The Role of Cognitive Functioning in Medication Adherence of Children and Adolescents with HIV Infection

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Objective To evaluate the relationship between cognitive functioning and medication adherence in children and adolescents with perinatally acquired HIV infection. **Methods** Children and adolescents, ages 3–18 ($N = 1,429$), received a cognitive evaluation and adherence assessment. Multiple logistic regression models were used to identify associations between adherence and cognitive status, adjusting for potential confounding factors. **Results** Children's average cognitive performance was within the low-average range; 16% of children were cognitively impaired (MDI/FSIQ <70). Cognitive status was not associated with adherence to full medication regimens; however, children with borderline/low average cognitive functioning (IQ 70–84) had increased odds of nonadherence to the protease inhibitor class of antiretroviral therapy. Recent stressful life events and child health characteristics, such as HIV RNA detectability, were significantly associated with nonadherence. **Conclusion** Cognitive status plays a limited role in medication adherence. Child and caregiver psychosocial and health characteristics should inform interventions to support adherence.

Key words adolescents; children; cognitive functioning; HIV; medication adherence.

Advances in medical treatment, through combination antiretroviral therapy (ART) and highly active ART (HAART) with protease inhibitors (PIs), have resulted in improved health outcomes among children with human immunodeficiency virus (HIV) infection (DeMartino et al., 2000; Gortmaker et al., 2001). Adherence to HAART regimens is difficult, however, due to the demanding nature of antiretroviral treatment and other unique challenges faced by children and adolescents with HIV and their caregivers. Antiretroviral medications, particularly regimens containing PIs, share characteristics that amplify the inherent difficulties of medication adherence in children and adolescents: poor palatability, heavy pill burden, dietary restrictions, acute and long-term side effects, and restrictions on daily schedules (Reddington et al., 2000; Van Dyke et al., 2002). Children and adolescents with HIV often face other life stressors that affect their ability to achieve adherence, including parental HIV disease, poverty, and limited or inconsistent social support (Steele, Nelson, & Cole, 2007). Adherence failure is dangerous in HIV disease as it may result in diminished treatment efficacy, development of genotypically resistant mutations, viral rebound, and subsequent reduction in HIV treatment options.

Despite the importance of adherence in HIV disease, our understanding of factors predictive of adherence in children and adolescents remains incomplete. Prior studies of adherence in children with HIV infection, while often atheoretical, have identified multiple contextual factors associated with adherence, including disease characteristics, features of the medication regimen, and characteristics of the caregiver and family, such as caregiver education and problem-solving skills, caregiver relationship to the child, and child and caregiver stress (Hammani et al., 2004; Martin et al., 2007; Mellins, Brackis-Cott, Dolezal, & Abrams, 2004; Naar-King et al., 2006; Pontali, 2005). Child and adolescent developmental issues, including

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older age, knowledge of HIV diagnosis, and adjustment to chronic illness have also been implicated, although findings remain inconsistent (Simoni et al., 2007; Williams et al., 2006).

Neurocognitive impairment, due to the neuropathological effects of HIV infection, is a significant complication of perinatally acquired HIV infection (Van Rie, Harrington, Dow, & Robertson, 2007). It has been associated with nonadherence in adults with HIV (Hinkin et al., 2004) and may provoke similar risk in children and adolescents. Global or mild cognitive deficits, if present, may impede or delay development of those functional skills essential for adherence, such as understanding and following parental and provider directions, remembering schedules and dosage, and communicating needs effectively.

The purpose of this study was to examine cognitive functioning in children and adolescents with HIV, and to evaluate its relationship with medication adherence. We hypothesized that adherence to ART and HAART with PIs will be compromised in the presence of neurocognitive deficits in children and adolescents with HIV infection. We also evaluated potential confounding factors, including demographic characteristics, biological markers of health, medication and adherence factors, and child and family psychosocial characteristics that have been associated with medication adherence in previous investigations.

Methods

Participants

Our analyses used cross-sectional data from Pediatric AIDS Clinical Trials Group (PACTG) Late Outcomes Protocol 219C (P219C), a prospective cohort study designed to assess long-term effects of HIV infection and ART treatment (Gortmaker et al., 2001). Children and adolescents were enrolled at over 80 participating P219C sites (see Appendix) in urban and rural areas of the US and Puerto Rico. Eligibility criteria for the present analysis were: perinatally acquired HIV, age 3–18 years, on ART during participation in P219C, at least one cognitive evaluation during the study, and an adherence assessment closest to and within 6 months of the cognitive evaluation. The study was approved by human subject research review boards at all participating sites. Written informed consent was obtained from children's parents or legal guardians or from older adolescents who could self-consent. Written assent was obtained from children ages 12 through 17 in accordance with local IRB guidelines.

In April 2004, there were 2,384 perinatally infected children enrolled in P219C; 2,191 were 3- to 18-years old at some point during study follow-up. Of these 2,191 participants, 1,682 (77%) had at least one cognitive evaluation, and 1,537 of these 1,682 (91%) had an ART adherence assessment within 6 months of the most recent cognitive evaluation. Within this subgroup of 1,537, 1,429 (93%) completed the age-appropriate cognitive measure and obtained valid scores. These 1,429 children and adolescents comprise the cohort for this study.

Approximately one-half (52%) of the participants were female, 52% were between 9 and 15 years of age, and 84% self-identified as either African-American (58%) or Latino (26%) (Table I). Forty-three percent had undetectable viral loads (HIV RNA <400 copies/ml), and 26% had a CDC class C diagnosis (severely immunocompromised). Seventy-two percent of participants received HAART with PIs. Children and adolescents lived with biological parents (42%), adult relatives (28%), such as grandparents, aunts, and cousins, and nonrelative adults (28%), including foster and adoptive parents. Fifty-six percent of caregivers had a high school education or less and 52% reported at least one recent life stressor. Forty-seven percent of participants knew their HIV diagnosis and 22% reported on their own medication adherence. Overall adherence rates were high, with 85% reporting complete adherence to all ART drugs in their regimen, and 87–90% reporting complete adherence to individual drug classes.

Measures

Cognitive Functioning

Cognitive testing was conducted at 3-year intervals, beginning at age 3 years. The Bayley Scales of Infant Development–Second Edition (Bayley-II; Bayley, 1993) were used for children between 36 and 42 months of age. Age-appropriate Wechsler tests were used for older children: Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R; Wechsler, 1989) for ages 3.5 to <6 years; Wechsler Intelligence Scale for Children, Third Edition (WISC-III; Wechsler, 1991) for ages 6–16; and Wechsler Adult Intelligence Scale, Third Edition (WAIS-III; Wechsler, 1997) for ages 17 and 18 years. We used the most recent cognitive assessment conducted between the ages of 3 and 18 years. Tests were administered according to standardized procedures. For those children and adolescents whose primary language was Spanish ($N = 236$; 16.5%) or other non-English language ($N = 40$; 2.8%), cognitive testing was provided by an examiner fluent in the child's primary language, or a professional translator was used.

The Mental Development Index (MDI) of the Bayley-II and the Full Scale Intelligence Quotient (FSIQ) of the Wechsler tests were used to measure general cognitive ability. The MDI and FSIQ are standardized scores based

Table I. Demographic, Health, and Psychosocial Characteristics of Participants ($N = 1,429$)

Characteristic	*N* (%)
Female	742 (52)
Race/ethnicity	
White	204 (14)
African-American	825 (58)
Latino	373 (26)
Other	27 (2)
Age at adherence visit (years)	
3–6	195 (14)
>6–9	349 (24)
>9–12	439 (31)
>12–15	296 (21)
>15–18	150 (10)
Primary caregiver	
Biological parent	605 (42)
Nonrelative adult	407 (28)
Adult relative	404 (28)
Other	9 (<1)
Self[a]	4 (<1)
Education of caregiver	
Grade 1–11	354 (25)
High school graduate	444 (31)
Some college/technical school	351 (24)
College graduate or higher	171 (12)
Other/not reported	109 (8)
Knows HIV status	677 (47)
Person assessing adherence	
Biological parent	512 (36)
Other nonrelative adult	319 (22)
Adult relative	282 (20)
Self[a]	316 (22)
CD4 + (%)	
≤15	137 (10)
15–25	285 (20)
≥25	1,007 (70)
HIV-1 viral load (copies/ml)	
≤400	617 (43)
≥400–10,000	455 (32)
≥10,000	357 (25)
CDC class C[b]	
No	1,059 (74)
Yes	367 (26)
Complete adherence over prior 3 days	
To all ART drugs	1,216 (85)
To NRTIs	1,229/1,420 (87)
To NNRTIs	446/494 (90)
To PIs	918/1,055 (87)
On PI at adherence visit	1,055 (74)
Antiretroviral regimen	
HAART with PI	1,024 (72)
HAART with NNRTI	147 (10)
Single NRTI	15 (1)
Dual NRTI	150 (10)
≥3 NRTIs	54 (4)
Other combination therapy	39 (3)
Duration of HAART (years)	
<2	443 (31)
2–4	600 (42)
>4–6	326 (23)
>6	60 (4)
Memory prompt required	415 (27)
Recent life stressors	
None	644 (45)
At least one	738 (52)
Missing	47 (3)
Type of life stressors	
Financial stressful event	329 (23)
Family structure stressful event	299 (21)
Illness/death in family/friend	416 (29)
Any of above	738 (52)
Type of ART reminders[c]	
Activity of daily living	389 (27)
Pillboxes	226 (16)
Buddy system	110 (8)
Labels	186 (13)
Physical/social role functioning[d]	
Limited activities due to illness	160 (11)
Limited school attendance	169 (12)
Repeated a grade	341 (24)
Participated in sports	773 (54)
Attended special class/help	438 (31)

[a]Includes three children who had the assistance of another in reporting adherence.
[b]Three missing observations.
[c]Participant may report use of more than one type of ART reminder.
[d]Each category had between 173–176 missing observations.

on the general US population ($M = 100$, $SD = 15$). We also included the Wechsler Verbal IQ (VIQ), Performance IQ (PIQ), and Verbal Comprehension (VC), Perceptual Organization (PO), Freedom from Distractibility/Working Memory (FD/WM), and Processing Speed (PS) indices. Impairment was defined as scores that were two or more *SD*s below the population mean (MDI and Wechsler scores <70). We excluded data from children who were unable to complete the age-appropriate cognitive tests due to cognitive or behavioral limitations, whose raw scores were

below test norms, or whose data were considered invalid due to non-English primary language or sensory or motor handicaps. Comparison of children and adolescents who were excluded ($N = 62$) with those included in the analysis revealed significant differences in the proportion of females (39% female vs. 52%, Fisher's exact test, $p = .05$) and attendance in special class (64% vs. 35%, Fisher's exact test, $p = .01$). The mean MDI/FSIQ of the non-English speaking participants ($M = 80$, $SD = 15.1$) was lower than that of the English-speaking participants ($M = 86$, $SD = 16.3$) (two-sample t-test for means: $t = 5.2$, $p < .0001$). However, there were no significant differences between these groups in adherence to the whole medication regimen or to PIs.

Medication Adherence

Medication adherence was assessed with a validated self-report measure (Van Dyke et al., 2002), using a scripted interview with the person who self-identified as responsible for medication administration, whether parent/caregiver or child/adolescent. Respondents identified each medication in the ART regimen and reported the number of doses of each medication missed during each of the preceding 3 days, which may have included weekends and holidays. The adherence report reflected the respondent's ability to administer the medication regimen and/or the willingness and ability of the child/adolescent to take the medicine. Medication burden (the total number of expected doses over the past 3 days) was recorded. The need to prompt respondents for names of ART medications was identified, as were the types of aids utilized as reminders, including pillboxes, buddy system, and activities of daily living. We defined separate indicators of adherence for each drug class: nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and PIs, since PIs are sometimes considered more burdensome than other medication classes (Reddington et al., 2000). Complete adherence was defined as taking all prescribed ART medications during the 3 days preceding the study visit. Adherence was self-assessed by 12% of participants with cognitive impairment, 22% of those in the 70 to <85 range, 25% of those in the 85–100 range, and 27% of those in the >100 range.

Procedures

Data collection for PACTG 219C has been previously described (Williams et al., 2006) and is briefly reviewed. Socio-demographic information, including age, gender, race/ethnicity, primary language, and caregiver characteristics, were collected at study entry, as were detailed medical histories, including clinical diagnoses and medication history. We examined measures of virologic and immunologic status that are assessed every 3 months in PACTG 219C, including HIV-1 RNA viral load and CD4+ T-lymphocyte count and percentage, to account for the complex role played by child and adolescent HIV disease status, which may influence adherence behaviors (Martin et al., 2007; Reddington et al., 2000; Williams et al., 2006). HIV-1 RNA viral load provides a quantitative measurement of HIV viremia in peripheral blood and CD4+ T-lymphocyte percentage provides an indication of immunologic status (higher viral levels and lower CD4 percentage are correlated with increased risk of clinical progression of HIV disease). CDC classification of HIV disease (Center for Disease Control and Prevention, 1994) was also recorded every 3 months at follow-up visits, as was information regarding the current use of ART medications and adherence. Adherence information closest to and within 6 months of the cognitive evaluation was used in the analysis.

Psychosocial information, such as occurrence of stressful life events and presence or absence of physical/social role limitations, was obtained from the General Health Assessment for Children (GHAC), a validated health-related quality-of-life measure, completed annually (Gortmaker et al., 1998). Caregivers reported the occurrence of negative life events during the prior 12 months, including parental job loss, hospitalization of family member, death in the family, and others. Eighteen different stressful life events were categorized into one of three groups involving changes in financial stability, family structure, and family health (Lee, Gortmaker, McIntosh, Hughes, & Oleske, 2006). We identified whether the participant experienced at least one stressor in any of these three categories. Physical/social role functioning was evaluated for participants over 5 years of age. Five different physical/social role functioning events were classified as having occurred or not and included repeating a grade in school, receiving special help in school, participating in sports, or having limitations in physical activity or school attendance.

Data Analytical Strategy

Fisher's Exact tests were used to compare the proportions of children with complete adherence between those with and without cognitive impairment (MDI or FSIQ <70), and Pearson chi-squared tests were used to compare adherence levels across four levels of cognitive impairment (MDI or FSIQ <70, 70–84, 85–100, >100). The Wilk–Shapiro, Kolmogorov–Smirnov, and Anderson–Darling tests were used to assess whether the IQ scores followed a normal distribution. One-sample tests based on Student's t

distribution were used to evaluate the deviation of mean IQ scores from the population mean, and one-sample tests based on the standard normal distribution were used to evaluate whether impairment rates (i.e., percent with cognitive impairment) deviated significantly from general population norms. The two-sample *t*-test was used to compare cognitive scores of children with English as primary language versus those with Spanish or other primary languages.

Demographic characteristics (gender, age, race/ethnicity, and non-English primary language), biological markers of HIV disease (CD4 + count and percent, viral load >400 copies per milliliter, and CDC class C diagnosis), medication and adherence factors (ART and other medication use, duration on HAART, person assessing adherence, medication burden, need for prompting, types of reminders used), child and family psychosocial characteristics (child knowledge of HIV status, primary caregiver, caregiver education level, occurrence of recent stressful life events, and physical/social role functioning limitations), and child psychiatric/neurological profiles (medication and diagnosis history) that have been associated with medication adherence in previous investigations were included in the analyses as covariates (Martin et al., 2007; Mellins et al., 2004; Naar-King et al., 2006; Pontali, 2005; Simoni et al., 2007; Williams et al., 2006). Multiple logistic regression models were used to evaluate associations of adherence with cognitive functioning, adjusting for the identified covariates. Model selection using backward elimination and a 10% level of significance was used to identify significant predictors of nonadherence.

Results

Cognitive Functioning

The children's average performance was within the low-average range on the Bayley-II and Wechsler measures of cognitive ability (Table II), and the mean MDI/FSIQ ($M = 85$, $SD = 16$) for the cohort was lower than the general population mean (one-sample *t*-test for means: $t = 35.44$, $p < .0001$). Of the 1,429 children, 232 (16%) were in the <70 IQ range, 502 (35%) were in the 70 to <85 range, 457 (32%) were in the 85–100 range, and 238 (17%) were in the >100 range. The percentage of children with cognitive impairment (16% with MDI or FSIQ <70) was significantly higher than expected (one-sample *z*-test for proportions: $z = 33.17$, $p < .01$), with the highest impairment rates in VIQ and VCI and the lowest rates in PSI.

Cognitive Functioning and Adherence

We found no significant association between levels of cognitive functioning (MDI or FSIQ <70, 70–84, 85–100,

Table II. Bayley-II and Wechsler Scores and Prevalence of Cognitive Impairment ($N = 1,429$)

Test	N[a]	FSIQ/MDI	VIQ	PIQ	VC	PO	FD/WM	PS
BSID-II								
Mean (*SD*)	30	83 (15)						
Percentage with score <70		20						
WPPSI-R								
Mean (*SD*)	188	84 (14)	84 (14)	87 (15)				
Percentage with score <70		13	15	10				
WISC-III								
Mean (*SD*)	1188	85 (17)	84 (16)	88 (17)	85 (16)	88 (17)	86(16)	93(17)
Percentage with score <70		17	18	13	18	13	16	8
WAIS-III								
Mean (*SD*)	36	87 (16)	86 (16)	91 (16)	89 (17)	92 (18)	83 (15)	86(13)
Percentage with score <70		11	14	6	3	6	26	12
Overall								
Mean (*SD*)	1429	85 (16)	84 (16)	88 (17)	85 (16)	88 (17)	86 (16)	93(17)
Percentage with score <70		16	17	13	17	13	16	8
Z-statistic[b]		33.17^{++}	35.52^{++}	24.12^{++}	32.92^{++}	22.34^{++}	29.89^{++}	8.98^{++}
T-statistic[c]		36.07^{++}	37.22^{++}	27.70^{++}	31.67^{++}	23.77^{++}	29.75^{++}	11.02^{++}

Cognitive impairment defined as standard score <70.

[a]Maximum number with any single test score.

[b]This corresponds to the upper-tailed one-sample *z*-test for the true proportion of impairment in this population (*p*-value <.05 implies impairment rate is significantly higher than the general population rate of 2.5%).

[c]This corresponds to the lower-tailed *t*-test for the true mean score (*p*-value <.05 implies mean score is significantly smaller than the general population mean of 100).

$^{++}p < 0.01$, one-tailed.

Table III. Percent of Participants with Complete (100%) Adherence by Drug Class and Levels of Cognitive Functioning

	Mental development index/Full scale IQ level				
Drug class	**<70**	**70–<85**	**85–100**	**>100**	**Overall**
Entire regimen	205 (88)	413 (82)	391 (86)	207 (87)	1,216 (85)
	($n = 232$)	($n = 502$)	($n = 457$)	($n = 238$)	($n = 1429$)
NRTIs	207(89)	419 (84)	396 (87)	207 (88)	1,229 (87)
	($n = 232$)	($n = 498$)	($n = 454$)	($n = 236$)	($n = 1,420$)
NNRTIs	70 (95)	163 (88)	145(89)	68 (94)	446 (90)
	(n = 74)	($n = 185$)	($n = 163$)	($n = 72$)	($n = 494$)
PIs[a]	166 (91)	305 (83)	297 (89)	150 (88)	918 (87)
	($n = 183$)	($n = 368$)	($n = 333$)	($n = 171$)	($n = 1,055$)

[a]Pearson's chi-squared test ($\chi^2 = 9.25$, $df = 3$, $p = .03$).

or >100) and adherence to the entire medication regimen (Pearson's chi-squared test: $\chi^2 = 5.85$, $df = 3$, $p = .12$). Further, there were no significant associations between cognitive status and adherence to the NRTI drug class (Pearson's $\chi^2 = 4.37$, $df = 3$, $p = .22$) and the NNRTI drug class (Pearson's $\chi^2 = 4.31$, $df = 3$, $p = .23$) (Table III).

There was a significant association between cognitive status and adherence to the drug class of PIs (Pearson's chi-squared test: $\chi^2 = 9.25$, $df = 3$, $p = .03$). Children who function within the borderline/low-average range of cognitive ability (MDI/FSIQ = 70–84) were less adherent to PI therapy compared to those below and above that range (83% vs. 91% adherent, Fisher's exact test, $p = .01$; and 83% vs. 89%, $p = .02$, respectively).

Final Models of Predictors of Nonadherence

Entire Regimen

In the final multiple logistic regression model, cognitive functioning, as measured by MDI and FSIQ, was not predictive of nonadherence to the entire medication regimen (Table IV). Factors significantly associated with higher odds of nonadherence included occurrence of a recent life stressor [odds ratio (OR): 1.74, $p = .001$) and HIV RNA detectability (>400 copies/ml) (OR: 1.58, $p = .01$). Factors associated with higher odds of complete adherence included: more years on HAART (OR: 0.86, $p = .001$), higher caregiver education (OR: 0.83, $p = .02$), having a nonrelative (OR: 0.60, $p = .04$) or relative (OR: 0.56, $p = .02$) adult responsible for medication, and repeating a grade in school (OR: 0.63, $p = .02$).

Table IV. Final Multiple Logistic Regression Model for Predictors of Nonadherence to Entire ART Regimen ($n = 1,429$)[a]

Predictor	**Estimated OR**	**95% confidence interval**	***p*-value**
Cognitive functioning			.18
Impaired: (MDI/FSIQ: <70)	1.00	–	(ref)
MDI/FSIQ: 70–<85	1.42	0.84–2.40	.19
MDI/FSIQ: 85–100	1.10	0.63–1.90	.74
MDI/FSIQ: >100	0.86	0.45–1.62	.63
Age group (years)			.85
3–<6	1.00	–	(ref)
6–12	1.26	0.57–2.79	.57
>12–18	1.29	0.52–3.17	.58
Adherence assessor			.005
Biological parent	1.00	–	(ref)
Self or self plus other	1.28	0.79–2.07	.32
Relative	0.56	0.34–0.91	.02
Other adult	0.60	0.37–0.99	.04
Recent life stress	1.74	1.25–2.44	.001
HIV–1 RNA >400 copies/ml	1.58	1.11–2.24	.01
Reminder: Pillbox	1.47	0.97–2.24	.07
Child knows HIV status	1.40	0.92–2.14	.12
Memory prompt required	1.36	0.96–1.93	.09
Participation in sports	1.35	0.95–1.90	.09
Duration of HAART[b]	0.86	0.78–0.94	.001
Caregiver education level	0.83	0.72–0.97	.02
Reminder: daily activities	0.70	0.47–1.04	.08
Repeated a grade	0.63	0.43–0.94	.02
Reminder: buddy system	0.52	0.25–1.06	.07

Higher values for estimated OR indicate higher risk of nonadherence.

[a]A total of 178 observations were deleted due to missing values for the response or the explanatory variables.

[b]Corresponds to every additional year on HAART.

PIs Alone

After adjusting for hypothesized covariates, we found a marginal association between cognitive functioning and nonadherence to the individual drug class of PIs ($p = .06$) (Table V). Children in the borderline to low-average range of cognitive functioning had marginally higher odds of nonadherence to PIs than those with cognitive impairment (OR: 1.94, $p = .05$). Additional factors associated with higher odds of nonadherence to PIs included: HIV RNA detectability (OR: 2.07, $p = .001$), limitations in daily

Table V. Final Multiple Logistic Regression Model for Predictors of Nonadherence to Protease Inhibitors ($N = 1{,}055$[a] Participants on PIs)

Predictor	Estimated odds ratio	95% confidence interval	*p*-value
Cognitive functioning			.06
Impaired (MDI/FSIQ: <70)	1.00	–	(ref)
MDI/FSIQ: 70–<85	1.94	0.99–3.79	.05
MDI/FSIQ: 85–100	1.07	0.53–2.19	.85
MDI/FSIQ: >100	1.23	0.56–2.69	.61
Age group (years)			.14
3–<6	1.00	–	(ref)
6–12	2.69	0.79–9.23	.12
>12–18	3.61	0.99–13.19	.05
Adherence assessor			.04
Biological parent	1.00	–	(ref)
Self or self + other	1.26	0.71–2.23	.43
Relative	0.52	0.28–0.98	.04
Other adult	0.62	0.34–1.15	.13
HIV-1 RNA >400 copies/ml	2.07	1.34–3.22	.001
Activities limited	1.98	1.11–3.55	.02
Recent life stress	1.72	1.12–2.64	.01
Participated in sports	1.51	0.97–2.35	.07
Medication burden[b]	1.25	1.05–1.48	.01
Duration of HAART[c]	0.82	0.71–0.93	.003
Reminder: activities of daily living	0.60	0.37–0.98	.04
CD4 count <200	0.40	0.16–1.02	.06

Higher values for estimated odds ratio indicate higher risk of nonadherence.
[a]157 observations were deleted due to missing values for the response or the explanatory variables.
[b]Corresponds to every additional drug dose per day.
[c]Corresponds to every additional year on HAART.

activities (OR: 1.98, $p = .02$), recent life stress (OR: 1.72, $p = .01$), and higher medication burden (OR: 1.25, $p = .01$). Factors associated with higher odds of complete adherence to PIs included: more years on HAART (OR: 0.82, $p = .003$), using activities of daily living as an adherence support (OR: 0.60, $p = .04$), and having an adult relative responsible for medication (OR: 0.52, $p = .04$).

Effect of Age

We included age, grouped into three categories (3 to <6 years, 6–12 years, >12–18 years), in the final models; however, results were not significant. Moreover, the parameter estimates corresponding to the three cognitive levels in the models remained essentially unchanged (<10% change) when age group was included in the models. Age group was not significantly associated with nonadherence to the entire medication regimen or with nonadherence to PIs. In a supportive analysis, with age excluded in the final models, results regarding the association of cognitive functioning with nonadherence to PIs were slightly stronger ($p = .05$).

Discussion

The cognitive functioning of children in this investigation is consistent with recent studies of children with HIV infection (Jeremy et al. 2005; Mialky, Vagnoni, & Rutstein, 2001; Nozyce et al., 2006). The mean score of the children in this cohort was within the low-average range of cognitive functioning, and their performance in most areas, including verbal, memory, and perceptual organization, was below expectations for the general population. Sixteen percent of children in this cohort were cognitively impaired (MDI or FSIQ <70). This finding is consistent with recent studies that describe a decrement in rates of progressive HIV encephalopathy but not elimination of significant neurocognitive impairment among children with HIV during the HAART era (Chiriboga, Fleishman, Champion, Gaye-Robinson, & Abrams, 2005).

Contrary to our hypothesis, the cognitive status of children and adolescents in this study, whether impaired or not, was not significantly associated with adherence to their full medication regimen. In fact, high rates of complete adherence to medication regimens were consistently observed among children with cognitive impairment, in contrast to the adult experience (Hinkin et al., 2004). This finding suggests the presence of adequate caregiver vigilance and active participation in the process of adherence with these children and is supported by the limited number of children with cognitive impairment who assume primary responsibility for their medication. Caregivers of children with cognitive impairment may recognize that their children are less knowledgeable about their medication regimen and have limited ability to understand the immediate and long-term consequences of nonadherence. As these children progress through adolescence and transition into adult health care programs, sensitive support and surveillance of adherence will be critical for the well-being of the individual as well as for the protection of public health.

Adherence to PI therapy was of special interest in this investigation due to its unique challenges among ART drug classes. Earlier longitudinal studies indicated that PI therapy is initiated sooner among children with more advanced disease, is difficult to administer or take due to large pill size or poor palatability of liquid formulations, and may have complex acute and long-term side-effects (Gortmaker et al., 2001; Storm et al., 2005). In addition, some PIs have inadequate penetration to the central nervous system and may be limited in their impact on the presence and severity

of neurocognitive involvement, despite effective suppression of systemic HIV infection (Ferrando, Rabkin, van Gorp, Lin, & McElhiney, 2003). Among those children with PI-containing medication regimens in this investigation, child cognitive status conferred modest additional risk for nonadherence to PIs. Children with cognitive scores in the borderline to low-average range were marginally less successful adhering to PIs than those with cognitive impairment and those whose scores were at or above age level. Their cognitive and learning difficulties may be less appreciated by caregivers than the problems of children with greater neurocognitive impairment, and as a result, the supports necessary for adherence to difficult medications may be inadequate. It is also possible that these children were entrusted to manage their own adherence before they achieved readiness for this level of independence. The observed trend of lower rates of adherence among children with borderline/low average cognitive status across all drug classes attests to the clinical importance of ongoing adherence supervision for these children. Further research is necessary to better articulate the specific deficits that contribute to higher risk for nonadherence among these children and adolescents, particularly with respect to PIs.

Our investigation highlights the important role of the caregiving environment for medication adherence, given children's dependence on their caregivers for health care management, and is consistent with earlier investigations. Recent life stressors have been associated with poorer psychological outcomes (Moss, Bose, Wolters, & Brouwers, 1998) and with nonadherence in earlier studies (Mellins et al., 2004; Williams et al., 2006) and have been related to cognitive impairment among HIV positive adults (Pukay-Martin, Cristiani, Saveanu, & Bornstein, 2003). In this study, recent life stressors, which were experienced by more than half (52%) of the participants, were associated with higher odds of nonadherence, suggesting that adherent behavior is sensitive to variations in child and family well-being. Families affected by HIV are unfortunately often vulnerable to both sudden and chronic stress due to the impact of HIV as a multigenerational, stigmatized illness, and due to shared characteristics of families with HIV, such as minority group membership, poverty, discrimination, inadequate housing, and exposure to crime and violence (Brown, Lourie, & Pao, 2000).

Several caregiving factors, including higher caregiver education and the nature of the child–caregiver relationship, appeared to be protective and reduced the risk for medication nonadherence in children with HIV infection. Children whose medications were administered by caregivers such as relatives (e.g., aunts, grandparents) or nonrelative adults (e.g., foster/adoptive parents) demonstrated lower risk for nonadherence. These caregivers may have more personal resources and be less burdened by the psychological and physical health complications often experienced by biological parents with HIV disease. Parents with HIV disease may require increased social support to ensure medication success for their children, particularly if their current or chronic life stress is high (Bauman, Silver, Draimin, & Hudis, 2007). Of interest, the regular use of specific aids for adherence, such as linking medication-taking to daily activities and using a buddy system were marginally associated with complete adherence, in keeping with studies showing the benefits of daily routines and social support for medication adherence in chronic illness (Greening, Stoppelbein, Konishi, Jordan, & Moll, 2007; Lyon et al., 2003). In contrast, the need for a memory prompt to recall medication names and the use of a pillbox, which organizes medications and provides a visual memory cue, were marginally associated with nonadherence. It is possible that pillboxes are initiated in the presence of adherence failure or in the context of declining caregiver supervision and increased child participation in the task of taking medicine on a daily basis.

Several child health and developmental factors, as well as specific medication factors, were associated with medication adherence. In our investigation, children with longer time on complex treatment regimens and those with advanced HIV disease were more likely to be adherent. These findings are consistent with studies of adults and children with HIV infection who were more adherent as HIV disease progressed or symptoms developed (Eldred, Wu, Chaisson, & Moor, 1998; Giacomet et al., 2003; Gibb et al., 2003). Caregivers, children, and adolescents may become or remain more vigilant about medication-taking behaviors when children's health becomes more precarious. In contrast, recent inadequate virologic control, as indicated by detectable viral load, as well as high medication burden and health-related limitations in children's daily activities were associated with higher risk for nonadherence, and reflect the current impact of HIV disease and its treatment upon health behaviors. It is important to note, however, that detectable viral load may be observed in the context of perfect adherence, especially among heavily treated children and adolescents who sometimes experience suboptimal suppression of viral replication and antiretroviral drug resistance.

Earlier studies and clinical observation suggest a relationship between older age and nonadherence to medication among children and adolescents with HIV

(Mellins et al., 2004; Williams et al., 2006). However, our results did not support such a relationship, perhaps because the variance associated with age was accounted for by other, more explanatory covariates, such as occurrence of stressful life events that may increase in frequency as children age, and adherence assessor. When modeling for nonadherence to PIs, for example, age of child was significant when adherence assessor was removed from the model but was nonsignificant when adherence assessor was retained in the model. Adherence assessor, on the other hand, remained significant regardless of whether age of child was in the model or not, suggesting that adherence assessor was the more important covariate in the model.

This study was limited by the use of a cross-sectional design to explore dynamic developmental processes. Participants in P219C who completed valid cognitive evaluations may represent an inherently more adherent subgroup of children and adolescents with HIV; thus, our results may not adequately reflect the medication adherence of all children and adolescents with HIV due to selection bias in P219C. We were unable to compare the cognitive functioning of our cohort with a demographically matched sample of children. Additional measures of child adaptive functioning, memory, and executive functioning as well as information regarding the physical and psychological well-being of caregivers were not available in P219C but would contribute information relevant to families' health maintenance behaviors. Overall, medication adherence rates of children and adolescents in this study (85%) were high relative to earlier investigations, which measured adherence over longer time periods of 1 week to 1 month (Mellins et al., 2004; Reddington et al., 2000). Our use of a single, 3-day self-report measure of adherence may underestimate the true prevalence of nonadherence, possibly due to social desirability, improved adherence immediately prior to a medical visit, limitations in the integrity of children's and parents' memories, and the restricted time frame for reporting. However, Williams et al. (2006) provided support for the validity of our adherence measure, identifying a clear trend for improved adherence with declining levels of viral load.

This investigation has important strengths. To date, this is the largest sample of children with HIV infection whose adherence and cognitive status were examined concurrently at different ages. Our large sample size allowed us to identify risk and protective factors for medication adherence among children with HIV. It is clear that multiple factors influence the adherence process, including individual child characteristics, health and medication factors, and the social context within which adherence occurs.

Our findings can assist families and health care providers to target preventive, multilevel interventions to support children and families at highest risk for nonadherence, particularly when medication regimens are initiated. Developmentally appropriate education, deliberate practice of emerging and complex self-care routines, and ongoing monitoring of adherence are essential for all children, regardless of cognitive status, especially during early adolescence when caregivers and teens anticipate greater independence. Children and families who experience stressful life events, even if short-lived, may require additional psychosocial support and monitoring to enhance adherence. Stress management and problem-focused coping skills may be particularly useful for children and caregivers and could be facilitated in a primary care setting in which culturally sensitive mental health care and case management are available. Prospective longitudinal studies are needed to further delineate children's adherence needs as they develop and to evaluate the efficacy of targeted strategies for adherence support.

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Conflicts of interest: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Allergy and Infectious Diseases or the National Institute of Health.

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Appendix

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