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RELATIONSHIP BETWEEN VIRAL LOAD AND SELF-REPORT MEASURES OF MEDICATION ADHERENCE AMONG YOUTH WITH PERINATAL HIV INFECTION

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Abstract

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Poor adherence to antiretroviral therapy (ART) contributes to disease progression and emergence of drug-resistant HIV in youth with perinatally acquired HIV infection (PHIV+), necessitating reliable measures of adherence. Although electronic monitoring devices have often been considered the gold standard assessment in HIV research, they are costly, can overestimate non-adherence and are not practical for routine care. Thus, development of valid, easily administered self-report adherence measures is crucial for adherence monitoring. PHIV+ youth aged 7–16 (n=289) and their caregivers, enrolled in a multisite cohort study, were interviewed to assess several reported indicators of adherence. HIV-1 RNA viral load (VL) was dichotomized into $\geq$ / $<$ 400 copies/ml. Lower adherence was significantly associated with VL $\geq$ 400 copies/ml across most indicators, including 1 missed dose in past 7 days [youth report OR=2.78 (95% CI 1.46–5.27)]. Caregiver and combined youth/caregiver reports yielded similar results. Within-rater agreement between various adherence indicators was high for both youth and caregivers. Inter-rater agreement on adherence was moderate across most indicators. Age $\geq$ 13 years and living with biological mother or relative were associated with VL $\geq$ 400 copies/ml. Findings support the validity of caregiver and youth adherence reports and identify youth at risk of poor adherence.

Keywords

HIV; adherence; antiretroviral; pediatric

INTRODUCTION

During the past decade, combination antiretroviral therapy (ART) has slowed HIV disease progression, increasing the lifespan of youth with perinatal HIV infection (PHIV+) and transforming it into a chronic disease. However, high rates of medication adherence are necessary to achieve viral suppression and prevent the emergence of drug-resistant HIV and disease progression (Lima et al., 2009; Sethi, Celentano, Gange, Moore, & Gallant, 2003). Unfortunately, poor ART adherence among children and, particularly, adolescents is common (Reisner et al., 2009; Steele & Grauer, 2003). In one review, 23 of 32 pediatric HIV studies reported less than 75% ART adherence across all measurement methods, with caregiver adherence reports ranging from 34–100% and youth self-reported adherence from 20–97% (Simoni et al., 2007). Factors (beyond actual adherence) contributing to these variations include measurement methods, sample size, participant age range, assessment interval, and question phrasing. Assessing youth adherence is complicated by diffusion of responsibility between caregivers and youth, the need to consider multiple respondents, and potential for recall and social desirability bias on self-report measures (Allison et al., 2010; Simoni et al., 2007). Adherence is influenced by multiple factors: youth and family characteristics, disease severity, medication regimen, social setting and resources, and even the patient-provider relationship. In other pediatric chronic conditions, and increasingly with youth with HIV, adherence interventions have focused on promoting social support, enhancing family communication, providing education and skills training, and teaching behavioral management strategies (Reisner et al., 2009; Simoni et al., 2007). Since PHIV+ youth will require a lifetime of ART, accurate and practical adherence measures, awareness of modifiable barriers, and the ability to identify and intervene with those at highest risk for poor adherence are crucial.

Objective methods (i.e., electronic monitoring systems (EMS), serum assays, pharmacy refill records) frequently show higher associations with biomedical indicators such as HIV RNA viral load (VL) than self-report but have proved impractical for long-term use in most care settings (Bangsberg, 2008; Berg & Arnsten, 2006). While self-report can overestimate adherence and be subject to forgetfulness, social desirability, and ceiling effects (Levine et al., 2006; Simoni et al., 2006), self-reported adherence correlates significantly with objective adherence measures, VL, incident HIV drug resistance, and CD4 response in both adults and children (Berg & Arnsten, 2006; Simoni et al., 2006; Van Dyke et al., 2002; Williams et al., 2006) prompting efforts to validate and refine self-report measures. For example, revised measures that: a) inquire about longer time periods (previous 7 days or past month), thus capturing adherence on weekdays and weekends; b) ask for reports on adherence “in general” or estimates of doses taken/missed using visual analogue scales or percentages; or c) use multi-item rating scales have demonstrated association with VL across multiple studies (Deschamps et al., 2008; Doró et al., 2011; Kalichman et al., 2009; Lu et al., 2008; Munoz-Moreno et al., 2007; Simoni et al., 2006). Additionally, easily administered adult adherence measures using several brief questions (versus detailed medication dose recall) have shown strong association with health outcomes, providing information equivalent to that obtained from objective measures (Apisarnthanarak & Mundy, 2010; Glass et al., 2008; Julian, Martin, & Erickson, 2010; Mannheimer et al., 2006). Efforts to refine child and adolescent measures have been more limited, but are critical for optimizing youth adherence assessment in research and clinical settings.

VL remains the gold standard for monitoring the efficacy of HIV treatment and measuring the validity of adherence reports. If a patient’s virus is known to be sensitive to current therapy, a detectable VL likely represents poor adherence. Utilizing data from a large, national cohort study of PHIV+ youth, we examined the validity of questions assessing antiretroviral medication-taking behaviors, using youth and caregiver reports, to identify which questions most accurately reflect adherence behaviors as indicated by viral load. We examined the association between these questions and VL, and between VL and key participant sociodemographic and personal characteristics.

METHODS

Participants

Participants included PHIV+ youth and their caregivers enrolled in the Adolescent Master Protocol (AMP) of the Pediatric HIV/AIDS Cohort Study (PHACS). AMP is an ongoing prospective cohort study examining the impact of HIV infection and ART on health, behavioral, and neuropsychological outcomes in children and adolescents with perinatal HIV. Participants were recruited from 15 urban sites in the United States and Puerto Rico. Criteria for AMP enrollment included: 1) perinatal HIV-infection, 2) aged 7 to < 16 years, 3) engaged in HIV medical care, and 4) availability of HIV medical history, including ART since birth.

Procedures

Institutional Review Boards (IRB) at the participating AMP sites and Harvard School of Public Health approved research protocols. Written informed consent was obtained for youth from their parent or legal guardian and from primary caregivers for their own participation. Written assent was obtained from the youths in accordance with local IRB guidelines.

Biomedical and psychosocial evaluations and interviews were performed every six months. Demographic information was collected at study entry; laboratory data, including VL, were collected during each visit. ART adherence interviews were administered separately to youth and caregivers, in English or Spanish, by personnel not involved in the youth's clinical care. ART adherence data used in this analysis are from the 6-month visit (+/- 2 months), the first study visit in which adherence was assessed. Data were obtained between May 2007 and March 2010.

Measures

Youth Adherence—ART adherence was assessed with a structured questionnaire based, in part, on a self-report medication questionnaire developed by the Adult AIDS Clinical Trials Group (ACTG) (Chesney et al., 2000) and adapted by the Pediatric AIDS Clinical Trials Group (PACTG) (Van Dyke et al., 2002). In both the PACTG and the modified AMP questionnaire, participants were queried about the youth's current ART regimen (i.e. medications, number of doses prescribed daily), but while the PACTG questionnaire asked the number of medication doses missed over the previous three days, the AMP questionnaire asked the number of medication doses missed over the previous seven days. The PACTG question "When was the *last time* you/your child missed any medications?" (never, past 3 days, past week, 1–2 weeks ago, 3–4 weeks ago, 1–3 months ago, >3 months ago) was retained. Finally, the AMP measure also assessed general adherence behavior: "*In general*, over the past 6 months, how often did you/your child miss taking any medications?" (hardly ever take any of my medicines, miss most of my medicines, miss about half of my medicine, miss my medicines a little bit of the time, never miss any of my medicine).

Laboratory Values and Youth Health Data—CD4+ T-lymphocyte counts (cells/uL), HIV-1 RNA VL (copies/mL), current ART regimen, and years on ART were collected at study visits or abstracted from medical records. VL and CD4+ counts closest to the 6-month study visit were used in this analysis (window included 6 months prior to and 1 month after). Since ultrasensitive HIV-1 RNA testing was not available at every site, we dichotomized VL into 400 copies/mL and >400 copies/mL.

Covariates—Demographic information included youth age, gender, race, ethnicity, primary language, household income, caregiver relationship to youth, caregiver education, and caregiver cognitive functioning, estimated using the Full Scale IQ (FSIQ) from the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999).

Data Analysis

Response options to the three adherence indicator questions were categorized as follows:

Question	Response Categories
1. How many ART doses were missed in the past 7 days (for each medication)?	1. “Not missed” vs. “Missed at least one dose” ¹
2. When was the <i>last time</i> you/your child missed your/his/her medications?	2. a) “Not in last week” vs. “Missed in last week” b) “Not in last month” vs. “Missed in last month”
3. <i>In general</i> , over the past 6 months, how often did you/your child miss your/his/her medications?	3. “Never missed” vs. “Miss some”.

Each variable was analyzed three ways: youth response, caregiver response, and a combined youth/caregiver response when both were available. In analyses of combined youth/caregiver responses, the participant was considered non-adherent if either respondent reported non-adherence.

Associations between adherence and patient characteristics or VL were assessed using the Wilcoxon or Fisher’s exact test. Logistic regression modeling determined youth, caregiver, and combined youth/caregiver reported adherence associations with VL >400 copies/mL, adjusted for other characteristics significantly associated with VL in the bivariate analyses. Kappa statistics were used to evaluate agreement between youth and caregiver adherence reports and within-rater agreement between responses to the “Missed in last week” category and reporting at least one missed ART dose in the past 7 days. Agreement between youth and caregiver was evaluated overall and stratified by youth age (<13 vs. ≥13). Youth and caregiver reports of number of prescribed ART medications/week were evaluated with Kappa statistics; agreement on number of medication doses/week was analyzed with the Pearson correlation coefficient. Analyses were conducted using SAS Version 9.1.3; statistical significance was based on $p < 0.05$.

Results

Youth were included if they had VL information, were prescribed ART, and completed an adherence interview. Of 364 youth who completed their 6-month visit (first visit adherence data is collected), 75 (21%) were missing adherence and/or VL information, for a final sample of 289. Those missing data were more likely to be female or Hispanic; otherwise, characteristics of youth with missing data were similar to the final sample.

For the final 289 youth, youth adherence data were available from 233 youth, 275 caregivers, and 219 youth/caregiver dyads. Youth reports were reduced primarily due to caregiver concerns about inadvertent HIV disclosure or the youth’s ability to understand interview questions. Seventy-five percent of youth had their VL measured within three days of the adherence assessment; 84% (243) of participants had their VL measured within 7 days, 7% (20) within 8–30 days, and 9% (26) had >31 days between VL measurement and adherence assessment.

¹Total of missed doses for all medications. This variable was dichotomized due to the large number of respondents reporting 100% adherence in the past 7 days.

Youth and Caregiver Characteristics (Table 1)

The number of male and female participants was similar with 54% younger than 13 years. The majority of youth identified as African American and non-Hispanic with English as their primary language. Slightly more youth resided with their biological mother than with either a biological relative or a non-relative. Most caregivers had no more than a high school education; median estimated full-scale IQ was higher for non-relative caregivers than for either biological mothers or biological relatives. Three-quarters of youth had VL >400 copies/mL.

Association between youth characteristics and VL (Table 2)

Factors associated with having a VL >400 copies/mL were: older age, living with their biological mother or relative, a lower household income, and a lower estimated caregiver IQ. Gender, race, ethnicity, youth knowledge of his/her HIV status, number of prescribed ART medication doses per week, primary language, and caregiver education were not significantly associated with VL (data not shown).

Reported adherence (Table 3)

Sixty-four of 232 youth (28%) and 61 of 274 caregivers (22%) reported the youth missed at least one ART dose in the past 7 days. When queried as to the last time medication was missed, youth reported higher rates of non-adherence for medications missed in the last week, in the last month, and in general over the past 6 months than did caregivers.

Association of adherence indicators with VL (Table 3)

Both youth and caregiver reports of non-adherence to ART were significantly associated with VL >400 copies/mL across all adherence indicators. Among youth who reported missing at least one ART dose in the past 7 days, 45% had VL >400 copies/mL. Only 21% of those who reported not missing a dose in the past 7 days had VL >400 copies/mL ($p < .001$).

Asked to recall the *last time* a medication was missed, more youth (48%) who reported missing within the last week had VL >400 copies/mL than did those reporting no missed doses (19%) ($p < .001$). Results were similar when youth were asked for a *general estimate* of missed medications over the last six months: 32% of those reporting missing “some” or more during the last six months had VL >400 copies/mL compared to 19% who reported never missing ($p = 0.04$). Caregiver and combined youth/caregiver reports yielded similar results for all adherence indicators.

Estimated association of adherence indicators with VL >400 copies/mL. (Figure 1)

Logistic regression models associating adherence with VL were also adjusted for youth age and caregiver type. Income and FSIQ, strongly associated with caregiver type, were not included in the multivariable models. All primary adherence indicators remained significantly associated with VL >400 copies/mL in adjusted models, with the exceptions of separate youth and caregiver reports of general adherence over last six months.

Between and within-rater agreement on medication and adherence indicators

We found moderate agreement between youth and caregiver reports (overall and stratified by youth age) for all four indicators of adherence (Table 4). Additionally, within-rater agreement was strong for youth (Kappa = 0.80; 95% CI 0.72, 0.89) and caregiver (Kappa = 0.71; 95% CI 0.61, 0.81) reports of adherence. There was also considerable agreement between youth and caregiver reports regarding the total number of ARV medications in the regimen (Kappa = 0.95, 95% CI 0.91, 0.99) and of doses per week ($r = 0.98$; $p < 0.001$).

Discussion

We found strong associations between VL and youth and caregiver reports of ART adherence among PHIV+ youth, with poorer adherence significantly associated with VL >400 copies/mL across most adherence indicators used in this study. Although similar VL-adherence associations have been reported in the pediatric and adult literature (Khan et al., 2009; Nieuwkerk & Oort, 2005; Simoni et al., 2006; Williams et al., 2006), the data here come from one of the largest cohort studies of PHIV+ youth in the US and thus lend support to the usefulness of self-reported adherence data in general and, more specifically, the validity of youth and caregiver reports of youth adherence. Adjusting for age and caregiver relationship, we found two indicators (*recall of one or more missed ARV doses in past 7 days* and the question “*When was the last time you/your child missed your medications?*”) significantly associated with VL whether caregiver and youth responses were analyzed independently or combined. A third question, asking for *an estimate of general adherence over the past six months*, was significantly associated with VL only for combined youth/caregiver responses.

While others have found low inter-rater agreement rates for ART adherence variables within caregiver/youth dyads (Dolezal et al., 2003), agreement between youth and caregiver responses in this study was moderate across most behavioral indicators and very high with regard to number of ARV medications and doses. Furthermore, analyses of youth and caregiver data demonstrated consistency across adherence indicators, suggesting that youth and caregiver reports of youth adherence can be reliably measured.

Consistent with previous research, rates of reported non-adherence were high, with almost one-third of youth and/or caregivers reporting a missed dose in the past 7 days and more than half reporting one in the past month. Substantial numbers of youth with VL >400 copies/mL reported missing medications during the referenced time frame and, for all questions, youth reported more missed medications than did caregivers.

As in other studies, youth knowledge of HIV status and the number of prescribed weekly doses were not associated with VL. Age, however, was; youth 13 and older were more likely to have VL >400 copies/mL than younger participants, an often-observed pattern in pediatric chronic conditions (Haberer & Mellins, 2009; Khan et al., 2009; McQuaid, Kopel, Klein, & Fritz, 2003; Williams et al., 2006). Adolescence is characterized by a desire for greater control over decision-making. Caregivers often allow adolescents such control, regardless of cognitive and/or emotional readiness. Other factors contributing to non-adherence may

include failure to prioritize medication-taking, a desire to “fit-in” and feel “normal”, fears of unintended disclosure, and treatment fatigue (Haberer & Mellins, 2009; Simoni et al., 2007).

Family structural and social characteristics (i.e., biological mother or relative as caregiver, lower household income, lower caregiver IQ) were also associated with VL >400 copies/mL. For biological mothers, difficulties managing their own HIV infection may complicate coping with their child’s illness. Limited economic resources reduce options and opportunities for functional support, and lower levels of cognitive functioning may make it harder to master complicated treatment plans and understand implications of non-adherence (Mellins et al., 2004; Wagner, 2002). Additional factors associated with increased risk for poor adherence among youth with HIV include higher caregiver stress, lower caregiver quality of life, problems in parent-child communication, inadequate knowledge of HIV and medications, social stigma, and psychological functioning of both patient and caregiver (Mellins et al., 2004; Reisner et al., 2009; Simoni et al, 2007). Family support has been found crucial for adherence in HIV-infected and other chronically ill youth (DeLambo, Ievers-Landis, Drotar, & Quittner, 2004; Marhefka et al., 2008; Martin et al., 2007), and enhancing family efficacy may be important in improving youth adherence.

This study’s limitations include cross-sectional data analysis, which limits inferences of causality. Also, our participants, recruited at primary and tertiary clinics, have extensive research experience and may not represent all PHIV+ youth. The higher rates of missing data from females and Hispanics may have biased the results. Furthermore, mental health and medication side effects, which likely impact youth adherence, were not examined. Health disparities, stigma, discrimination, and social, psychological, and environmental stressors also affect health care behaviors and warrant future studies with this population (Marhefka et al., 2008; Simoni et al., 2007).

Major strengths of this study, beyond sample size, include using multiple questions assessing adherence in different ways over varying time intervals and having interviews conducted by research staff not directly involved in patient care, thus likely minimizing recall and socially desirable response bias.

In summary the indicators *recall of one or more missed ARV doses in past 7 days* and “*When was the last time you/your child missed your medications?*” were significantly associated with VL and, most likely, adherence behaviors, regardless of respondent. The former was used in the context of a broader inquiry into ART medication adherence knowledge and behavior. The latter was a discrete question with multiple response options. Offering a range of responses may detect various adherence patterns, from previously non-adherent individuals who just resumed taking medications to usually adherent individuals experiencing life changes, stress, or disruptions to their routine. Results indicate youth and caregivers can accurately and reliably report youth adherence behaviors. We see these specific questions as particularly valuable in monitoring adherence and alerting providers to those at high risk for treatment failure, and we urge their adoption in both clinical and research settings.

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Figure 1. Association of adherence with HIV-1 RNA viral load >400 copies/mL, estimated from logistic regression models, adjusted for age and caregiver relationship, PHACS-AMP, 2007–2010

Table 1

Demographic and health characteristics of the 289 participants at the time of their adherence assessment, PHACS-AMP, 2007–2010

Characteristic	N=289
Age (years)	12.7 (10.7–14.6)
Male	143 (49%)
Race	
Black or African-American	214 (74%)
White	58 (20%)
Other/More than one race/Unknown	17 (6%)
Ethnicity: Hispanic or Latino	59 (20%)
Primary Language	
English	257 (89%)
Spanish	15 (5%)
Bilingual	17 (6%)
Caregiver Relationship	
Biological Mother	110 (38%)
Biological Relative	94 (33%)
Non-relatives	85 (29%)
Caregiver Education: More than High School ¹	103 (36%)
Caregiver IQ: WASI Full Scale ¹	87 (78–100)
Biological Mother	87 (77–95)
Biological Relative	82 (76–88)
Non-relative	103 (83–113)
Yearly Household Income >20K ¹	148 (55%)
HIV-1 RNA Viral Load: >400 copies/mL	73 (25%)
CD4+ Lymphocyte Count (cells/mm ³)	753 (548–1,003)
Years on ART	9.0 (7.0–10.2)
Youth: Current Number ARV Medications Reported ²	
1–2	56 (24%)
3	130 (56%)
4 or more	46 (20%)
Caregiver: Current Number of Youth ARV Medications Reported ²	
1–2	63 (23%)
3	156 (57%)
4 or more	55 (20%)

NOTE: PHACS-AMP = Pediatric HIV/AIDS Cohort Study-Adolescent Master Protocol

¹ Had missing values: Education=1, IQ=78, Income=18

² 232 youth, 274 caregiver reports

Median (25th–75th) is presented for continuous variables, N (%) for categorical variables

Table 2

Association of selected participant characteristics with HIV-1 RNA viral load, PHACS-AMP, 2007–2010

Characteristics	HIV-1 RNA Viral Load		P-value ¹
	400 copies/mL (N=216)	>400 copies/mL (N=73)	
Age (years)			
Median (25 th –75 th)	12.2 (10.1–14.5)	13.3 (12.1–14.8)	0.01
<13	125 (80%)	32 (20%)	0.04
13 and older	91 (69%)	41 (31%)	
Caregiver Relationship			
Biological Mother	76 (69%)	34 (31%)	0.002
Biological Relative	65 (69%)	29 (31%)	
Non-Relatives	75 (88%)	10 (12%)	
Caregiver IQ (WASI) ^{2,3}			
Median (25 th –75 th)	88 (78–102)	81 (77–89)	0.008
Household Income ⁴			
\$20K or less	84 (68%)	39 (32%)	0.05
\$>20K	117 (79%)	31 (21%)	

NOTE: PHACS-AMP = Pediatric HIV/AIDS Cohort Study-Adolescent Master Protocol

Row percentages are reported

¹Wilcoxon test on continuous variables, Fisher's Exact test on categorical variables²WASI – Wechsler Abbreviated Scale of Intelligence³Missing from 78 participants (50 with viral load < 400 copies/mL, 28 with viral load >400 copies/mL)⁴Missing from 18 participants (15 with viral load < 400 copies/mL, 3 with viral load >400 copies/mL)

Table 3

Association of adherence indicators with HIV-1 RNA viral load, PHACS-AMP, 2007–2010

Adherence Indicator		HIV-1 RNA Viral Load		P-value ¹
Responder	Response	400 copies/mL (N=216)	>400 copies/mL (N=73)	
7 Day Recall - Number of missed doses in past 7 days ²				
Youth	Not missed	133 (79%)	35 (21%)	<.001
	Missed at least one dose	35 (55%)	29 (45%)	
Caregiver	Not missed	174 (82%)	39 (18%)	<.001
	Missed at least one dose	37 (61%)	24 (39%)	
Youth/Caregiver	Not missed	164 (82%)	37 (18%)	<.001
	Missed at least one dose	52 (59%)	36 (41%)	
When was the last time you/your child missed your/his/her medicines? ³				
Youth	Not in last week	135 (81%)	32 (19%)	<.001
	Missed in last week	34 (52%)	32 (48%)	
Caregiver	Not in last week	175 (80%)	43 (20%)	0.008
	Missed in last week	35 (63%)	21 (37%)	
Youth/Caregiver	Not in last week	162 (83%)	34 (17%)	<.001
	Missed in last week	54 (58%)	39 (42%)	
Youth	Not in last month	90 (83%)	18 (17%)	<.001
	Missed in last month	79 (63%)	46 (37%)	
Caregiver	Not in last month	123 (83%)	25 (17%)	0.007
	Missed in last month	87 (69%)	39 (31%)	
Youth/Caregiver	Not in last month	109 (85%)	19 (15%)	<.001
	Missed in last month	107 (66%)	54 (34%)	
In general over last 6 months, how often did you/your child miss your/his/her medicines? ³				
Youth	Never miss	64 (81%)	15 (19%)	0.044
	Miss some	105 (68%)	49 (32%)	
Caregiver	Never miss	94 (83%)	19 (17%)	0.042
	Miss some	116 (72%)	45 (28%)	
Youth/Caregiver	Never miss	76 (84%)	14 (16%)	0.013
	Miss some	140 (70%)	59 (30%)	

NOTE: PHACS-AMP = Pediatric HIV/AIDS Cohort Study-Adolescent Master Protocol

233 youth and 275 caregivers responded.

Row percentages are reported.

¹ Fisher's Exact Test² One youth and one caregiver did not respond.³ One caregiver did not respond.

Table 4

Youth and caregiver agreement on adherence indicators, overall and by age of youth, PHACS-AMP, 2007–2010

Adherence Indicator	Between Rater Agreement: Kappa (95% CI)		
	Overall	Youth age < 13	Youth age ≥ 13
7 Day Recall: missed <u>at least</u> 1 dose in last 7 days ¹	0.53 (0.41, 0.66)	0.49 (0.30, 0.68)	0.58 (0.41, 0.75)
Last time missed medicines: in last week ²	0.37 (0.23, 0.51)	0.39 (0.19, 0.59)	0.35 (0.16, 0.55)
Last time missed medicines: in last month ²	0.61 (0.50, 0.71)	0.64 (0.50, 0.79)	0.57 (0.42, 0.72)
General adherence past 6 months: missed some ²	0.58 (0.47, 0.69)	0.65 (0.50, 0.80)	0.51 (0.34, 0.67)

NOTE: PHACS-AMP = Pediatric HIV/AIDS Cohort Study-Adolescent Master Protocol

219 caregiver-youth dyads responded to at least one adherence indicator (107 < 13 years, 112 ≥ 13 years).

¹ 217 dyads responded.

² 218 dyads responded.