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Assessing Medication Adherence of Perinatally HIV-Infected Children Using Caregiver Interviews

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Abstract

Medication adherence is critical for children's HIV treatment success, but obtaining accurate assessments is challenging when complex measurement technologies are not feasible. Our goal was

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to evaluate a multidimensional adherence interview designed to improve upon existing adherence measures. Data from caregivers ($N = 126$) of perinatally infected children were analyzed to determine the ability of the revised interview guide to detect potential treatment non-adherence. Questions related to viral load (VL) on a bivariate level included proportion of doses taken in the previous 3 days and 6 months, caregivers' knowledge of prescribed dosing frequencies, and caregivers' reports of problems associated with medication administration. VL was not associated with 3-day recall of missed doses. In multivariate analyses, only caregiver knowledge of prescribed dosing frequencies was uniquely associated with VL. Our modified interview appears to successfully identify family struggles with adherence and to have the capacity to help clinicians address medication adherence challenges.

Keywords

adherence assessment; HIV disease; knowledge of prescribed dosing frequency; pediatrics

The development of antiretroviral (ARV) medications has drastically changed the face of HIV disease among children and adolescents in the United States, significantly reducing morbidity and mortality (Gortmaker et al., 2001). However, adherence rates as high as 95% are likely needed for patients receiving certain ARV regimens in order to ensure maximal suppression of viral replication in both adults (Harrigan et al., 2005) and youth (Gibb et al., 2003). Gaining an accurate assessment of adherence to pediatric regimens among children living with HIV remains a challenging task. Many assessment techniques (e.g., self-report, pharmacy refill, pill counts, and electronic monitoring) exist, each with their own unique benefits and drawbacks (Simoni et al., 2007).

Caregiver or patient self-report is the most commonly used strategy. It is easy, costs little, and can be used in resource-limited settings. However, data are subject to desirability bias, as respondents may inflate adherence to satisfy clinicians. Studies seeking to validate self-report as an adherence assessment strategy in the pediatric setting have yielded conflicting results (Simoni et al., 2007). Several studies have shown that self-reported adherence is associated with health measures. For example, undetectable viral load (VL; VL <400 copies/mL) has been associated with 3-day recall of missed doses in a pediatric HIV clinical trial population (Van Dyke et al., 2002) and in a cohort study (Williams et al., 2006), although in this latter study associations were weaker for younger children than for adolescents. In a smaller study ($n = 90$), undetectable VL was associated with no missed doses reported by caregivers over the previous week (Reddington et al., 2000). However, other studies have documented the overestimation of adherence when using 3-day recall by caregivers of HIV-infected children when compared to pill counts (Steele et al., 2001) and electronic monitoring (Farley, Hines, Musk, Ferrus, & Tepper, 2003; Steele et al., 2001).

Methods

To improve the utility of caregiver adherence reports and to determine the questions most likely to identify children at risk for non-adherence, we modified the procedures and questions of the Pediatric AIDS Clinical Trials Group (PACTG, 2001) adherence interview, a commonly used assessment in pediatric HIV trials. Procedural modifications were made in order to decrease social desirability and self-enhancement bias. Specifically, before asking caregivers to report on their dosing failures (that is, the number of doses they did not give to the children), they were asked to talk about the difficulties they encountered with the medications and the strategies they had tried to address the problems. By first recognizing their challenges and acknowledging their efforts, we anticipated that caregivers might feel less defensive and more comfortable admitting to having missed doses. We examined the extent to which reports of

these difficulties and strategies, as well as caregiver successes (number of doses given rather than missed), were predictive of adherence as measured by the child's VL. The goals of these analyses were to: (a) examine the relationship between VL and caregiver report on a number of adherence questions within the modified caregiver adherence interview, and (b) identify those that could be easily used to screen for possible adherence problems.

Participants

From October 1985 until September 1999 the U.S. Centers for Disease Control and Prevention (CDC) funded the Perinatal AIDS Collaborative Transmission Study (PACTS), which enrolled HIV-infected pregnant and peripartum women and their newborns. The primary purpose of PACTS was to examine the rate of and risk factors for perinatal HIV transmission in four U.S. locations (Atlanta, GA; Baltimore, MD; Newark, NJ; New York, NY). HIV-infected children were followed for the duration of the study; uninfected children were not formally followed after about 18 months of age when their seroreverter status was confirmed (Simonds et al., 1998).

Between March 2001 and March 2003, children formerly enrolled in PACTS were enrolled into the HIV Follow-up Of Perinatally Exposed Children study (PACTS-HOPE). The goal of PACTS-HOPE was to gain a better understanding of the biomedical and psychosocial development of perinatally HIV-infected children. The source population included all living HIV-infected children not lost to follow-up throughout the duration of PACTS ($n = 204$), of which 182 were enrolled. HIV-uninfected but perinatally exposed children, while not included in these analyses, were also enrolled in PACTS-HOPE. Freedman and colleagues (2006) provided information on the sampling plan, procedures, and outcomes of frequency matching.

Study participants for the current analysis were 126 HIV-1-infected children and adolescents and their primary caregivers. Criteria for a child's inclusion in these analyses were: infection with HIV, prescribed ARV treatment at baseline, completed caregiver adherence interview, and blood draw with VL conducted within ± 90 days of the adherence interview. Of the 182 HIV-infected children enrolled in PACTS-HOPE, 56 children were not included in the analyses. Of these 56 children, 23 were not on medication at the baseline assessment, 5 had caregivers who did not complete the adherence interview, and 25 did not have VL data within the acceptable time frame. Three additional participants were excluded because the adherence interview was conducted exclusively with the child. Data presented in this report focus exclusively on the initial adherence interview within PACTS-HOPE.

Procedures

Prior to the initiation of data collection, institutional review board approvals were obtained from the CDC and all participating institutions. Research assistants from all participating sites were centrally trained on general interviewing skills and administration of the adherence interview. Following consent, research assistants or research nurses administered a baseline interview with the caregiver, which lasted approximately 1 hour. Interview measures included assessment of demographics, family structure, and medication knowledge and adherence. The interview was conducted with the primary caregiver (i.e., parent or legal guardian) unless the child was 10 years of age or older, fully informed of his/her HIV status, and had sole responsibility for taking the medications; children who had sole responsibility for medication-taking completed the questionnaires individually and were thus excluded from these analyses. All participants were either English speaking or bilingual, and all interviews were conducted in English. All interviews were conducted in the hospital clinics where the child received his or her medical care. Interviewers read questions and answer options aloud. Also, caregivers were given response cards listing all response categories. Children and their caregivers were compensated with a \$25 gift certificate for the adherence interview. Data regarding each child's

current prescribed medication regimen (medication name, color, type and expected number of doses) were extracted from the child's medical chart prior to the adherence interview. Information about the prescribed medicine was necessary for the adherence interview and was later compared with the caregiver's reports of the prescribed regimen.

Adherence interview

As noted previously, the current adherence interview was based on the PACTG adherence interview; however, a number of changes were made in order to try to decrease social desirability and ultimately increase the utility of the interview questions/format. In accordance with standard administration of the PACTG adherence interview, the interviewer first acknowledged how difficult adherence could be, in an attempt to create a non-judgmental interview context. Then the caregiver was asked to identify the child's ARV medications and number of doses prescribed for each day. If all of the child's prescribed ARV medications identified during chart review were not reported, the caregiver was prompted regarding any omitted medications.

Next, instead of asking about missed doses, the new interview approach engaged caregivers in a discussion regarding their experiences administering medications and inquiring about any side effects that the children had experienced. Among the problems encountered, caregivers were asked if there was *a particular medication that is harder than others to administer?*, if there were *any medications that your child refuses to take?*, and *did the child experience side effects from one or more of the medications?* The hope was that by first recognizing their challenges and acknowledging their efforts, caregivers might feel more comfortable acknowledging missed doses.

The final portion of the interview was consistent with the PACTG adherence interview, wherein caregivers were asked to report on the number of missed doses for each medication taken over each of the previous 3 days. A dichotomous variable was created whereby children were coded as either having taken all of their medication over the past 3 days or having missed at least one dose. Two additional questions were added to evaluate the relation between health and self-reported adherence over a longer period of time, and to examine the effects of a more positively framed question. Caregivers were asked to recall adherence over the previous 6 months:

Thinking back over the past 6 months (that would be since [fill in the month]), what proportion of (child's name)'s HIV medication doses has (s)he taken? and Over the past 6 months, what percent of doses would you say were missed? Responses for the 6-month recall were initially given on a five-category scale. However, because the data were skewed and because high levels of adherence are deemed necessary for maximal viral suppression (Gibb et al., 2003; Harrigan et al., 2005), 6-month recall responses were collapsed into dichotomous variables. For the question asking about the percentage of medications taken over the previous 6 months, the variable was collapsed into those reporting that their children had taken at least 90% of medications and those reporting less than 90%. For the question asking about the proportion of missed medications over the previous 6 months, the variable was collapsed into those who did not report missing any medications and those who reported that they missed at least some.

A ratio of the number of caregiver-reported prescribed doses to documented prescribed doses (ascertained from medical chart review) was calculated for each child to represent the caregiver's knowledge of the child's prescribed dosing frequency. A caregiver knowledge ratio of 1.0 indicated that the caregiver reported the exact same number of doses as was documented in the medical chart. A ratio falling below 1.0 indicated that the caregiver believed that the child had been prescribed fewer doses of medication than what was documented in the medical chart, while a ratio greater than 1.0 revealed that the caregiver reported the child was taking more doses than prescribed. Throughout the rest of the paper this ratio will be referred to as caregiver knowledge of prescribed dosing frequency.

Clinical Monitoring of VL

Blood draws for VL measurement were scheduled and obtained based upon the clinical monitoring needs of individual subjects. VL data from these visits were obtained for the study through medical chart review. As noted above, participants were excluded if VL data were not available within 90 days of the adherence interview. Assays were performed by either the Roche Amplicor reverse-transcribed PCR method (range 400–750,000 copies/mL of plasma; 88.1%), the Roche Ultrasensitive Amplicor (10.3%), the Organon NASBA (0.8%), or another method (0.8%). All results were log₁₀-transformed. Results below 400 or above 750,000 copies/mL were assigned values of 399 or 750,000, respectively, before log transformation. After log₁₀ transformation, VL data were used as a continuous variable.

Data Analyses

Correlation analyses were conducted to examine the interrelationships between VL, 3-day recall (percentage missed), 6-month recall (percentage taken and percentage missed), caregiver knowledge of dosing frequency and report of medication administration difficulties (*yes/no*). Chi-square tests and Pearson product-moment correlation coefficients were calculated depending on whether the data were categorical or continuous. Significant bivariate associations between VL and the other measures were identified. Multivariate linear regression models were used to examine the extent to which variables that were significantly associated with VL in bivariate analyses were independently associated with VL. All analyses were two-tailed, and a *p* value of < .05 was established as the threshold for significance. Analyses were performed using SPSS 13.0 for Windows (SPSS, Inc., Chicago, IL).

Results

Participants

The sample included 126 HIV-infected children and the children's primary caregivers. Children ranged in age from 2.9 to 15.1 years old ($M = 7.7$, $SD = 2.7$); 61% were female (See Table 1). In all cases, caregivers and children were identified as having the same racial and ethnic background. Seventy-six percent of the families were non-Hispanic African-American, 16% Hispanic, 6% non-Hispanic Caucasian, and 2% other or unknown.

Children who were not included in the analyses did not differ from those who were included with respect to VL, gender, race, or relationship to caregiver. However, children included in analyses were significantly younger than children who were ineligible for this analysis (mean age [years]: 7.7 vs. 9.1; $p < 0.001$). One possible explanation for this age difference is that children who completed the adherence interview independently were excluded from analyses and these children tended to be older.

Prescribed Therapy and Viral Suppression

Children were prescribed a median of three (range: 1–6) ARV formulations for treatment of their HIV infection. Children had been on their current regimens for an average of 2.63 years. Twenty-three (18%) were prescribed four or more formulations, 78 (62%) were prescribed three formulations, and 25 (20%) were prescribed one or two formulations. The majority of children (87%) were prescribed a twice-a-day regimen, while the remaining 13% were on a three-times-a-day regimen. All but 21 (17%) children were prescribed a regimen including one or more protease inhibitors (PI) and/or a non-nucleoside reverse transcriptase inhibitor (NNRTI). Three children were prescribed triple nucleoside analogue therapy, 15 were prescribed dual nucleoside analogue therapy, and 3 were prescribed didanosine monotherapy. Twenty-eight percent took all their medications as liquids, 26% were prescribed pills only, and 2% took only medications distributed as powders. Thirty-eight percent took a combination of

liquids and pills. The remaining 6% had a combination of powders, liquids, pills, and/or injections. Lastly, 28% of the children were instructed to take at least one of their medications on an empty stomach.

Of the 126 children, 36% had VLs ≤ 400 copies/mL, 6% had 401–1,000 copies/mL, 32% had 1,001–9,999 copies/mL, 18% had 10,000–99,999 copies/mL, and 9% had 100,000–750,000 copies/mL. The median was 2,121 copies/mL.

Adherence and Viral Load

Three-day recall—Full adherence over the previous 3 days was reported by 109 (87%) caregivers. Seventeen caregivers (13%) reported at least one missed dose, with a total of 41 missed doses of nine different medications. Lamivudine (3TC) and stavudine (d4T) were the most frequently missed medications, with nine missed doses each. No differences were found between demographic characteristics (child's age, or caregiver's age, race, level of education, or monthly income) of families reporting missed doses compared to families not missing doses. Additionally, there were no differences in mean VL between families that reported missing doses and those who did not (See Table 2); similar results were found after restricting the analysis to 67 children who had a VL test the same day as their adherence interviews.

Caregiver knowledge of regimen and dosing frequency—Most caregivers ($n = 101$; 80%) reported the correct dosing frequencies (ratio 1.0). Approximately 13% of caregivers believed their child had been prescribed fewer doses of medication than what was documented in the medical chart (ratio < 1.0); 4% of caregivers reported that their children were supposed to be taking more doses than prescribed (ratio > 1.0). Data were missing for 3% of caregivers. Dosing frequency reports were related to the child's VL ($r = -0.23$, $p = 0.01$), such that the children of caregivers with more accurate dosing frequency reports had lower VLs (See Table 2).

Six-month recall—Eighty-seven (69%) caregivers reported that over the prior 6 months their children took *almost all* of their doses, 16% reported that their children took *most* of their doses, 2% reported that they took *less than half*, while 4% of the caregivers reported that their children took *none* of their medications. Data were missing from approximately 9% of the caregivers. When asked to report *missed* doses over the prior 6 months, 47% of the caregivers reported that their children did not miss any doses, 37% reported that their children missed *less than half*, 4% reported their children missed *more than half*, and 6% reported *almost all* doses missed. Responses were missing from 6% of the caregivers. Neither recall of doses taken nor recall of doses missed was associated with demographic characteristics of the child or caregiver. Recall of doses taken over the past 6 months was significantly related to VL ($r = -0.25$, $p = 0.006$), while the reporting of missed doses in the previous 6 months approached significance ($r = 0.17$, $p = 0.08$; See Table 2).

Identified Problems and Viral Load

Forty-four (35%) caregivers identified 10 different medications as being *harder than others to administer*. The most commonly cited were the PIs, ritonavir (RTV) and nelfinavir (NFV). Approximately 25% also reported that a child refused to take a medication. Of the 10 medications children were reported to refuse, half were PIs and half were nucleoside analogue reverse transcriptase inhibitors (NRTIs). Liquid RTV was mentioned most frequently among drugs refused. Refusing to take a medicine was associated with caregivers reporting at least one medication that was harder to administer ($\chi^2 (1, N = 120) = 31.5$, $p < 0.001$). Refusing medication was associated with younger mean age of caregivers (39.7 years vs. 45.3 years; $t (115) = 2.4$; $p < 0.05$) and was marginally associated with younger mean age of children (6.8 vs. 7.9 years; $t (118) = 1.85$; $p = 0.07$). Difficulty administering any (vs. no) medication and

child refusing (vs. not refusing) medication were associated with higher VLs ($t(123) = -2.22$, $p = 0.03$; $t(118) = -2.65$, $p = .009$ respectively). Just over 16% of caregivers reported that their children experienced at least one side effect, but the presence of side effects was unrelated to demographic characteristics or VL.

Interrelationships Between Adherence Questions

Answers to several adherence questions were interrelated (See Table 2). Three-day recall of missed doses was significantly related to 6-month recall of percentage of missed doses ($\chi^2 [1, N = 118] = 6.9$, $p < 0.01$). Accuracy of caregiver-reported dosing frequency was significantly associated with the 6-month recall of percentage of taken doses ($r = 0.19$, $p < 0.05$). Percentage of doses taken over the previous 6 months was significantly associated with percentage of doses missed over the same time period ($\chi^2 [1, N = 113] = 8.1$, $p < 0.01$). Difficulty administering medication and child refusing medication were also significantly related ($\chi^2 [1, N = 120] = 31.5$, $p < 0.001$).

Predictors of Adherence: Multivariate Modeling

Adherence covariates that were significantly associated with VL ($p < 0.05$ criteria) in bivariate analyses (caregiver knowledge of dosing frequency, percentage of doses taken over the previous 6 months, admission of difficulty in administering medications, and child's refusal to take medications) were simultaneously entered into a linear regression model. Covariates not meeting the $p < 0.05$ level of significance during bivariate analyses were not entered into the multivariate model. None of the demographic variables were entered into the multivariate model given that none of them were significantly related to VL at the bivariate level. With the exception of a statistically significant relationship between caregiver knowledge of dosing frequency and the child's VL ($\beta = -.23$, $p < 0.05$), none of the other variables contributed uniquely to the variance in VL when the variance associated with the other variables in the equation was statistically controlled. Overall the adherence interview responses entered into the multiple regression explained 14% of the variance in VL ($R^2 = 0.14$).

Discussion

Our study explored the utility of an enhanced caregiver interview for assessing adherence to pediatric ARV regimens. Findings from this multi-site study indicated that several questions from our enhanced adherence interview were associated with VL, including the question involving recall of doses taken over the previous 6 months, questions assessing problems associated with the administration of medications, and questions about prescribed dosing frequency.

A positively framed adherence question inquiring about a longer time period appeared to increase accuracy of caregiver reports. In a recent systematic review of self-reported adherence among adult HIV patients, Simoni and colleagues (2006) found a non-statistically significant trend toward longer recall periods being more strongly associated with VL. Our study provided partial support for longer recall periods but also suggested that positivity or negativity of question framing may be critical. In our analyses, 3-day recall of missed doses was not related to VL, contrasting with findings from a larger cohort study (Williams et al., 2006). Reports of $\geq 90\%$ doses taken over the previous 6 months were associated with having a higher VL and yet reports of doses missed were not. It might be that questions focused on missed doses inadvertently create pressure for caregivers to respond in a socially desirable manner. Questions about doses taken, particularly over a longer time period, might be more predictive because they: (a) reduce caregivers' inclinations to respond in a socially biased manner (Johnson, 1993); (b) eliminate the effects of "white coat" adherence (Podsadecki, Vrijens & Tousset, 2006), in which families adhere better to medication regimens immediately before

and after medical appointments; and (c) include assessment of weekend adherence, which might differ from week-day adherence, and might not be captured in 3-day recall assessments (Levine et al., 2005).

A caregiver's report of a child's medication dosing frequency was significantly associated with VL at the bivariate and multivariate levels. Regimen knowledge is an important, necessary component of medication adherence and one that has been gaining attention by researchers in this area (Marhefka et al., 2004; Martin et al., 2007). However, a unique finding from this study was that it was not the caregiver's identification of the child's medications that was related to the VL, but the caregiver's knowledge of the child's prescribed dosing frequency. Caregivers with gaps in knowledge regarding medication dosing frequency (17% in this study) may inaccurately believe that they are being 100% adherent, while they are actually under- or over-dosing. Interestingly, caregiver knowledge of dosing frequency has been examined in at least one previous study and has not been found to be inaccurate (Marhefka et al., 2004). It might be that as children and caregivers age and encounter changing medication regimens, it becomes difficult for some families to keep track of the prescribed regimen. Results suggest that clinicians need to monitor families' awareness of prescribed dosing, especially when changes are made to the dosing schedule.

Caregivers who reported difficulty administering medications had children with significantly higher VLs than those who did not report any problems. Previous work has suggested that compared to caregivers who report no adherence barriers, caregivers who report at least one adherence barrier tend to have children with detectable VLs (Marhefka et al., 2004) and report lower rates of adherence (Marhefka et al., 2008). Asking caregivers about difficulties with medication administration can be a compassionate, nonjudgmental approach to understanding families' adherence experiences, which also provides opportunities for identifying specific intervention needs.

Adherence questions entered into the multivariate analysis were found to explain 14% of the variation in VL, yet a significant amount of the variation is not captured with these questions. Additional factors that were not assessed but that have been found to predict VL in other studies include dose timing (Liu et al., 2006) and the presence of genotypic mutations (Kamya et al., 2007). Future studies should consider including resistance profiles and, therefore, the likelihood of a child's current regimen resulting in an undetectable VL in order to more accurately predict variability in VL.

The present study has a number of strengths including the large, multi-site sample and inclusion of biological markers of disease progression. Further, the sample demographics are representative of the HIV epidemic among perinatally-infected children in the United States (Lindgren et al., 1999). There are also several limitations. First, the cross-sectional design used in this study was unable to capture the dynamic nature of medication adherence over time (Mannheimer, Friedland, Matts, Child, & Chesney, 2002). Secondly, due to the age of the children ($M = 7.7$ years of age), only caregivers' reports were included in the analyses. As this population continues to age, it is important that children are included in conversations with their medical care providers about treatment and adherence, as well as in research studies. Caregiver adherence estimates may overestimate adherence rates. Anecdotal evidence suggests that caregivers are not always aware of when their children miss a dose and that some children may be more willing to admit missed doses to health care providers than to caregivers. Including both a child and caregiver's report of adherence may offer a more representative understanding of adherent behaviors.

Findings from this study have implications for researchers and health care providers working with HIV-infected children and their families, particularly in clinical and resource-limited

settings where complex or electronically enhanced adherence assessments are not practical and laboratory tests of VL are rarely feasible. While the focus in the literature has been on the assessment of adherence for recent doses in order to minimize bias and maximize recall (Chesney et al., 2000), these findings suggest that only including questions regarding recent missed doses will result in limited information about the child's overall adherence. Study results stress the inclusion of multiple adherence questions, in particular, asking about doses taken over the previous 6 months, assessing a caregiver's precise knowledge of the child's dosing regimen, and asking about problems associated with administration of the child's medications. Additionally, framing questions so that caregivers report on doses taken (vs. missed) may result in more accurate reports of adherence. The inclusion of these questions into the routine care of perinatally-infected children can help to identify children and families that are struggling with adherence. Lastly, these questions can help clinicians determine how to intervene. Examples include the identification of a need for more education surrounding a child's medication dosing or the need to implement behavioral strategies to address disruptive behaviors associated with the administration of ARV medications.

In summary, our study used an adapted interviewing approach with expanded questioning to identify questions that could be predictive of adherence. Health care providers need rapid strategies for assessing adherence in clinical settings—especially when infrastructure and economics prevent routine VL testing. This study suggests that adding several additional questions to existing adherence assessments may greatly improve the utility of self-report assessments, while adding just several minutes to an adherence interview.

Clinical Considerations

- When assessing adherence to pediatric ARV regimens through interviews with caregivers, relying only on questions regarding recent missed doses may provide limited or inaccurate information.
- Accuracy of pediatric ARV adherence assessments can be improved by adding questions regarding proportion of doses taken over a longer period of time (e.g., 6 months), and determining the caregiver's knowledge of the child's dosing frequency.
- In addition to phrasing questions regarding non-adherence in an accepting and nonjudgmental manner, assessment approaches that ask caregivers to describe both adherence challenges and adherence successes may yield more honest portrayals of non-adherence and provide valuable information that can be used to develop adherence interventions.

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Table 1

Characteristics of Study Participants

Variable	<i>M (SD)/%</i>	Range
Children <i>n</i> = 126		
Age	7.7 (2.7)	2.9 – 15.1
Gender		
Female	61.1%	
Race		
African-American	76.2%	
Caucasian	5.6%	
Hispanic	15.9%	
Other	2.4%	
Knew diagnosis	22.2%	
Caregivers		
Age	44.3 (11.3)	22– 70
Relationship to child		
Biological parent	40.4%	
Grandparent/other relative	28.6%	
Unrelated foster/adoptive	31.0%	
High School Diploma	53.7%	
Monthly Income		
\$0 – \$ 250	8.7%	
\$251 – \$1,000	40.5%	
\$1,001 – \$ 2,000	33.3%	
>\$2,000	5.6%	
Unknown	12.0%	

Table 2

Correlations Between Measures of Adherence Among HIV-Infected Children on Antiretroviral Therapy, PACTS-HOPE, 2001–2003

	Any missed doses over previous 3 days ^a	Caregiver knowledge of prescribed dosing frequency	% doses taken over previous 6 months ^a	% doses missed over previous 6 months ^a	Medication problem: hard to take ^b	Medication problem: refuses ^b	Medication problem: side effects ^b
Any missed doses over previous 3 days ^a	--						
Caregiver knowledge of prescribed dosing frequency	-.084 ^c .355	--					
% doses taken over previous 6 months ^a	2.673 ^d .102	.186 ^c .048 [*]	--				
% doses missed over previous 6 months ^a	6.872 ^d .009 ^{***}	-.042 ^c .653	8.147 ^d .004 ^{***}	--			
Medication problem: hard to take ^b	.001 ^d .993	.085 ^c .354	6.264 ^d .012 [*]	4.023 ^d .045 [*]	--		
Medication problem: refuses ^b	.020 ^d .887	.073 ^c .435	10.775 ^d .001 ^{***}	1.190 ^d .275	31.482 ^d <.001 ^{***}	--	
Medication problem: side effects ^b	.870 ^d .351	.141 ^c .120	4.331 ^d .037 [*]	.063 ^d .802	.003 ^d .957	1.066 ^d .302	--
Viral load ^e	.057 ^c .529	-.230 ^f .010 ^{***}	-.254 ^c .006 ^{***}	.170 ^c .065	.196 ^c .029 [*]	.237 ^c .009 ^{***}	.047 ^b .605

Note: PACTS-HOPE = Pediatric AIDS Collaborative Transmission Study--HIV Follow-up of Perinatally Exposed Children

^a dichotomized variable: 3-day recall (any vs. none); 6 month taken (almost all vs. ≤ 80%); 6 month missed (any vs. none)

^b dichotomous variable (yes or no)

^c point biserial correlation

d Chi-square test for independence
 e viral load log10 transformation
 f Pearson product-moment correlation
* $p < 0.05$
** $p < 0.01$