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HIV Treatment Adherence Measurement and Reporting Concordance in Youth with Perinatally Acquired HIV Infection and Their Caregivers

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Abstract

We examined youth-caregiver adherence report concordance and association of different adherence self-report items with HIV RNA viral load (VL) in perinatally HIV-infected adolescents assessed in 2003–2008. Youth ($n = 194$; 9–19 years) and their caregivers completed a multi-step 2-day recall, one item on last time medications were missed, and one item on responsibility for managing youths' medications. Across early (9–12 years), middle (13–15 years), and late (16 + years) adolescence, both youth and caregivers reported having primary responsibility for youths' medication regimens and demonstrated poor to moderate youth–caregiver concordance on adherence items. Responses to the last-time-missed item had greater association with VL than did the 2-day recall, particularly for longer times (e.g., past month). By age group, significant associations with VL were found for caregiver reports in early adolescence, caregiver and youth reports in middle adolescence, and youth reports in late adolescence, suggesting that caregivers offer better reports of youth adherence during early adolescence, but by later adolescence, youth are better informants. Although design limitations preclude definitive conclusions about the reliability and validity of specific adherence items, this study suggests important issues related to age group, caregiver vs. youth informants of adherence, and recall periods for child adherence assessment that warrant further research.

Introduction

Approximately 3.4 million children and adolescents (< 15 years) are living with HIV/AIDS worldwide.[1] By the end of 2009, nearly 11,000 US children had been diagnosed with HIV before age 13—and most had acquired HIV perinatally.[2] Although mother-to-child transmission in the US has decreased significantly, large numbers of perinatally HIV-infected (PHIV +) children are surviving into adolescence and young adulthood, with staggering numbers to follow internationally, particularly in low resource settings.[3] For most of their lives, many PHIV + children and adolescents have been on numerous antiretroviral therapy (ART) medications, requiring daily adherence, often to complex regimens. Medication adherence difficulties have been documented among youth living with a range of chronic medical conditions,[4,5] and increasing numbers of studies suggest high rates of ART nonadherence among PHIV + youth that, similar to other chronic illnesses, increase with age.[6–11] ART nonadherence is particularly significant because of the potential for development of drug-resistant virus,[7] resulting in diminished drug efficacy and treatment failure. In fact, recent studies indicate that perinatally HIV-infected adolescents, in both resource-rich and resource-limited settings, have worse health outcomes than HIV + adults, including a higher percentage who fail to reach viral suppression.[3,10]

A major barrier to understanding, tracking, and addressing ART adherence problems among adolescents and young adults in both clinical and research settings is the lack of a

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gold standard for adherence assessment. Indeed, studies of adherence among PHIV+ children and adolescents report adherence rates that range from 20% to 100% depending on the type of instrument used, the informant, and the timing of assessment.[8,12] Adherence measurement tools typically are characterized as objective (e.g., medical event monitoring systems, pill counts, pharmacy refill records) or subjective (e.g., patient and/or caregiver recall of doses taken or missed).[13] Objective measures are considered to be more valid, more reliable, and less influenced by social desirability and patient recall errors.[13] However, these objective tools, which are primarily used in research, can be expensive and difficult to use correctly and may overestimate nonadherence.[12,13] In contrast, despite problems with reliability, self-report measures are widely used in clinical settings because they are inexpensive and easy to administer, thereby improving feasibility and scalability. Because it is unlikely that most objective measures of adherence can be widely used in busy clinics or low-resource settings in the US or globally, self-report measures may be the only routinely available option.

For many years, the majority of self-report measures used a comprehensive 2- to 4-day recall of medication doses that involved listing all medications, prescribed doses, and doses taken for each day separately. However, a number of studies suggested this procedure was onerous, was subject to social desirability or white coat effects, led to different results depending on whether the previous days included weekends, and was difficult for patients who might not recall exact prescribed doses.[6,10,14–16] More recently, investigations of adults living with HIV have begun to use more general questions that involve rating adherence over longer time frames that include weekends. Wilson and colleagues have found that respondents are more willing to report nonadherence with this strategy and also that these measures have stronger associations with both health outcomes and more objective measures of adherence.[17]

Measuring adherence in children and adolescents differs from adult HIV+ populations, particularly in the involvement of caregivers and the potential role of developmental stage in youth adherence and reporting behaviors. Caregivers generally assume responsibility for administering drugs for young children, shifting this responsibility to older children or adolescents over time. During this transition of responsibility, there are often periods when both caregivers and youth are involved in medication management; yet caregiver–youth communication barriers may contribute to neither person being completely aware of what is required of the regimen or what is actually happening regarding pill-taking.[12] For instance, caregivers may believe and report that youth are adherent to their regimens when that is not the case.

Only a few studies address child and caregiver concordance on reports of adherence,[18–20] and very few include adolescents older than 16 years or analyze the data by age group. For instance, although Usitalo et al.[20] found high rates of agreement among adolescents aged 7–16 years (mean age = 12) and their caregivers on reports of ART use, the majority of youth had undetectable HIV RNA viral load (VL; < 400 copies/mL), indicating a fairly adherent sample, and no older adolescents or young adults were included. These authors also found that the likelihood of having detectable VL was greater in youth aged ≥ 13 years, suggesting that older youth may be at higher risk for nonadherence and related health problems. No further analyses by age or developmental stage were reported.

Few studies have followed PHIV+ youth into older adolescence, when they may assume greater responsibility for managing their medications and when adherence problems may increase substantially.[6–9] Given developmental differences in cognitive and behavioral functioning, as well as varying levels of caregiver involvement across early, middle, and late adolescence,[21] a greater understanding of the types of adherence self-report questions and informants that are valid and reliable at different developmental stages is important for identifying PHIV+ youth who are at high risk of adherence difficulties and for developing appropriate interventions.

To address these issues, we analyzed data by adolescent developmental stage from a large cohort study of PHIV+ youth and their caregivers living in New York City, a major US metropolitan AIDS epicenter. We operationalized developmental stages of adolescence as early (9–12 years of age); middle (13–15 years of age); and late (16–19 years of age). Although there is variability in the ages at which children reach different stages of adolescent development based on physical maturity, puberty, cognitive development, and social interactions,[21] there is no gold standard to assess when youth achieve these milestones; thus, age is still the most commonly used proxy. In the absence of more nuanced physical, cognitive, and social testing to determine each participant's developmental stage, we used age as the best indicator of development as recommended by other investigators.[21]

The specific aims of these analyses were to examine (1) adherence self-reports by type of reporter (youth, caregiver), developmental stage (early, middle, late adolescence), and assessment method (multi-step, single-item, short/long-term); (2) concordance between youth and caregivers across items and developmental periods; and (3) the utility of different types of adherence questions and reporters at different adolescent developmental stages by comparing adherence reports to VL, a biological indicator that may reflect adherence. Although VL may be influenced by a number of factors other than adherence (e.g., viral resistance and drug metabolism), VL is still often used as a biomedical marker of adherence[21] and was used as such in this study.

Methods

Participants and procedures

Data came from two time points, 18 months apart [i.e., Baseline and Follow-Up-1 (FU-1)] in Project CASAH, a longitudinal psychosocial study of behavioral health outcomes in PHIV+ and PHIV- youth during the transition from childhood through adolescence.[22] Community-based participatory research with PHIV+ youth, their caregivers, and their providers revealed that an 18-month interval between baseline and FU-1 was considered ideal for capturing change without presenting undue burden on a population of youth who already have considerable demands on their time due to biomedical appointments every 3 months and participation in biomedical clinical trials.

Participants (youth and their primary caregivers) were recruited between 2003 and 2008 from four New York City medical centers that provide primary and tertiary care to HIV-affected families. Inclusion criteria at recruitment were

(1) youth ages 9–16 years with perinatal exposure to HIV (confirmed by medical providers and medical charts); (2) English or Spanish speaking; and (3) caregiver with legal ability to sign consent for youth participation. Exclusion criteria were severe cognitive impairments in youth (e.g., autism, severe mental illness) precluding understanding of the research procedures and questions. Three hundred and twenty-five youth (196 PHIV+) and their caregivers completed the full Baseline interview, and 278 (164 PHIV+) completed the full FU-1 interview. Present analyses include only PHIV+ youth and their caregivers, and data sources were caregiver and youth interviews and medical chart data on VL from Baseline and FU-1. Note that, because the study was funded only for psychosocial interviews and to avoid placing more burden on participants, we could only obtain biomedical data (e.g., VL and CD4+ cell count) by accessing medical chart data from the youth's medical clinic visit (closest to interview time). Adherence self-report and VL data for at least one time point were available for 194 PHIV+ youth and for both time points for 162 PHIV+ youth.

Trained bachelor-level research assistants conducted separate but simultaneous interviews with caregivers and youth. All youth were interviewed in English, and caregivers could choose to complete their interviews in either English or Spanish. Institutional Review Board approval was obtained from all sites; caregivers provided written consent for themselves and permission for youth who were less than 18 years. Youth provided written assent (or consent, if ≥18 years). Monetary compensation for time and transportation was provided.

Measures

Demographics. Youth demographics included age, gender, race/ethnicity, and HIV disclosure status. Caregiver variables included gender, age, reported HIV status, caregiver relationship to youth (e.g., biological parent, adoptive parent, or other relative), employment, education, income, and household size.

Assessment of youth ART adherence. Youth ART adherence was assessed by youth and caregiver self-report using two types of items derived from the Adult AIDS Clinical Trials Group (AACTG)[14] and Pediatric AIDS Clinical Trials Group (PACTG)[15,23] modified structured questionnaires. In the first item, a multistep approach was used. Youth and caregivers were asked to identify the youth's antiretroviral medications and, for each medication, the number of prescribed daily doses and the number of doses missed yesterday and the day before. The percentage of doses missed in the past 2 days (number of doses missed divided by the number of doses prescribed) was then calculated as a continuous variable, herein referred to as *2-day recall*. In addition, to account for skewed distribution, we dichotomized responses to create a categorical variable, herein referred to as *any dose missed in the past 2 days* (yes vs. no).

The second assessment item included one question: ''When was the last time you/your child missed any medications?'' The response options included (a) past week, (b) 1–2 weeks ago, (c) 3–4 weeks ago, (d) 1–3 months ago, (e) >3 months ago, and (f) never. Following several previous publications,[18–20] we then created two dichotomized adherence indicators: (1) missed doses vs. no missed doses in the past week (i.e., a vs. b-f; referred to as *Missed within Past Week*), and (2) missed doses vs. no missed doses in the past month (i.e., a–c vs. d–f; referred to as *Missed within Past Month*). We also analyzed data using a cut point of missed within the past 3 months (i.e., a–d vs. e–f); because the results were very similar to those for the past month (data not shown, available from authors), we present only *Missed within Past Week* and *Missed within Past Month* analyses here.

Youth and caregivers were also asked about the level of responsibility each had for overseeing the youth's medication regimen: ''Who is responsible for giving you/your child your/his or her medications?'' (i.e., youth, caregiver, other adult living in home, other non-adult living in home, home health aide/nurse, other).

Youth HIV outcomes. CD4+ T-lymphocyte counts (cells/uL; CD4+) and plasma HIV RNA viral load (VL) values (copies/mL), as close to the date of interview as possible, were obtained from medical records (Mean time between interview and CD4/VL data: Baseline: $M = 1.3$ months, range = 0–6 months; FU-1: $M = 1.5$ months, range 0–6 months). Because an ultrasensitive HIV-1 RNA assay was not routinely used clinically for the entire cohort, we dichotomized viral load as ≤400 and >400 copies/mL.

Analytic strategy

To determine whether youth and caregiver reports of missed doses were associated with VL in each developmental stage, we fit Generalized Linear Models (GLM) with a logit link function. Note that the mean 18-month interval between Baseline (age range 9–16 years) and FU-1 (age range 10–19 years) assessments allowed some youth to contribute two observations at the same developmental stage. Therefore, we employed Generalized Estimating Equation (GEE) methodology with unstructured working correlation matrices to account for the within-subject correlation caused by these repeated measures (see Table 4).

We used the same analytic approach to evaluate whether the adherence outcome correlated with youth's gender, race/ethnicity, or youth knowledge of HIV status to adjust for potential confounding when appropriate. Analyses were conducted using SPSS Version 21.0; statistical significance was based on $p < 0.05$. However, given that there are relatively few studies of adherence over time in perinatally infected youth, that the majority of studies have relatively small samples, that no studies to date have looked at developmental stage and adherence, and the importance of this topic, particularly internationally where there will be staggering numbers of perinatally HIV-infected youth,[1] we are also reporting findings that approached significance ($p < 0.10$) because of their potential to inform future studies.

Results

Sample characteristics (Table 1)

The mean age of youth aged 9–12 years ($n = 157$) was 11.2 ($SD = 1.08$), aged 13–15 years ($n = 145$) was 14.4 ($SD = 0.87$), and aged 16–19 years ($n = 53$) was 17.1 ($SD = 0.80$). The majority ($n = 161$; 83%) of the youth completed two interviews; 93 contributed two data points to one age group; 68 contributed

Table 1. Demographic and HIV Characteristics of PHIV+ Youth and Their Caregivers by Entire Sample and Adolescent Developmental stages

Characteristics	*Total*[a] *(N = 194)*	*9–12 years (n = 157)*	*13–15 years (n = 145)*	*16–19 years (n = 53)*
Youth characteristics	*N* (%)	*n* (%)	*n* (%)	*n* (%)
Female	95 (49)	89 (57)	68 (47)	21 (40)
Age[b]	12.7 (2.19)	11.2 (1.08)	14.4 (0.87)	17.1 (0.80)
African American	93 (48)	79 (50)	69 (48)	24 (45)
Latino	67 (35)	53 (34)	50 (35)	20 (38)
Black Hispanic	25 (13)	16 (10)	20 (14)	7 (13)
HIV-status disclosed	135 (70)	80 (52)	127 (90)	45 (100)
CD4+ cell count (cells/mm^3)[c]	566 (330)	635* (345)	494* (300)	421* (243)
CD4+ < 200 cells/mm^3	20 (10)	10 (6)	17 (12)	9 (17)
HIV RNA Viral load copies/mL[c]	3,246 (26,960)	1,753 (22,845)	2,221 (29,290)	5,370 (33,196)
VL ≤ 400 copies/mL	66 (34)	96 (61)	91 (63)	37 (70)
Caregiver characteristics				
Female	168 (87)	133 (86)	120 (85)	42 (93)
Age[b]	49.6 (11.8)	49.8 (11.8)	50.2 (11.5)	49.2 (13.6)
HIV+	57 (29)	55 (36)	35 (26)	13 (30)
African American	101 (52)	88 (56)	74 (51)	24 (45)
Latino	72 (37)	50 (32)	55 (38)	23 (43)
Biological parent	67 (35)	62 (40)	44 (31)	11 (24)
Employed	55 (28)	35 (23)	53 (39)	14 (32)
Education[b]	11.7 (3.3)	11.7 (3.2)	11.8 (3.3)	12.1 (3.2)
Household income[b,d]	5.9 (2.9)	5.7 (3.0)	6.1 (2.8)	6.2 (2.7)
Household size[b]	4.4 (1.8)	4.5 (1.9)	4.3 (1.8)	4.2 (1.8)

[a]Total sample at Baseline. Each participant contributed one or two data points as we combined observations from Baseline and Follow-Up 1 assessments.
[b]Mean (standard deviation).
[c]Median (standard deviation).
[d]Income assessed using a categorical variable for which a score of 5 = $20,001–$25,000 and a score of 6 = $25,001–$30,000; *$p < 0.05$.

two data points to two age groups. At Baseline, the majority of caregivers (*M* age = 49.6, *SD* = 11.8) were African American (52%) or Latina/o (37%), HIV-negative or unknown serostatus (71%), and a non-birth parent relative (e.g., aunt, grandmother; 28%) or non-biological guardian (38%). The majority of youth at each developmental stage knew their own HIV status: 52% of 9–12 year olds, 90% of 13–15 year olds, and 100% of 16–19 year olds. At Baseline, median CD4+ was 566 cells/mm^3 (*SD* = 330) and median VL was 3,246 copies/ml (*SD* = 26,960); only 34% of youth had VL ≤ 400 copies/mL. There was a significant difference across the three age groups in CD4+ cell counts (median = 635, 494, 421 cells/mm^3 respectively), but not in VL. Also, none of the adherence items from either caregiver or youth self-report were significantly associated with youth's gender, race/ethnicity, or youth's knowledge of their own HIV status, caregiver type (biological or non-biological), and caregiver HIV status; results not shown.

Over the study period, 2003–2008, there was enormous diversity of antiretroviral drugs and regimens prescribed to participants. Participants reported receiving monotherapy, and dual, triple, and multi-drug regimens that included as many as 8 agents. Regimens were composed of one, two, and three drugs classes (non-nucleoside reverse transcriptase, nucleoside reverse transcriptase, and protease inhibitors) in a variety of combinations. Three children received injectable T-20 (enfuvirtide). Specific drugs reported over the duration of the study period included abacavir, amprenavir, atazanavir, atripla, combivir, darunavir, delavirdine, didanosine, efavirenz, emtricitibine, enfuvirtide, epzicom, etravirine, fosamprenavir, indinavir, lamivudine, lopinavir/ritonavir, maraviroc, nelfinavir, nevirapine, raltegravir, ritonavir, saquinavir, stavudine, tenofovir, tipranavir, trizivir, truvada, zalcitabine, and zidovudine.

Responsibility for HIV medication regimens

The majority of both caregivers and youth reported that they were responsible for youth medication regimens. Across age groups, youth report of their own primary responsibility for their medication regimens increased with age, from 58% at 9–12 years to 81% at 16–19 years. Caregiver endorsement of caregiver primary responsibility for youth medication regimens decreased as youth aged, but was still high: from 98% at 9–12 years to 71% at 16–19 years.

Nonadherence across adherence indicators (Table 2)

2-Day recall. Based on the multistep PACTG procedure for assessing adherence, both youth and caregivers reported 91–100% adherence in the past 2 days, and neither youth nor caregiver report of percent missed doses at any developmental stage was associated with VL (data not shown). Given the very limited variance in the percent of missed doses, all other analyses using the 2-day recall item were conducted using the dichotomized variable (yes/no) for *any missed doses*. Across developmental stages, only 8–23% of youth and 11–15% of caregivers reported any missed doses on this item.

Last time missed. Responses to the single-item adherence question assessing the last time youth missed a dose indicated higher rates of reported nonadherence across developmental

Table 2. Reported Missed Doses on Different Adherence Measures by PHIV+ Youth and Caregivers by Adolescent Developmental Stage

	9–12 years		*13–15 years*		*16–19 years*	
Item	N	n (%)	N	n (%)	N	n (%)
2-Day recall[a]						
Youth	70	16 (23)	102	18 (18)	38	3 (8)
Caregiver	121	14 (12)	107	12 (11)	27	4 (15)
Missed within past week						
Youth	127	39 (31)	124	31 (25)	43	10 (23)
Caregiver	132	30 (23)	123	20 (16)	30	8 (27)
Missed within past month[b]						
Youth	127	49 (39)	124	47 (38)	43	18 (42)
Caregiver	132	50 (38)	123	42 (34)	30	17 (57)

[a]2-Day recall yes/no.
[b]Past month represents cumulative nonadherence at any point within that time period.

stages in the past week and past month compared to the 2-day recall. Youth reports of any missed dose within the past week were highest for ages 9–12 (31%) and decreased to 25% and 23%, respectively, for the two older age groups; caregiver reports of any missed dose within the past week were highest for youth ages 16–19 (27%). Reports of any missed dose within the past month by youth and caregivers were somewhat higher. At ages 9–12, 39% of youth reported any missed dose within last month rising slightly to 42% at ages 16–19. Again, caregiver report of youth nonadherence was greatest (57%) for youth in the oldest age range.

Concordance between youth and caregivers (Table 3)

On average, concordance between youth and caregiver reports of missed doses was poor to moderate across items and developmental stages. Concordance between youth and caregiver report of missed doses was not associated with VL at any developmental stage (data not shown).

2-Day recall. At 9–12 and 13–15 years, agreement between youth and caregiver reports for any missed dose on 2-day recall was on average moderate (2-day recall dichotomized: kappa = 0.40 and 0.43, respectively). However, at 16–19 years, youth and caregiver agreement on 2-day recall was very poor and less than expected by chance (kappa = −0.11).

Last time missed. Agreement for *Missed within Past Week* was poor across all developmental periods (kappa range = 0.26–0.32). For *Missed within Past Month*, agreement between youth and caregiver reports across developmental stages ranged from poor to moderate (kappa = 0.20–0.41).

Adherence and viral load (≤ 400 or > 400) (Table 4)

2-Day recall. On the 2-day recall dichotomized item, reports at only one developmental stage showed a significant association with VL. Specifically, youth report of nonadherence was significantly associated with VL >400 ($p = 0.033$) during middle adolescence (13–15 years).

Last time missed—Missed within past week. Although associations between reports of nonadherence within the past week and VL varied and were not significant, some approached significance. At 9–12 years, neither caregiver ($p = 0.985$) nor youth ($p = 0.144$) reports of nonadherence were associated with VL. At 13–15 years, the association of caregiver report of nonadherence with VL >400 was just shy of significance ($p = 0.054$). At 16–19 years, the association of youth report of nonadherence with VL >400 was also just shy of significance (0.064).

Last time missed—Missed within past month. Youth reports of nonadherence within the past month were significantly correlated with VL >400 ($p = 0.007$) at one developmental stage, late adolescence (16–19 years). Caregiver reports of nonadherence among early adolescents were significantly associated with VL >400 ($p = 0.045$), and the association was just shy of significance among middle adolescents ($p = 0.064$).

Discussion

As is the case among adults living with HIV, there is no gold standard for ART adherence assessment among PHIV+ youth. Given the importance of self-report measurement of adherence in low-resource and/or clinic settings, a number of

Table 3. Concordance of Reported Missed Doses on Different Adherence Measures by PHIV+ Youth and Caregivers by Adolescent Developmental Stage

	9–12 years			*13–15 years*			*16–19 years*		
Item	N[b]	n[c](%)	*kappa*	N[b]	n[c](%)	*kappa*	N[b]	n[c](%)	*kappa*
2-Day recall[a]									
Youth	68	15 (22.1)	0.40	87	16 (18.4)	0.43	24	2 (8.3)	−0.11
Caregiver		6 (8.8)			11 (12.6)			3 (12.5)	
Missed within past week									
Youth	117	33 (28.2)	0.32	118	30 (25.4)	0.31	30	9 (30.0)	0.26
Caregiver		25 (21.4)			19 (16.1)			8 (26.7)	
Missed within past month									
Youth	117	43 (36.8)	0.30	118	43 (36.4)	0.20	30	14 (46.7)	0.41
Caregiver		43 (36.8)			40 (33.9)			17 (56.7)	

[a]2-Day recall yes/no.
[b]Total number of dyads included in analyses.
[c]Number of youth or caregivers who reported missed doses.

Table 4. Association of Reported Missed Doses with HIV RNA Viral Load of PHIV+ Youth and Caregivers by Adolescent Developmental Stage

		9–12 years (n = *157*)			*13–15 years* (n = *145*)			*16–19 years* (n = *53*)		
		VL ≤400	*VL >400*		*VL ≤400*	*VL >400*		*VL ≤400*	*VL >400*	
Response		n *(%)*	n *(%)*	p[b]	n *(%)*	n *(%)*	p[b]	n *(%)*	n *(%)*	p[b]
2-Day recall[a] *– any missed doses in the past two days*										
Youth	Missed at least one dose	7 (44)	9 (56)	0.371	3 (17)	15 (83)	0.033	0 (0)	3 (100)	0.283
	Not missed	30 (56)	24 (44)		38 (45)	46 (55)		14 (40)	21 (60)	
Caregiver	Missed at least one dose	7 (50)	7 (50)	0.559	3 (25)	9 (75)	0.267	1 (25)	3 (75)	0.498
	Not missed	45 (42)	62 (58)		40 (42)	55 (58)		10 (44)	13 (56)	
Missed within past week										
Youth	Missed at least one dose	13 (33)	26 (67)	0.144	10 (32)	21 (68)	0.446	1 (10)	9 (90)	0.064
	Not missed	41 (47)	47 (53)		38 (41)	55 (59)		14 (42)	19 (58)	
Caregiver	Missed at least one dose	13 (43)	17 (57)	0.985	4 (20)	16 (80)	0.054	2 (25)	6 (75)	0.555
	Not missed	44 (43)	58 (57)		45 (44)	58 (56)		8 (36)	14 (64)	
Missed within past month										
Youth	Missed at least one dose	17 (35)	32 (65)	0.131	15 (32)	32 (68)	0.250	2 (11)	16 (89)	0.007
	Not missed	37 (47)	41 (53)		33 (43)	44 (57)		13 (52)	12 (48)	
Caregiver	Missed at least one dose	16 (32)	34 (68)	0.045	12 (29)	30 (71)	0.064	4 (24)	13 (76)	0.139
	Not missed	41 (50)	41 (50)		37 (46)	44 (54)		6 (46)	7 (54)	

[a]2-Day recall yes/no.
[b]The *p* value corresponds to the comparison of proportion of youth with VL >400 copies/mL between youth who reported missing at least one dose and those who reported not missing any doses during the given time period.

studies among HIV+ adults have examined the validity and reliability of self-report adherence questions.[17,24,25] However, similar work is rare among PHIV+ children and adolescents, with even fewer studies reporting on older adolescence—a time when caregiver responsibility decreases and adherence problems typically increase across chronic health conditions.[4,5] This study is one of the first to use the frame of developmental stage, using age groups as a proxy, to examine concordance between perinatally HIV-infected youth and their caregivers on different self-report adherence items, as well as the association of different items by different reporters at different stages with viral load, a biomedical marker of adherence.

Our findings of extremely low to, at best, moderate concordance between youth and caregiver adherence reports using all three reporting periods (missed within past 2 days, past week, and past month) suggest the need for interventions to increase youth–caregiver discussions about adherence and medical regimen management. In addition, the majority of *both* youth and caregivers reported that they each had primary responsibility for managing the youth's medications, further indicating a discordant perspective on medication management. Youth reports of having primary responsibility increased with age to 81% of the youth at 16–19 years of age; yet 71% of caregivers of these older youth still reported that they—not the youth—had primary responsibility. Without additional information on specific medication-related communications between caregivers and youth—in particular how they divide medication regimen tasks (e.g., obtaining refills and mapping/tracking dose schedule)—or direct observation of medication-taking, we do not know which informant is describing responsibility more accurately.

Moreover, there are factors influencing caregiver–youth relationship dynamics and subsequent adherence behaviors that we did not assess in this study. For example, caregivers and youth may get into power struggles over medication-taking. Caregivers decide when to begin transitioning responsibility for medication regimens and other aspects of disease management to youth based on factors such as youth's age, maturity, and neurocognitive functioning.[7] As youth age, some caregivers may retain responsibility for a significant number of—if not all—tasks related to youth HIV medication regimen.[18,26] It is unclear how caregivers in this study made decisions about the transition of responsibility and how useful consideration of these factors was to that process. Also, caregiver type (e.g., birth mother, adoptive parent, or relative) and caregiver HIV status can influence decisions and communication about ART adherence. Unfortunately, because by definition all birth mothers were HIV+ (and almost all birth parents were mothers) we can not distinguish between the role of caregiver HIV status and caregiver type in our analyses. Future studies focused on medication management during adolescent transitions and how such decisions are made and by whom could be very helpful in informing interventions to promote adherence in older adolescents.

It is also unclear how youth motivation to improve adherence might be influenced by increasing medication responsibility from early adolescence through emerging adulthood. Studies among youth with other chronic health conditions (e.g., cystic fibrosis, diabetes) suggest that moving from caregiver-only to joint responsibility has both positive and negative consequences. Across adolescent developmental stages, joint or shared responsibility has been found to be adaptive in many ways, such as easing burden, addressing complexity of regimens, and allowing caregivers to model appropriate self-care. It is also strongly associated with better health outcomes among older adolescents.[27–29] However, shared responsibility in which youth and caregivers alternate the tasks for which each is responsible might result in worse

adherence due to inconsistencies, misunderstandings, and assumptions of what ''the other'' is doing. Additionally, the belief that each one is ''in charge'' of the youth's regimen may significantly increase the likelihood of a reporting bias, whereby the individual who feels more responsible for the youth's regimen is less likely to endorse nonadherence, and, conversely, the individual who feels less responsible is more likely to endorse nonadherence. Such problems in distribution of responsibility and communication about that responsibility between caregivers and youth are suggested by our finding of poor agreement on whether doses were missed.

On average, we found that both youth and caregivers reported high adherence rates (91–100%) across developmental stages when using the multi-step PACTG procedure to calculate 2-day recall, and this ''ceiling effect'' (i.e., nearly all responses >90%) may limit the utility of this self-report strategy. Indeed, reports of missed doses on the single-item rating scale (e.g., last time missed) were, in general, better associated with VL. In addition, caregiver reports of missed doses were generally better associated with worse VL outcomes for longer reporting periods (past month) rather than for past 2 days. Youth and caregiver reports of high adherence rates in the past few days may be due to ''a white coat'' effect—the tendency to increase medication-taking right before and after medical visits or interviews, knowing that they will be asked about adherence, with a return to ''typical behavior'' within one month after the visit.[16,30] Alternatively, it may be more difficult to acknowledge missed doses in the recent past. Finally, it is possible that, because of the time gap between the interview and chart data, the longer reporting time frames more accurately correlate with the viral load measures.

Our findings also document some differences in reported adherence across developmental stages. In early adolescence, only caregiver report of missing at least one dose in the past month was significantly associated with detectable viremia. By late adolescence, no caregiver report was associated with VL, perhaps reflecting caregivers' lack of true knowledge of the youths' medication-taking behaviors. For youth report, in early adolescence, none of the items was associated with VL. However, during middle adolescence, youth 2-day recall was significantly associated with VL, and the association of youth report of *missed within past week* was just shy of statistical significance. Among late adolescents, youth report of any doses *missed within the past month* was significantly associated with VL >400—the strongest association between an adherence item and VL of any age group. These findings suggest that, as youth age and perhaps have more perceived or actual responsibility for taking their medications, they are more aware of their adherence and/or feel more comfortable accurately reporting having missed a dose over a longer, rather than shorter, timeframe.

These data correspond with an increasing number of studies of adults and children reporting that longer timeframes appear important for accurately assessing ''typical adherence'' behaviors. For example, Farley et al.[19] found an association with VL of both caregiver and youth self-reported missed doses in the past month but not in the past 3 days (90% of children were 8–16 years old). Among adults living with HIV, single-item rating scales assessing adherence over a one-month period have been shown to significantly predict VL[25] and produce significantly less over-reporting of adherence as compared to medication event monitoring system data.[24]

There are several limitations to this study. This is a convenience sample of PHIV+, research-experienced youth recruited from HIV primary care clinics beginning in 2003. Thus, the sample may not fully reflect the larger population of PHIV+ youth outside of New York City or those who are not engaged in care. In addition, because treatment efficacy and, thus, VL outcomes are influenced by a number of factors (e.g., antiretroviral treatment history, archived drug resistance, and HIV disease status), lack of correspondence between adherence report and VL may not reflect inaccuracy of the adherence report. For instance, given the ages of the participating youth, many may have been exposed to multiple suboptimal treatment regimens during earlier childhood before combination ART became available and, therefore, may have developed viral resistance. Related, since these analyses used data collected before the availability of newer drugs that treat multi-drug resistant HIV, high VL may reflect ineffective treatment regimens unable to fully suppress viral replication rather than actual inadequate adherence to medication.[31] Moreover, although VL data were retrieved from charts as close to the interview dates as possible—within a mean of 1.3–1.5 months (and not more than 6 months) before or after the assessment for Baseline and FU-1, respectively—there was not optimal correspondence between date of VL testing and date of adherence self-report; as noted earlier, drawing additional blood for viral load assays was beyond the scope of this study and would have imposed undue burden on participants. Thus, there are some limitations on the conclusions that can be drawn about reliability and validity of adherence assessment items. Future combined biomedical and psychosocial studies that closely link these data over time are needed, particularly with the availability of newer regimens and drug resistance testing and in contexts in which the epidemic is most prevalent, such as sub-Saharan Africa.

These data were collected between 6 and 11 years ago before the use of recent combination antiretroviral regimens that may impose less of an adherence burden on patients.[32] However, our focus in this article is on the validity of adherence reporting rather than on adherence to specific drugs. Furthermore, adherence—and the ability of clinical care providers and researchers to assess it—will remain an important public health issue for HIV+ youth in the US and around the world. In particular, perinatally infected adolescents, many of whom have been on a range of ART regimens over their lifetimes—often with suboptimal adherence—may still need to take multiple pills and medications with side-effects, and adherence is expected to remain an important issue, not only for their own health but for that of their future sexual partners.

Finally, our assessment of developmental stage is not perfect as children may be developmentally delayed or have precocious pubertal development and thus function at a different stage than indicated by age alone, although it is the best proxy that we had. Future work could consider more complex indicators of adolescent development in examining adherence.

Overall, our results are similar to those from some adult studies that suggest that one adherence item focused on a longer timeframe (i.e., past 1 month in this study) may be more accurate and easier to use than multi-step assessments focused on shorter time periods. In addition, the latter multi-step assessments take much longer to conduct, thereby

limiting feasibility in busy clinic settings, and may be more susceptible to social desirability and ''white coat'' effects.

This study also offers insights into the particular challenges of assessing (and addressing) adherence across developmental stages of adolescence. Regarding the reporting period, for both youth and caregivers, the one-month period seems the most appropriate. However, attention must be paid to the most appropriate informant. Whereas caregiver adherence reports over past month may be more useful for understanding adherence among early and middle adolescents, during late adolescence older youth alone may be better informants. This may reflect both the fact that older youth indeed have primary responsibility for managing their own medications and, thus, know their medication-taking behavior better than do caregivers, and that they more accurately report as a function of later developmental stage. As highlighted in this study, caregiver involvement and oversight of medication regimens is still likely to be warranted across early and middle adolescence.[29] Given the complexity of medical management for youth perinatally infected with HIV, even into late adolescence, clinicians can encourage communication between youth and caregivers to help caregivers understand their role as youth autonomy increases and ask more detailed questions about the regimen to determine specific interventions that may be needed as youth progress through adolescence.[33] The measurement issues identified in this study can inform future studies of self-report adherence instruments, especially among the aging perinatally-infected population in the US and abroad, as well as among youth coping with other chronic medical conditions. Lastly, given that there are few longitudinal studies on adherence in any population,[34] future studies using prospective cohorts with concurrent assessment of adherence, VL, and other psychosocial factors will be important for informing much-needed targeted interventions.

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Author Disclosure Statement

The authors declare no conflict of interest.

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