building on previously validated measures. Earlier studies demonstrated that the GHAC has good internal

consistency and reliability among 5- to 11-year-old children and provided evidence of the instrument's validity among HIV-infected children.[15,20] This study used the GHAC for children 5 to 11 years of age and the version for children ≥12 years of age to examine QOL in the domains of health perceptions, physical functioning, psychologic functioning, social/school functioning, and HIV symptoms.

In the health perceptions domain, caregivers rate the child's health in the past 3 months on a 10-point scale, from the very worst he/she ever felt to the very best he/she ever felt, in each of 4 areas, ie, overall, physically, emotionally, and schoolwork (age 5–11 years) or daily activities/schoolwork/job/housework (age ≥12 years). The 6-item physical functioning domain addresses 2 levels of activity, ie, energy-demanding tasks (vigorous activities, moderate activities, and walking uphill) and basic activities of daily living (walking 1 block, bending/lifting, and eating/dressing/bathing/toileting). Children's health-related activity limitations in the past 4 weeks are graded on a 5-point scale ranging from not at all to extremely limited.

Psychologic functioning is assessed with the Behavior Problems Index, an instrument that examines areas of behavior covered by the Child Behavior Checklist.[21] Caregivers describe 28 child behaviors in the past 3 months with a 3-point scale, ie, often true, sometimes true, or not true. Four of the items are age specific and differ between the GHAC module for 5- to 11-year-old children and the module for ≥12-year-old children.

Social/school functioning is assessed with 5 dichotomous items, adapted from the National Health Interview Survey, that reflect specific social/school limitations. The HIV symptom scale examines 20 physical symptoms. Caregivers are asked to rate the levels of these symptoms in the past 4 weeks on a 6-point scale, ie, not at all distressing, very mildly distressing, mildly distressing, moderately distressing, very much distressing, or extremely distressing.

The GHAC does not yield an overall summary score. Each QOL domain is scored separately. Thirty-five cases with missing data limited to 1 or 2 individual domain items were retained. Missing data were replaced with the mean item score for the sample before calculation of the domain score. Review of missing items did not suggest any pattern according to domain or participant. In calculations of scale scores, raw item scores were reversed when necessary, summed, and then transformed to a scale ranging from 0 to 100, with higher scores indicating better QOL, as follows: transformed score = [(actual raw score − lowest possible score)/(highest possible score − lowest possible raw score)] × 100. Strong internal consistency/reliability, ranging from 0.89 to 0.96, was observed for all domain scales except social/school functioning, which suggests this is an index of more diverse indicators. For this reason, both social/school functioning scores and individual limitations were evaluated.

The Behavior Problems Index, which was used to assess psychologic functioning, includes several subscales with demonstrated reliability and validity that can be scored separately, ie, antisocial, anxious/depressed, headstrong, hyperactive, and peer conflict.[21,22] The subscales are composed of 5 items, except for the 3-item peer conflict subscale. We also created a 3-item gastrointestinal subscale for the HIV symptoms domain, because gastrointestinal symptoms are common side effects of PIs. Subscale scores were calculated as the sum of raw item values minus the total number of items, where higher scores denote fewer behavioral problems or symptoms and better QOL, as with the complete domain scales.

For additional analyses characterizing QOL outcomes, individual items were recoded and/or categorized. Physical functioning was recoded as a dichotomous variable indicating the absence (score of 100) or presence (score of <100) of limited physical functioning, an approach similar to that used in a study of adults with HIV infection.[23] Behavior Problems Index scores were calculated as the sum of items on the psychologic functioning scale that were rated as sometimes true or often true. The presence of extreme behavioral problems, defined as a score of ≥14 problem behaviors, reflects scores in the ≥90th percentile.[24] Some of the items on the HIV symptom scale were grouped for assessment of different types of symptoms, ie, respiratory (3 items), pain (7 items), gastrointestinal (3 items), and fatigue and sleep (2 items). Responses were also recoded according to severity ratings, to denote mild (very mildly or mildly distressing) or moderate (moderately distressing or greater) symptoms.

Sociodemographic Variables

Sociodemographic variables included age, gender, race/ethnicity, primary language, primary caregiver, maternal/primary caregiver educational attainment, and GHAC respondent. Race/ethnicity was categorized as non-Hispanic white, non-Hispanic black, Hispanic, or other. Because only a few children (12 of 940 children, 1%) were categorized as other race, they were grouped with non-Hispanic white children in the analyses. Years of schooling completed by the mother or primary caregiver was used as an indicator of socioeconomic status. The relationship of the GHAC respondent to the participant was assigned to 1 of 3 categories, ie, biological parent; other relative; or adoptive parent, foster parent, or other.

Statistical Analyses

Descriptive statistics were used to characterize participants in the sample as a whole and in the 2 treatment groups. Group differences in continuous variables were examined with Student's t test, whereas χ^2 or Fisher's exact tests were used to examine proportional differences. Studies showed that PI therapy was initiated sooner among children with lower $CD4^+$ cell counts and lower height and weight z scores, which introduces the need to control for confounding by severity of illness with indication for treatment.[11,13,17] Mean differences in QOL scores between treatment groups were initially estimated with univariate linear regressions. Multivariate regressions were then used to estimate differences between treatment groups while controlling for clinical factors associated with receipt of PI therapy and sociodemographic characteristics. Logistic regressions that adjusted for covariates were used to analyze variables with 2 response categories, eg, individual social/school limitations and the presence or absence of symptoms. Sociodemographic covariates included age, gender, race/ethnicity, primary caregiver/maternal education, and GHAC respondent. Severity of illness covariates included $\log_{10}$ $CD4^+$ cell counts, height or weight z scores at the 1999 QOL visit, and AIDS status at study entry. The $\log_{10}$ $CD4^+$ cell count was used in these analyses because it was a better predictor of QOL scores than $CD4^+$ cell percentage. In a previous study, the $\log_{10}$ $CD4^+$ cell count was also found to be a better predictor of mortality rates.[11] Clinical indicators of severity of illness as correlates of QOL were examined in multivariate models that controlled for sociodemographic variables and the use of PI therapy. Anthropometric indices were calculated with NutStat Epi Info 2000 (www.cdc.gov/epiinfo). Analyses were performed with SAS version 8.2 (SAS, Cary, NC). Two-tailed P values are reported, and $P < .05$ (2-tailed) was set as the criterion for statistical significance.

RESULTS

Sample Characteristics

As shown in Table 1, the majority (77%) of participants in this school-aged sample were 5 to 11 years of age. Most children were non-Hispanic black (54%) or Hispanic (31%), and 49% of the participants were female. A biological parent was identified as the primary caregiver for only 40% of the children, which is consistent with the multigenerational impact of perinatally acquired HIV infection. For 22% of participants, a language other than English, usually Spanish, was the primary language spoken at home. At the 1999 QOL visit, 14% of children had severe immune suppression (<15% $CD4^+$ cells), on the basis of the Centers for Disease Control and Prevention Pediatric Classification System.[25] Notably, $CD4^+$ cell percentages were ≥25% (indicating no immune suppression) for 62% of children. Participants did exhibit some lag in growth; mean height and weight z scores of −0.70 and −0.20 place the mean height and weight in the 33rd and 45th percentiles, respectively, on age- and gender-adjusted growth curves. Twenty-eight percent of the children were reported to have AIDS at study entry.

TABLE 1. Sociodemographic and Clinical Characteristics of 940 PACTG 219 Participants and Differences According to Treatment Group

Characteristic*	No. (%)			*P* Value
	All Participants	PI Therapy	Non-PI Therapy	
Total	940	677 (72)	263 (28)	
Age				
5–8 y	416 (44)	287 (42)	129 (49)	.287
9–11 y	306 (33)	227 (34)	79 (30)	
12–14 y	172 (18)	127 (19)	45 (17)	
15–18 y	46 (5)	36 (5)	10 (4)	
Age, y, mean (SD)	9.71 (2.9)	9.86 (3.0)	9.33 (2.9)	.014
Gender				
Male	480 (51)	367 (54)	113 (43)	.002
Female	460 (49)	310 (46)	150 (57)	
Race/ethnicity				
White non-Hispanic	131 (14)	95 (14)	36 (14)	.894
Black non-Hispanic	504 (54)	359 (53)	145 (55)	
Hispanic	293 (31)	215 (32)	78 (30)	
Other	12 (1)	8 (1)	4 (2)	
Primary caregiver				
Biological parent	375 (40)	262 (39)	113 (43)	.299
Other relative	276 (29)	208 (31)	68 (26)	
Foster/adoptive/other	289 (31)	207 (31)	82 (31)	
GHAC respondent				
Biological parent	378 (40)	264 (39)	114 (43)	.142
Other relative	265 (28)	203 (30)	62 (24)	
Foster/adoptive/other	297 (32)	210 (31)	87 (33)	
Maternal/caregiver education				
<12 y	324 (34)	238 (35)	86 (33)	.212
12 y	276 (29)	206 (30)	70 (27)	
>12 y	265 (28)	178 (26)	87 (33)	
Missing	75 (8)	55 (8)	20 (8)	
Primary language				
English	730 (78)	530 (78)	200 (76)	.0412
Spanish	189 (20)	137 (20)	52 (20)	
Other	21 (2)	10 (1)	11 (4)	
Pediatric immune suppression category				
None (≥25%)	586 (62)	409 (60)	177 (67)	.044
Moderate (15–24%)	225 (24)	164 (24)	61 (23)	
Severe (<15%)	129 (14)	104 (15)	25 (10)	
$CD4^+$ cells, %, mean (SD)	27.2 (11.3)	26.6 (11.6)	28.8 (10.2)	.005
$CD4^+$ cell no./mm^3	695.6 (454.6)	699.2 (474.8)	686.1 (398.3)	.670
AIDS	266 (28)	215 (32)	51 (19)	<.001
Height *z* score, mean (SD)	−0.70 (1.21)	−0.80 (1.18)	−0.43 (1.24)	<.001
Weight *z* score, mean (SD)	−0.20 (1.21)	−0.32 (1.19)	0.09 (1.22)	<.001

Sociodemographic and clinical characteristics were assessed at or within 6 months of the 1999 QOL visit except for AIDS status, which was based on the report from the PACTG 219 enrollment visit (1993–1999).
* Because of rounding, percentages may not sum to 100.

Children receiving PI therapy were slightly older than children in the non-PI group and were more likely to be male (Table 1). There were no differences between treatment groups according to race/ethnicity, primary caregiver, or primary caregiver/maternal education. Almost 75% of children from either English- or Spanish-speaking homes received PI therapy. Children with other primary languages were slightly underrepresented in the PI treatment group, but numbers were small. Children receiving PI therapy had characteristics consistent with more advanced disease. They had lower mean $CD4^+$ cell percentages, height *z* scores, and weight *z* scores, compared with participants receiving non-PI therapy, and were more likely to have AIDS at study entry. The apparent gender difference in receipt of PI therapy may be attributable to confounding by disease stage. A previous longitudinal study of the effect of PI therapy on mortality rates found that lower $\log_{10}$ $CD4^+$ cell counts independently predicted earlier initiation of PI therapy, whereas demographic differences in the initiation of PI therapy did not persist after adjustment for severity of illness.[11]

Antiretroviral Therapy

Antiretroviral therapy is described in Table 2. Almost three fourths of the participants (72%) received PI combination regimens, most often with nelfinavir or ritonavir. Use of >1 PI was reported for 30% of children receiving PIs; this number reflects changes in therapy in addition to treatment with >1 PI. Children receiving PI therapy were more likely to receive a NNRTI than were those receiving non-PI therapy (38% vs 10%, $P < .001$). There were also some differences in NRTIs, with stavudine being used more often for children receiving PIs, whereas zidovudine and didanosine were used more often for children receiving non-PI therapy (Table 2). Twenty-five children in the non-PI group had received PIs previously, including 6 children who were receiving

TABLE 2. Differences in Antiretroviral Medications Received According to Treatment Group

Antiretroviral Drug	No. (%)*		*P* Value
	PI Therapy	Non-PI Therapy	
Total	677 (72)	263 (28)	
NRTIs			
Abacavir	39 (6)	11 (4)	.412
Didanosine	180 (27)	98 (37)	.002
Lamivudine	456 (67)	162 (62)	.108
Stavudine	481 (71)	96 (37)	<.001
Zalcitabine	33 (5)	3 (1)	.007
Zidovudine	262 (39)	140 (53)	<.001
NNRTIs			
Delaviradine	5 (1)	0 (0)	.323
Efavirenz	79 (12)	9 (3)	<.001
Nevirapine	184 (27)	20 (8)	<.001
PIs			
Amprenavir	45 (7)		
Indinavir	55 (8)		
Nelfinavir	429 (63)		
Ritonavir	312 (46)		
Saquinavir	93 (14)		
No. of PIs			
0		230 (100)	
1	472 (70)		
2	158 (23)		
≥3	47 (7)		
Total no. of antiretroviral drugs			
0	0 (0)	14 (5)	<.001
1	0 (0)	25 (10)	
2	47 (7)	178 (68)	
≥3	630 (93)	46 (17)	

* Percentages are based on the total number in the treatment group and can sum to >100%.

monotherapy or no antiretroviral drugs. Characteristics of the 39 children who were receiving monotherapy or no antiretroviral drugs were generally similar to those of children in the non-PI group; however, only 1 of these children had severe immune suppression, and their mean weight and height parameters were near or above the mean normative values for age and gender (data not shown).

QOL Domain Scores

The GHAC was usually completed in English (84%), and approximately one half (53%) of the questionnaires were self-administered. QOL scores are presented in Table 3. Although some ceiling effects were present in all domains, particularly physical and social/school functioning, few or no children demonstrated minimum scores. Health perceptions ratings for most children were at the upper end of the scale, whereas 25% of children ranged over the lower 70% of possible scores. Almost one half of the children had at least some limitations in physical functioning, with more frequent limitations in energy-demanding activities (46%) than in basic activities of daily living (32%). The distribution of psychologic functioning scores was similar to that of health perceptions. However, the mean Behavior Problems Index (9.34) and the proportion of children with extreme scores (23%) were consistent with values reported for chronically ill children and those at social and economic risk.[21,24,26]

One or more limitations in social/school function-

TABLE 3. Description of QOL Domain Scores and Comparison of QOL Scores Between Treatment Groups

QOL Domain*	All Children (n = 940)			PI Therapy (n = 677), Mean Score (SD)	Non-PI Therapy (n = 263), Mean Score (SD)	Crude Observed Difference	Adjusted Difference‡
	Median Score (Q1–Q3)†	% at Maximum Score; % at Minimum Score	Mean Score (SD)				
Health perceptions	83.3 (72.2–94.4)	15; <1	80.3 (17.8)	80.2 (17.6)	80.9 (18.0)	−0.7	0.14
Physical functioning	100.0 (75–100)	53; 3	81.6 (29.0)	81.9 (28.6)	81.0 (30.1)	0.9	2.01
Psychologic functioning	83.9 (69.6–92.9)	8; 0	80.3 (15.9)	80.3 (16.3)	80.1 (15.9)	0.2	0.63
Antisocial	9.0 (7.0–10.0)	34; <1	8.2 (1.9)	8.2 (2.0)	8.2 (1.9)	0	0.04
Anxiety/depression	9.0 (7.0–10.0)	31; 0	8.3 (1.7)	8.3 (1.7)	8.3 (1.8)	0	0.06
Headstrong	8.0 (6.0–9.0)	22; 0.6	7.4 (2.4)	7.4 (2.3)	7.3 (2.5)	0.1	0.21
Hyperactivity	8.0 (6.0–10.0)	25; <1	7.5 (2.2)	7.5 (2.2)	7.4 (2.2)	0.1	0.18
Peer conflict	6.0 (5.0–6.0)	71; 0	5.5 (1.0)	5.5 (1.0)	5.5 (0.9)	0	−0.07
Social/school functioning	80.0 (60–100)	42; 1	79.5 (23.1)	78.3 (23.3)	82.4 (22.5)	−4.1§	−1.60
HIV symptoms	95.0 (88–98)	15; 0	91.3 (10.4)	91.0 (10.7)	92.1 (9.6)	−1.1	−0.58
Gastrointestinal symptoms	15.0 (13.0–15.0)	53; <1	13.5 (2.3)	13.4 (2.4)	13.9 (1.9)	−0.5§	−0.50§

* Scores for complete QOL domains range from 0 to 100. Psychologic functioning subscale scores range from 0 to 10, except for the peer conflict subscale, which ranges from 0 to 6. Gastrointestinal symptom subscale scores range from 0 to 15. In each case, higher scores indicate better QOL.
† Values for the first and third quartiles of the distribution.
‡ Values reflect mean adjusted differences between treatment groups estimated from regression equations controlling for sociodemographic variables (age, gender, race/ethnicity, maternal/caregiver education, and GHAC respondent) and severity of illness (AIDS, log $CD4^+$ cell counts, and height z scores).
§ Differences between treatment groups significant at $P < .05$.

ing were reported for 58% of children. Individual limitations included health-related limitations in activities (13%) or school attendance (17%), spending ≥1 day in bed during the past 4 weeks (19%), repeating a grade (21%), or receiving special help in school (32%) (Table 4). Approximately 15% of children had no reported symptoms. Thirty-eight percent of children experienced ≥1 symptoms that were at least moderately distressing. These included respiratory symptoms (18%), pain (16%), gastrointestinal symptoms (14%), and fatigue and sleep problems (8%). Approximately one fourth of the children experienced very mild or greater nausea/vomiting/abdominal pain, diarrhea, and/or loss of appetite (Table 4).

PI Therapy and QOL

Health perceptions, physical functioning, psychologic functioning, and HIV symptom scores did not differ between children receiving PI therapy and those receiving non-PI therapy (Table 3). Furthermore, no treatment group differences were evident in additional analyses that evaluated the proportions of children with physical limitations (data not shown) or psychologic subscale scores. Adjustment for sociodemographic characteristics and severity of illness ($\log_{10}$ $CD4^+$ cell count, AIDS status, and height and weight *z* scores) did not alter the findings for any of the domains.

Children receiving PI therapy did exhibit significantly worse social/school functioning than did those receiving non-PI therapy, but this difference was eliminated with adjustment for covariates. When specific limitations were examined, only health-limited school attendance differed with receipt of PI therapy, and the association did not persist after adjustment for covariates (Table 4).

Although the overall HIV symptom scores did not differ according to treatment group, comparison of gastrointestinal symptom subscale scores indicated that children receiving PI therapy had significantly greater gastrointestinal symptoms than did children in the non-PI group, a difference that was not altered with adjustment for covariates (Table 3). When individual symptoms were evaluated, as shown in Table 4, the occurrence of nausea/vomiting/abdominal pain or loss of appetite did not differ between treatment groups. In contrast, PI therapy was independently associated with an increased rate of diarrhea, after adjustment for covariates. The occurrence of diarrhea was approximately doubled among children receiving PI therapy, with increases in both very mild/mild diarrhea (21% vs 10%) and moderate or worse diarrhea (7% vs 3%).

Severity of Illness

Multivariate models were used to examine the association between clinical indicators of severity of illness and QOL domain scores, with adjustment for sociodemographic characteristics and treatment group. Because weight *z* scores and height *z* scores were strongly correlated, they were evaluated separately. Coefficient estimates for each indicator were consistent with expected relationships between less severe illness and better QOL in all domains except psychologic functioning (Table 5). The overall model for psychologic functioning did not reach the criterion for statistical significance. Higher $\log_{10}$ $CD4^+$ cell counts and height *z* scores at the 1999 QOL visit and the absence of AIDS at study entry each contributed independently to better QOL in social/school functioning and HIV symptom domains. In the domains of health perceptions and physical functioning, independent associations with severity of illness were limited to $\log_{10}$ $CD4^+$ cell counts for health perceptions and to height *z* scores for physical functioning. When scored as the presence or absence of physical limitations, both $\log_{10}$ $CD4^+$ cell counts and

TABLE 4. Proportions of Children Experiencing Social/School Limitations and Gastrointestinal Symptoms, With Comparisons Between Treatment Groups

QOL Domain	Proportion, %			Odds Ratio (95% CI)†	Adjusted Odds Ratio (95% CI)‡
	All Children (*n* = 940*)	PI Therapy (*n* = 677)	Non-PI Therapy (*n* = 263)		
Social/school limitations					
≥1 bed day in 4 wk	19	19	19	1.00 (0.70–1.43)	0.92 (0.63–1.34)
Health limited activities	13	15	9	1.56 (0.99–2.47)	1.27 (0.79–2.05)
Health limited school attendance	17	19	11	1.81 (1.18–2.77)	1.50 (0.96–2.34)
Receives special school help	32	33	30	1.17 (0.86–1.59)	1.05 (0.76–1.44)
Repeated a grade	21	22	18	1.32 (0.92–1.90)	1.07 (0.72–1.57)
Gastrointestinal symptoms					
Any nausea/vomiting/abdominal pain	28	29	25	1.25 (0.90–1.72)	1.24 (0.89–1.74)
Very mild/mild	22	23	20		
Moderate	6	7	5		
Any loss of appetite	24	25	21	1.28 (0.90–1.81)	1.21 (0.84–1.73)
Very mild/mild	16	16	16		
Moderate	8	9	5		
Any diarrhea	24	28	13	2.58 (1.73–3.84)	2.59 (1.74–3.85)
Very mild/mild	18	21	10		
Moderate	6	7	3		

* *n* ranged from 938 to 940 for individual items.
† CI indicates confidence interval.
‡ Estimated from logistic regressions comparing any symptom to no symptoms, controlling for sociodemographic variables (age, gender, race/ethnicity, maternal/caregiver education, and GHAC respondent) and severity of illness (AIDS, log $CD4^+$ cell counts, and height *z* scores).

TABLE 5. Multivariate Models of Clinical Indicators of Severity of Illness Associated With QOL Domain Scores ($n = 940$)

QOL Domain	Clinical Indicator*	Coefficient Estimate† (SE)	*P* Value
Health perceptions	AIDS diagnosis	−1.73 (1.31)	.188
	Log_{10} $CD4^+$ cell count	4.23 (1.48)	.004
	Height *z* score	0.42 (0.51)	.403
Physical functioning	AIDS diagnosis	−3.72 (2.13)	.081
	Log_{10} $CD4^+$ cell count	2.77 (2.40)	.249
	Height *z* score	2.48 (0.82)	.003
Psychologic functioning	AIDS diagnosis	−2.07 (1.19)	.082
	Log_{10} $CD4^+$ cell count	−0.32 (1.34)	.809
	Height *z* score	−0.74 (0.46)	.103
Social/school functioning	AIDS diagnosis	−3.26 (1.65)	.049
	Log_{10} $CD4^+$ cell count	7.51 (1.86)	<.001
	Height *z* score	2.90 (0.64)	<.001
HIV symptoms	AIDS diagnosis	−2.16 (0.77)	.005
	Log_{10} $CD4^+$ cell count	3.30 (0.86)	<.001
	Height *z* score	0.68 (0.29)	.022

* Data on clinical indicators were obtained at or within 6 months of the 1999 QOL measurement except for AIDS status, which was based on the report from the PACTG 219 enrollment visit (1993–1999).
† Estimated from multivariate linear regressions with adjustment for sociodemographic variables (age, gender, race/ethnicity, maternal/caregiver education, and GHAC respondent) and use of PI therapy.

height *z* scores were independently associated with physical functioning (data not shown). In contrast to findings with log_{10} $CD4^+$ cell counts, relative $CD4^+$ cell counts ($CD4^+$ cell percentages) were not independently associated with QOL scores (data not shown). Multivariate models including weight *z* scores demonstrated that weight *z* scores were not independently associated with any of the domain scores (data not shown).

DISCUSSION

Dramatic reductions in mortality and morbidity rates that have occurred with the introduction of PI therapy have revolutionized clinical care and outcomes for HIV-infected children in the United States. However, the impact and burden of treatment and remaining disease morbidity on children's QOL have not been assessed. This study provides the first overall evaluation of QOL among school-aged children living with perinatally acquired HIV infection during the era of PIs. Evaluation of QOL in the context of changing therapy is complicated by the fact that new emerging treatments are often offered to and accessed by sicker children first. Longitudinal studies showed that children with more advanced HIV infection initiated PI therapy earlier than did those with less advanced disease.[11,13] Our findings indicate that QOL among children receiving PI therapy differs little from that among children receiving non-PI therapy, despite indications of more advanced disease. Importantly, we found no evidence of direct negative effects of PI therapy, other than an increased rate of diarrhea, on QOL outcomes. This observation seems particularly noteworthy in light of differences in the number, type, complexity, and palatability of medications between PI-containing and non—PI-containing regimens.

Almost all (93%) children receiving PI therapy received ritonavir and/or nelfinavir. These were the only PIs with approved pediatric formulations at the time of this analysis, and they continue to be strongly recommended for the treatment of pediatric HIV infection, according to the most recent antiretroviral guidelines.[2] Currently, the only other PI in the strongly recommended category for the treatment of HIV-infected children is lopinavir/ritonavir, which has palatability problems similar to those of ritonavir in liquid formulation, although it does have a lower pill burden.

Gastrointestinal symptoms are commonly reported side effects of PI combination therapies among children. Although the incidence and severity vary among studies, symptoms are characterized generally as mild or transient and do not often require discontinuation of treatment.[27] Pediatric clinical trials of nelfinavir- and/or ritonavir-containing regimens found that approximately one fourth of children experienced moderate nausea and vomiting.[4,5] Diarrhea was reported for 18% of participants in a trial of a nelfinavir-based regimen.[6] In our study, approximately one fourth of all children experienced very mild or greater nausea/vomiting/abdominal pain, loss of appetite, and/or diarrhea. Although PI therapy was associated with greater gastrointestinal symptoms, only diarrhea differed significantly between treatment groups. The increased rate of diarrhea was independently associated with PI use and was not related to severity of illness. The finding that gastrointestinal symptoms in our cohort tended to be milder, with less frequent moderate symptoms than reported in clinical treatment trials, is probably related to a number of factors, including the study's 4-week time frame for assessment, the transient nature of gastrointestinal symptoms occurring with initiation of PI therapy, effective treatment of side effects, change of therapy when problems were severe or persistent, and less stringent adherence in routine ongoing care.

Although parents and clinicians have voiced concerns that PI combination therapies may adversely affect children's behavior, we found no indication that psychologic functioning differed among chil-

dren receiving PI therapy, on the basis of comparisons of total or subscale scores. The mean Behavior Problems Index in our sample (9.34) was almost identical to that of a 1995 PACTG 219 cohort of 5- to 11-year-old children (9.5).[15] In a national sample of children 5 to 17 years of age, the mean Behavior Problems Index was higher among children with asthma and other comorbid conditions than among children without chronic conditions (7.3 and 5.4, respectively).[26] Social and economic factors, such as family disruption and poverty, also place children with HIV infection at risk of experiencing a greater number of behavioral problems.[24,26] Mellins et al[28] recently reported similar high rates of behavioral problems among HIV-infected and HIV-exposed children. Irrespective of cause, high rates of behavioral problems among HIV-infected children pose a significant concern for clinicians and families, because they may affect treatment adherence and impair school performance.

This study demonstrates that severity of illness is associated with QOL among children with HIV infection, although relationships vary according to indicator and among domains. The finding that $\log_{10}$ $CD4^+$ cell counts and height *z* scores at the 1999 study visit and AIDS status at study entry (1993–1999) were each independently associated with social/school limitations and HIV symptoms suggests that they have a cumulative impact on QOL outcomes. Independent relationships of $\log_{10}$ $CD4^+$ cell counts and height *z* scores with QOL outcomes suggest that treatment-mediated changes in these indicators can improve QOL. However, the associations of AIDS status at study entry and height *z* scores but not weight *z* scores with QOL among children are also consistent with long-term effects of disease progression. A recent analysis of data from an earlier clinical trial of NRTI treatment by Benjamin et al[29] demonstrated that increases in height *z* scores were more strongly related to reduced risk of clinical disease progression than were increases in weight *z* scores. Only increases in height *z* scores were associated with reduced risk of failing to increase $CD4^+$ cell percentages.

Our findings on QOL among school-aged children with HIV infection are generally consistent with observed effects of antiretroviral treatment and severity of illness among HIV-infected adults. Adult studies suggest that PI combination therapy can improve, maintain, or attenuate declines in QOL over time.[30–33] Call et al[34] noted that lower viral loads and higher $CD4^+$ cell counts predicted better QOL in some domains, including general health and physical and role functioning, but did not predict mental health scores. In the HIV Cost and Services Utilization Study, adults' physical functioning depended on symptom status or AIDS diagnosis.[35] However, psychologic functioning was impaired among both asymptomatic and symptomatic patients and was significantly worse, compared with the general population and with patients with other chronic diseases except depression.

The demographic and social characteristics of our sample are generally representative of those of the population of school-aged children with perinatally acquired HIV infection in the United States.[36] Inherent limitations of the study involve issues related to QOL measurements among children, available information, confounding attributable to unmeasured differences in disease severity, and use of observational cross-sectional data. Our findings provide additional evidence of the validity of the GHAC for QOL assessment among children with HIV infection. Domain scores were associated with selected indicators of disease severity in a pattern similar to that observed among HIV-infected adults. Furthermore, the symptom scale was able to detect a difference in the occurrence of diarrhea, a common side effect of PIs, between treatment groups. The GHAC assesses caregivers' perspectives of their children's QOL. Children's own reports may provide additional unique information about their health and functioning. Although both perspectives are valuable, caregiver reports are particularly important in examination of the association of new, complex, antiretroviral treatment and children's QOL, because parents and guardians are responsible for making health care decisions and for initiating and managing therapy.

Although it was not possible to determine the exact regimen or duration of treatment when QOL assessments were completed, this study characterized QOL 1 to 2 years after PIs became widely available for children, during a period when PI use was changing rapidly. Treatment adherence and HIV RNA measurements were not obtained in PACTG 219 during this period. However, the immunologic competence of the sample was substantially improved, compared with a 1995 PACTG 219 cohort of children and youths 0 to 20 years of age. The proportion of children with no immune suppression almost doubled, from 33% to 62%, whereas the proportion with severe immune suppression was reduced by one half, from 30% to 15%.[11,13] Using a cross-sectional design, we were not able to determine whether the absence of QOL differences between treatment groups was attributable to uncontrolled differences in illness severity before the initiation of therapy.

Strong infrastructure for the clinical care of HIV infection in the United States, made possible by support from the Ryan White CARE Act, facilitated the rapid widespread introduction of PI combination therapy. With reduced morbidity and mortality rates, the concept of QOL has become increasingly important in our efforts to understand how the disease and its treatment affect children and families. In light of the metabolic complications of antiretroviral therapy, which include lipodystrophy, dyslipidemia, and osteonecrosis, it will be important to monitor the long-term effects of therapy. Gaughan et al[20] noted that, whereas painful diagnoses decreased from 1995 to 1999 among children with HIV infection, the prevalence of caregiver-reported pain remained constant at ~20%. Pain was associated with a number of factors, including age and gender. More frequent reports of pain with increasing age highlight the developmental issues that complicate QOL assessments and outcomes among children.

Observed relationships between severity-of-illness indicators and QOL are consistent with long-term effects of disease progression and illustrate mechanisms for improved QOL, particularly through the well-documented effects of PI therapy to increase $CD4^+$ cell counts. Our findings suggest that the ability of PI therapy to increase $CD4^+$ cell counts, improve height growth, and slow or prevent disease progression have the potential to improve QOL among children, although this will require confirmation in future longitudinal analyses.

Children with HIV infection remain at health and social risk because of the chronicity of the disease. Many children experience a constellation of functional impairments indicated by behavioral problems and clinical symptoms, with limitations in activities and in school performance. Comprehensive health services will continue to be required to minimize long-term illness and disability and to maximize children's potential as they move into adolescence and adulthood.

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