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# Cognitive, Academic and Behavioral Correlates of Medication Adherence in Children and Adolescents with Perinatally Acquired HIV Infection

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## Abstract

**Objective—**Medication adherence is critical to the success of antiretroviral therapies for children and youth with perinatally acquired HIV. Factors that influence successful transition of medication responsibility from caregivers to youth are poorly understood. The purpose of this study was to evaluate the relationship of medication adherence with demographic, cognitive, academic, and behavioral characteristics.

**Method—**Randomly selected youth, N = 151, age 8-18, completed cognitive and academic measures, and they and their caregivers completed questionnaires assessing behavior and emotional well-being. An announced pill count and questionnaires completed by youth and their caregivers were used to evaluate adherence.

**Results—**Of 151 participants, 100 completed all adherence measures. Adherence rates varied by assessment method. Non-adherence (<90%) by pill count was associated with older child age, greater youth responsibility for medications, and other demographic and medication regimen variables. Verbal impairment predicted better self-reported adherence and reading problems predicted better self- and caregiver-reported adherence. Youth-reported locus of control was associated with pill count non-adherence, and poor relationships with parents were associated with youth-reported non-adherence.

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**Conclusion—**Consideration of youth cognitive or academic status may be helpful in evaluating medication adherence in patients with perinatally acquired HIV infection, particularly when using self- or caregiver reports to assess adherence. Vigilance for adherence problems is indicated when youth are older, responsible for medications, report poor caregiver relationships, and/or sense a lack of control over their lives.

### Keywords

HIV; children; adherence; antiretroviral therapy

## INTRODUCTION

Despite advances in preventing perinatal transmission of HIV, an estimated 2.5 million infants and children were living with HIV worldwide as recently as 2009, and an estimated 370,000 new infections occurred in people under age 15[1]. Almost 354,000 children worldwide were receiving antiretroviral (ARV) medications in 2009, unfortunately representing a minority of the children who would benefit from treatment. As children with perinatally acquired HIV infection reach adolescence and young adulthood, their ability to maintain ARV adherence independently gains greater importance. Poor adherence to highly active antiretroviral therapy (HAART) increases the risk of treatment failure and development of drug resistance, which can limit treatment options and present public health concerns if the youth engages in high-risk sexual behaviors. Unfortunately, treatment for HIV presents special challenges for adherence, such as demanding dosing schedules and significant adverse side effects such as nausea, fatigue, peripheral neuropathy, and body fat redistribution, among others. Studies of adherence in people with other chronic diseases, such as diabetes, indicate adherence is especially problematic for adolescents[2], a pattern seen in perinatal HIV infection as well[2]. Clinicians caring for youth with HIV infection need to understand what factors influence an adolescent's ability and readiness to follow a complex treatment regimen.

Factors previously identified as potential contributors to poor adherence in children with perinatally acquired HIV infection include environmental and family issues (e.g. stressful life events, family history of substance abuse and psychiatric disorders[3,4] and child and caregiver disagreement regarding responsibility for medication tasks[5]); child characteristics (e.g., female gender, older age, academic problems, depression or anxiety[3]); and regimen characteristics such as complexity, formulation, and palatability[6,7]. In adults with HIV infection, research has shown that cognitive factors such as memory impairment relate to poorer medication adherence[8,9,10]. Children and adolescents with perinatally acquired HIV infection are at risk for cognitive deficits, both globally and in specific areas such as language, memory, and academic achievement, particularly if they have a history of AIDS-defining illness[11,12,13,14]. The relationship of specific cognitive factors with adherence in youth with perinatally acquired HIV has not previously been examined, although a recent study by Malee and colleagues[15] suggests that global cognitive functioning has a significant, but limited, relationship. Emotional and behavioral issues that affect this population, such as depression, impulsivity, or oppositional behavior, also have the potential to decrease adherence by affecting motivation to follow medication regimens and relationships with caregivers and medical providers[16].

To date, no studies of perinatally HIV-infected youth have placed adherence in context by including detailed cognitive/behavioral assessments and measures of medication responsibility. The current study explored the contribution of cognitive and behavioral factors, as well as demographic, psychosocial, medical, and treatment regimen variables, to medication adherence in youth with perinatally acquired HIV infection. The study focused

on children and adolescents age 8 through 18 to cover the age range during which young people typically would be expected to assume partial and ultimately complete medication responsibility based on our clinical experience and findings that children with other chronic diseases such as asthma may have partial medication responsibility as young as age seven[17]. Child and caregiver ratings of responsibility for medications were included due to previous studies indicating that non-adherence increases as youth assume greater responsibility for their own medication tasks[3]. It has been suggested that the relationship between increased age and non-adherence in children and adolescents may result at least in part from premature delegation of medication responsibility to youth who are not yet cognitively or emotionally ready to perform this important health task independently[3]. Cognitive assessment instruments were chosen to measure key areas hypothesized to have potential contributions to adherence success, including memory, attention, language comprehension, academic skills, and global intellectual functioning. Both youth self-report and caregiver ratings of youths' behavior, emotional well-being, and relationships were included, as well as demographic and health-related variables.

The measurement of adherence is a complex issue; we previously have shown that different measures of adherence demonstrate limited correlations with one another and different associations with potential predictors of adherence (Farley et al., 2008). Although pill bottles and dispensers that incorporate electronic measurement are considered the gold standard, these generally are not available in clinical practice and self-report of adherence is standard. For the analyses reported herein, pill count was used as the primary measure of adherence; however, because of difficulties in obtaining pill counts in both clinical and research settings, both child and caregiver subjective ratings of adherence also were included. One purpose of our analyses was to examine the differential associations of these measures with demographic, cognitive, and behavioral predictors of adherence.

The goal of this exploratory study was to identify factors associated with non-adherence that might be evaluated in future studies to provide guidance for clinicians in assessing adherence readiness and to target domains for evaluation or intervention to promote adherence in this vulnerable group of youth with HIV infection. We hypothesized that poorer functioning in global cognition and specific cognitive domains (including verbal memory, language comprehension, and reading), and depression and acting-out behaviors would be positively related to ARV non-adherence. This study also provided the opportunity to examine the contribution of demographic, psychosocial, and treatment regimen variables to non-adherence, assess the contribution of medication responsibility to the relationship between cognitive and emotional functioning and adherence, and to explore differences in the relationship of study variables to different measures of adherence.

## METHODS

### Study Design and Participants

This cross-sectional evaluation used data from Pediatric AIDS Clinical Trials Group (PACTG) 1042S (P1042S), a substudy of PACTG 219C (P219C), a long-term observational study that followed HIV-infected (N = 2869) and uninfected (N = 1787) infants, children and adolescents at 38 sites throughout the United States (U.S.) from September 2000 through May 2007 (please see the Acknowledgments section for a list of participating sites.) HIV disease markers (HIV RNA viral load, CD4 counts and percentages), antiretroviral medication use, self- or caregiver-report adherence evaluations, assessments of global cognitive functioning and behavior, and quality of life evaluations were among the data collected in 219C. Further details are available in other publications based on this study[3,18].

For P1042S, a subset of 159 participants with perinatally acquired HIV infection, age 8 through 18 years, were enrolled from a group of 420 randomly selected P219C participants who met the following criteria: actively enrolled in P219C; planned to be on an ARV regimen during study duration with no treatment interruption; youth primary language either English or Spanish; and due for a P219C cognitive evaluation within 3 months prior to entry into P1042S. Random selection of participants was stratified by age (<12 years and ≥12 years) to insure adequate representation of children and adolescents in the analysis. P1042S was reviewed and approved by respective institutional review boards (IRBs) at all 38 participating sites. Written informed consent and assent were obtained from parents, caregivers, legal guardians, and youth participants according to local IRB requirements.

## Measures

Participants completed the following battery of adherence, cognitive, behavior, and questionnaire measures within 12 weeks of study entry.

**Adherence Measures—**Four measures of adherence to ARV medication regimen (pill count, child/adolescent and parent/caregiver questionnaires, and three-day adherence recall interview) were employed in P1042S to evaluate the utility of different measures of medication adherence in youth with perinatally acquired HIV infection. Detailed information about the adherence measures and their associations with markers of disease severity were presented by Farley and colleagues[19]. The analyses reported here used the following three measures, which were validated by their significant association with HIV RNA[19].

1. Pill Count: A 30-day announced pill count was scheduled 4 to 8 weeks after study enrollment and approximately 30 days after ARV medications were due to have been refilled. The pill count was performed by study staff outside of the presence of participants. The percentage of pills taken, or volume of liquid or powder medication consumed, for the whole regimen over the 30-day interval was computed. Based on our previous analyses showing that using a 90% adherence cutoff was significantly associated with log(RNA) viral load and had significant agreement with viral load <400 copies/mL in this cohort[19], pill count adherent was defined as having taken at least 90% of prescribed medication during the reported interval.
2. P1042S Child/Adolescent Questionnaire: Participants responded to an item asking for the approximate time since the youth last missed a dose of ARV medication: within the last week, 1-2 weeks ago, 3-4 weeks ago, 1-3 months ago, more than 3 months ago, or never. Self-reported adherent was defined as having reported no missed doses in the last month prior to the adherence assessment, a definition that provided the strongest association with log(RNA) viral load in this cohort[19].
3. P1042S Parent/Caregiver Questionnaire: Parents or caregivers responded to an analogous item regarding the last time the youth missed a dose of ARV medication. Caregiver-reported adherent was defined as the youth having no missed doses in the last month prior to the adherence assessment. Modest but significant inter-rater agreement for the two questionnaire measures was observed (Kappa = 0.56, 95% CI: 0.41, 0.70).

**Measures of Cognitive, Academic and Behavioral Functioning—**The P219C protocol included periodic administration of a standardized measure of general cognitive functioning, the Wechsler Intelligence Scale for Children-Third Edition (WISC-III)[20] for children age 6-16 or the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III)[21] for youth age 17 and older. These versions of the Wechsler tests were used rather than the more

recent Fourth Edition since the latter were released while the longitudinal P219C study was ongoing. These tests provide standardized composite (Index) scores reflecting verbal comprehension, perceptual organization, working memory (referred to as Freedom from Distractibility on the WISC-III), and processing speed. Because administration of one subtest required to compute the Processing Speed Index was optional in 219C, this index was available for only a subset of participants. The analyses for P1042S included the Index scores of the age-appropriate Wechsler test administered within 3 months of entry into P1042S.

Additional P1042S-specific measures were administered to assess domains of functioning relevant to the study hypotheses. These domains of functioning and associated measures were as follows: (1) Verbal memory: Immediate and delayed recall of two brief stories (Immediate and Delayed Stories subtests from the Children's Memory Scale [CMS[22]] for participants age 8-16 or the Wechsler Memory Scale-III [WMS-III[23]] for participants 17-18 years old); (2) Nonverbal memory: recall of scenes of everyday activities (CMS or WMS-III Family Pictures Immediate and Delayed recall subtests); (3) Attention and working memory: rapid production and manipulation of common series (CMS or WMS-III Sequences subtest); (4) Language comprehension: following increasingly complex verbal commands, and answering questions about paragraphs read by the examiner (Concepts and Directions and Listening to Paragraphs subtests from the Clinical Evaluation of Language Fundamentals-3 [CELF-3[24]]); (5) Academic achievement: word reading, reading comprehension, and mathematical reasoning subtests of the Wechsler Individual Achievement Test, 2nd Edition (WIAT-II[25]); (6) Behavioral and social-emotional functioning: self-report and caregiver-report questionnaires regarding behavior and emotional areas listed in Table 3 (Behavior Assessment System for Children: BASC SRP [youth self-report] and BASC PRS [parent/caregiver report[26]]). All of these measures are standardized, individually administered paper-and-pencil tests with the exception of the measures of behavioral and social-emotional functioning, which are standardized questionnaires completed separately by both the participant and the caregiver.

All assessments were administered according to standardized procedures by licensed psychologists or psychometricians working under the supervision of a licensed psychologist. The examiners rated the validity of each test administration, and assessments considered invalid were excluded from the analyses. Eight participants with Spanish as their primary language were administered, in Spanish, those tests for which published Spanish versions were available; those tests not available in Spanish (CMS, WMS and WIAT) were excluded for those participants. Twelve caregivers completed study questionnaires in Spanish. For both children and caregivers who had difficulty reading (less than sixth grade level in the judgment of site personnel), the questionnaires were administered as interviews; this included the majority (67/100) of the child questionnaires and 29/100 of the caregiver questionnaires. All analyses were based on age-standardized scores published in the test manuals. For each index or scale, impairment was defined as scores that fell more than two standard deviations (SDs) below the population mean for cognitive tests or more than two SDs from the mean in a direction considered maladaptive for the BASC. "At-risk" scores for the BASC were defined as scores falling between one and two SDs from the mean in a maladaptive direction.

**Medical, Treatment, Demographic, and Psychosocial Variables—**The following measures were collected as part of the P219C protocol. Those closest to and within 6 months of the P1042s adherence assessments were included in P1042S analyses: HIV disease markers (HIV RNA viral load, CD4 counts and percentages), ARV medication use, demographic information (age, gender, race, identity and education of caregiver), and quality-of-life data collected via caregiver questionnaire regarding stressful life events, HIV-

related limitations in participant school attendance, and participant history of special education services.

### Statistical Analysis

Both univariate and multiple logistic regression modeling were used to determine which of the cognitive, academic and behavioral outcomes were associated with each of the three adherence measures. Separate univariate logistic regressions of adherence on each of the cognitive, academic and behavioral outcomes were performed. Binary representations of adherence were used, with adherent and non-adherent defined as described above for the pill count, the Child/Adolescent Questionnaire, and the Parent/Caregiver Questionnaire. To adjust for participant, caregiver, disease or regimen characteristics also associated with non-adherence, multiple logistic regression modeling of non-adherence on selected cognitive, academic and behavioral outcomes was performed. If in the univariate logistic regression analyses any other cognitive, academic or behavioral outcomes had p-value < 0.25, then those outcomes also were subjected to multiple logistic regression analyses. Each cognitive, academic and behavioral outcome was represented as a binary outcome (impaired/at-risk versus unimpaired) in the analyses to enhance the clinical relevance of the findings.

All of the demographic, health, medication and other characteristics listed in Table 1 were considered as potential covariates of the cognitive and behavioral outcomes in the multiple logistic regression modeling of non-adherence as well as potential adherence predictors in their own right. Information about youth participants' ARV medication regimen (protease inhibitor (PI) or non-PI; HAART or non-HAART) and medication burden (maximum daily dosage, number of pills per day, and medicine not in tablet or capsule form) were obtained as part of the adherence evaluations completed for P1042S. For analyses of age effects, the sample was stratified into two age groups: those 8 through 11 years old and those 12 through 18 years old at the time of the adherence assessment.

Medication responsibility was derived from a set of questions on the P1042S Parent/Caregiver Questionnaire, administered at study entry, asking the respondent to report whether the child, the caregiver, or both were responsible for medication-related activities[27]. The caregiver report was chosen for the regression analyses based on its more robust association with other study measures[27]; however, child/adolescent and parent/caregiver reports of medication responsibility were significantly correlated with one another ($r = .30$, $p<.01$). Additional details and analyses regarding medication responsibility are reported in Naar-King et al.[27]. Medication responsibility was analyzed as a continuous outcome with values ranging from 1 (caregiver fully responsible) to 3 (youth fully responsible). Values between 1 and 3 showed some degree of shared responsibility

Forward selection with a 10% level of significance for including variables was used to determine the final models. The cognitive and behavioral outcomes were highly correlated, thus separate final models were determined for each outcome. Cognitive and behavioral outcome, age, and medication responsibility were forced into the final models.

## RESULTS

### Study Participants

Of 420 patients randomly selected from P219C participants, 159 agreed to participate and were enrolled in P1042S. Of the remaining 261 participants randomly selected, 99 refused to enroll (volunteered reasons included concerns about logistics and time required), 91 were deemed ineligible, 62 were never approached because the study was prematurely closed to accrual due to funding changes for the PACTG, and for 9, no information was available.

Reasons for ineligibility included being outside the required window for 219C testing, not being on ART at time of selection, or discontinuation from the 219C study.

Among the 159 participants who enrolled in the study, 151 were considered evaluable. The remaining eight participants were considered nonevaluable due to eligibility failure after enrollment, randomization entry error, withdrawal of consent prior to study completion, or failure to complete evaluation due to inability to get to clinic. Comparison of participants in P1042S with all eligible P219C participants indicated that a higher proportion of participants in P1042S had a viral load less than 400 copies/mL (59% vs 48%, p=.04), and a higher proportion of participants in P1042S were on HAART, having been prescribed three or more ARV medications from two or more classes (94% vs 79%, p<0.01).

Of the 151 participants with evaluable data, 100 participants completed all three adherence measures described above and were included in analyses for this paper. Selected participant, caregiver, disease, or regimen characteristics of these 100 participants are shown in Table 1. A comparison of the 100 participants completing all adherence measures with the remaining 51 evaluable participants showed that only knowledge of HIV status differed significantly between the two groups (79% versus 58%, respectively, Fisher's exact test p-value = 0.02).

## Adherence

**Pill Counts—**Participants (n = 120) completed a pill count within one month after study entry. Pill counts were not performed for 31 (21%) participants due to non-return of all medication bottles (10), missed visit (10), prescribed drug holiday (3), participant refusal (3), forgetting or overwhelmed (2), caregiver illness (1), participant's death (1), and loss to follow-up (1). Eight were considered invalid because of missing data for at least one ARV medication in the regimen or the calculated percentage of pills taken was over 110%. Of the 112 valid pill counts, 58 (52%) were at least 90% adherent; this percentage was unchanged when only the 100 participants with all three adherence measures were considered. A more detailed description of the baseline pill count data from this study is provided in Farley et al.[19]

**Youth Self-Reported and Caregiver-Reported Adherence—**The Child/Adolescent Questionnaire was completed and considered valid for 132 participants; 55% reported not missing a dose of ARV medication within the last month. The Parent/Caregiver Questionnaire was completed and considered valid for 138 caregivers; 64% reported that the youth participant had not missed a dose within the last month[19]. When only the 100 participants with all three adherence measures were considered, the percentages of youth not missing a dose within the last month were similar (53% for the Child/Adolescent Questionnaire and 61% for the Parent/Caregiver Questionnaire).

## Correlates of Non-adherence

**Pill count-based non-adherence—**Non-adherence was defined as taking < 90% of prescribed medications. Table 2 shows the participant, caregiver, disease, and regimen characteristics with significant associations with pill count-based non-adherence. For all analyses, odds ratios and confidence intervals are shown in the tables. The following variables had a significant association ($p < .05$) with higher odds of pill count-based non-adherence: older child age, greater participant responsibility for medications, regimen with a drug not in pill form, and African-American race/ethnicity. The following variables had a significant association with lower odds of pill count-based non-adherence: on HAART, greater number of pills per day, and participation in sports.

Table 3 shows the cognitive and behavioral variables significantly associated with pill count-based non-adherence. After adjusting for the variables in Table 2 listed above, only impairment or at-risk on the BASC SRP Locus of Control scale had a significant association with higher odds of pill-count based non-adherence.

**Youth self-reported non-adherence—**Table 2 shows the participant, caregiver, disease, and regimen characteristics with significant associations with youth self-reported non-adherence (missed dose within the last month). Greater participant responsibility for medications had a significant association with higher odds of youth self-reported non-adherence. The following variables had a significant association with lower odds of youth self-reported non-adherence: higher CD4 percent and caregiver education of 12 years (high school graduate) or less.

Table 3 shows the cognitive and behavioral variables with significant associations with youth self-reported non-adherence. After adjusting for the variables with significant associations in Table 2, the following behavioral variables had significant associations with higher youth self-reported non-adherence: impairment or at-risk on the BASC SRP Relation to Parents scale. Impairment on the following variables was significantly associated with lower odds of youth self-reported non-adherence: WISC-III Verbal Comprehension Index, WIAT-II Reading Comprehension subtest, and WIAT-II Word Reading subtest.

**Caregiver-reported non-adherence—**Table 2 shows the participant, caregiver, disease, and regimen characteristics with significant associations with caregiver-reported non-adherence (missed dose within the last month). Log(RNA) viral load had a significant association with higher odds of caregiver-reported non-adherence. No variable had a significant association with lower odds of caregiver -reported non-adherence.

Table 3 shows the cognitive and behavioral variables with significant associations with caregiver-reported non-adherence (youth missed dose within the last month). After adjusting for the variables in Table 2 with significant associations with caregiver-reported non-adherence, impairment on the WIAT-II Word Reading subtest was significantly associated with lower odds of non-adherence.

## DISCUSSION

The findings of this study demonstrate considerable non-adherence to ARVs in our sample of children and adolescents with perinatally acquired HIV infection. A variety of demographic, psychosocial, and treatment regimen variables, some aspects of youth cognitive abilities, and youth emotional and behavioral functioning were associated with medication non-adherence. Three measures of adherence previously validated by their association with viral load[19] were employed in the study. Although pill count is generally considered the least subject to bias of the measures used, self- and caregiver-reported adherence also were included because of their potential as easily obtained and cost-effective clinical measures. The striking differences between results obtained with the three adherence measures were not unexpected given the different processes involved in these measures and their poor agreement with one another as previously reported[19]; these differences emphasize the need to consider the source of adherence information carefully in clinical practice, as noted below.

A number of demographic, psychosocial, and treatment regimen variables were significantly associated with pill count-based non-adherence and provide guidance regarding the need for greater adherence resources for families. Greater non-adherence as measured by pill count was seen in youth who were older, African-American, or had at least one medication not in

pill form. The findings regarding age are largely in agreement with other investigators[3,4] and further emphasize the need for vigilance and support regarding adherence as children with perinatally acquired HIV infection enter and navigate adolescence. As youth naturally withdraw from adult supervision over many aspects of their lives, ensuring that they have an adequate understanding of the importance of medication adherence and education and support regarding how to achieve and maintain it is critical for their survival.

Children and youth of African-American descent had significantly higher odds of non-adherence as measured by pill count in this study. It is possible that the successful assumption of responsibility for medication adherence is particularly complicated by the disparities in access to health care and other services and increased family stress associated with low income, minority status[28]. Information about caregiver income, found to be strongly associated with adherence for children with perinatally acquired HIV[29] in other studies, was unavailable for this study, and information regarding extrafamilial factors was limited. It should be noted that, in our sample, African-American caregivers were significantly more likely to have completed high school than White or Hispanic caregivers. However, neither caregiver education nor recent stressful life events were significantly associated with pill-count measured adherence, suggesting that consideration of other factors is needed. Although refusal rates for the study and completion of pill counts did not differ by race, differential sampling or attrition for the available participants also should be considered; for example, participating clinics may have made a concerted effort to retain minority patients with adherence problems in care due to concerns about this population's access to health care. Follow-up studies are needed to clarify this finding and identify points of intervention, if needed. In the meantime, our findings suggest that particular care should be directed at ensuring that African-American youth receive adequate support as they take on responsibility for their own health care and medication adherence.

Inclusion of a medication not in pill form in the regimen was strongly associated with non-adherence and should warrant close monitoring by care providers. Although the availability of medications in liquid form may facilitate adherence for younger children who are unable to swallow pills easily[7,31], objectionable taste and required volume considerations may present a greater obstacle as children reach school age and adolescence. Adults who switched from pill to a liquid formulation of ritonovir because of problems obtaining pills were found to decrease adherence[30]. Another possible explanation for our finding is that a child in the 8-16 age range who is still taking liquid formulations may have oral aversions that preclude swallowing tablets and present obstacles to taking liquid medications as well. Although this study did not specifically assess pill swallowing ability as a barrier to adherence or obtain information regarding why older youth were on liquid rather than pill formulations, these findings provide additional emphasis for the need to provide interventions to combat pill-swallowing difficulties and aversions, such as described by Garvie and colleagues[31]. In general, the degree to which medication-related factors such as formulation or side effects serve as or are perceived as barriers to adherence may be of importance in making clinical decisions to facilitate adherence. A questionnaire regarding a variety of potential barriers to adherence, including such medication factors as side effects and taste, was administered to both youth and caregivers as part of this study and findings are reported elsewhere[32].

Youth with greater responsibility for their own medication tasks also had poorer adherence, as measured by either pill count or youth self-report, reinforcing the need for greater supervision of medication management during the transition of responsibility from caregiver to child[27]. Youth on HAART or who had greater pill burden had better pill-count measured adherence. This is consistent with other reports of better adherence with higher pill burden and may reflect that adherence tends to improve as children become more symptomatic[33],

although higher pill burden could also reflect other factors such as resistance to a component of commonly used combination medications.

A novel feature of this study was the inclusion of several hypothesis-driven tests of the association between cognitive and academic functioning and medication adherence. Consistent with Malee and colleagues[16], cognitive measures had only modest associations with adherence behavior as measured by pill count, and no relationships reached statistical significance. The finding that cognitive functioning is not significantly related to pill count adherence, while reassuring in some respects, differs from the prevailing literature regarding adherence in adults[34,35]. Limited power due to the small sample size in this study may have contributed to the lack of an association between cognitive functioning and adherence. It is also possible that the greater schedule and environmental structure imposed on youth by school and families decreases the impact of cognitive impairment on adherence and that this impact will become more apparent as the youth achieve greater independence. It should be noted that both youth who do and do not show cognitive impairments relative to others their age still face limitations related to normal developmental processes. These would include immaturity of cognitive functions such as planning, problem solving, and inhibition, and prioritization of the usual tasks of adolescent development such as gaining independence over illness management, all of which have the potential to affect adherence adversely.

The variables associated with self- and caregiver-reported non-adherence are strikingly different from those that show significant relationships with pill count, raising a cautionary note for clinicians against considering the information gained from different adherent assessment instruments equivalent. Relationships with demographic and regimen variables are weaker, with poorer youth-reported adherence associated significantly only with greater youth responsibility for medications, lower CD4 percent, and primary caregiver with greater than high school education, and no significant associations between caregiver-reported non-adherence and demographic variables. The relationship of youth- and caregiver-reported adherence with cognitive and behavioral measures differs in pattern from that of pill-count measured adherence. Impairment on a measure of single word reading was associated with better adherence, as measured by both youth and caregiver report, and impairment on measures of verbal comprehension and reading comprehension were associated with better youth-reported adherence. Impairments in these areas may be particularly apparent to caregivers and others due to their impact on school performance and interpersonal interaction and thus prompt increased supervision of the child or adolescent. This explanation would be consistent with Malee and colleagues' finding that children with either no or significant cognitive impairment showed better adherence than those with borderline cognitive functioning[16], possibly because the need for adherence supervision was not as readily recognized for children with subtle impairments. However, it is also possible that youth may be less likely to be aware of or to report adherence failures in the presence of cognitive impairment or academic impairment or disadvantage (the latter would also be consistent with less reporting of adherence failure by youth whose caregivers have lower educational attainment.) Clinicians should consider assessment of the youth's cognitive status and possibly reading skills when evaluating adherence assessments based on youth self-report or caregiver report. Although self and caregiver reports of adherence were validated through their association with treatment response[19] and provide valuable insight into family perceptions of medication taking, the presence of youth cognitive or academic impairments may complicate their use and interpretation. Supplementing with measures that do not rely on self-report such as pill count or pharmacy refills, at least until the accuracy of self-report is determined, may be advisable when cognitive or reading skills are in question.

Contrary to our prediction, neither youth nor caregiver ratings of depressive symptoms or other emotional and behavioral symptoms were significantly related to non-adherence.

However, youth self-report of poor relationships with parents or caregivers was significantly associated with youth reports of missed doses, and youth self-report of external locus of control (perceived lack of control over life events or low self efficacy) was associated with adherence failure as measured by pill count. Together, these findings support the value of assessing youths' perceptions of interpersonal relationships, family support, and control over their lives in identifying the need for family intervention to promote adherence.

This study has several limitations. Pill count data were not available for a significant number of participants. Although those participants with and without complete adherence data differed only in knowledge of HIV status, this must be acknowledged as a limitation of the study, and in fact as a limitation of using pill count data as an adherence measure in general. The youth and caregivers who participated in P1042S were randomly selected from an ongoing longitudinal study of HIV infection in children and adolescents (P219C), and there were a large number of refusals. The families willing to make the time commitment to participate in P219C, and to devote further time to P1042S, may not be representative of all families affected by pediatric HIV, particularly those with limited time resources or with significant life stress that would make study participation difficult. The cognitive battery focused on widely used clinical tests; future studies should include focused measures of cognitive constructs such as executive functioning or prospective memory, particularly as youth gain more responsibility for medication taking. Finally, information about socioeconomic, demographic, and cultural factors that would help to clarify the significant effect for race was not available for these analyses and indicates the need for further research in this area.

In summary, each adherence measurement technique has strengths and limitations that should be considered carefully when a clinician examines medication taking in young patients with perinatally acquired HIV infection. Clinicians may wish to be especially vigilant for adherence problems, including using multiple measures of adherence, for youth who are older, members of disadvantaged groups, taking medications not in pill form, cognitively or academically impaired, or showing signs of strained family relationships and perception of low control over their lives. The youth's perception of family support, particularly relationships with parents, should be solicited. Inquiring about the division of responsibility for medication-related tasks and being alert for indications that responsibility is being transferred prematurely from caregiver to youth are indicated. In addition, the study results highlight the importance of appreciating both youth and caregiver characteristics when interpreting self-reports of adherence. Determining an adolescent patient's readiness to assume medication responsibility is complex and calls for both using multiple measures of adherence in clinical practice, and bearing in mind the limitations and potential contributions of each measure at all times.

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## Appendix

The following institutions and individuals participated in PACTG Protocol 1042S, by order of enrollment: Children's Hospital Boston: K. McIntosh, B. Kammerer, S. Burchett; University of Maryland School of Medicine: S. Allison, V. Tepper, C. Hilyard: State University of New York at Stony Brook School of Medicine: S. Nachman, J. Perillo, M. Kelly, D. Ferraro: St. Christopher's Hospital for Children: J. Foster, J. Chen, D. Conway, R. Laguerre; Children's Memorial Hospital: R. Yogev, E. Chadwick, K. Malee; Jacobi Medical Center: A. Wiznia, Y. Iacovella, M. Burey, R. Auguste; University of California San Francisco School of Medicine: D. Wara, M. Muskat, N.Tilton; St. Jude Children's Research Hospital: P. Garvie, D. Hopper, M. Donohoe, S. Carr; Tulane Medical School - Charity Hospital Medical Center of Louisiana at New Orleans: R. Van Dyke, P. Sirois, C. Borne, S. Bradford, K. Jacobs, A. Ranftle; Children's Hospital - University of Colorado at Denver and Health Sciences Center: R. McEvoy, S. Paul, E. Barr, M. Abzug; University of Medicine and Dentistry of New Jersey, New Jersey Medical School: J. Oleske, L. Bettica, L. Monti, J. Johnson; Texas Children's Hospital: M. Paul, C. Jackson, L. Noroski, T. Aldape; Baystate Medical Center: B. Stechenberg, D. Fisher, S. McQuiston, M. Toye; University of Miami Miller School of Medicine: G. Scott, C. Mitchell, E. Willen, L. Taybo; University of California San Diego: S. Spector, S. Nichols, State University of New York Downstate Medical Center: H. Moallem, S. Bewley, L. Gogate; San Juan City Hospital: E. Jimenez, J. Gandia, D. Miranda; Duke University School of Medicine: O. Johnson, J. Simonetti, K. Whitfield, F. Wiley; Harlem Hospital Center: E. Abrams, M. Frere, D. Calo, S. Champion; University of Puerto Rico: I. Febo, R. Santos, N. Scalley, L. Lugo; Children's National Medical Center: D. Dobbins, M. Lyon, V. Amos, H. Spiegel; Bronx-Lebanon Hospital Center: E. Stuard, A. Cintron; Johns Hopkins University: N. Hutton, B. Griffith; University of North Carolina at Chapel Hill School of Medicine: T. Belhorn, J. McKeeman; New York University School of Medicine: W. Borkowsky, S, Deygoo, E. Frank, S. Akleh; Yale University School of Medicine: W. Andiman, M. Westerveld; State University of New York Upstate Medical University: R. Silverman, J. Schueler-Finlayson; Los Angeles County/ University of Southern California Medical Center: A. Stek, A. Kovacs; University of Alabama at Birmingham: R. Pass, J. Ackerson, H. Charlton, M. Crain; Medical College of Georgia School of Medicine: C. Mani; North Broward Hospital District, Children's Diagnostic & Treatment Center: A. Puga, J. Blood, A. Inman; Children's Hospital of Philadelphia: S. Douglas, R. Rutstein, C. Vincent, G. Koutsoubis; Long Beach Memorial Medical Center: A. Deveikis, R. Seay, S. Marks; J. Batra; ; Howard University Hospital: S. Rana, O. Adeyiga, R. Rigor-Mator, S. Wilson; Children's Hospital and Research Center Oakland: A. Petru T. Courville; Phoenix Children's Hospital: J. Piatt, M. Lavoie

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## Table 1

Selected Characteristics of Participants (N = 100)

| Characteristic | n | % |
|---|---|---|
| Female | 46 | 46% |
| Age | | |
| 8-<12 y | 34 | 34% |
| 12-<16 y | 56 | 56% |
| 16-<19 y | 10 | 10% |
| Race/ethnicity | | |
| White/others | 17 | 17% |
| African-American | 54 | 54% |
| Hispanic | 29 | 29% |
| Spanish primary language | | |
| No | 87 | 87% |
| Yes | 13 | 13% |
| Primary caregiver | | |
| Biological parent | 41 | 41% |
| Relative | 24 | 24% |
| Other adult | 34 | 34% |
| Shelter/home | 1 | 1% |
| Education level of primary caregiver | | |
| Grade 1-11 | 25 | 25% |
| High school graduate | 29 | 29% |
| Some college/technical school | 27 | 27% |
| College graduate or higher | 10 | 10% |
| Other/not reported | 9 | 9% |
| CD4 percent | | |
| ≤15% | 8 | 8% |
| 15-25% | 26 | 27% |
| ≥25% | 62 | 65% |
| Missing | 4 | — |
| HIV viral load (copies/mL) | | |
| ≤400 copies | 57 | 59% |
| 400-10,000 copies | 22 | 23% |
| 10,000-100,000 copies | 13 | 13% |
| >100,000 copies | 5 | 5% |
| Missing | 3 | — |
| CDC class C | | |
| No | 65 | 65% |
| Yes | 35 | 35% |
| On PI at adherence visit | | |
| No | 22 | 22% |

| Characteristic | n | % |
|---|---|---|
| Yes | 78 | 78% |
| On HAART at adherence visit | | |
| No | 8 | 8% |
| Yes | 92 | 92% |
| Maximum daily drug dosage | | |
| Once a day | 4 | 4% |
| Twice a day | 94 | 94% |
| Three times a day | 2 | 2% |
| Prescribed number of pills per day | | |
| 1-<5 | 21 | 21% |
| 5-<10 | 38 | 38% |
| 10-<15 | 25 | 25% |
| ≥15 | 16 | 16% |
| Regimen with drug not in pill form | | |
| No | 81 | 81% |
| Yes | 19 | 19% |
| Responsibility for medication (caregiver-reported) | | |
| Caregiver fully responsible | 53 | 54% |
| Child and caregiver shared responsibility | 36 | 36% |
| Child fully responsible | 10 | 10% |
| Missing | 1 | — |
| Had recent life stress | | |
| No | 53 | 55% |
| Yes | 43 | 45% |
| Missing | 4 | — |
| School attendance limited by illness | | |
| No | 85 | 89% |
| Yes | 10 | 11% |
| Missing | 5 | — |

CDC, center for disease control and prevention; PI, protease inhibitor; HAART, highly active antiretroviral therapy.

## Table 2

Adjusted and Unadjusted Odds Ratios of Selected Participant, Caregiver, Disease, and Regimen Characteristics by Adherence Measure

| Patient Characteristics | Unadjusted Odds Ratio (95% Limits) | Unadjusted *p* | Adjusted Odds Ratio[a] (95% Limits) | Adjusted *p* |
|---|---|---|---|---|
| Pill count-based nonadherence | | | | |
| Age in years at adherence visit: 12-<19 y | 2.78 (1.19, 6.50) | .019 | 18.88 (3.62, 98.40) | <.001 |
| Degree of youth medication responsibility (caregiver-reported) | 1.25 (0.67, 2.33) | .476 | 2.75 (1.06, 7.17) | .038 |
| On HAART at adherence visit | 0.12 (0.01, 0.97) | .047 | 0.02 (0.001, 0.55) | .020 |
| Number of pills per day | 0.98 (0.96, 1.01) | .187 | 0.91 (0.85, 0.99) | .020 |
| Regimen with drug not in pill form | 1.64 (0.60, 4.49) | .340 | 152.41 (7.72, 3009.84) | .001 |
| Race/ethnicity | | .006 | | <.001 |
| White/other | 1.00 | — | — | (ref) |
| Black non-Hispanic | 4.08 (1.25, 13.28) | .020 | 65.55 (4.78, 898.24) | .002 |
| Hispanic | 1.08 (0.29, 3.99) | .908 | 4.11 (0.30, 55.89) | .288 |
| Participated in sports | 0.35 (0.15, 0.86) | .022 | 0.20 (0.05, 0.84) | .028 |
| Youth-reported nonadherence | | | | |
| Age in years at adherence visit: 12-<19 y | 1.07 (0.47, 2.41) | .872 | 0.64 (0.25, 1.67) | .364 |
| Degree of youth medication responsibility (caregiver-reported) | 2.08 (1.06,4.08) | .033 | 2.28 (1.08, 4.78) | .030 |
| CD4 percent | 0.96 (0.92, 1.00) | .035 | 0.94 (0.90, 0.99) | .018 |
| Primary caregiver: high school grad or less | 0.45 (0.20, 1.03) | .058 | 0.39 (0.15, 0.97) | .042 |
| Caregiver-reported nonadherence | | | | |
| Age in years at adherence visit: 12-<19 y | 0.76 (0.33, 1.73) | .505 | 0.64 (0.26, 1.58) | .331 |
| Degree of youth medication responsibility (caregiver reported) | 1.22 (0.65, 2.27) | .537 | 1.36 (0.70, 2.64) | .368 |

HAART, highly active antiretroviral therapy.</.>

## Table 3

Cognitive and Behavioral Correlates of the Three Adherence Measures (Adjusted Effects of Important Cognitive and Behavioral Outcomes[a])

| Cognitive/Behavioral Assessment[a] | Odds Ratio | 95% LCI | 95% UCI | *p* |
|---|---|---|---|---|
| Pill count-based nonadherence | | | | |
| BASC-SRP locus of control impairment/at-risk | 9.72 | 1.33 | 70.93 | .025 |
| Youth-reported nonadherence | | | | |
| Verbal comprehension index impairment | 0.14 | 0.03 | 0.81 | .028 |
| WIAT-II reading comprehension impairment | 0.25 | 0.07 | 0.92 | .037 |
| WIAT-II word reading impairment | 0.13 | 0.03 | 0.52 | .004 |
| BASC-SRP relation to parents impairment/at-risk | 3.14 | 1.01 | 9.75 | .048 |
| Caregiver-reported nonadherence | | | | |
| WIAT-II word reading impairment | 0.26 | 0.07 | 0.92 | .036 |

LCI, • • •; UCI, • • •; BASC-SRP, Behavior Assessment System for Children-Self-Report of Personality; WIAT-II, Wechsler Individual Achievement Test—Second Edition.

[a]Adjusting for all variables that were retained in the model selection, in addition to age and caregiver-reported medication responsibility (see Table 2).