ARTICLE

Predictors of Adherence to Antiretroviral Medications in Children and Adolescents With HIV Infection

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ABSTRACT

BACKGROUND. Most evaluations of adherence to antiretroviral therapy in children with HIV infection have focused on validation of adherence measures via their association with virological outcomes. However, few studies have fully explored associations with other factors to guide development of adherence interventions.

METHODS. In this study, we examined the relationship of self-reported medication adherence to health, demographic, and psychosocial characteristics of children and their caregivers, using data from an ongoing multicenter prospective observational study of long-term outcomes of HIV infection conducted by the Pediatric AIDS Clinical Trials Group. Child and caregiver characteristics were evaluated for association with adherence via univariate and multiple logistic regression models.

RESULTS. Of the 2088 children and adolescents, 84% reported complete adherence to antiretroviral therapy medications over the past 3 days. The median viral load was ~10 times higher among nonadherent than adherent children, and the strength of this association increased with age. Factors associated with at least marginally significant increases in nonadherence in a multiple logistic regression model included increasing age in years, female gender, detectable HIV viral load, occurrence of recent stressful life events, repeating a grade in school, self-assessment of adherence by the subject, and diagnosis of depression or anxiety. Having an adult other than the biological parent as the primary caregiver, using a buddy system to remember to take antiretroviral therapy medications, higher caregiver education level, previous adherence assessments, and taking antipsychotic medications were each associated with improved adherence. After controlling for these characteristics, there was no significant association of adherence with race, knowledge of HIV status, medication burden, CD4 percentage, or current antiretroviral therapy.

CONCLUSIONS. Rates of self-reported adherence were relatively high and were influenced by multiple child and family characteristics. These findings identify targets for adherence interventions and highlight the importance of evaluating and supporting the family environment to optimize adherence.

Key Words: medication adherence, HIV, family environment, child behavior, adolescents, stressful life events

Abbreviations: ART—antiretroviral therapy; HAART—highly active antiretroviral therapy; REACH—Reaching Excellence in Adolescent Care and Health; PACTG—Pediatric AIDS Clinical Trials Group; NRTI—nucleoside reverse transcriptase inhibitor; PI—protease inhibitor; PCG—primary caregiver; CDC—Centers for Disease Control and Prevention; ADHD—attention-deficit/hyperactivity disorder; CI—confidence interval; OR—odds ratio

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Establishing and maintaining adherence to medication is a difficult goal for individuals with chronic illness, even when the treatment regimen is simple and the patient is clearly symptomatic. Antiretroviral therapy (ART) for HIV disease is often highly demanding, requiring multiple medications and frequent dosing, with significant negative adverse effects. Children and adolescents with HIV infection may face additional and unique obstacles to achieving adherence, such as cognitive deficits, parental illness, depression, or behavioral problems. Adherence failure may result in early ART failure, development of resistance to ART, and subsequent reduction of treatment options.

Despite the importance of adherence in the successful clinical management of pediatric HIV infection, studies in children and youth are limited. Studies in clinical settings or adherence reports that are part of a multicenter antiretroviral treatment trial have focused on evaluating methods of adherence assessment or have examined the association between adherence and virological outcomes. For example, a 3-day recall tool was shown to be a useful surrogate marker for monthly adherence and predicted virological response to highly active ART (HAART) in a randomized trial of protease inhibitor-containing combination regimens in children with HIV infection. Similarly, the largest study to date outside the clinical trial setting found that children whose caregivers reported no missed doses in the previous week were more likely to have an undetectable viral load (<400 copies per mL). Although these studies suggest that self-report measures of adherence may be valid, other investigations of self-reported adherence outside of the clinical trial setting found that this assessment method overestimated adherence compared with both pill count and electronic monitoring results.

Studies in older adolescents with HIV infection have begun to investigate factors associated with adherence. Results from 231 adolescents on HAART participating in the Reaching Excellence in Adolescent Care and Health (REACH) trial suggested that later HIV disease stage, more alcohol use, dropping out of high school, and lower CD4 count were associated with decreased adherence to ART regimens. The subjects included in the REACH study were infected as teens, primarily through sexual behavior, and were old enough (mean age: 18.4 years; range: 15–22 years) that they reported on their own medication adherence.

Identifying children and adolescents who have assumed responsibility for medication administration, along with factors associated with taking on such responsibility, is important, because such knowledge helps target interventions for improving adherence. In particular, behavioral and learning problems might reduce a child’s motivation or ability to assume and maintain responsibility for taking medications in a systematic manner. Thus, evaluating the adherence levels among those who assume this responsibility for their own medications may also aid in developing adherence strategies.

Although existing studies have suggested some factors associated with adherence outcomes in pediatric HIV infection, most have been relatively small and have focused on a narrow age range, such as older adolescents or younger children. These study characteristics have limited the ability to evaluate specific factors predictive of adherence in children of different ages, demographic and family environment backgrounds, and health status. Such an understanding is necessary to provide a foundation for the development of targeted adherence interventions. The primary goals of this study were to characterize adherence to ART in a cohort of perinatally infected children aged 3 to 18 years, to evaluate the association of the 3-day recall adherence instrument with virological functioning, and to identify predictors of adherence in children and adolescents with perinatally acquired HIV infection. Secondary objectives were to characterize children and adolescents responsible for their own ART medications and to evaluate predictors of nonadherence within this subgroup.

Methods

This cross-sectional evaluation was based on data collected as part of the Pediatric AIDS Clinical Trials Group (PACTG) 219C cohort study, which has been enrolling and following both HIV-infected and uninfected perinatally exposed children in the United States since September 2000. PACTG 219C was a revised version of the original PACTG 219, which was a protocol initiated in 1993 to study long-term effects of in utero ART exposure and complications of HIV infection in children, as described in greater detail elsewhere. The original PACTG 219 study allowed enrollment only of children who were co-enrolled in another PACTG treatment trial or of children whose mothers participated in such a trial. The revised version, PACTG 219c, extended enrollment to any HIV-infected or HIV perinatally exposed child aged ≥21 years. Children were enrolled by direct contact with study staff at 1 of the 89 participating PACTG 219c sites (see “Acknowledgments”); these sites represented a mix of both urban and rural sites across the United States, including Puerto Rico. The study protocol for PACTG 219C was reviewed and approved by the institutional review board at each of the participating sites, and written informed consent was obtained from each child’s parent/guardian or from older participants who could self-consent. Written assent was obtained from children ≥12 years when appropriate.

At the time of enrollment into PACTG 219C, clinical records were abstracted to obtain medical and clinical histories, including a complete history of ART medications and clinical and neurologic diagnoses. In addition, CD4+ T-lymphocyte percentages and HIV viral loads were measured and sociodemographic and quality-of-life data were collected. These data were used to calculate adherence using multiple methods, including pill count, electronic monitoring, and self-report measures. The primary goals of this study were to characterize adherence to ART in a cohort of perinatally infected children aged 3 to 18 years, to evaluate the association of the 3-day recall adherence instrument with virological functioning, and to identify predictors of adherence in children and adolescents with perinatally acquired HIV infection. Secondary objectives were to characterize children and adolescents responsible for their own ART medications and to evaluate predictors of nonadherence within this subgroup.
life information was obtained as reported by the child and/or caregiver. Every 3 months, follow-up visits were conducted to collect information on the use of ART and other medications, HIV immunologic and virologic parameters, neurologic and psychiatric diagnoses, quality of life, and adherence to ART. The criteria for reporting neurologic and psychiatric diagnoses require that they be based on adequate source documentation from a mental health practitioner or with school documentation (eg, for mental retardation). Children eligible for the present evaluation must have been perinatally HIV infected and have had an adherence assessment at a PACTG 219C study visit while aged 3 to 18 years along with a viral load measurement taken within 6 months of their adherence assessment. Although the PACTG 219C study also includes children infected via routes other than perinatal exposure, these participants compose <10% of the subjects and were felt to represent a distinct group; thus, they were not included in our assessment. The latest available adherence assessment as of April 2004 was used in this analysis, along with most recent measures of health status, child and caregiver characteristics, quality-of-life measures, and ART regimens before the adherence assessment.

We defined adherence based on a self-report measure that has been validated as described previously, and which is currently used as part of standard practice in primary therapy PACTG studies. The questionnaire uses a standardized script to ask the person responsible for medication administration to report on missed doses for each drug that the subject was currently taking over the 3 days before the study visit. The adherence questionnaire is administered by the study nurse or other clinical care research team member with experience completing ACTG forms. Before the study visit, the study nurse completes the information on the expected doses of each ART medication according to the prescription for that study subject. Site personnel administering the form are instructed to read the script exactly as written until the assessment is completed. The instructions also provide information to the site personnel administering the form on the importance of maintaining a nonjudgmental and supportive attitude. We defined complete adherence as taking all of the ART medications during the previous 3 days and also defined separate indicators of adherence for each drug class: nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors, and protease inhibitors (PIs). A small number of subjects (<20) who were not able to recall whether or not they had missed doses were also classified as nonadherent within that specific drug class and overall. Because other research has suggested that ≥95% adherence levels may be sufficient for maintaining viral suppression, we also considered a cutoff of 95% or better adherence as “adherent” and conducted a sensitivity analysis to compare final model results for this cutoff. Information was also collected on the total expected number of doses over the past 3 days (as a measure of medication burden), the need to prompt subjects or caregivers for names of ART medications included in their prescription, and indicators of techniques used to help remember to take medications, such as pillboxes or buddy systems. In some cases, the primary person responding to the questionnaire was the subject rather than the parent/caregiver, and a separate analysis evaluating predictors of adherence was conducted for this subgroup, in addition to an analysis evaluating predictors of which subjects were responsible for their own medications as based on their adherence self-assessment.

Adherence was characterized by calculating the proportion of subjects taking all of the medications (ie, denying any missed doses on 3-day recall interview). Associations with viral load were conducted using Fisher’s exact test for comparing proportions with viral load ≤400 copies per mL and using Wilcoxon rank sum tests for comparing median viral load. We used κ statistics as measures of the strength of agreement between viral load >400 copies per mL and adherence.

To evaluate potential predictors of nonadherence, we first fit age-adjusted logistic regression models both overall and within the subset of participants who self-assessed adherence. We then fit multiple logistic regression models including all of the predictors with \( P < 0.25 \) in the above age-adjusted models. The covariates included for consideration as predictors of nonadherence included demographic variables (gender, race/ethnicity, non-English primary language, and primary caregiver [PCG] and their education level), immunologic and virologic measures of health status (CD4%, viral load ≥400 copies per mL, Centers for Disease Control and Prevention [CDC] class), adherence-related measures (person assessing adherence, knowledge of HIV status, medication burden, need for prompting, and types of reminders for taking ART), ART use (past and current PI and HAART use and duration on HAART), and psychiatric medication use (use of any psychiatric medication or medications within specific classes, including attention-deficit/hyperactivity disorder [ADHD]), quality-of-life measures (recent stressful life events; social and role functioning measures, such as repeating a grade, limitations on activities, sports, or school attendance; and receiving special help in school), and history of neurologic/psychiatric diagnoses (encephalopathy, cerebral palsy, ADHD, and others). Stressful life events occurring since the last study visit included a list of 18 events relating to changes in the financial stability of the subject and/or household; illness or death of a family member or close friend; and changes in family structure as a result of marriage, divorce, or change in PCG. Although this was a cross-sectional analysis, we also had information from previous visits to ascertain how many previous adherence assessments had been conducted for each subject; this covariate was also incorporated into our models to adjust for...
potential bias because of previous exposure to the adherence instrument.

The same logistic regression modeling approach described above was used to evaluate potential predictors of whether adherence was self-assessed or not. For all of the multiple logistic regression models, subjects missing covariate values were excluded, but final models were confirmed by refitting with and without these predictors. In particular, social and role functioning measures were not collected for subjects under age 5 years, because they were age inappropriate. Both forward and backward selection approaches were used to assess robustness of model results, and C statistics and the Akaike Information Criterion criteria were used to compare and evaluate model fit. All of the analyses were conducted by using SAS 8.1 software (SAS Institute Inc, Cary, NC) and included data submitted to our data management center by April 2004.

RESULTS
As of April 2004, a total of 2384 children and adolescents with perinatally acquired HIV infection had enrolled in PACTG 219C. Of these, 2088 had both an adherence assessment while aged 3 to 18 years and a viral load assessment conducted within 6 months of the adherence assessment; these subjects form the study population for this analysis. These 2088 subjects had been followed on study for a median of 2.3 years before the most recent adherence assessment (interquartile range: 1.2–3.0 years). Of the remaining 296 subjects not included, 24 were >18 years at entry, 81 were still <3 years as of their last study visit, 108 were missing adherence assessments, and 83 were missing viral load within 6 months of their adherence assessment. Thus, excluding those outside the age range of interest, the study population of 2088 subjects represented 92% of the target population. The study population was predominantly nonwhite (86%), and 19% identified a language other than English as their primary language (predominantly Spanish). Almost 60% had a PCG other than a biological parent. The median age was 11.5 years, and 37% had assessed their own adherence. The use of psychiatric medications was relatively common (15%), and 27% of subjects had ≥1 reported neurologic or psychiatric diagnosis before the adherence assessment. Health and demographic characteristics are summarized in Table 1, and characteristics of the adherence assessment are presented in Table 2. The characteristics of all of the study subjects are presented, as well as the subgroup of youth assessing their own adherence.

Overall Adherence and Association With Viral Load
We found that 84% of the subjects were adherent overall, with similar rates of adherence within each drug class. The underlying distribution of percentage of adherence to the overall ART regimen was as follows: 100% adherence: 1764 subjects (84%); 95% to 99% adherence: 4 subjects (<1%); 75% to 94% adherence: 140 subjects (7%); 50% to 74% adherence: 78 subjects (4%); 1% to 49% adherence: 30 subjects (2%); and 0% adherence: 72 subjects (3%). Adherence rates tended to decline with age, with the worst adherence rates among 15- to 18-year-olds (76% overall, as compared with 83%–89% for younger children). The percentage of children with undetectable viral load (=400 copies per mL) was significantly higher among fully adherent children than among nonadherent children (50% vs 27%; P < .001), and median viral load was ~10 times higher among nonadherent than adherent children (median: 4065 vs 414.5 copies per mL). This association held within all of the age groups except the 3- to 6-year-olds (because of a more limited sample size in this group), and the association with viral load became stronger as the age level increased. Despite the significant association between adherence rates and viral load, many adherent subjects still had detectable viral load, and some nonadherent subjects had undetectable viral load, which resulted in a fairly low level of agreement between HIV RNA detectability and adherence (overall κ = 0.13; 95% confidence interval [CI]: 0.10–0.16).

Because we only expect complete adherence to result

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Study Subjects (N = 2088)</th>
<th>Subjects With Self-assessed Adherence (N = 772)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>1076 (52)</td>
<td>404 (52)</td>
</tr>
<tr>
<td>Age, median (interquartile range)</td>
<td>11.5 (8.7–14.1)</td>
<td>14.4 (12.6–16.5)</td>
</tr>
<tr>
<td>Race/ethnicity, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White/others</td>
<td>332 (16)</td>
<td>131 (17)</td>
</tr>
<tr>
<td>Black</td>
<td>1231 (59)</td>
<td>429 (56)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>525 (25)</td>
<td>212 (27)</td>
</tr>
<tr>
<td>Non-English primary language, n (%)</td>
<td>404 (19)</td>
<td>153 (20)</td>
</tr>
<tr>
<td>Primary caregiver, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biological parent</td>
<td>898 (43)</td>
<td>278 (36)</td>
</tr>
<tr>
<td>Relative or other adult</td>
<td>1162 (55)</td>
<td>471 (61)</td>
</tr>
<tr>
<td>Shelter/home</td>
<td>16 (1)</td>
<td>13 (2)</td>
</tr>
<tr>
<td>Self</td>
<td>12 (1)</td>
<td>12 (2)</td>
</tr>
<tr>
<td>Education level of primary caregiver, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1–11</td>
<td>503 (24)</td>
<td>167 (22)</td>
</tr>
<tr>
<td>High school graduate</td>
<td>624 (30)</td>
<td>227 (29)</td>
</tr>
<tr>
<td>Some college/technical school</td>
<td>484 (23)</td>
<td>190 (25)</td>
</tr>
<tr>
<td>College graduate or higher</td>
<td>255 (12)</td>
<td>90 (12)</td>
</tr>
<tr>
<td>Other/not reported</td>
<td>222 (11)</td>
<td>98 (13)</td>
</tr>
<tr>
<td>CD4% level, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤15%</td>
<td>206 (10)</td>
<td>107 (14)</td>
</tr>
<tr>
<td>15%–25%</td>
<td>413 (20)</td>
<td>175 (23)</td>
</tr>
<tr>
<td>≥25%</td>
<td>1469 (70)</td>
<td>490 (63)</td>
</tr>
<tr>
<td>HIV-1 viral load, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1000 copies per mL</td>
<td>961 (46)</td>
<td>336 (44)</td>
</tr>
<tr>
<td>1000–10 000 copies per mL</td>
<td>652 (30)</td>
<td>246 (32)</td>
</tr>
<tr>
<td>≥10 000 copies per mL</td>
<td>495 (24)</td>
<td>190 (24)</td>
</tr>
<tr>
<td>CDC class C, n (%)</td>
<td>562 (27)</td>
<td>210 (27)</td>
</tr>
</tbody>
</table>
in undetectable viral load for subjects on effective regimens, we examined the relationship restricting our interest to those on HAART with or without PI, which accounted for 82% of subjects. There was a significant association between adherence and viral load detectability within this subgroup (P < .001), whereas no association was detected for those not on standard HAART or on ≥3 NRTIs. In addition, the adherence rates increased with decreasing viral load (see Fig 1). The adherence rates were higher for those on HAART than for those on ≥3 NRTIs (85% vs 74%) but similar to those on other non-HAART combination regimens (84%). In addition, a lower percentage of those on HAART had detectable viral load (50% as compared with 74% on either ≥3 NRTIs or other combination ART). Although the association between HIV RNA detectability and adherence was stronger for those on HAART, the overall degree of agreement remained low (κ = 0.13; 95% CI: 0.09–0.16).

In addition to measuring the overall rate of adherence, we found that 25% of those reporting adherence required ≥1 prompt to recall the child’s current prescription or were unable to recall all ART medications. More than half (56%) of participants were taking ≥6 doses of ART drugs each day. Subjects used a variety of tools and techniques to help them remember to take medications; the most common of these were “triggers based on activities of daily living” (25%; ie, at or before certain mealtimes, before bed, etc), pillboxes (15%), buddy systems (8%), and labels (8%; see Table 2). Self-reported adherence rates increased with exposure to the adherence assessment tool; adherence rates ranged from 77% adherent among those with no previous assessment to 88% for those with ≥7 previous adherence assessments.

Identifying predictors of adherence is important for preventing regimen failure, increases in viral load, and subsequent viral resistance. However, many factors associated with adherence rates are also confounded by age. Thus multivariate models that adjust for age and other potential confounders are most appropriate for identifying meaningful predictors. We first present age-adjusted measures of associations of nonadherence within each area of interest (see Tables 3 and 4): demographic characteristics, health indicators, ART and psychiatric medication use, adherence assessment characteristics, quality of life measures, and neurologic/psychiatric diagnoses. We then present our final multivariate model, which incorporates the important predictors from each of these areas (Table 5).

### Association With Demographic and Health Measures
As noted previously, adherence levels varied significantly by age (odds ratio [OR]: 1.10; P < .001), with a 10% increase in the odds of nonadherence per year of age. After adjustment for age, those with an adult other than their biological parent as PCG had reduced odds of nonadherence, and each additional level of PCG education (as defined in Table 2) was associated with a 20% decrease in the odds of nonadherence (see Table 3). Those with RNA >400 copies per mL and those with CD4% <15% had 2.6 and 1.6 times the odds of nonadherence, respectively. Female subjects and those without English as their primary language had a marginally significant increase in the odds of nonadherence. There was no association with CDC class or race/ethnicity.

### Association With ART Regimens and Adherence Assessment Characteristics
After adjustment for age, there was an almost twofold increase in the odds of nonadherence for children and adolescents receiving ≥3 NRTIs as compared with those on HAART, whereas there was no difference in adherence between those on other combination therapies as compared with HAART. The odds of nonadherence were reduced almost by half if the person assessing adherence (assumed to also be the person administering medication) was an adult or relative other than the biological parent. Subjects using a buddy system as an aid to remembering to take ART had significantly improved adherence (OR: 0.62; P = .05). Each increase in level of

**TABLE 2.** Characteristics of ART and Medication Adherence Assessment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Study Subjects (N = 2088, n (%))</th>
<th>Subjects With Self-assessed Adherence (N = 772, n (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person assessing adherence</td>
<td>Self (with or without help from others) 772 (37)</td>
<td>772 (100)</td>
</tr>
<tr>
<td></td>
<td>Biological parent 612 (29)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Relative or other adult 704 (34)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subject knows HIV status 1199 (57)</td>
<td>603 (90)</td>
</tr>
<tr>
<td>Antiretroviral regimen</td>
<td>HAART with PI 1478 (71)</td>
<td>528 (63)</td>
</tr>
<tr>
<td></td>
<td>HAART without PI 244 (12)</td>
<td>98 (13)</td>
</tr>
<tr>
<td></td>
<td>Triple NRTI therapy 98 (5)</td>
<td>45 (6)</td>
</tr>
<tr>
<td></td>
<td>Other ART therapy 268 (12)</td>
<td>101 (13)</td>
</tr>
<tr>
<td></td>
<td>Currently receiving PIs 1519 (73)</td>
<td>548 (71)</td>
</tr>
<tr>
<td>Medication burden</td>
<td>≤3 doses per d 208 (10)</td>
<td>108 (14)</td>
</tr>
<tr>
<td></td>
<td>4–5 doses per d 709 (34)</td>
<td>311 (40)</td>
</tr>
<tr>
<td></td>
<td>6–7 doses per d 932 (45)</td>
<td>290 (39)</td>
</tr>
<tr>
<td></td>
<td>≥8 doses per d 239 (11)</td>
<td>63 (8)</td>
</tr>
<tr>
<td>Assessor needed prompting for any ART drug</td>
<td>None (first assessment) 170 (8)</td>
<td>55 (7)</td>
</tr>
<tr>
<td></td>
<td>1–2 475 (23)</td>
<td>135 (17)</td>
</tr>
<tr>
<td></td>
<td>3–6 1305 (62)</td>
<td>532 (69)</td>
</tr>
<tr>
<td></td>
<td>≥7 138 (7)</td>
<td>50 (6)</td>
</tr>
<tr>
<td>Types of ART reminders</td>
<td>Daily activity 540 (26)</td>
<td>208 (27)</td>
</tr>
<tr>
<td></td>
<td>Pill boxes 307 (15)</td>
<td>161 (21)</td>
</tr>
<tr>
<td></td>
<td>Buddy system 175 (8)</td>
<td>89 (12)</td>
</tr>
<tr>
<td></td>
<td>Labels 175 (8)</td>
<td>61 (8)</td>
</tr>
<tr>
<td>No. of previous adherence assessments</td>
<td>None (first assessment) 170 (8)</td>
<td>55 (7)</td>
</tr>
<tr>
<td></td>
<td>1–2 475 (23)</td>
<td>135 (17)</td>
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</tr>
<tr>
<td></td>
<td>≥7 138 (7)</td>
<td>50 (6)</td>
</tr>
</tbody>
</table>
previous adherence assessments (as defined in Table 2) was associated with a 24% decrease in the odds of nonadherence (OR: 0.76; \( P < .001 \)). We found no association of adherence with either medication burden or a need to prompt the adherence respondent for ART regimen information.

**Association With Neurologic/Psychiatric Diagnoses, Psychiatric Medications, and Quality of Life**

After adjustment for age, there was no significant association of nonadherence with any individual neurologic or psychiatric diagnosis, but those with \( \geq 1 \) neurologic diagnosis had a marginally significant decrease in odds of

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**FIGURE 1**

Percent adherence according to characteristics of the participants: A, age group; B, HIV-1 RNA viral load level among those on HAART; C, PCG, and D, education level of the PCG.
nonadherence (OR: 0.76; P = .06; see Table 4). Subjects receiving ADHD medications and those receiving antipsychotic medications tended to have reduced odds of nonadherence (OR: 0.58 and OR: 0.12, respectively), leading to a marginally significant benefit of psychiatric medications overall (OR: 0.71; P = .06). Almost half of the subjects (46%) had experienced a stressful life event since the last study visit, which was associated with a significant increase in the odds of nonadherence (OR: 1.38; P = .01). In particular, those who experienced a recent financial stress or change in family structure had the greatest increases in odds of nonadherence, whereas we found no significant association of adherence with illness or death of a family member or friend. Repeating a grade in school (26%) was also associated with a significant increase in the odds of nonadherence (OR: 1.32; P = .004).

**Final Multiple Logistic Regression Model for Nonadherence**

In the final multiple logistic regression model, factors associated with at least marginally significant (P < .10) increases in nonadherence included: detectable HIV viral load (OR: 2.46), self-assessment of adherence by the subject (OR: 1.90), occurrence of recent stressful life events (OR: 1.55), female gender (OR: 1.36), repeating a grade in school (OR: 1.36), increasing age in years (OR: 1.05), and a diagnosis of depression or anxiety (OR: 1.85; see Table 5). Improved adherence was associated with higher caregiver education level, having a relative or adult other than the biological parent as the PCG, more previous adherence assessments, taking antipsychotic medications, and using a buddy system to remem-

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**TABLE 3** Age-Adjusted Estimates of Demographic and Health Effects on Nonadherence From Logistic Regression Model in 2088 Children and Adolescents

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Estimated OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
</table>

Demographic and health characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Estimated OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.10 (1.07–1.14)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Female</td>
<td>1.25 (0.98–1.58)</td>
<td>.07</td>
</tr>
<tr>
<td>Nonwhite race</td>
<td>1.20 (0.84–1.70)</td>
<td>.32</td>
</tr>
<tr>
<td>Primary language not English</td>
<td>1.29 (0.96–1.71)</td>
<td>.09</td>
</tr>
<tr>
<td>Adult PCG other than biological parent</td>
<td>0.60 (0.47–0.77)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PCG education level</td>
<td>0.80 (0.73–0.89)</td>
<td>.001</td>
</tr>
<tr>
<td>HIV-1 RNA &gt;400 copies per mL</td>
<td>2.55 (1.96–3.33)</td>
<td>.001</td>
</tr>
<tr>
<td>CD4s &lt;15%</td>
<td>1.59 (1.12–2.25)</td>
<td>.01</td>
</tr>
<tr>
<td>CDC class C</td>
<td>0.97 (0.74–1.27)</td>
<td>.84</td>
</tr>
</tbody>
</table>

Characteristics of ART and adherence assessment

<table>
<thead>
<tr>
<th>Adherence assessed by</th>
<th>Characteristic</th>
<th>Estimated OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biological parent</td>
<td>1.00 (Reference)</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>Other relative or adult</td>
<td>1.09 (0.76–1.55)</td>
<td>.64</td>
<td></td>
</tr>
<tr>
<td>Subjects knows HIV status</td>
<td>1.12 (0.81–1.55)</td>
<td>.48</td>
<td></td>
</tr>
<tr>
<td>Current ART regimen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current HAART use</td>
<td>1.00 (Reference)</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>On ≥3 NRTIs</td>
<td>1.80 (1.11–2.90)</td>
<td>.02</td>
<td></td>
</tr>
<tr>
<td>Other combination therapy</td>
<td>1.04 (0.73–1.48)</td>
<td>.83</td>
<td></td>
</tr>
<tr>
<td>Current PI use</td>
<td>0.84 (0.65–1.09)</td>
<td>.18</td>
<td></td>
</tr>
<tr>
<td>Medication burden (no. doses per day)</td>
<td>0.96 (0.88–1.05)</td>
<td>.39</td>
<td></td>
</tr>
<tr>
<td>Prompting for ART drugs required</td>
<td>1.12 (0.86–1.47)</td>
<td>.41</td>
<td></td>
</tr>
<tr>
<td>Buddy system ART reminder</td>
<td>0.62 (0.38–1.01)</td>
<td>.05</td>
<td></td>
</tr>
<tr>
<td>No. of previous adherence assessments</td>
<td>0.76 (0.65–0.89)</td>
<td>&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 4** Percentage of Subjects With Neurologic/Psychiatric Diagnoses and Associated Medication Use and Corresponding Age-Adjusted Effects on Nonadherence From Logistic Regression Model

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>% With Characteristic</th>
<th>Estimated OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic and psychiatric diagnoses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Encephalopathy (HIV or other)</td>
<td>10</td>
<td>0.54 (0.21–1.37)</td>
<td>.19</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>3</td>
<td>1.02 (0.48–2.20)</td>
<td>.96</td>
</tr>
<tr>
<td>Depression/anxiety</td>
<td>3</td>
<td>1.56 (0.85–2.89)</td>
<td>.15</td>
</tr>
<tr>
<td>ADHD/behavioral problem</td>
<td>11</td>
<td>0.78 (0.53–1.16)</td>
<td>.23</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>6</td>
<td>0.73 (0.41–1.30)</td>
<td>.29</td>
</tr>
<tr>
<td>Epilepsy/seizures/spasms</td>
<td>4</td>
<td>0.61 (0.30–1.23)</td>
<td>.17</td>
</tr>
<tr>
<td>Any of the above</td>
<td>27</td>
<td>0.76 (0.57–1.01)</td>
<td>.06</td>
</tr>
<tr>
<td>Psychiatric medication use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADHD</td>
<td>8</td>
<td>0.58 (0.35–0.96)</td>
<td>.04</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>4</td>
<td>0.76 (0.41–1.39)</td>
<td>.37</td>
</tr>
<tr>
<td>Antianxiety</td>
<td>1</td>
<td>1.10 (0.37–3.25)</td>
<td>.87</td>
</tr>
<tr>
<td>Antipsychotic</td>
<td>2</td>
<td>0.12 (0.02–0.85)</td>
<td>.03</td>
</tr>
<tr>
<td>Antiepileptic or anticonvulsant</td>
<td>2</td>
<td>0.88 (0.39–1.99)</td>
<td>.76</td>
</tr>
<tr>
<td>Any of the above</td>
<td>15</td>
<td>0.71 (0.50–1.02)</td>
<td>.06</td>
</tr>
<tr>
<td>Social and role functioning characteristics (a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repeated a grade</td>
<td>26</td>
<td>1.32 (1.03–1.71)</td>
<td>.004</td>
</tr>
<tr>
<td>School attendance limited</td>
<td>11</td>
<td>1.10 (0.76–1.59)</td>
<td>.63</td>
</tr>
<tr>
<td>Normal activities limited</td>
<td>12</td>
<td>1.05 (0.73–1.51)</td>
<td>.79</td>
</tr>
<tr>
<td>No participation in school sports</td>
<td>37</td>
<td>0.88 (0.68–1.14)</td>
<td>.35</td>
</tr>
<tr>
<td>Special classes or special help</td>
<td>34</td>
<td>0.97 (0.75–1.26)</td>
<td>.84</td>
</tr>
</tbody>
</table>

(a) A total of 54 subjects with missing information on stressful life events were excluded from these models.

---

**TABLE 5** Final Multiple Logistic Regression Model for Predictors of Nonadherence

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Estimated OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.05 (1.00–1.10)</td>
<td>.07</td>
</tr>
<tr>
<td>Female</td>
<td>1.36 (1.05–1.77)</td>
<td>.02</td>
</tr>
<tr>
<td>Adult PCG other than biological parent</td>
<td>0.66 (0.51–0.86)</td>
<td>.002</td>
</tr>
<tr>
<td>PCG education level</td>
<td>0.84 (0.75–0.95)</td>
<td>.003</td>
</tr>
<tr>
<td>HIV-1 RNA &gt;400 copies per mL</td>
<td>2.46 (1.85–3.26)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diagnosis of depression or anxiety</td>
<td>1.85 (0.95–3.61)</td>
<td>.07</td>
</tr>
<tr>
<td>Repeating a grade in school</td>
<td>1.36 (1.03–1.81)</td>
<td>.03</td>
</tr>
<tr>
<td>Recent stressful financial life event</td>
<td>1.55 (1.14–2.09)</td>
<td>.005</td>
</tr>
<tr>
<td>Adherence assessed by subject</td>
<td>1.90 (1.36–2.65)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Antipsychotic medication</td>
<td>0.12 (0.02–0.88)</td>
<td>.04</td>
</tr>
<tr>
<td>Buddy system ART reminder</td>
<td>0.58 (0.34–0.98)</td>
<td>.04</td>
</tr>
<tr>
<td>Number of previous adherence assessments</td>
<td>0.79 (0.65–0.95)</td>
<td>.01</td>
</tr>
</tbody>
</table>

A total of 171 subjects with missing values for stressful life events or social/role functioning were excluded from this model.
significant trend of increasing ORs for viral load between viral load and age and verified a marginally fit a supporting model, which allowed an interaction viral load with adherence over increasing age levels, we statistics. Given the finding of increased association of model, and the ART reminder were no longer included in the final measures shown in Table 5 can still be considered a summary ORs for viral load were in the same direction and ranged between 1.7 and 4.5 for our age range, thus, a summary overall model but with a reduced impact on nonadherence (OR: 1.39 vs 1.65). We also evaluated a finer breakdown of the adult caregiver into relative (other than biological parent) versus other adult (ie, foster parent, legal guardian, etc); these predictors were similarly associated with reduced odds of nonadherence (OR: 0.68 and OR: 0.63, respectively), but the model containing these 2 predictors rather than a single indicator of other adult PCGs did not provide as good a fit based on model fit statistics, such as Akaike Information Criterion and C statistics. Given the finding of increased association of viral load with adherence over increasing age levels, we fit a supporting model, which allowed an interaction between viral load and age and verified a marginally significant trend of increasing ORs for viral load >400 copies per mL with increasing age. However, all of the ORs for viral load were in the same direction and ranged between 1.7 and 4.5 for our age range, thus, a summary measure shown in Table 5 can still be considered relevant. When the significance level was set at .05 rather than .10, age and use of a buddy system for an ART reminder were no longer included in the final model, and the P value for a diagnosis of depression or anxiety fell to .03.

Self-assessed Adherence: Characteristics, Predictors, and Adherence Levels

Secondary objectives of this analysis were to describe subjects who assess their own adherence in terms of their background characteristics and evaluate predictors of whether subjects self-assessed their own adherence. Among the 2088 subjects, 772 (37%) assessed their own adherence, alone or with the help of another person. Based on the adherence assessment instructions, we interpret this to mean that these subjects were responsible, at least in part, for their own medication administration. These subjects were generally older than those who did not self-assess adherence (median age: 14.4 years vs 9.8 years), and almost all (90% vs 57%) knew their HIV status (see Table 5). In a multiple logistic regression model (see Table 6), factors associated with increased odds of adherence self-assessment included older age (OR: 1.67), knowledge of HIV status (OR: 2.94), use of pill-boxes as reminders for taking ART (OR: 1.61), a history of either stressful family events (OR: 1.37) or financial events (OR: 1.35), and taking antipsychotic medications (OR: 2.41). Subjects were significantly less likely to assess their own adherence if they had limitations on activities because of illness (OR: 0.47), had repeated a grade or received special help at school (OR: 0.66 and OR: 0.65, respectively), or had ADHD (including taking ADHD medications, OR: 0.55) (see Table 6). Adherence rates tended to be lower among those assessing their own adherence than overall (78% vs 84%); this was partly attributable to the older age of these subjects, but the lower adherence rates in this subgroup persisted even after adjustment for age, viral load, and other covariates, as shown by the final multivariate model in Table 5.

A separate analysis of predictors of nonadherence was conducted within the subgroup of those who self-assessed. The final multiple logistic regression model included many of the same predictors as for the overall population (see Table 5), including gender, adult PCG, PCG education level, viral load, and depression/anxiety, with very similar estimated ORs. Additional predictors of nonadherence for this subgroup included absolute CD4 count at levels 0 to 200, 200 to 500, 500 to 1000, or >1000 cells per mm$^3$ (OR: 0.80; P = .04) and a previous diagnosis of encephalopathy (OR: 0.39; P = .06).

**DISCUSSION**

The results of this investigation suggest that adherence to medication in children with HIV infection is a complex process that is influenced by multiple factors, including demographic, health, medication characteristics, and psychosocial characteristics of the child and family. The results highlight the importance of considering the family context of the child when decisions regarding medication management are made and emphasize that

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Estimated OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.67 (1.58–1.77)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Knowledge of HIV status</td>
<td>2.94 (2.13–4.06)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HIV-1 RNA &gt;400 copies per mL</td>
<td>0.75 (0.58–1.07)</td>
<td>.03</td>
</tr>
<tr>
<td>ADHD diagnosis or medication</td>
<td>0.55 (0.39–0.78)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Need to prompt about regimen</td>
<td>1.53 (1.16–2.03)</td>
<td>.003</td>
</tr>
<tr>
<td>Repeating a grade in school</td>
<td>0.66 (0.50–0.87)</td>
<td>.003</td>
</tr>
<tr>
<td>Special classes or gets special help</td>
<td>0.65 (0.50–0.85)</td>
<td>.002</td>
</tr>
<tr>
<td>Activities limited because of health</td>
<td>0.47 (0.32–0.68)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Antipsychotic medication</td>
<td>2.41 (1.07–5.42)</td>
<td>.03</td>
</tr>
<tr>
<td>History of family stressful event</td>
<td>1.37 (1.05–1.79)</td>
<td>.02</td>
</tr>
<tr>
<td>History of financial stress</td>
<td>1.35 (1.03–1.77)</td>
<td>.03</td>
</tr>
<tr>
<td>Pill box as ART reminder</td>
<td>1.61 (1.16–2.23)</td>
<td>.004</td>
</tr>
</tbody>
</table>

A total of 187 subjects with missing values for stressful life events or social/role functioning predictors were excluded from this model.
psychosocial support for families is crucial when medication adherence is a goal.

The rate of adherence observed in this study (84%) is higher than that observed in other investigations of pediatric populations that used self-report measures or the Medication Event Monitoring System. The higher rate that we observed might be attributable in part to the increased attention given to adherence at PACTG sites at both clinic visits and study visits or may be indicative of a higher rate of overall motivation of those who agree to participate in such research studies. Because we observed that self-reported rates increased with the number of previous adherence assessments, the higher rates that we found may be in part attributable to the long-term follow-up of these subjects (median: 2.3 years). In addition, the self-report of medication taking during the previous 3 days may not adequately capture periods of nonadherence that are intermittent or present over more extended time periods. Others have found 40% to 45% nonadherence rates over longer time periods before the study visit, ranging from a week to a month or since the previous clinic visit. Given the association identified in this study between nonadherence and stressful life events, the limited 3-day time frame may miss nonadherence that occurs during periods of increased stress in the family. Van Dyke et al found that 70% were completely adherent over the last 3 days using the same tool, but this study was initiated around the time that pediatric PI formulations were first being used, so the lower adherence in that study may have been attributable to less experience with these more complicated regimens. In addition, palatability of PI formulations in children has improved somewhat over time, and this cohort included many older children more likely to have mastered pill swallowing. Finally, the higher rate of adherence that we noted might be because of improved adherence just before the health care visit or overreporting of adherence by participants because of social desirability. Although it is generally acknowledged that self-report measures tend to overestimate adherence, the reports of missed medication doses would be expected to identify those nonadherent to medications.

We found a strong association between viral load and complete adherence to ART medications, both when viral load was dichotomized (≤400 vs >400 copies per mL) and based on a clear trend for improved adherence with decreasing levels of viral load, providing additional support for the validity of our adherence self-report measure. However, there remained a large number subjects who reported nonadherence but had low viral load or who were completely adherent yet had higher viral load. It is possible that some of the latter subjects may have had previous treatment with less-than-optimal regimens, which may have resulted in drug resistance and suboptimal suppression of viral replication, despite maintaining good adherence. Greater difficulty in achieving optimal viral suppression in children as compared with adults is well recognized and has been attributed to higher baseline viral load and differences in viral dynamics. Furthermore, those for whom full adherence was reported may not have taken their medications as directed with respect to timing of dosages and food consumption, which could reduce medication effectiveness. Giacomet et al noted that whereas 79% reported no missed doses in the past 4 days, only 11% of caregivers indicated that they gave medications at the correct times. In addition, the reduced capture of nonadherence over longer time frames or during stressful periods noted above, that is, episodic nonadherence, may weaken the agreement between viral load and adherence. In our evaluation, as much as 6 months could have elapsed between the viral load measurement and the adherence assessment, which could also weaken the association. However, in practice, we observed that 89% of the 2088 subjects had both their adherence assessment and viral load measurement on exactly the same date, whereas only 66 (3%) had >3 months elapsed between measurements.

Other research in this area has also commented on the fact that fully adherent patients do not always achieve and maintain viral suppression. For example, Watson and Farley note that approximately half of the adherent subjects in their study failed to achieve and maintain nondetectable viral loads, whereas 10% of nonadherent subjects did achieve viral load below detectable levels despite filling <75% of ART prescriptions. They suggest that this may be because of high initial viral loads in children, previous development of resistance, or use of regimens of insufficient potency. These observations suggest that use of viral load detectability as the only way of validating adherence measures may not be ideal.

We identified multiple factors as influencing adherence in children and adolescents with HIV infection. Older age was associated with increased likelihood for nonadherence in this investigation, consistent with findings of Mellins et al in 3- to 13-year-old HIV-infected children. Studies of medication adherence in other chronic illnesses also indicate that adherence decreases over time. This finding may also be related to our observation that older children in this study were given more responsibility for their own medication management. This assumption of responsibility, whether total or shared, may be premature for some, given that some adolescents with HIV infection may have cognitive or emotional difficulties that influence their ability to function independently. At the same time, they are facing the normal challenges of adolescence that may affect their willingness and/or ability to assume an important health maintenance behavior, such as medication adherence.
We found that female gender was associated with a marginally significant increase in odds of nonadherence, consistent with the findings of several studies of adults with HIV. However, Murphy et al found that male gender was associated with marginally significant odds for nonadherence in adolescents. These findings may be partly explained by the difference in both age and perinatal exposure status of the 2 populations, because the REACH study evaluated by Murphy et al was restricted to adolescents (>15 years) with HIV because of risk behaviors, whereas we studied a generally younger group (median age: 11.5 years) of perinatally infected children. Even among adolescents, those who are perinatally infected are more likely to have parents who are ill and unable to provide adequate care; this history may exert greater influence on girls' behavior than boys, because daughters are told about parental HIV illness more often than sons.

The child's relationship with the PCG was identified as a key factor in medication adherence. Children with a relative or other adult as PCG reported better adherence than those cared for by a biological parent, perhaps because biological parents reveal intermittent adherence difficulties more readily than other caregivers. It is also possible that adherence behavior is more successful in the absence of parental HIV illness and associated psychosocial risk factors. Parental HIV illness may disrupt healthy parenting and adherence behaviors, which place children at increased risk for adverse outcomes. Biological parents may be more likely than other caregivers to be of lower socioeconomic status. Poverty places families at increased risk for many stressful life events and has been shown to be strongly associated with child nonadherence.

Higher education level of the caregiver also showed a positive association with adherence rates in our study. This association was not detected by Mellins et al but their sample was much smaller. This association of education level with adherence has been observed in adults with HIV, along with greater confidence in the benefits of ART. The benefit of a positive social support system was also suggested by the higher rates of adherence for the effect of detectable viral load across all of the age groups and fairly consistent estimates of effects for other predictors. However, refitting the model without this particular effect (to allow inclusion
of all of the subjects with nonmissing values of other covariates) had minimal impact on the parameter estimates for the other predictors, although the significance level of age increased (OR: 1.06; P = .01).

Our analysis relied on an outcome of adherent versus nonadherent. We recognize that analysis of a continuous underlying outcome, like percentage adherence rather than a dichotomized outcome, typically provides increased power to detect effects. However, in the case of our data, there are 3 problems with this approach. First, the distribution of percent adherence shown above is highly skewed and, thus, does not satisfy the assumption of a normal distribution required for a standard linear regression model. In fact, because there is a single point mass with 84% of the sample (at 100%), no transformation of this distribution will help to approximate a normal distribution. The second problem lies in the interpretation of results. Although one could fit a generalized estimating equation model to evaluate the percentage adherence, which would not require the strict assumption of normality, the estimates provided by such a model would be for “shifts” in the baseline level of percentage adherence. However, this type of interpretation would be inappropriate when 84% of the subjects overall report 100% adherence. For certain combinations of predictors, we could even end up estimating >100% adherence; in fact, using the final model covariates in Table 5 for predicting percentage adherence (rather than nonadherent versus completely adherent) results in predicted percent adherence >100% for 9% of the study population. Third, when we evaluate a distribution like that observed above, with 84% of the subjects at the upper boundary, the use of regression methods for continuous outcomes gains only minimal power over a dichotomized outcome. Our use of the dichotomized indicator of adherence was, thus, chosen for both improved interpretability and minimal loss of power.

Other publications have noted that adherence levels of ≥95% are often sufficient for maintaining viral suppression. However, we found that only 4 of the 2088 subjects (<0.5%) had ≥95% adherence to their overall ART regimen but not 100% adherence, so there was minimal impact on the subjects self-reported to be adherent. In addition, all of the analysis results were confirmed using the definition of ≥95% adherence, and, not surprisingly, the results were almost identical.

This investigation has many strengths, particularly its large size (>2000 subjects), and its wide range of age groups. These study characteristics provided a unique opportunity to evaluate multiple demographic, health, medication, and family and child psychosocial characteristics. The adherence questionnaire used in our evaluation is a standardized tool used in many other studies. However, this study also had recognized limitations. First, the single self-report of adherence may underestimate the prevalence of nonadherence because of both overreporting and inability to capture intermittent nonadherence over longer time periods. Secondly, the cross-sectional design only allows us to evaluate the association between adherence and other factors, rather than the variability and consistency of adherence over time.

Finally, the subjects considered in this evaluation are a subset of those enrolled in PACTG 219C and may not be completely representative of the general pediatric HIV population.

Despite these limitations, the study has several important implications. First, the results suggest that child and family characteristics should be evaluated before initiation of ART medications in perinatally HIV-infected children to identify those at higher risk of nonadherence. Such an evaluation will allow preventive education and intervention efforts to be initiated early if risks to adherence are apparent. In addition, clinical staff must be sensitive to changes in family structure or financial status and develop social and financial supports to reduce these stresses. Although such support systems require additional resources, the benefit in reducing later health problems will likely outweigh the costs. It is particularly important that social support systems exist for adolescents as they strive for autonomy and as parents and caregivers withdraw their supervision of their children’s medication adherence during adolescence.

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