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Factors Associated With Nonadherence to Antiretroviral Therapy Among Young People Living With Perinatally Acquired HIV in England

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Abstract

Young people living with perinatally acquired HIV may be at risk of poor adherence to antiretroviral therapy; identification of predictors, using a conceptual framework approach proposed previously by others, is important to identify those at higher risk. In 261 young people with perinatally acquired HIV in England, 70 (27%) reported 3-day nonadherence, 82 (31%) last month nonadherence, and 106 (41%) nonadherence on either measure. Of those reporting nonadherence on both measures, 52% (23/44) had viral load of <50 copies/ml, compared with 88% (127/145) of those reported being fully adherent. In multivariable analysis, young person and medication theme factors were associated with nonadherence. The main predictors of 3-day nonadherence were antiretroviral therapy containing a boosted protease inhibitor and poorer quality of life. Predictors of last month nonadherence were having told more people about one's HIV status, worse self-perception about having HIV, and boosted protease inhibitor–based regimens. The consistency of individual young person and medication factors in predicting nonadherence gives insight into where interventions may best be targeted to improve adherence.

Key words: adherence, adolescents and young adults, conceptual framework, HIV, perinatal, young people

Young people (adolescents and young adults ages 10–24 years) living with perinatally acquired HIV (PHIV) may be at particular risk of poor antiretroviral adherence due to several factors. First, across many chronic conditions requiring long-term treatment, maintenance of medication adherence can be problematic (Patton et al., 2016). Advances in antiretroviral therapy (ART) have led to simplified regimens and also single tablet regimens, but the behavior required to adhere to treatment is a challenge to sustain over time (Kacanek et al., 2019). Second, the adolescent period can exacerbate adherence challenges, at a time when responsibility for disease management may transfer from the caregiver to the young person (Anon, 2016). This period is characterized by significant physiological and psychosocial change, maturation of emotional development, and dynamic brain development, which all impact on short-term and long-term goal setting and decision-making processes, which in turn may affect adherence (Patton et al., 2016). Studies show that medication adherence generally declines as children with chronic conditions enter adolescence (Penazzato et al., 2018; Virella Perez et al., 2019). Third, the context of perinatal HIV may generate its own issues, including secrecy about HIV within the family and stigma (Kawuma-Kagawa et al., 2014). Also, people living with PHIV may have more difficulties adhering to ART than peers living with nonperinatal HIV, due to having lived with HIV for a longer period (MacDonell et al., 2013). They may have more complex ART treatment regimens

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Members of the Adolescents and Adults Living with Perinatal HIV (AALPHI) Steering Committee are listed in Appendix 1.

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http://dx.doi.org/10.1097/JNC.0000000000000171

and may have experienced the death of parent(s) early in life, and have anxiety around disclosing their HIV status to others (Xu et al., 2017).

Poor ART adherence compromises virological suppression and increases the risk of developing HIV drug resistance, disease progression, and transmission of the virus to others (Ammon et al., 2018; Hudelson & Cluver, 2015). Thus, ongoing monitoring of ART adherence and identification of predictors is important to identify those at higher risk for ART nonadherence. However, few large studies to date have focussed specifically on PHIV or have been able to capture the diverse range of predictors that have shown to be associated with ART adherence in young people, including medication-related, patient-related, family-related, and psychosocial predictors (Adejumo et al., 2015; Altice et al., 2019; Enane et al., 2018; Evangeli, 2018; Hudelson & Cluver, 2015; Kim et al., 2014).

A conceptual framework for the wide range of factors associated with ART adherence has been proposed by Haberer and Mellins (2009). This conceptual framework was used in a systematic review of adherence to ART therapy in adolescents living with HIV (Hudelson & Cluver, 2015), incorporating four key themes influencing adherence: adolescent, caregiver, medication (including caregiver vs. young person administration and disclosure, due to their associations with medication nonadherence), and social and physical environment. Although the review was unable to identify factors consistently associated with nonadherence across the studies included, using the conceptual framework, the authors were able to detect important themes such as gender, knowledge of HIV diagnosis, family structure, type of ART regimen, attitudes about medication, geographical location, and having missed clinic appointments (Hudelson & Cluver, 2015). Therefore, this framework provides an evidence-based model that can help clinicians conceptualize the complex interplay between factors influencing ART adherence across heterogeneous populations globally.

In this study, we explore the prevalence of ART nonadherence in all young people living with HIV participating in the Adolescents and Adults Living with Perinatal HIV (AALPHI) cohort. We used the conceptual framework approach, by grouping potential predictors of nonadherence into four themes, to explore the association between ART adherence and a wide range of factors collected in the AALPHI cohort.

Methods

Adolescents and Adults Living with Perinatal HIV is a prospective study evaluating the impact of HIV infection and ART exposure on PHIV in England and comparing outcomes with HIV-uninfected young people, across multiple areas of inquiry, including cognitive function (Judd et al., 2016); cardiac function, anxiety, and depression (Le Prevost et al., 2018); sexual and reproductive health (Judd et al., 2018); and self-harm (Copelyn et al., 2019). This analysis includes only young people in AALPHI with PHIV. Three hundred sixteen young people with PHIV, ages 13–21 years, were recruited into the AALPHI study between 2013 and 2015; these participants were also in the nationwide U.K. and Ireland Collaborative HIV Paediatric Study (CHIPS; Collins et al., 2017). The young people recruited were broadly representative of young people with PHIV in the United Kingdom and Ireland (Judd et al., 2016). All young people meeting the study inclusion criteria were approached in 18 HIV clinics and four community service locations in England, and voluntarily provided informed consent. Young people younger than 18 years were allowed to consent to participation in the study themselves if they were deemed by the study research nurses as having the capacity to consent. This involved study research nurses having discussions with clinicians and/or voluntary sector staff about the young person's physical and emotional state and their capacity to consent, before the young person being approached to participate in the study. Furthermore, to ensure young people had adequate information to decide whether to participate in the study, research nurses read the patient information sheet to the young person and answered any queries. In addition, all the points in the consent form were discussed and questions posed throughout the consent process to help the research nurse decide if the young person had the ability and maturity to consent to participating in the study. Participants provided written informed consent, except where they lacked the capacity, in which case parents or guardians provided written informed consent and the young person provided written assent. Full ethical approval was granted from Leicester Research Ethics Committee. The sample size for the study was based on power to detect comparisons between the PHIV and HIV-uninfected groups, and no specific power calculations were undertaken to detect differences within the PHIV group only.

Participants underwent a 2-hour face-to-face interview, with a trained research nurse, which included a computer-assisted self-interviewing section where data were collected on ART adherence. The two adherence measures assessed medication taking behavior—missing any doses in the last 3 days ("3 day nonadherence") and also having missed more than 2 days' of doses in a row in the last month ("last month nonadherence"), which have been used in previous studies (Harrison et al., 2013). Although these specific measures have not been validated against an

external reference, similar questions (e.g., missing doses in the last 2 days, and number of days in last month not taking drugs as prescribed) have been validated and/or correlated with viral load (VL; Scott et al., 2018). Respondents also reported whether any doses were particularly hard to take, reminders that were used, and reasons for nonadherence. VL and $CD4^+$ T-cell data closest to the AALPHI interview date (±6 months) were extracted from routine laboratory tests collected in CHIPS.

This analysis differs from other publications from AALPHI because it takes a quantitative approach to assessing ART adherence and its predictors in all PHIV in AALPHI. A previous publication on ART adherence in a small subset (29 participants) of the PHIV group in AALPHI looked at young people who took their medication inconsistently (i.e., periods of adherence and nonadherence in the same participant; Hawkins et al., 2016). Therefore, the analysis of the adherence data from all the young people with PHIV in the cohort in this article is appropriate because of the lack of studies to date investigating adherence in young people with PHIV, which have a large sample size and with a wide range of data collected on potential predictors.

Data Analysis

Participants were included in the analysis if they had completed the adherence questionnaire in the main interview, as described above. These participants may have been included in the analysis in previous publications from this cohort; however, the data collected specifically on adherence, which is the focus of this article, have not been analyzed or reported previously. The effects of potential predictors on 3-day and last month nonadherence were explored using logistic regression. Potential predictors of nonadherence were grouped into four conceptual framework themes, based on previous studies (Haberer & Mellins, 2009; Hudelson & Cluver, 2015). All instruments used in the study are described in Table 1.

Young person–related factors included sex, age at interview, ethnicity, and being born outside the United Kingdom, which were considered *a priori* to be associated with both 3-day and last month nonadherence. Other young person–related factors were cognitive function (six-domain summary neuropsychological *z* score [NPZ-6], calculated as the mean *z* score across six cognitive domains; Judd et al., 2016) and mental health measures, including anxiety and depression symptoms (Hospital Anxiety and Depression Scale; Zigmond & Snaith, 1983), health-related quality of life (Pediatric Quality of Life Inventory 4.0; Varni, 2012; Varni et al., 1999), self-esteem (Rosenberg Self-esteem Scale; Rosenberg, 1965), and self-perception about having HIV (composite score of level of upset, worry, sadness, loneliness, and concern about future health; developed by the authors).

Caregiver-related factors were death of one or both parents, whether fostered or adopted, number of main caregivers (different adults taking responsibility for and living with the participant during childhood), and main language spoken at home.

Medication-related factors were age at ART start, Centers for Disease Control and Prevention stage, diagnosis of encephalopathy (as reported by the clinic to the CHIPS study), years taking ART, total number of tablets taken per day, frequency of taking ART each day, class of ART regimen, and having transferred to adult care. Other medication-related factors were the number of people whom the young people had told about their HIV, number of people they were able to talk to about their HIV, and whether everyone in the family home was aware of their HIV status, which were all self-reported by the young person.

Social- and physical-related factors were residential deprivation score (Income Deprivation Affecting Children Index; Department for Communities and Local Government, 2015), current education/employment status, and whether living with parents. These predictors have been used in previous publications from this cohort, although have not previously been grouped into themes.

Results are presented for nonmissing values; missing values were less than 10% of study participants unless specified. Variables attaining a p value of $<.1$ in univariable logistic regression analyses were considered in multivariable analysis using backward selection, as well as the *a priori* variables (sex, age at interview, ethnicity, and being born outside the United Kingdom), and a two-tailed p value of $<.05$ was considered statistically significant (Bursac et al., 2008). A similar analysis approach has been used in previous publications from this cohort, albeit with different outcome variables. Years taking ART and total number of tablets taken per day were not considered in multivariable analysis because they were highly correlated with class of ART regimen and excluded due to collinearity concerns (Armitage, Berry, & Matthews, 2002). Data were analyzed using STATA version 15 (Stata Corp, College Station, TX).

Results

A total of 261 PHIV young people taking ART answered questions on ART adherence. Of these, 238 (91%) were on once-daily regimens, of whom 131 (55%) were taking ART combinations containing boosted protease inhibitors (PI) and 98 (41%) were taking nonnucleoside

Table 1. Instruments Used in the Study

Theme	Instrument/Measure	Scoring
Young person	NPZ-6	Mean z-score across 6 domains, documented previously (Judd et al., 2016)
	HADS	Scores range from 0 to 21, with higher scores indicating more severe anxiety or depression (Zigmond & Snaith, 1983)
	PedsQL	Teenage report for 13–18 years and young adult report for 18–25 years; scores range from 0 to 100 and a higher score indicates better social functioning (Varni, 2012; Varni et al., 1999)
	Rosenberg SES	Scores range from 0 to 30: higher scores indicate better self-esteem (Rosenberg, 1965)
Social and physical	IDACI	Scores range from 0 to 1; a higher score indicates more severe deprivation (Department for Communities and Local Government, 2015)

Note. HADS = Hospital Anxiety and Depression Scale; IDACI = Income Deprivation Affecting Children Index; NPZ = Neuropsychological *z* Score; PedsQL = Pediatric Quality of Life Inventory; SES = Self-esteem Scale.

reverse transcriptase inhibitor (NNRTI)–based regimens. Of the 23 young people on twice-daily regimens, 18 (78%) and 2 (9%) were taking PI- and NNRTI-based regimens, respectively.

Of the 261 total participants, the median age was 16 years (interquartile range, 15–18), 112 (43%) were male, 85% Black African, 59% born outside of the United Kingdom, and the majority studying and living with their parents (Table 2). At the time of the interview, 78% had a VL of <50 copies/ml, medium CD4 count was 629 cells/mm^3 (interquartile range, 465–814), and 61 (23%) had already transitioned from pediatric to adult care.

One quarter (n = 69/251, 27%) reported problems taking weekday doses, 98 of 252 (39%) weekend doses, and 50 of 251 (20%) both weekday and weekend doses. Half (n = 147, 56%) used reminders to help adherence, including family members (107/147, 73%), pill boxes (20%), timers (20%), daily routines (e.g., breakfast time; 10%), text messages (7%), and friends (7%).

Twenty participants (8%) reported missing doses on the day of the interview, 30 (11%) the preceding day, and 53 (20%) the day before that, with a total of 70 (27%) reporting 3-day nonadherence. One third (n = 82, 31%) reported last month nonadherence, and 41% (106/261) reported nonadherence on either measure. Of those taking ART once daily, 94 of 238 (40%) reported nonadherence on either measure compared with 12 of 23 (52%) taking ART twice daily, and a higher proportion of young people on boosted PI-based regimens (68/149, 46%) reported nonadherence on either measure compared with those on NNRTI-based regimens (29/100, 29%). The main reasons for missing ART doses were forgetting (72/106, 68%), being away from home (37%), being asleep at the time the dose should be taken (30%), feeling too tired (29%), not being able to deal with ART that day (24%), not wanting others to know (23%), school hours interfering with adherence (23%), and running out of ART drugs (15%), with no difference in the reasons given by daily frequency or class of ART regimen (data not shown).

Of those reporting 3-day and last month nonadherence, only 52% (23/44) had a suppressed VL of <50 copies/ml, compared with 70% (16/23) for those reporting 3-day nonadherence only, 77% (27/35) for those reporting last month nonadherence only, and 88% (127/145) for those reporting adherence on both measures. There was no difference in VL suppression by daily frequency of ART (data not shown); however, a lower proportion of young people had suppressed VL if they were taking boosted PI-based regimens (95/141, 67%) compared with NNRTI-based regimens (91/96, 95%; $p < .001$).

In univariable analysis (Table 3), only *young person* (Hospital Anxiety and Depression Scale depression score, PedsQL, Rosenberg Self-esteem Scale, HIV self-perception) and *medication* (years taking ART, total number of tablets taken per day, ART class, number of people told about HIV) theme factors, and not *caregiver* or *social- and physical*-related factors, were associated with 3-day nonadherence ($p < .1$). After adjustment for *a priori* variables (sex, age at interview, ethnicity, and being born outside the United Kingdom), those with poorer quality of life (adjusted odds ratio [aOR], 2.39 per 25 units worse; 95% confidence interval [CI], 1.31–4.36; p = .004), and

Table 2. Young Person, Caregiver, Medication, and Social and Physical Characteristics of Young People With PHIV Taking ART (n = 261)

Theme	Variable	Category	*N* (%) or Median [IQR]
Young person	Sex	Male	112 (43%)
	Age (years)		16 [15 to 18]
	Ethnicity	Black	221 (85%)
	Born outside of UK		153 (59%)
	NPZ-6[a]		−0.5 [−1.0 to 0.1]
	HADS anxiety[b]		6 [3 to 9]
	HADS depression[b]		3 [1 to 6]
	PedsQL[c]		77 [67 to 87]
	Rosenberg SES[d]		21 [17 to 25]
	Self-perception about HIV[e]		35 [22 to 44]
Caregiver	Death of one/both parents		87 (35%)
	Fostered/adopted[f]		14 (13%)
	Number of main carers		1 [1 to 2]
	Main language spoken at home	English only	136 (52%)
Medication	Age at ART start (years)		7 [3 to 11]
	CDC stage at interview	N/A/B	184 (70.5%)
		C	77 (29.5%)
	Ever HIV encephalopathy		9 (3%)
	Years taking ART		9 [5 to 13]
	No. tablets taken each day	1	38 (15%)
		2	64 (25%)
		≥3	151 (60%)
	Once daily regimen		238 (91%)
	ART class	NNRTI based	100 (39.5%)
		Boosted PI based	149 (59%)
		Other	4 (1.5%)
	Transferred to adult care		61 (23%)
	No. people young person has told about their HIV	0	143 (56%)
		1–2	62 (24%)
		3+	49 (19%)
	No. people young person has spoken to about HIV in last 12 months (family/ friends/ clinic)	0	94 (37%)
		1-2	79 (31%)
		3+	81 (32%)

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Table 2. (*continued*)

Theme	Variable	Category	*N* (%) or Median [IQR]
	Everyone in family home knows status		165 (69%)
Social, physical	IDACI score[g]		0.4 [0.3 to 0.5]
	Occupation	Education	242 (93%)
		Employment	5 (2%)
		Not in education/employment	12 (5%)
	Live with parents		236 (91%)

Note. ART = antiretroviral therapy; CDC = Centers for Disease Control and Prevention; HADS = Hospital Anxiety and Depression Scale; IDACI = Income Deprivation Affecting Children Index; IQR = interquartile range; PedsQL = Pediatric Quality of Life Inventory; SES = Self-esteem Scale; NNRTI = nonnucleoside reverse transcriptase inhibitor; PHIV = perinatally acquired HIV; PI = protease inhibitor; UK = United Kingdom.
[a] Summary score calculated as the mean z-score across six cognitive domains.
[b] Scores range from 0 to 21; higher scores indicate more severe anxiety or depression.
[c] Mean score over 23 questions, each question ranges from 0 to 100, and higher scores representing better health-related quality of life.
[d] Scores range from 0 to 30, with higher scores indicating better self-esteem.
[e] Composite total score ranges from 0 to 50, and higher scores indicate better feelings about having HIV.
[f] Unknown for 151 as question was introduced part way through the study.
[g] Score ranges from 0 to 1, with higher score indicating more severe deprivation; unknown for 34.

those taking boosted PI-based ART combinations (aOR, 2.67; 95% CI, 1.34–5.30 vs. NNRTI-based; $p = .005$), had higher odds of 3-day nonadherence.

In the model investigating predictors of last month nonadherence (Table 4), again, only *young person* and *medication* theme factors had an association. Worse self-perception about having HIV (aOR, 1.17 per 5 unit decrease; 95% CI, 1.06–1.30; $p = .003$), having told more people about their HIV status (1–2 persons aOR, 1.49; 95% CI, 0.72–3.10; ≥3 persons aOR, 3.29; 95% CI, 1.53–7.08 vs. none; $p = .009$), and taking boosted PI-based ART combinations (aOR, 2.25; 95% CI, 1.19–4.24 vs. NNRTI-based; $p = .013$) were associated with last month nonadherence.

Discussion

In this cohort of long-term survivors of perinatal HIV, two of five reported missing any doses in the 3 days before the study interview and/or missing more than 2 days of doses in a row in the last month. Twenty-one participants (8% of the total) reported missing doses on both of these ART adherence measures and had unsuppressed VL at interview. By far, the most common reason for missing doses was forgetting. Overall, the prevalence of nonadherence was in keeping with findings from other studies. A systematic review published in 2018 documented adherence levels varying from 64% to 90%, although nonadherence levels in the past week varied widely from 6% to 95% (Ammon et al., 2018). An earlier review found adherence in the 30 days before interview being 28% to 70% (Reisner et al., 2009). However, both included all young people with HIV, and not just those with PHIV, which was the focus of this article. Larger, more recent primary research studies included a study of 250 adolescents living with (primarily perinatally acquired) HIV recruited across three countries in Asia and followed them longitudinally for 3 years. In this study, 60% to 69% of adolescents reported adherence in the last month of ≤95% at the various time points of follow-up (Ross et al., 2019). In South Africa, 70% of 474 adolescents with PHIV reported no missed doses in the last 30 days (Brittain et al., 2018). More recent evidence from the United States highlights how in young people with PHIV followed longitudinally, around 40% reported missing an ART dose in the last week, and the presence of psychiatric disorders was strongly associated with missed doses (Bucek et al., 2018). This highlights how targeted interventions in this area may help improve adherence in young people.

The conceptual framework used in our study was developed to facilitate understanding of the varied challenges affecting adherence to ART among children and adolescents across heterogeneous populations worldwide (Haberer & Mellins, 2009). This model incorporates factors beyond those affecting other young people with chronic illnesses, by, for example, including caregiver characteristics such as vitality status and awareness of HIV in the home. Future studies might consider incorporating

Table 3. Prevalence, and Univariable and Multivariable Predictors of Missing Any Doses of ART in the Last 3 Days[a]

Variable (Theme)	Categories	Missing ≥ 1 Dose *n*/Total, % or *M (SD)*	Univariable			Multivariable		
			Odds Ratio	95% CI	*p*-Value	Odds Ratio	95% CI	*p*-Value
Sex (young person)	Male	25/112, 22%	1.00			1.00	—	
	Female	45/149, 30%	1.51	0.86–2.65	.156	1.11	0.56–2.19	.761
Age (years) at interview (young person)	*M* age, no missed dose	16.8 (2.3)	—	—	—	—	—	
	M age, missed dose	17.1 (2.1)	—	—	—	—	—	
	Per year increase	—	1.06	0.94–1.20	.317	1.06	0.92–1.23	.384
Ethnicity (young person)	Non-Black[b]	7/40, 18%	1.00			1.00	—	
	Black	63/221, 29%	1.88	0.79–4.47	.153	2.37	0.89–6.31	.083
Country of birth (young person)	United Kingdom	32/108, 30%	1.00			1.00	—	
	Outside of United Kingdom	38/153, 25%	0.78	0.45–1.36	.390	0.77	0.41–1.45	.420
HADS depression score (young person)	Normal/mild (<11)	61/232, 26%	—	—	—	—	—	—
	Moderate/severe (≥11)	4/11, 36%	—	—	—	—	—	—
	Per unit worse	—	1.08	0.99–1.18	.076	—	—	—
PedsQL (quality of life) (young person)	*M* score, no missed dose	78.4 (13.2)	—	—	—	—	—	—
	M score, missed dose	71.2 (13.6)	—	—	—	—	—	—
	Per 25 unit worse	—	2.62	1.55–4.44	<.001	2.39	1.31–4.36	.004
Rosenberg SES (self-esteem) (young person)	*M* score, no missed dose	21.2 (5.1)	—	—	—	—	—	—
	M score, missed dose	20.0 (5.7)	—	—	—	—	—	—
	Per 5 unit worse	—	1.26	0.97–1.64	.089	—	—	—
HIV self-perception (young person)	*M* score, no missed dose	33.1 (14.0)	—	—	—	—	—	—
	M score, missed dose	26.9 (15.9)	—	—	—	—	—	—
	Per 5 unit worse		1.15	1.05–1.26	.003	—	—	—

(*continued on next page*)

Table 3. (*continued*)

Variable (Theme)	Categories	Missing ≥ 1 Dose *n*/Total, % or *M (SD)*	Univariable			Multivariable		
			Odds Ratio	95% CI	*p*-Value	Odds Ratio	95% CI	*p*-Value
Years taking ART (medication)	*M* years, no missed dose	9.1 (4.9)	—	—	—	—	—	—
	M years, missed dose	10.4 (4.6)	—	—	—	—	—	—
	Per year increase		1.06	1.00–1.12	.061	—	—	—
Total number of tablets taken	1	5/38, 13%	1.00			—	—	—
per day (medication)	≥ 2	60/215, 28%	2.55	0.95–6.85	.062	—	—	—
ART class (medication)	NNRTI based	16/100, 16%	1.00			1.00		
	Boosted PI based	47/149, 32%	2.42	1.28–4.57	.007	2.67	1.34–5.30	.005
No. people told about HIV (medication)	None	31/143, 22%	1.00			—	—	—
	1–2	19/62, 31%	1.60	0.82–3.12		—	—	—
	≥ 3	19/49, 39%	2.29	1.14–4.60	.056	—	—	—

Note. ART = antiretroviral therapy; CI = confidence interval; HADS = Hospital Anxiety and Depression Scale; NNRTI = nonnucleoside reverse transcriptase inhibitor; PedsQL = Pediatric Quality of Life Inventory; PI = protease inhibitor; SES = Self-esteem Scale.

[a] Factors attaining an univariable p value $< .10$, and a priori variables (sex, age at interview, born in United Kingdom vs. abroad, ethnicity) are shown in the table.

[b] Non-Black includes White, mixed, Asian, and Chinese. Black includes Black Caribbean, Black African, and other Black.

Table 4. Prevalence, and Univariable and Multivariable Predictors of Missing More Than 2 Days of Doses in a Row in the Last Month[a]

Variable (Theme)	Categories	Missing > 2 Days *n*/Total, % or *M (SD)*	Univariable			Multivariable		
			Odds Ratio	95% CI	*p*-Value	Odds Ratio	95% CI	*p*-Value
Sex (*young person*)	Male	32/112, 29%	1.00			1.00	—	
	Female	50/149, 34%	1.26	0.74–2.15	.391	1.13	0.61–2.09	.706
Age (years) at interview (young person)	*M* age, no missed dose	16.8 (2.3)	—	—	—	—	—	—
	M age, missed dose	17.1 (2.2)	—	—	—	—	—	—
	Per year increase	—	1.06	0.95–1.19	.303	0.97	0.84–1.11	.653
Ethnicity (young person)	Non-Black[b]	12/40, 30%	1.00			1.00	—	
	Black	70/221, 32%	1.08	0.52–2.25	.834	1.40	0.60–3.24	.437
Country of birth (young person)	United Kingdom	40/108, 37%	1.00			1.00	—	
	Outside of United Kingdom	42/153, 27%	0.64	0.38–1.09	.101	0.57	0.31–1.05	.070
HADS depression score (young person)	Normal/mild (<11)	71/232, 31%	—	—	—	—	—	—
	Moderate/severe (≥11)	4/11, 36%	—	—	—	—	—	—
	Per unit worse	—	1.08	0.99–1.17	.087	—	—	—
PedsQL (quality of life) (young person)	*M* score, no missed dose	78.3 (13.0)	—	—	—	—	—	—
	M score, missed dose	72.3 (14.4)	—	—	—	—	—	—
	Per 25 unit worse	—	2.24	1.36–3.69	.002	—	—	—
Rosenberg SES (self-esteem) (young person)	*M* score, no missed dose	21.3 (4.9)	—	—	—	—	—	—
	M score, missed dose	20.0 (6.0)	—	—	—	—	—	—
	Per 5 unit worse	—	1.25	0.97–1.62	.083	—	—	—
HIV self-perception (young person)	*M* score, no missed dose	33.4 (13.7)	—	—	—	—	—	—
	M score, missed dose	27.1 (16.1)	—	—	—	—	—	—
	Per 5 unit worse		1.15	1.05–1.26	.002	1.17	1.06–1.30	.003

(*continued on next page*)

Table 4. (*continued*)

Variable (Theme)	Categories	Missing > 2 Days *n*/Total, % or *M* (*SD*)	Univariable			Multivariable		
			Odds Ratio	95% CI	*p*-Value	Odds Ratio	95% CI	*p*-Value
ART class (medication)	NNRTI based	20/100, 20%	1.00			1.00		
	Boosted PI based	56/149, 38%	2.41	1.33–4.35	.004	2.25	1.19–4.24	.013
No. people told about HIV (medication)	None	33/143, 25%	1.00			1.00	—	—
	1–2	21/62, 34%	1.52	0.80–2.91		1.49	0.72–3.10	—
	≥ 3	23/47, 47%	2.63	1.34–5.17	.018	3.29	1.53–7.08	.009

Note. ART = antiretroviral therapy; CI = confidence interval; HADS = Hospital Anxiety and Depression Scale; NNRTI = non-nucleoside reverse transcriptase inhibitor; PedsQL = Pediatric Quality of Life Inventory; PI = protease inhibitor; SES = Self-esteem Scale.

[a] Factors attaining an univariable *p* value < .10, and a priori variables (sex, age at interview, born in the United Kingdom vs. abroad, ethnicity) are shown in the table.

[b] Non-Black includes White, mixed, Asian, and Chinese. Black includes Black Caribbean, Black African, and other Black.

measurement of variables spanning the four framework themes contributing to adherence, to disentangle the relative effects of each in contrasting populations.

In our analysis, *young person* and *medicatio*n themes were the strongest predictors of nonadherence. Factors associated with nonadherence in both outcome models included poorer quality of life and worse self-perception about having HIV, as well as having told more people about their HIV status. Disclosure was also found to be predictive of loss to follow-up in a study from South Africa, which found that adults who had disclosed to partners and were open to family and friends about their HIV status had higher levels of disengagement from care (Evangeli et al., 2016). Thus, secrecy around HIV status may be associated with better adherence and warrants further investigation. Taking ART regimens containing boosted PIs was a consistent predictor across both models in our study; this likely reflects previous poor adherence and subsequent switching to a PI-based regimen, which has a higher genetic barrier to drug resistance (British HIV Association, 2016), the fact that most twice daily regimens were boosted PI-based, or suggest tolerability issues with PIs.

Three reviews to date have focused on predictors of adherence in young people with HIV (Adejumo et al., 2015; Hudelson & Cluver, 2015; Reisner et al., 2009). Literature review of Reisner et al. (2009) from the United States suggested that sociodemographics (age, sex, ethnicity) did not predict adherence, and in contrast, psychosocial factors (such as HIV stigma and discrimination by friends and family, lower levels of life satisfaction, depression, and anxiety) were most consistently associated with nonadherence across studies, similar to our study. Adejumo et al. (2015) similarly highlighted the importance of psychological, socioeconomic, individual, and treatment-related factors influencing adolescent adherence in sub-Saharan Africa. Hudelson and Cluver (2015) reviewed literature from low- and middle-income countries and noted that there were few consistent relationships across studies between measured factors and adherence, but important emerging themes included knowledge of serostatus, the influence of family structure, the impact of various ART regimens, and health care and environmental factors such as rural versus urban location and missed clinic appointments (Hudelson & Cluver, 2015).

Our study has a number of limitations. First, it is widely recognized that there is no gold standard measure of adherence. However, we did ask specific questions about missing any doses in the last 3 days and missing more than 2 days in the last month; it is possible that other periods of nonadherence were missed. To encourage truthful reporting of ART adherence, we used computer-assisted

self-interviewing and stressed confidentiality and disassociation of the study staff with medical staff treating study participants. Furthermore, wording of the ART adherence questions was constructed in a nonjudgemental way. The relatively short period of recall was specifically selected in an attempt to minimize recall bias. Second, although we applied a conceptual framework approach to variable grouping, we had fewer variables in some of the themes, which may make them less likely to have a predictor associated with the outcome. Third, we did not measure levels of felt stigma, preparedness to transition from pediatric to adult HIV services, responsibility for medication adherence, adherence motivation, behavioral skills and self-efficacy, levels of drug resistance, or psychiatric comorbidity, all of which could have been informative. Fourth, our data were collected at the baseline AALPHI interview, and so the temporal association between factors and adherence could not be ascertained. Thus, for example, poorer quality of life could have been a cause or a consequence of nonadherence.

In conclusion, two in five young people in our study reported some level of ART nonadherence, and of those having missed doses, one in 10 were virally unsuppressed at interview. Predictors of nonadherence were related to the individual young person and medication factors, highlighting the importance of these domains and, in particular, when thinking about transition to adult care. They give insight into where to focus additional resources on supporting young people with PHIV in England to improve adherence and virological suppression. Specifically, issues around poor self-perception about having HIV, and the implications of disclosure, may be addressed through interventions to support young people's adjustment to HIV, including peer-based, residential, and individual therapy approaches. In terms of specific ART drugs, our study was conducted in the preintegrase inhibitor era, and newer ART strategies have a higher genetic barrier to drug resistance, and together with long-acting injectables provide novel improved options for young people with PHIV for the future. Individualized transition programs with appropriate support may be required to help maintain optimal medication adherence in this group (Kowalska et al., 2019). Thus, individualizing medication to address varied challenges is important for young people transitioning to adult care and to enable them to achieve optimal health in adulthood.

Disclosures

The authors report no real or perceived vested interests related to this article that could be construed as a conflict of interest.

Acknowledgments

This study was funded by the Monument Trust (grant number MON5049, Principal Investigator—Ali Judd) and Paediatric European Network for Treatment of AIDS (PENTA) Foundation (Principal Investigator—Ali Judd). This work was supported by the Medical Research Council programme grant MC_UU_12023/26 awarded to the MRC Clinical Trials Unit. The funding sources had no role in the study design, collection, analysis, and interpretation of data; writing of the report; or decision to submit the paper for publication. We thank all young people, parents, and staff from all the clinics and voluntary services participating in AALPHI.

Appendix 1. Members of the Adolescents and Adults Living with Perinatal HIV (AALPHI) Steering Committee

Members of the Adolescents and Adults Living with Perinatal HIV (AALPHI) Steering Committee is as follows:
Project team: S. Brice, H. Castro, A. Judd, M. Le Prevost, A. Mudd, A. Nunn, K. Rowson, K. Sturgeon. Investigators: M. Conway, K. Doerholt, D. Dunn, C. Foster, D.M. Gibb, A. Judd (PI), S. Kinloch, N. Klein, H. Lyall, D. Melvin, K. Prime, T. Rhodes, C. Sabin, M. Sharland, C. Thorne, P. Tookey. MRC CTU Data Services: C. Diaz Montana, K. Fairbrother, M. Rauchenberger, N. Tappenden, S. Townsend. Neurocognitive subgroup: A. Arenas-Pinto, H. Castro, C. Foster, A. Judd, M. Le Prevost, D. Melvin, A. Winston. Steering Committee chairs: D. Gibb, D. Mercey (2012–2015), C. Foster (2016–). Patient and public involvement: Children's HIV Association Youth Committee NHS clinics (named alphabetically): LONDON: Chelsea and Westminster NHS Foundation Trust, F. Boag, P. Seery; Great Ormond Street Hospital NHS Foundation Trust, M. Clapson, V. Noveli; Guys and St Thomas' NHS Foundation Trust, A. Callahgan, E. Menson; Imperial College Healthcare NHS Trust, C. Foster, A. Walley; King's College Hospital NHS Foundation Trust, E. Cheserem, E. Hamlyn; Mortimer Market Centre, Central and North West London NHS Foundation Trust, R. Gilson, T. Peake; Newham University Hospital, S. Liebeschuetz, R. O'Connell; North Middlesex University Hospital NHS Trust, J. Daniels, A. Waters; Royal Free London NHS Foundation Trust, T. Fernandez, S. Kinloch de Loes; St George's University Hospitals NHS Foundation Trust, S. Donaghy, K. Prime. REST OF ENGLAND: Alder Hey Children's NHS Foundation Trust, S. Paulus, A. Riordan; Birmingham Heartlands, Heart of England NHS Foundation Trust J. Daglish, C. Robertson; Bristol Royal Infirmary, University Hospitals Bristol NHS Foundation Trust, J. Bernatonlene, L. Hutchinson, University Hospitals Bristol NHS Foundation Trust, M. Gompel, L. Jennings; Leeds Teaching Hospitals NHS Trust, M. Dowie, S. O'Riordan; University Hospitals of Leicester NHS Trust, W. Ausalut, S. Bandi; North Manchester General Hospital, Pennine Acute Hospitals NHS Trust, P. McMaster, K. Rowson; Royal Liverpool and Broadgreen University Hospitals NHS Trust, M. Chaponda, S Paulus. Voluntary services (named alphabetically): Blue Sky Trust, C. Dufton, B. Oliver; Body and Soul, A. Ash, J. Marsh; Faith in People, I. Clowes, M. Overton; Positively UK, M. Kiwanuka, A.

Namiba; Positive Parenting & Children, N. Bengtsson, B. Chipalo. Lead contact for the AALPHI Steering Committee: Prof Ali Judd, a.judd@ucl.ac.uk.

Key Considerations

- ❍ Young person and medication factors influence nonadherence to antiretroviral therapy and play an important role in understanding why young people with PHIV in England may have poor adherence
- ❍ Providing support to young people who choose to disclose their HIV status may help to improve adherence
- ❍ Tailoring treatment to fit with young people's lifestyles, minimizing medication side effects, and making medication easier to take may also improve adherence and help to maintain viral suppression

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