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Nonadherence and unsuppressed viral load across adolescence among US youth with perinatally acquired HIV

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Abstract

Objective: To identify factors associated with nonadherence and unsuppressed viral load across adolescence among youth with perinatally-acquired HIV (PHIV).

Design: Longitudinal study at 15 US clinical sites

Methods: Self-reported antiretroviral medication nonadherence (any missed dose, past week) and unsuppressed VL (HIV RNA >400 copies/mL) were assessed annually. Individual, caregiver, social and structural factors associated with nonadherence and unsuppressed VL were identified by age (years): 8–11 (“pre-adolescence”), 12–14 (“early adolescence”), 15–17 (“middle adolescence”), and 18–22 (“late adolescence/young adulthood”), utilizing multivariable generalized linear mixed effects models.

Results: During a median 3.3-year follow-up, 381 youth with PHIV contributed VL measurements and 379 completed 1190 adherence evaluations. From pre-adolescence to late

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adolescence/young adulthood, prevalence of nonadherence increased from 31% to 50% ($p<0.001$); prevalence of unsuppressed VL increased from 16% to 40% ($p<0.001$). In adjusted analyses, in pre-, middle-, and late adolescence/young adulthood, perceived antiretroviral side effects were associated with nonadherence. Additional factors associated with nonadherence included: in pre-adolescence, using a buddy system (as an adherence reminder); in early adolescence, identifying as black, using buddy system; in middle adolescence, CD4% $<15\%$, unmarried caregiver, indirect exposure to violence, stigma/fear of inadvertent disclosure, stressful life events. Associations with unsuppressed VL included: in early adolescence, youth unawareness of HIV status, lower income; in middle adolescence, perceived antiretroviral side effects, lower income; in late adolescence/young adulthood, distressing physical symptoms and perceived antiretroviral side effects.

Conclusion: Prevalence of nonadherence and unsuppressed VL increased with age. Associated factors varied across adolescence. Recognition of age-specific factors is important when considering strategies to support adherence.

Keywords

Medication adherence; adolescent development; young adult; viral load; social determinants of health; violence; youth

INTRODUCTION

Globally, ~1.8 million adolescents live with HIV [1]. In the United States, in 2016, ~12,000 children, adolescents and young adults were living with perinatally acquired HIV (PHIV), of whom 1814 were under the age of 13 and 10,101 were adolescents and young adults [2]. Among children, adolescents, and young adults with perinatally-acquired HIV infection (PHIV), achieving and maintaining adherence to antiretroviral therapy (ART) is challenging yet essential for viral suppression, prevention of resistant HIV strains [3–5], and reduced HIV transmission risk [6]. Adherence is especially complex during adolescence, a dynamic period of physical, cognitive, social and emotional changes that encompass increasing independence, experimentation, and identity development [7–9]. Across chronic health conditions, adolescents may be more adherent during some periods than others; thus, factors that affect adherence during early adolescence may be different than during late adolescence/young adulthood [9,10]. Multiple factors contribute to ART adherence throughout childhood and adolescence, including individual [11–15], family [11, 16–17], social [11] and structural characteristics [12, 18–20] that may shift over time.

Suboptimal ART adherence and loss of virologic suppression are more frequent among adolescents than younger children [11, 14, 16, 21–23] and adults [24–25]. However, little is known about whether factors associated with adherence vary at different stages of adolescence. Age ranges across studies vary, with few results disaggregated by age.

To intervene effectively at all stages of adolescence and young adulthood, longitudinal studies are needed to identify factors associated with adherence as youth age. This longitudinal study sought to: 1) determine the prevalence of nonadherence to ART and unsuppressed viral load (VL) as youth with PHIV age; and, 2) identify individual, family, social, and structural factors associated with nonadherence and unsuppressed VL across

stages of adolescence. We considered adherence in the context of developmental changes of adolescence and young adulthood [9]. Social ecological models of health behavior [26], which recognize the social and environmental context in which health behavior occurs, informed our approach. We hypothesized that family-level factors would be associated with nonadherence in pre- and early adolescence, and that social and structural factors would be associated with nonadherence during middle and late adolescence.

METHODS

We included children, adolescents, and young adults (ages 8–22, hereafter referenced as “youth”) with PHIV enrolled in the Adolescent Master Protocol (AMP) of the Pediatric HIV/AIDS Cohort Study (PHACS), a prospective study of the impact of HIV and ART on youth with PHIV. AMP enrolled children and adolescents with PHIV and their caregivers at 15 US clinical sites, including Puerto Rico, from March 2007–October 2009. Participants completed follow-up visits every 6 months (2007–2010), then annually (2010–). This analysis used data as of 7/1/2014. Visits include clinical examinations, medical record abstraction, and interviews. Inclusion criteria were: PHIV, age 7–15 years at entry, engaged in medical care, with available medical records. Institutional review boards at all sites and at Harvard T.H. Chan School of Public Health approved the protocol. Parents or legal guardians provided written informed consent; children and adolescents provided assent per local IRB guidelines. Upon turning 18, participating youth provided consent to continue study participation.

Included in this analysis were youth who indicated receipt of ART at enrollment or follow-up and also had 1 youth-reported or caregiver-reported adherence evaluation, and/or VL measurement in the adherence visit window.

Outcome Measures:

We assessed two ART nonadherence outcomes: 1) youth or caregiver-reported nonadherence; and 2) unsuppressed VL. Youths’ ART adherence was assessed annually from the 6 month to 2.5 year visits and from the 4 year visit onward during separate interviews with youth and caregivers using a questionnaire from the Pediatric AIDS Clinical Trials Group [27,28] modified by PHACS. AMP assessed (for each antiretroviral medication prescribed) the number of doses missed in the previous 7 days. Nonadherence was defined as youth or caregiver report of one or more missed ART doses in the past week, associated with unsuppressed VL in previous work [22]. HIV RNA data were abstracted from medical records at each visit. The measure obtained closest to and within \pm 3 months of each self-reported adherence assessment was included. Unsuppressed VL was defined as HIV-RNA >400 copies/mL.

Age Strata:

Using time-varying age in years, we defined four age strata corresponding to stages of adolescence [29]: pre-adolescence (8–11 years), early adolescence (12–14 years), middle adolescence (15–17 years), and late adolescence/young adulthood (18–22 years).

Covariates:

The most recent individual, family, social and structural-level covariates measured during each adherence assessment (unless indicated otherwise) were examined.

Individual Characteristics included youth's sex, race, ethnicity and nadir CD4% at baseline, ART regimen (combination ART [cART] defined as three or more drugs), medication burden (single vs. multiple dose regimen), distressing physical symptoms (youth and/or caregiver reports), perceived ART side effects, youth awareness of their HIV status, alcohol use, and emotional and behavioral health. Caregivers and youth were interviewed separately about youth's experience of 20 physical symptoms (e.g., dizziness, chest pain), rating symptom distress over the past 4 weeks. Presence of distressing symptoms was defined as reporting 1 moderately or more distressing physical symptom. Perceived ART side effects were defined as youth or caregiver report that the youth missed taking ART in the past 6 months sometimes or often because they "wanted to avoid side effects (feeling sick)." Youth awareness of their HIV status (reported by caregiver), was defined as whether the youth had been told they had HIV. Youth alcohol use reflected self-reported use in the past 3 months (assessed at 10 years of age via audio computer-assisted survey interview [ACASI]). Emotional problems were assessed with the Behavior Assessment System for Children-Second Edition (BASC-2) youth Self-Report of Personality (SRP) Emotional Symptoms Index (ESI) [30]. Behavioral problems were measured by the BASC-2 caregiver-reported Behavioral Symptoms Index (BSI). For both the ESI and BSI, presence of problems was defined as a score in or exceeding the "at risk" (T 60) range.

Family characteristics included caregiver's educational attainment, marital status, and living arrangement at baseline, annual household income, number of caregiver health limitations, and youth relationship with caregiver (measured with the BASC-2 Youth SRP Personal Adjustment Composite); presence of problems was defined as a score in the "at risk" or "clinically significant" (T 40) range.

Social characteristics included whether the youth currently had a boyfriend or girlfriend (assessed via ACASI), youth or caregiver-reported use of a "buddy system" to support adherence, and stigma/concern about inadvertent disclosure of youth's HIV status, defined as youth or caregiver reporting that the youth missed taking ART medication in the past 6 months "sometimes" or "often" because of not wanting others seeing the youth taking medications.

Structural Characteristics included exposure to violence between ages 8–15, and number of stressful life events. Self-reported exposure to violence was assessed at ages 8–15 as part of the Life Events Checklist (LEC) [31]. The LEC assesses self-reported exposure to stressful life events within the past year and has been used in other studies of children living with or affected by HIV [32]. Seven LEC items pertain to direct and indirect exposure to violence. Indirect exposure to violence was defined as report of 1 event in the past year including: a) witnessed a fight with a weapon; b) heard gunshots on their block; people in the neighborhood were c) hit by the police; or, d) murdered. Direct violence victimization was defined as report of 1 event in the past year, including having been: a) physically attacked; b) raped or sexually assaulted; or, c) robbed or burglarized. Any violence exposure was

defined as report of either indirect exposure to violence or direct violence victimization. Youth exposure to stressful life events was assessed annually from the 1-year through 5-year visit and biennially thereafter through interviews with caregivers and, beginning at age 12, also with youth. Participants were asked about occurrence of 18 events within the past year (e.g., parents separated, loss of health insurance). The number of events reported was summed and categorized (0, 1, 2, 3) for caregivers and youth. For adherence visits where a listed variable should have been measured but was not, we considered the data as missing.

Statistical analysis:

For both adherence outcomes, we compared baseline characteristics of adherent and nonadherent youth, using chi-square and Fisher's exact tests for categorical variables, and t tests and Wilcoxon rank sum tests for continuous variables, as appropriate. "Baseline" data for this analysis were data obtained beginning at the 1- and 1.5-year AMP visits since most covariates of interest were assessed beginning at the 1-year visit. Using data from all available follow-up visits, we estimated the prevalence of nonadherence during pre-adolescence, early adolescence, middle adolescence, and late adolescence/young adulthood. To evaluate associations of each covariate with nonadherence within each age stratum, unadjusted and adjusted generalized linear mixed effects models were fit to account for correlation in repeated longitudinal measures within each participant. Covariates with p-value ≤ 0.1 in unadjusted analyses were considered for inclusion in multivariable models and retained in a core model if p ≤ 0.1 . Final models for each age stratum included core model covariates and covariates with p ≤ 0.1 when added back to the core model. Variables with data missing for $\geq 25\%$ of participants within an age group were not considered for multivariable models.

Using data from the aggregate (not age-stratified) sample, we evaluated whether the association of each covariate with each outcome varied across developmental stage, by including an interaction between age group and each covariate. Interactions were first evaluated in unadjusted models including the interaction term and main effects of the two variables; when the interaction p-value was ≤ 0.10 , multivariable models were fit adjusting for covariates selected *a priori* (sex, race, caregiver living arrangement, and household annual income). When the interaction p-value was ≤ 0.05 in the adjusted model, we calculated predicted probabilities of the outcome at each age in those with and without the characteristic of interest. All analyses used SAS 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

RESULTS

Of 451 PHIV youth enrolled, 427 attended 1 protocol visit requiring an adherence evaluation as of July 1, 2014, of whom 426 reported ever receiving ART. Within this group, 410 youth (or caregivers) completed 1 valid adherence evaluation, 381 (1257 measurements) of whom had VL measurements obtained within 3 months of a scheduled adherence visit occurring after the 1-year follow up visit and were included in the VL analysis. A total of 379 of the 410 participants completed 1 adherence assessment after the 1-year follow-up visit, with 1190 total evaluations. Most characteristics of included

participants did not differ significantly from those of excluded participants; included participants more frequently received ART before or at enrollment (95% vs 78%), and had a caregiver living with a partner (51% vs. 32%) compared to excluded participants. Table 1 summarizes baseline characteristics of participating youth by adherence and VL status. The mean age was 13 years, 53% were female, 74% identified as Black, and 23% identified as Latinx. Thirty percent reported nonadherence, and 29% had unsuppressed VL (Table 1). At baseline, 36% of nonadherent youth vs. 21% of adherent youth had unsuppressed VL ($p=0.006$) (Data not shown in tables).

Of 1190 adherence evaluations completed, 14% were during pre-adolescence, 32% during early adolescence, 36% during middle adolescence, and 17% during late adolescence/young adulthood. Median duration from earliest to most recent included adherence and viral load evaluation was 3.4 years (range: 0–5 years). Thirty percent of participants contributed data to one, 59% to two, and 11% to three age groups. From pre-adolescence to late adolescence/young adulthood, prevalence of self-reported nonadherence increased from 31% to 50% ($p<0.001$) and prevalence of unsuppressed VL increased from 16% to 40% ($p<0.001$) (Figure 1). The distribution of most covariates did not differ across developmental stages, but the proportion of visits when youth reported alcohol use, having a boyfriend/girlfriend, or being aware of their HIV status increased with age (See Table, Supplemental Digital Content 1, which describes the distribution of covariates by developmental stage).

Factors Associated with Nonadherence

Table 2 summarizes multivariable analysis results within each age stratum. Factors associated with nonadherence included: during pre-adolescence, using a “buddy system” adherence reminder; during early adolescence, identifying as Black, and using a buddy system adherence reminder; during middle adolescence, nadir CD4% <15%, alcohol use, having an unmarried caregiver, indirect exposure to violence, stigma/concern about inadvertent disclosure, and stressful life events. During all but early adolescence, perceived ART side effects were associated with nonadherence, with the greatest magnitude in pre-adolescence and mid-adolescence (Table 2). Results from univariable analyses within each age stratum are summarized in eTable 2 (see Table, Supplemental Digital Content 2, which presents unadjusted associations of each covariate with nonadherence within each age stratum).

Factors Associated with Unsuppressed VL

Table 3 summarizes results from multivariable models of unsuppressed VL within each age stratum. Higher risk of unsuppressed VL was associated with: during early adolescence, youth being unaware of their HIV status and lower household income; during middle adolescence, perceived ART side effects and lower household income; and during late adolescence/young adulthood, experiencing distressing symptoms and perceived ART side effects. No statistically significant associations were observed during pre-adolescence. Unadjusted associations of each covariate with unsuppressed VL within each age stratum are summarized in eTable 3 (see Table, Supplemental Digital Content 3, which presents unadjusted associations of each covariate with unsuppressed VL within each age stratum).

The association of violence exposure with self-reported nonadherence was modified by age group, with stronger associations during middle adolescence compared to other developmental stages (Figure 2). Youth who reported violence exposure had an elevated risk of nonadherence during early adolescence [adjusted Odds Ratio (aOR) 2.10, 95% confidence interval (CI) 1.17–3.77] and middle adolescence [aOR 3.57, 95% CI 2.02–6.34], but not in pre-adolescence or late adolescence/young adulthood (interaction $p=0.02$).

There were observed interactions of Black race, Latinx ethnicity, unmarried caregiver, and perceived ART side effects with age group on unsuppressed VL in unadjusted models. However, associations were not statistically significant in adjusted models (data not shown).

DISCUSSION:

In this cohort of youth with PHIV, the prevalence of nonadherence and unsuppressed VL increased through adolescence and into young adulthood. Individual, family, social and structural factors contributed to nonadherence and unsuppressed VL, yet associations varied by developmental stage and outcome. As hypothesized, associations of structural factors with nonadherence were stronger in middle adolescence than in other periods. However, we also observed that multiple family factors were associated with nonadherence or unsuppressed VL during middle adolescence, highlighting the ongoing role of family resources. Although the pattern of increasing nonadherence with age is consistent with prior studies [13, 22–24], this study illuminates **targets** for adherence interventions tailored to stages of adolescent development and unique youth, family, and community strengths and challenges.

In pre- and early adolescence, youth who used a “buddy system” reported worse adherence, contrasting with previous studies [11,33]. It could be that this adherence aid was a marker for past or current adherence challenges. We did not distinguish the nature or quality of the relationship of the person providing adherence support. Adolescents ages 12–14 who often desire greater autonomy, may not view caregivers’ adherence reminders as desirable. Yang [34] identified a “mismatch between desired and received support” as an adherence barrier among adolescents living with PHIV in Botswana. Additionally, during early adolescence, youth in our study who knew their HIV status were more likely to have suppressed VL. The WHO recommends that children be disclosed their HIV status by 10–12 years old, yet in our study, 10% of study visits between ages 12–14 were among youth who were unaware of their HIV status. US guidelines do not recommend an age by which children should be disclosed their HIV status, and note that timing of disclosure should “be based on a comprehensive assessment of the psychosocial milieu and the needs of the child and family,” [35] including consideration of significant cognitive and/or emotional-behavioral difficulties, if present. Counseling caregivers to disclose children’s HIV status before early adolescence, if feasible, and addressing caregiver concerns about consequences of disclosure and HIV-related stigma for their children’s emotional health and safety, may optimize virologic outcomes once youth reach adolescence [36, 37].

In middle adolescence, multiple social and structural factors were associated with nonadherence. As peer relationships and the desire for social acceptance increase in

importance [38–39], mid-adolescents' growing awareness of societal expectations and norms may contribute to behavior that is inconsistent with health demands, such as ART nonadherence. HIV-related stigma, including fears about risk of inadvertent disclosure of HIV status, may eclipse health needs, contribute to feeling socially isolated, and reduce the salience of adherence as a goal, increasing the potential for virologic failure. Additionally, we found that exposure to community violence during mid-adolescence elevated risk of nonadherence, extending previous findings [20,40]. Many youth living with HIV and their families experience family and community violence [41], which may compromise youths' ability to manage normal developmental challenges, alter neurocognitive functioning [42], increase risk for mental health problems [43–44], and be associated with family disruption [41], all of which in turn may contribute to nonadherence. Violence could also be a marker for multiple family and community environmental stressors. During mid-adolescence, opportunities for youths' independent activity and risk-taking in community environments may increase, which may account for the stronger associations we observed during this period. We also observed that during early and mid-adolescence, youth living in households with low incomes had greater odds of unsuppressed VL, which could be due to food insecurity [45], insufficient resources to access quality care, or poverty-related stigma and psychosocial stress [46]. Additionally, as alcohol use during middle adolescence was associated with nonadherence, addressing risks to nonadherence in the context of alcohol and other substance use is important.

Adherence support for youth during middle adolescence must address potent social environmental risk factors. To diminish risks associated with nonadherence during middle adolescence, integrated services must include screening for violence exposure, and support to youth and their families who have experienced violence, economic hardship, and other adversities. Further, communication with youth about strategies to minimize the risk of and manage an inadvertent disclosure should be implemented early to prepare youth and families with strategies before this stage. Interventions that address economic and social inequity, including Suubi + Adherence [47], which has shown positive effects of economic empowerment on viral suppression among Ugandan HIV+ adolescents, and CHAMP+/VUKA [48–50], a family strengthening intervention which teaches and supports communication and problem-solving strategies for youth living with HIV infection and their families prior to high-risk time periods are critically important. Such interventions might catalyze communication between youth, families, peers and community stakeholders to share strategies to prevent or buffer the effects of direct and indirect exposure to violence to maintain adherence, and implement them through parental engagement, strengthened social networks and community supports for youth.

Across multiple developmental stages, the presence of side effects was associated with nonadherence and unsuppressed VL, consistent with previous studies [51,52]. Associations of side effects and distressing physical symptoms with both outcomes could be due to PHIV youths' long history of ART medication use, history of exposure to multiple regimens, leading to treatment fatigue [53], and/or to body composition changes that may carry stigma or lead to unwanted questions [54]. During middle and later adolescence/young adulthood, when youth seek peer acceptance and intimate relationships, and have concerns about physical appearance, interventions to support youth experiencing pronounced side effects

should assess youths' concerns about side effects, and how to manage them, through education, treatment, or switching the ART regimen.

This study has some limitations. The small sample size in some age strata limited statistical power to evaluate associations. Given that this is a clinic-based sample, results may not generalize to all youth with PHIV. Although self-reported adherence was correlated with viral suppression, adherence was assessed infrequently, limiting our ability to capture short-term fluctuations. A strength of this study is that it examined both adherence and VL longitudinally for a large sample of youth from childhood to early adulthood, with repeated assessments spanning up to five years, in contrast to previous studies with shorter observation periods [13,23].

Results of this study have implications for programs and policies to mitigate risk of nonadherence and unsuppressed VL among youth with PHIV as they transition through adolescence into adulthood: Services to help adolescents with PHIV navigate typical developmental challenges should recognize age-specific risks and build on sources of resilience at individual, family, social and structural levels. This involves creation and maintenance of a multi-systemic alliance that is respectful of unique and evolving characteristics of the child/adolescent within a dynamic family and social context, recognizing the youth's growing autonomy. At the same time, addressing social and structural factors associated with nonadherence, including stigma, violence and poverty, requires societal and policy changes and community advocacy to prevent their occurrence, and resulting health inequities. Future research should evaluate whether findings from this US study generalize to global settings, home to the majority of children and adolescents living with HIV. Intervention research is also urgently needed to reduce age disparities across adolescence in attainment of the UNAIDS 90–90–90 goals, and sustaining virologic suppression, through development and testing of multi-level, multi-sectoral adherence interventions which build on lessons from studies of children and adults [55,56], across all stages of adolescence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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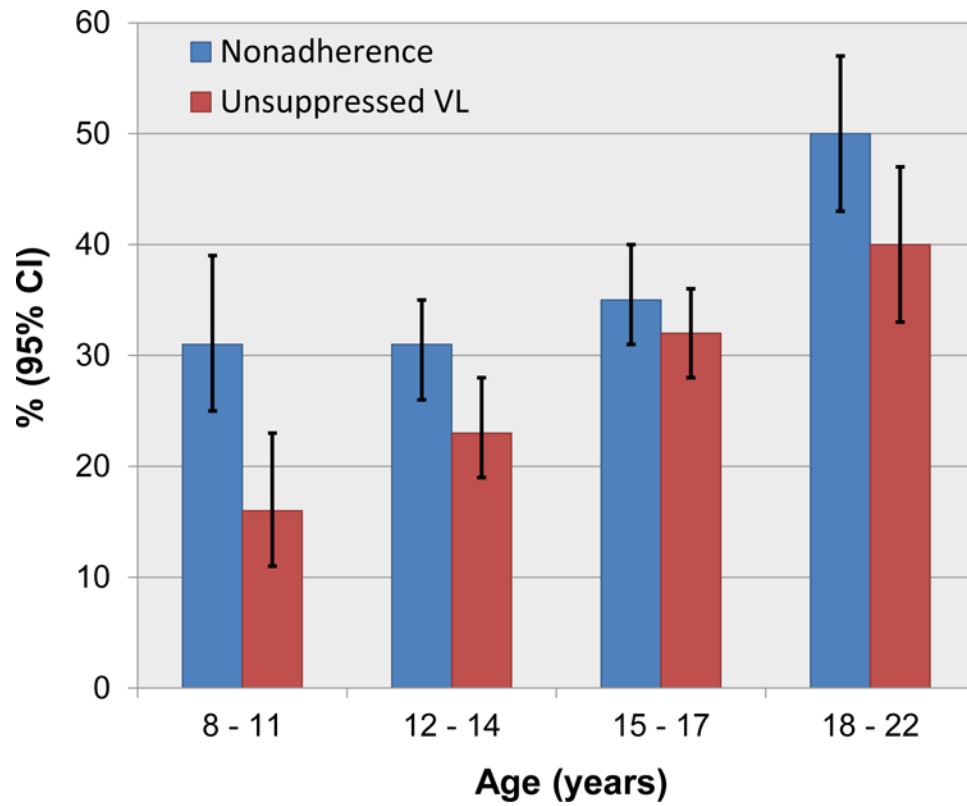


Figure 1:
Prevalence of Nonadherence and Unsuppressed Viral Load by Age in PHACS AMP.
N=1190 self- and/or caregiver-reported adherence evaluations of 379 youth; N=1257 viral load measurements from 381 youth
PHACS AMP=Pediatric HIV/AIDS Cohort Study Adolescent Master Protocol;
CI=Confidence Interval; VL=Viral load

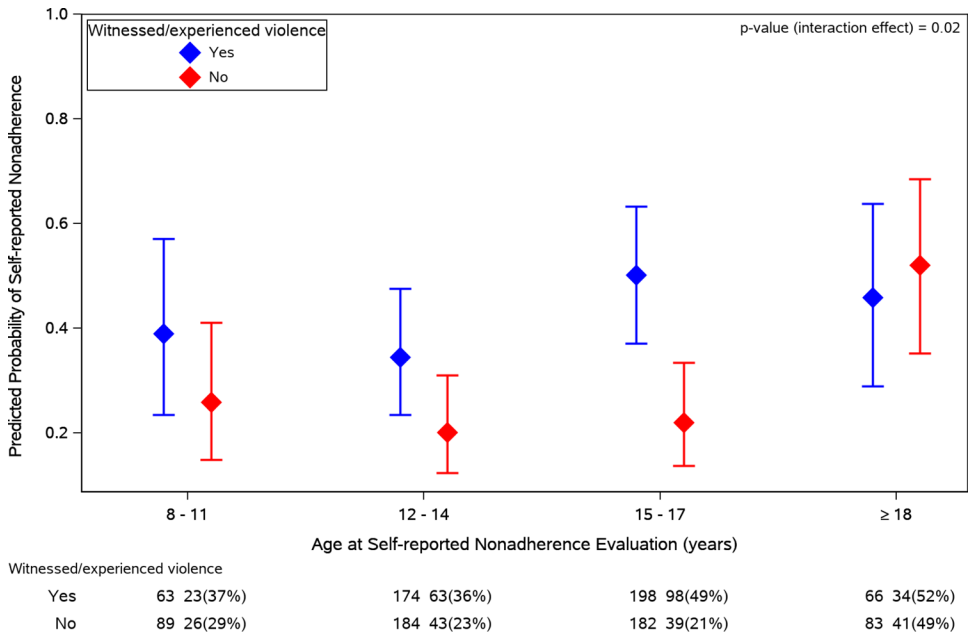


Figure 2: Adjusted Predicted Probabilities (with 95% Confidence Intervals) of Self-reported Nonadherence among Youth with vs. without Exposure to Violence in PHACS AMP. PHACS AMP=Pediatric HIV/AIDS Cohort Study Adolescent Master Protocol Model adjusted for sex, race, caregiver living arrangement, and household annual income. P-value was for testing the interaction between witnessed or experienced violence and age at self-reported nonadherence evaluation from the adjusted models. Predicted probabilities were among black males who lived in a household with annual income >\$10000–40000 and whose caregiver was living with a partner. The data table under the plot presents the number of participants with a specific characteristic and the number(%) with nonadherence (by self or caregiver report) among participants with the specific characteristic, within each group from unadjusted analysis.

Table 1:

Baseline Characteristics by Self-reported Nonadherence and Unsuppressed Viral Load among Youth with Perinatally-acquired HIV in the Pediatric HIV/AIDS Cohort Study Adolescent Master Protocol, 2007–2014

Characteristic	Self-reported ^a Nonadherence			Unsuppressed Viral Load			Total (N=381) n(%)
	Yes (N=112) n(%)	No (N=267) n(%)	P-Value	Yes (N=109) n(%)	No (N=272) n(%)	P-Value	
Individual							
Age (years)							
8 – 11	29 (26)	74 (28)	0.11	16 (15)	87 (32)	0.002	103 (27)
12 – 14	34 (30)	92 (34)		44 (40)	88 (32)		132 (35)
15 – 17	40 (36)	94 (35)		43 (39)	92 (34)		135 (35)
18 – 22	9 (8)	7 (3)		6 (6)	5 (2)		11 (3)
Female	69 (62)	132 (49)	0.03	64 (59)	139 (51)	0.18	203 (53)
Race: Black	83 (75)	187 (73)		77 (72)	198 (75)	0.55	275 (74)
Ethnicity: Latinx	26 (23)	68 (25)	0.64	29 (27)	60 (22)	0.34	89 (23)
Nadir CD4% prior to or at enrollment							
> 25%	26 (23)	58 (22)	0.37	16 (15)	66 (24)	0.03	82 (22)
15% - 25%	52 (46)	108 (40)		44 (40)	118 (43)		162 (43)
< 15%	34 (30)	101 (38)		49 (45)	88 (32)		137 (36)
ART regimen							
PI-containing cART	76 (68)	198 (74)	0.31	78 (72)	191 (70)	<0.001	269 (71)
NNRTI-containing cART	23 (21)	45 (17)		4 (4)	57 (21)		61(16)
NRTI-containing cART	3 (3)	11 (4)		4 (4)	10 (4)		14 (4)
Non-cART	10 (9)	13 (5)		10 (9)	12 (4)		22(6)
No ART	N/A	N/A		13 (12)	2 (1)		15 (4)
Single dose ART regimen	40 (36)	77 (29)	0.19	31 (36)	73 (29)	0.19	104 (30)
Distressing physical symptoms, caregiver-reported	34 (35)	66 (27)	0.18	24 (27)	79 (32)	0.38	103 (30)
Distressing physical symptoms, youth-reported	25 (35)	53 (33)	0.71	28 (37)	53 (33)	0.53	81 (34)
Perceived ART side effects	19 (17)	15 (6)	<0.001	13 (15)	15 (6)	0.01	28 (8)
Youth aware of HIV status	91 (81)	209 (78)	0.52	88 (81)	212 (78)	0.55	300 (79)
Alcohol use, past 3 months	22 (26)	20 (10)	<0.001	19 (25)	19 (10)	0.001	38 (14)
Emotional problem	13 (13)	29 (12)	0.98	7 (7)	31 (14)	0.22	38 (12)
Behavioral problem	20 (20)	39 (17)	0.54	14 (18)	45 (19)	0.78	59 (18)
Family							
Household annual income							
\$10,000	24 (22)	52 (20)	0.40	29 (27)	46 (17)	0.01	75 (20)
> \$10,000 - \$40,000	63 (58)	144 (54)		62 (58)	146 (54)		208 (55)
> \$40,000	21 (19)	69 (26)		16 (15)	76 (28)		92 (25)
Caregiver education							
< High school	35 (31)	62 (23)	0.26	35 (32)	61 (22)	<0.10	96 (25)
High school/GED	38 (34)	102 (38)		39 (36)	98 (36)		137 (36)

Characteristic	Self-reported ^a Nonadherence			Unsuppressed Viral Load			Total (N=381) n(%)
	Yes (N=112) n(%)	No (N=267) n(%)	P-Value	Yes (N=109) n(%)	No (N=272) n(%)	P-Value	
> High school	39 (35)	103 (39)		35 (32)	113 (42)		148 (39)
Caregiver Marital Status							
Married	33 (29)	120 (45)	0.01	28 (26)	125 (46)	0.001	153 (40)
Separated/divorced/widowed	34 (30)	76 (28)		40 (37)	70 (26)		110 (29)
Single, never married	45 (40)	71 (27)		41 (38)	77 (28)		118 (31)
Caregiver living with partner/spouse	47 (42)	148 (55)	0.02	44 (40)	148 (54)	0.01	192 (50)
Number of caregiver functional limitations							
0	50 (52)	136 (57)	0.23	52 (60)	134 (55)	0.77	186 (57)
1 – 2	21 (22)	59 (25)		19 (22)	57 (24)		76 (23)
3	25 (26)	42 (18)		16 (18)	51 (21)		67 (20)
Personal adjustment at risk/ clinically significant	18 (17)	38 (14)	0.20	17 (19)	38 (17)	0.74	55 (16)
Social							
Buddy system ART reminder	36 (32)	47 (18)	0.002	13 (12)	64 (24)	0.06	77 (20)
Concern about inadvertent disclosure	18 (16)	16 (6)	0.002	13 (15)	13 (5)	0.002	26 (8)
Youth has a boyfriend/girlfriend	65 (77)	118 (61)	0.01	59 (77)	125 (65)	0.06	184 (68)
Structural							
Any violence exposure	45 (54)	64 (30)	< 0.001	38 (48)	68 (32)	0.01	106 (36)
Indirect exposure to violence	38 (46)	54 (25)	<0.001	34 (43)	56 (26)	0.01	90 (31)
Direct violence victimization	16 (19)	21 (10)	0.03	12 (15)	24 (11)	0.39	36 (12)
Number of stressful life events, youth-reported							
0	23 (32)	80 (49)	0.01	26 (35)	80 (49)	0.009	106 (45)
1	16 (23)	40 (25)		17 (23)	38 (23)		55 (23)
2	12 (17)	24 (15)		17 (23)	21 (13)		38 (16)
3	20 (28)	18 (11)		15 (20)	23 (14)		38 (16)
Number of stressful life events, caregiver-reported							
0	40 (39)	131 (53)	0.004	46 (49)	134 (52)	0.17	180 (51)
1	23 (23)	66 (27)		22 (24)	67 (26)		89 (25)
2	20 (20)	25 (10)		10 (11)	36 (14)		46 (13)
3	19 (19)	23 (9)		15 (16)	21 (8)		36 (10)

^aSelf-reported defined as youth and/or caregiver report.

Abbreviations: ART=Antiretroviral therapy; PI=Protease inhibitor; NNRTI=Non-nucleoside reverse transcriptase inhibitor; NRTI=Nucleoside reverse transcriptase inhibitor; Data presented as number (percentage) of participants in each column unless indicated otherwise. Those with missing responses were not included in the % calculation. The following numbers of participants whose data were missing for a particular variable at baseline for the nonadherence and unsuppressed viral load analysis samples, respectively, were excluded: Race, n=12, n=10; distressing physical symptoms, caregiver-reported, n=40, n=41; distressing physical symptoms, youth-reported=146, n=143; emotional problem, n=41, n=55; behavioral problem, n=50, n=65; alcohol use, n=103, n=112; annual household income, n=6, n=6; number of caregiver functional limitations, n=46, n=52; personal adjustment composite, n=41, n=55; Buddy system ART reminder n=0, n=39; concern about inadvertent disclosure n=0, n=39; perceived ART side effects n=0, n=39; youth has a boyfriend or girlfriend, n=102, n=111; any violence exposure n=83, n=89; youth-reported stressful life events, n=146, n=144; caregiver-reported stressful life events, n=32, n=30

Table 2: Adjusted Associations of Covariates with Self-reported Nonadherence at Different Age Stages (N=1190 Evaluations of 379 Youth)

Covariates	Age (years) at Time of Adherence Evaluation					
	8 – 11 (N ^d =172)	12 – 14 (N ^d =383)	15 – 17 (N ^d =432)	18 – 22 (N ^d =203)	OR (95% CI)	P-value
Race: Black (ref: White, Asian/Pacific Islander, Native American, or Alaskan Native)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	P-value
	18.75 (1.91, 183.84)	2.32 (1.11, 4.83)	2.40 (0.91, 6.32)	1.66 (0.82, 3.37)	3.74 (1.17, 11.94)	0.02
Nadir CD4% prior to or at enrollment						
15% - 25% (ref: > 25%)		0.93 (0.47, 1.86)	2.40 (0.91, 6.32)	1.66 (0.82, 3.37)	3.74 (1.17, 11.94)	0.08
< 15% (ref: > 25%)		0.58 (0.26, 1.30)	3.06 (1.17, 8.03)	1.66 (0.82, 3.37)	3.74 (1.17, 11.94)	0.02
Multidose ART regimen (ref: single dose)		0.58 (0.33, 1.02)				0.06
Distressing physical symptoms, youth-reported ^b (ref: 0)						
Perceived ART side effects (ref: Never/Rarely)	0.01	2.35 (0.90, 6.12)	5.23 (1.90, 14.40)	3.74 (1.17, 11.94)	3.74 (1.17, 11.94)	0.002
Alcohol use, past 3 months ^c			1.95 (0.98, 3.87)			0.06
Annual household income						
>\$10,000 – 40,000 (ref: > \$40,000)				1.96 (0.82, 4.66)	1.96 (0.82, 4.66)	0.13
\$10,000 (ref: > \$40,000)				2.41 (0.79, 7.39)	2.41 (0.79, 7.39)	0.12
Caregiver marital status						
Separated, divorced, widowed (ref: married)			1.56 (0.69, 3.54)			0.29
Single, never married (ref: married)			2.88 (1.35, 6.11)			0.01
Buddy system ART reminder	2.72 (1.22, 6.07)	1.85 (1.04, 3.30)				0.04
Indirect exposure to violence ^d		1.67 (0.96, 2.91)	2.82 (1.50, 5.31)			0.001
Number of stressful life events, caregiver-reported ^e						
1 (ref: 0)			1.28 (0.60, 2.72)			0.52
2 (ref: 0)			2.45 (1.01, 5.93)			0.05
3 (ref: 0)			2.18 (0.83, 5.70)			0.11
Concern about inadvertent disclosure (ref: Never/Rarely)			4.41 (1.56, 12.47)			0.01

Abbreviations: ART=Antiretroviral therapy; PI=Protease inhibitor; NNRTI=Non-nucleoside reverse transcriptase inhibitor; NRTI=Nucleoside reverse transcriptase inhibitor; OR=Odds Ratio of self-reported nonadherence for participants with vs. without a specific characteristic; CI=Confidence interval

^aNumber of evaluations/records from participants within each age group. The number of unique participants within each age group is: 103 in 8–11; 211 in 12–14; 250 in 15–17; and 122 in 18 – 22 age group.

^bData were collected at 1-year visits for age 12 or older; variable was excluded from analysis for age 8 – 11.

^cData were collected for age 10 or older; variable was excluded from analysis for age 8 – 11.

^dData were collected at 1-year visits for ages 8–15.

^eData were collected at 1-year visits.

Additional covariates excluded from the multivariable analyses for age 8–11: Have a boyfriend/girlfriend; Alcohol use in the past 3 months; Youth-reported stressful life events; Youth-reported distressing physical symptoms.

Additional covariates excluded from the multivariable analyses for age 18: youth awareness of HIV status; Caregiver functional limitation; Caregiver-reported behavioral problem; Youth-reported violent events (experienced or witnessed); Caregiver-reported distressing physical symptoms.

The following pairs of covariates may be correlated with each other, thus if both covariates were significant in univariable analyses then only one was included in multivariable analyses as indicated; however, if only one was significant in univariable analyses then the significant covariate was included: 1) caregiver education and household income (used household income); 2) violence exposure and youth-report stressful life events (used violence exposure); 3) caregiver marital status and living arrangement (used marital status); 4) ART regimen and regimen dose (used ART regimen).

Table 3: Adjusted Associations of Covariates with Unsuppressed Viral Load at Different Age Stages (N=1257 Measurements from 381 Youth)

	Age (years) at Time of Viral Load Measure							
	8 – 11 (N ^a =178)	P-value	12 – 14 (N ^a =391)	P-value	15 – 17 (N ^a =462)	P-value	18 – 22 (N ^a =226)	P-value
	OR (95% CI)		OR (95% CI)		OR (95% CI)		OR (95% CI)	
Race: Black (ref: White, Asian/Pacific Islander, Native American, or Alaskan Native)							2.70 (0.77, 9.41)	0.12
PI-containing cART regimen							2.41 (0.84, 6.90)	0.10
Distressing physical symptoms, youth-reported ^b (ref: 0)							2.54 (1.01, 6.43)	0.05
Perceived ART side effects (ref: Never/Rarely)							4.41 (1.16, 16.72)	0.03
Youth aware of HIV status		0.32 (0.12, 0.81)	0.02					
Behavioral problem: (ref: Normal)		0.23 (0.05, 1.15)	0.07					
Annual household income							8.79 (3.52, 21.97)	< 0.001
> \$10,000 – \$40,000 (ref: > \$40,000)	7.60 (0.83, 69.72)	0.07	1.86 (0.70, 4.94)	0.21	4.29 (1.80, 10.27)	0.001		
\$10,000 (ref: > \$40,000)	3.66 (0.33, 40.85)	0.29	3.28 (1.06, 10.18)	0.04	5.62 (2.04, 15.52)	< 0.001		
Caregiver not living with partner (ref: Living with partner/spouse)								
Buddy system ART reminder		2.80 (0.96, 8.18)	0.06				0.50 (0.24, 1.06)	0.07
Indirect exposure to violence ^c								
Concern about inadvertent disclosure (ref: Never/Rarely)			3.06 (0.97, 9.63)	0.06				
							1.82 (0.67, 4.92)	0.23

Abbreviations: ART=Antiretroviral therapy; PI=Protease inhibitor; NNRTI=Non-nucleoside reverse transcriptase inhibitor; NRTI=Nucleoside reverse transcriptase inhibitor; OR=Odds Ratio of unsuppressed viral load for participants with vs. without a specific characteristic; CI=Confidence interval

^aNumber of records within each age group. The number of unique participants within each age group is: 103 in 8–11; 219 in 12–14; 259 in 15–17; and 135 in 18–22 age group.

^bData were collected at 1-year visits for age 12 or older; variable was excluded from analysis for age 8–11.

^cData were collected at 1-year visits for ages 8–15.

Covariates with 25% missing data in any age group were excluded from the multivariable analyses for all age groups: for age 8–11: Have a boyfriend/girlfriend; Alcohol use in the past 3 months; Youth-reported stressful life events; Youth-reported distressing physical symptoms.

Additional covariates excluded from the multivariable analyses for age 18–22: HIV disclosure status; Caregiver functional limitation; Caregiver-reported behavioral problem; Youth-reported violent events (experienced or witnessed); Caregiver-reported stressful life events; Caregiver-reported distressing physical symptoms.

The following pairs of covariates may be correlated with each other, thus if both covariates were significant in univariable analyses then only one was included in multivariable analyses as indicated; however, if only one was significant in univariable analyses then the significant covariate was included: 1) caregiver education and household income (used household income); 2) violence exposure and youth-report stressful life events (used violence exposure); 3) caregiver marital status and living arrangement (used marital status); 4) ART regimen and regimen dose (used ART regimen).