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ORIGINAL PAPER

Association of Adolescent- and Caregiver-Reported Antiretroviral Therapy Adherence with HIV Viral Load Among Perinatally-infected South African Adolescents

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Abstract

Accurate measurement of antiretroviral therapy (ART) adherence remains challenging and there are few data assessing the validity of self-reported adherence among perinatally HIV-infected adolescents. We examined adolescent and caregiver reports of adolescent adherence among perinatally-infected adolescents aged 9–14 years in Cape Town, South Africa, and explored factors that may modify associations between reported adherence and elevated viral load (VL). Among 474 adolescents (median age 12.0 years; median duration of ART use 7.5 years), elevated VL and caregiver- and adolescent-report of missed ART doses were common. Elevated VL was particularly prevalent among older, male adolescents. Low-moderate concordance was observed between caregiver and adolescent report. Among adolescents aged ≥ 12 years, caregiver- and adolescent-reported adherence was associated with elevated VL across most items assessed, but few significant associations were observed among adolescents < 12 years of age. Refined adherence measures and tools to identify adolescents who require adherence interventions are needed in this context.

Keywords Adherence · Self-report · Adolescent · HIV · Viral load

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Introduction

Improved access to paediatric antiretroviral treatment has resulted in increasing numbers of perinatally HIV-infected infants surviving to adolescence and beyond [1–3]. Sustained adherence to antiretroviral therapy (ART) is needed in order to achieve optimal health outcomes, particularly in resource-limited settings where alternative regimens may not be readily available [2, 4]. However, ART adherence among young people may be poor [5, 6], with commonly reported barriers to adherence including forgetting, needing a break from taking medications and not wanting to be reminded of HIV [7]. Advanced adolescence is a well-documented risk factor for suboptimal adherence [8–12], while there are contrasting findings regarding the impact of gender [8, 13].

Adherence is a dynamic behaviour that needs to be assessed continuously [8], but objective electronic or biochemical measures of adherence may not be practical for long-term use in routine care settings [14, 15]. Despite concerns regarding recall and social desirability bias [4, 16], self-report of adherence may thus be the most feasible measure in poorly resourced areas [17, 18], and is the

most commonly used adherence measure in both clinical and research settings [4, 14]. However, accurate measurement remains challenging [5]. Efforts to improve self-report in general HIV-infected populations include the use of computer-assisted self-interviews, cognitive interviewing, or item response theory to combine information from multiple items [4], as well as attempts to optimise recall periods or the wording of items such that suboptimal adherence is presented as normalized [18, 19]. However, there have been limited efforts to refine child and adolescent self-report measures [9, 20]. Most research seeking to identify valid measures of adherence among perinatally HIV-infected adolescents has been conducted in the United States, and there are few data from sub-Saharan Africa, where the highest prevalence of adolescent HIV-infection is found and where objective measures of adherence are not readily available.

Among perinatally-infected youth, assessing adherence is further complicated as responsibility for adherence is often shared between caregivers and adolescents and may change over time as adolescents age [9, 15, 20–22]. An early review suggested that child or adolescent report of adherence can be considered when developmentally appropriate [23], given that the ability to recall and accurately report develops as children age, but it is unclear at what age and under what circumstances adolescent report becomes valid. An early study conducted in the United States suggested that caregiver report of adherence generally performs better than adolescent report [24], and studies have shown poor to moderate concordance between caregiver and adolescent report [15, 20, 21, 24]. In sub-Saharan Africa, there are few comparisons of adolescent versus caregiver report, and the validity of adolescent report of adherence is unclear. In addition, concern has been raised that sociodemographic characteristics may affect the validity of self-report measures of adherence [19], but there are again few data from sub-Saharan Africa.

Identifying adolescents with adherence difficulties is critical to target counselling interventions and more intensive adherence monitoring, and there is an urgent need to refine adherence assessments to identify adolescents requiring intervention and additional support. Given the increasing number of perinatally-infected children who are surviving to adolescence and beyond, and the limited availability of objective measures of adherence in resource-limited settings, data on the validity of self-report measures of adherence in sub-Saharan Africa are required. In addition, identifying basic sociodemographic factors associated with suboptimal adherence and investigating how these factors may affect the validity of adherence reports is important to ensure that adherence measures perform well in high-risk groups. We aimed to investigate adolescent and caregiver report of adolescent adherence across multiple adherence items in a cohort of perinatally HIV-infected adolescents in South Africa, and explored associations between these items and elevated HIV viral load (VL), while considering sociodemographic characteristics that may modify these associations. VL was used as a surrogate marker of clinical impact, as has been widely used elsewhere [19], given that objective measures of adherence are not routinely available in this setting. In a secondary analysis, we explored associations between adolescent characteristics and elevated VL.

Methods

This is a cross-sectional analysis of enrolment data from the Cape Town Adolescent Antiretroviral Cohort (CTAAC), a longitudinal study of perinatally HIV-infected adolescents on ART in Cape Town, South Africa. The broader CTAAC study seeks to investigate markers of chronic disease processes and progression in five key areas (general adolescent development, neurocognitive function, pulmonary disease, cardiovascular function, and musculoskeletal disease) at study visits conducted 6-monthly for 48 months.

Participants

For the purposes of the broader CTAAC study, perinatally HIV-infected adolescents were recruited from seven routine ART services across Cape Town, and were eligible to participate if they were aged 9–14 years, had been on ART for longer than 6 months, and knew their HIV-status. The primary caregiver of each adolescent provided written informed consent prior to participation, and child assent was obtained. The study was approved by the University of Cape Town's Faculty of Health Sciences Human Research Ethics Committee. For the purposes of the present analysis, participants were included if complete adolescent and caregiver report of adolescent adherence as well as VL measures from the enrolment visit were available.

Measures

All participants were accompanied to study visits by a caregiver, who for the vast majority of participants was the primary caregiver. Detailed clinical data were abstracted from routine clinical records, and included age at ART initiation, ART regimen history and current ART regimen. At enrolment, basic sociodemographic characteristics were assessed, including age, gender, educational attainment and household circumstances. A composite poverty score was developed and calculated based on housing type, access to household assets and caregiver employment status, based on the approach used in the South African Stress and Health Study [25]. Participants were categorised into three groups (representing 'most disadvantaged', 'moderately disadvantaged'

and 'least disadvantaged') of approximately equal size based on this score to facilitate comparisons within the study sample. Participants underwent phlebotomy at enrolment, and CD4 cell count and VL testing (Abbott RealTime HIV-1) was conducted by the South African National Health Laboratory Services.

At enrolment, trained interviewers administered measures of adolescent adherence to adolescents and their accompanying caregiver separately. Interviews were conducted in participants' home language. Adherence was assessed across multiple items adapted from a family-based intervention developed and piloted in South Africa [26], with analogous items administered to adolescents and their caregivers. Primary responsibility for adherence was assessed by asking "Who is usually responsible for making sure you take your ARVs every day?". For the purposes of the present analysis, 3 items assessing adolescent adherence were included. The first, a *30-day recall of missed doses* item, assessed adherence as follows: "During the last 30 days, on how many days did you miss at least one dose of your ARVs?". In analysis, this item was assessed as both a binary (missed dose(s) on ≥ 1 days versus no missed doses) and a continuous variable. This binary variable is the recommended approach, given the well-documented 'ceiling effect' observed in self-reported adherence, whereby measures are positively skewed [4, 19]. The second, a *30-day rating of adherence* ("During the last 30 days, how would you rate how good a job you did with taking your ARVs in the way that you are supposed to?") assessed adherence on a Likert scale using the following response options: Very poor (a score of 1), Poor (2), Fair (3), Good (4), Very good (5), and Excellent (6). Finally, a *rating of adherence-related difficulties* ("How hard is it for you to take your ARVs in the way you are supposed to?") assessed adherence on a Likert scale using the following response options: Extremely hard (a score of 1), Very hard (2), Somewhat hard (3), Not very hard (4), and Not hard at all (5).

Although all reasonable attempts were made to assess adherence in all adolescents and caregivers present, interviewers were given the option to opt out of administering adolescent assessments where they deemed it necessary to do so and following discussion with the CTAAC Medical Officer. In cases where adolescents were deemed unable to adequately complete the assessment, either because of cognitive impairment or a lack of insight into their own adherence, often owing to having only been recently disclosed to about their HIV-status, interviewers opted out and assessments were incomplete.

Data Analysis

Data were analysed using Stata 12 (StataCorp Inc, College Station, Texas, USA). The concordance between adolescent and caregiver report across adherence items was examined using Cohen's kappa for binary variables and rating scales and Spearman's rank correlation for the continuous *30-day recall of missed doses* measure; only data from adolescents and caregivers where both had completed adherence assessments were included in order to explore concordance. In a sub-analysis, concordance was explored across categories of caregiver relationship to participant. Associations between individual adherence items and elevated VL (VL ≥ 50 copies/mL) were explored across adolescent and caregiver report using χ^2 or Fisher exact tests for binary variables and Wilcoxon rank sum tests (Mann–Whitney tests) for non-normally distributed continuous variables. All results were stratified by age category (with 'younger adolescents' aged < 12 years and 'older adolescents' aged 12 years and older) in order to assess the impact of increasing age on concordance with caregiver report and on the validity of self-report. In addition, the effect of adolescent gender and primary responsibility for adherence on the validity of adherence reports was explored in stratified analyses. In a secondary analysis, a multivariable logistic regression model was built to examine independent associations between adolescent characteristics and elevated VL. Sensitivity analyses used VL ≥ 1000 copies/mL in order to ensure that results were consistent at a higher VL threshold, with both thresholds selected based on international guidelines.

Results

A total of 515 adolescents were enrolled between July 2013 and February 2015 inclusive; 474 (92%) were included in this analysis. Reasons for exclusion included incomplete caregiver adherence questionnaire (n = 4), incomplete participant adherence questionnaire (n = 36), and no VL measure at enrolment (n = 1). Adolescents who were excluded from the present analysis were significantly younger compared to those included (median age, 10.9 versus 12.0 years; $p < 0.001$).

Sociodemographic and Clinical Characteristics

Detailed sociodemographic and clinical characteristics are presented in Table 1. Among 474 adolescents included (median age 12.0 years; 49% female), most (64%) had a primary caregiver who was a biological parent while 26% and 10% of caregivers were other family members and non-family members, respectively. The median age at ART initiation among adolescents was 4.5 years [inter-quartile range (IQR): 2.1–7.7 years], with a median duration of ART use of 7.5 years (IQR: 4.5–9.2 years). A total of 172 participants (36%) were currently taking a protease inhibitor-based regimen (PI), with current PI use more common

Table 1 Adolescent sociodemographic and clinical characteristics, by age at enrolment

Variable	Total sample—*n* (%)	Younger—*n* (%)	Older—*n* (%)
Number of participants	474	235 (50)	239 (50)
Sociodemographic characteristics			
Median age [IQR]	12.0 [10.7, 13.4]	10.7 [10.0, 11.4]	13.4 [12.7, 14.1]
Gender—female	230 (49)	126 (54)	104 (44)
Ethnicity—Black/African	437 (92)	217 (92)	220 (92)
Current education			
Not in regular schooling system	5 (1)	3 (1)	2 (0.9)
Median [IQR] current grade	5 [4, 6]	4 [3, 5]	6 [5, 7]
Primary caregiver relationship			
Biological parent	305 (64)	159 (68)	146 (61)
Other family member	123 (26)	55 (23)	68 (28)
Non-family member	46 (10)	21 (9)	25 (10)
Participant lives in a care facility	15 (3)	4 (2)	11 (5)
Housing type			
Informal	159 (34)	88 (37)	71 (30)
House/flat	315 (66)	147 (63)	168 (70)
Median [IQR] number of household members	5 [4, 6]	5 [4, 6]	5 [3, 7]
Primary caregiver employed	248 (52)	132 (56)	116 (49)
Poverty level			
Least disadvantaged	176 (37)	87 (37)	89 (37)
Moderately disadvantaged	172 (36)	82 (35)	90 (38)
Most disadvantaged	126 (27)	66 (28)	60 (25)
Clinical characteristics			
Median [IQR] age at ART initiation	4.5 [2.1, 7.7]	2.9 [1.2, 5.1]	6.8 [4.0, 9.5]
0–2 years	167 (35)	123 (52)	44 (18)
3–5 years	125 (26)	67 (29)	58 (24)
6–14 years	174 (37)	43 (18)	131 (55)
Median [IQR] years on ART	7.5 [4.5, 9.2]	8.1 [5.5, 9.1]	6.7 [3.8, 9.8]
Current ART regimen			
2xNRTI + NNRTI	284 (60)	121 (51)	163 (68)
2xNRTI + PI	172 (36)	104 (44)	68 (28)
Number of molecules used since ART initiation			
Median [IQR]	4 [4, 5]	4 [4, 5]	4 [3, 5]
Still taking initial regimen	114 (24)	47 (20)	67 (28)
HIV viral load			
< 50 copies/mL	359 (76)	191 (81)	168 (70)
50–999 copies/mL	54 (11)	23 (10)	31 (13)
≥ 1000 copies/mL	61 (13)	21 (9)	40 (17)
Median [IQR] CD4 cell %	29.9 [24.3, 34.2]	31.5 [26.0, 36.4]	27.8 [23.0, 32.5]
Median [IQR] CD4 cell count	710 [564, 949]	777 [606, 1033]	666 [531, 812]

Younger: < 12 years of age; Older: 12 years of age and older

among younger adolescents. At enrolment, VL ≥ 50 copies/mL was observed in 19% of younger and 30% of older adolescents, respectively (p = 0.005). Marked differences in viraemia were observed across gender, with older male participants more likely to have VL ≥ 50 copies/mL at enrolment (Fig. 1a). A similar trend was observed for VL ≥ 1000 copies/mL (Fig. 1b).

Adolescent and Caregiver Report of Responsibility for Adherence

Caregiver primary responsibility for adherence was reported by 66% of adolescents and 73% of caregivers, with the proportion reporting caregiver primary responsibility decreasing with increasing age (Table 2). Adolescent primary

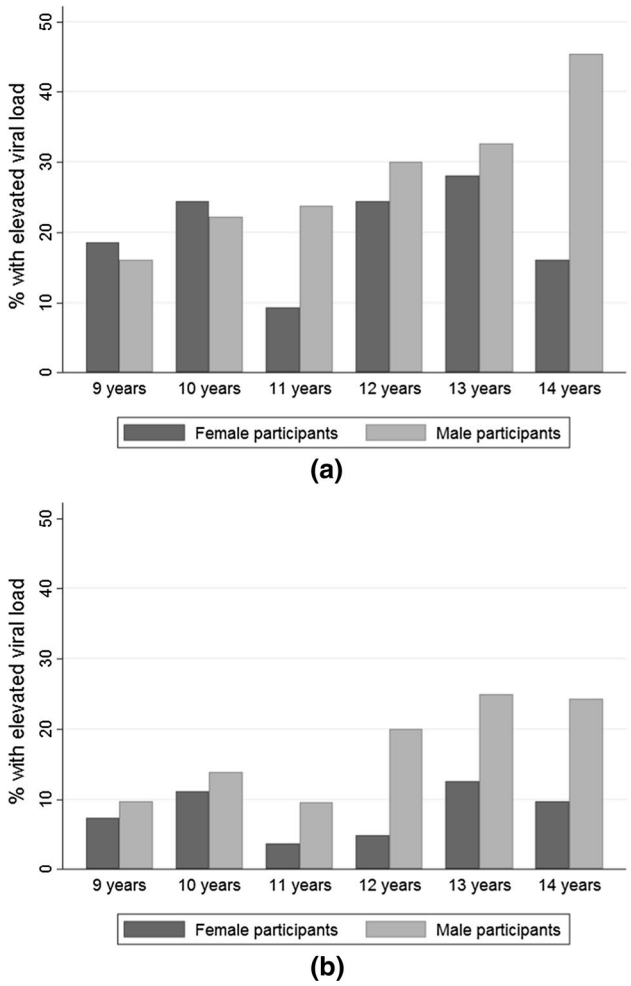

Fig. 1 **a** Elevated HIV viral load (VL ≥ 50 copies/mL) by adolescent age and gender **b** Elevated HIV viral load (VL ≥ 1000 copies/mL) by adolescent age and gender

responsibility for adherence was uncommon, while shared responsibility increased with increasing age. Moderate concordance was observed between adolescent and caregiver report of primary responsibility for adherence [Cohen's kappa (κ): 0.43]. In a sub-analysis of adolescent and caregiver report of responsibility for adherence by caregiver relationship to participant, higher concordance was observed between adolescent and caregiver report among adolescents whose primary caregiver is a biological parent, compared to those whose primary caregiver is another family member or non-family member, respectively (Supplementary Table 1).

Adolescent and Caregiver Report of Adherence

Using *30-day recall of missed doses*, 30% of adolescents reported missing doses on ≥ 1 days during the preceding 30 days, compared to 24% of caregivers (κ: 0.35; Table 2). Both report of non-adherence and agreement between caregiver and adolescent report were relatively consistent across age categories. The mean number of days on which adolescents reported missing doses during the preceding 30 days was 0.5, compared to 0.4 reported by caregivers [Spearman's rho (ρ): 0.28], with the correlation between adolescent and caregiver report relatively consistent across age categories. Using *30-day rating of adherence*, adolescents and caregivers reported a mean score of 4.5 and 4.6 out of a maximum score of 6 (where 6 represents the most positive rating, or "Excellent"), respectively (κ: 0.31). Using *rating of adherence-related difficulties*, a mean score of 4.3 out of a maximum score of 5 was reported by both adolescents and caregivers (where 5 represents the least amount of difficulty, or "Not hard at all"), with relatively poor concordance between adolescent and caregiver report (κ: 0.21). Across both rating items, concordance was lower among older adolescents compared to younger adolescents. In a sub-analysis of reported adherence by caregiver relationship to participant, concordance between adolescent and caregiver report across adherence items was generally higher among adolescents whose primary caregiver is a biological parent (Supplementary Table 1).

Associations Between Report of Adherence and Elevated HIV Viral load

Associations between adherence and elevated VL were assessed across individual adherence items and across adolescent and caregiver report. Each of *30-day recall of missed doses* (treated as a binary and as a continuous variable) and *30-day rating of adherence* were significantly associated with elevated VL ≥ 50 copies/mL across both adolescent and caregiver report in the total sample (Table 3). However, marked differences were observed across age categories: for adolescent report of missed doses, significant associations between reported adherence and elevated VL were observed among older but not younger adolescents (p value for difference across groups: binary adherence measure: $p = 0.021$; continuous adherence measure: $p = 0.040$). The *30-day rating of adherence* measure was similarly significantly associated with elevated VL among older but not younger adolescents, although the difference in effect size across groups was not significant ($p = 0.447$). The *rating of adherence-related difficulties* measure was not associated with elevated VL among either older or younger adolescents. Among younger adolescents, the only significant associations observed were between caregiver *30-day rating of adherence* and *rating of adherence-related difficulties* and elevated VL. No significant differences in effect size were observed across age categories for caregiver report of adherence. When stratified by adolescent gender, the effect sizes for associations between individual adherence items and elevated VL did not differ across groups (Supplementary

Table 2 Adolescent and caregiver report of responsibility for adherence and adolescent ART adherence by adolescent age

Variable	Total sample ($n = 474$)	Younger ($n = 235$)	Older ($n = 239$)
Primary responsibility for adherence			
Adolescent report—*n* (%)			
Adolescent responsibility	17 (4)	3 (1)	14 (6)
Caregiver responsibility	313 (66)	181 (77)	132 (55)
Shared responsibility	144 (30)	51 (22)	93 (39)
Caregiver report—*n* (%)			
Adolescent responsibility	9 (2)	2 (0.9)	7 (3)
Caregiver responsibility	346 (73)	184 (78)	162 (68)
Shared responsibility	119 (25)	49 (21)	70 (29)
Cohen's kappa of adolescent versus caregiver report	0.43	0.47	0.38
Adolescent ART adherence: 30 day recall of missed doses (binary measure)			
Adolescent report—*n* (%)			
No missed doses	334 (70)	170 (72)	164 (69)
Missed dose(s) on ≥ 1 days	140 (30)	65 (28)	75 (31)
Caregiver report—*n* (%)			
No missed doses	360 (76)	189 (80)	171 (72)
Missed dose(s) on ≥ 1 days	114 (24)	46 (20)	68 (28)
Cohen's kappa of adolescent versus caregiver report	0.35	0.38	0.31
Adolescent ART adherence: number of days on which doses were missed during preceding 30 days (continuous measure)			
Adolescent report – mean (SD)	0.5 (1.1)	0.4 (1.1)	0.5 (1.1)
Caregiver report – mean (SD)	0.4 (0.9)	0.3 (0.9)	0.4 (0.9)
Spearman's rho between adolescent and caregiver report	0.28	0.31	0.26
Adolescent ART adherence: 30 day rating of ART adherence between 1 ("Very poor") and 6 ("Excellent")			
Adolescent report – mean (SD)	4.5 (1.0)	4.5 (1.0)	4.5 (1.1)
Caregiver report – mean (SD)	4.6 (1.1)	4.6 (1.1)	4.5 (1.1)
Cohen's kappa of adolescent vs caregiver rating	0.31	0.39	0.24
Adolescent ART adherence: rating of adherence-related difficulties between 1 ("Extremely hard") and 5 ("Not hard at all")			
Adolescent report – mean (SD)	4.3 (0.8)	4.2 (0.9)	4.4 (0.8)
Caregiver report – mean (SD)	4.3 (0.9)	4.3 (1.0)	4.3 (0.9)
Cohen's kappa of adolescent vs caregiver rating	0.21	0.28	0.14

Younger: < 12 years of age; Older: 12 years of age and older

Table 2). Similarly, effect sizes across groups did not differ when stratified by either adolescent (Supplementary Table 3) or caregiver (Supplementary Table 4) report of primary responsibility for adherence.

Adolescent Characteristics Associated with Elevated HIV Viral Load

In a secondary analysis, the associations between sociodemographic and clinical characteristics and elevated VL were explored in logistic regression models (Table 4). After adjustment for gender, poverty and current ART regimen, VL ≥ 50 copies/mL was significantly associated with older age, with older adolescents having a 2.4 times [95% confidence interval (CI) 1.49–3.88] increased odds of elevated VL compared to younger adolescents. In a sensitivity analysis examining VL ≥ 1000 copies/mL, elevated VL was significantly associated with older age, male gender, and higher levels of poverty. Older adolescents had a 2.98 times (95% CI 1.52–5.82) increased odds of elevated VL compared to younger adolescents, and male adolescents had a 2.2 times (95% CI 1.15–4.20) increased odds of elevated VL compared to female adolescents.

Discussion

This research explored adolescent and caregiver reports of adolescent ART adherence and associations with VL among perinatally HIV-infected South African adolescents. High levels of elevated VL were found, particularly among older, male participants; and report of missed ART doses during the preceding 30 days was common. Moderate concordance was observed between caregiver and adolescent report of

Table 3 Associations between report of adolescent adherence and HIV viral load (VL) ≥ 50 copies/mL across adolescent age, by adolescent and caregiver report

Variable	Total sample ($n = 474$)		Younger ($n = 235$)		Older ($n = 239$)		*P* value for comparison[a]
	Odds ratio [95% CI]	*P* value	Odds ratio [95% CI]	*P* value	Odds ratio [95% CI]	*P* value	
Adolescent ART adherence: 30 day recall of missed doses (binary measure)							
Adolescent report							
No missed doses	Reference		Reference		Reference		
Missed dose(s) on ≥ 1 days	1.70 [1.09–2.64]	0.019	0.85 [0.40–1.79]	0.662	2.61 [1.45–4.67]	0.001	0.021
Caregiver report							
No missed doses	Reference		Reference		Reference		
Missed dose(s) on ≥ 1 days	2.29 [1.45–3.63]	< 0.001	2.01 [0.95–4.24]	0.068	2.28 [1.26–4.13]	0.006	0.792
Adolescent ART adherence: Number of days on which doses were missed during preceding 30 days (continuous measure)							
Adolescent report	1.21 [1.00–1.45]	0.046	0.85 [0.57–1.26]	0.422	1.50 [1.14–1.97]	0.003	0.040
Caregiver report	1.30 [1.04–1.62]	0.019	1.31 [0.94–1.81]	0.110	1.27 [0.94–1.72]	0.119	0.906
Adolescent ART adherence: 30 day rating of ART adherence between 1 ("Very poor") and 6 ("Excellent")							
Adolescent report	0.76 [0.62–0.93]	0.010	0.84 [0.60–1.18]	0.315	0.71 [0.54–0.93]	0.012	0.447
Caregiver report	0.65 [0.53–0.80]	< 0.001	0.72 [0.54–0.97]	0.031	0.60 [0.45–0.80]	< 0.001	0.415
Adolescent ART adherence: rating of adherence-related difficulties between 1 ("Extremely hard") and 5 ("Not hard at all")							
Adolescent report	0.92 [0.72–1.18]	0.532	0.88 [0.62–1.26]	0.492	0.90 [0.63–1.28]	0.551	0.952
Caregiver report	0.76 [0.62–0.95]	0.014	0.68 [0.50–0.92]	0.014	0.85 [0.63–1.14]	0.279	0.330

Younger: < 12 years of age; Older: 12 years of age and older

[a]*P* value for comparison of odds ratios between younger and older adolescents

Table 4 Adolescent characteristics associated with elevated HIV viral load (VL) ≥ 50 copies/mL (**A**) and ≥ 1000 copies/mL (**B**)

Variable	(**A**) VL ≥ 50 copies/mL				(**B**) VL ≥ 1000 copies/mL			
	Unadjusted odds ratio [95% CI]	*p* value	Adjusted odds ratio [95% CI]	*p* value	Unadjusted odds ratio [95% CI]	*p* value	Adjusted odds ratio [95% CI]	*p* value
Age								
<12 years	Reference		Reference		Reference		Reference	
12 years and older	1.83 [1.19, 2.82]	0.006	2.40 [1.49, 3.88]	< 0.001	2.05 [1.17, 3.59]	0.012	2.98 [1.52, 5.82]	0.001
Gender								
Female	Reference		Reference		Reference		Reference	
Male	1.65 [1.08, 2.54]	0.021	1.32 [0.83, 2.10]	0.236	2.52 [1.41, 4.51]	0.002	2.20 [1.15, 4.20]	0.017
Primary caregiver relationship								
Biological parent	Reference				Reference			
Other family member	0.90 [0.55, 1.46]	0.666			0.89 [0.48, 1.68]	0.729		
Non-family member	0.61 [0.27, 1.37]	0.233			0.79 [0.29, 2.10]	0.630		
Poverty level								
Least disadvantaged	Reference		Reference		Reference		Reference	
Moderately disadvantaged	1.34 [0.81, 2.21]	0.257	1.27 [0.74, 2.20]	0.384	1.74 [0.88, 3.44]	0.112	1.75 [0.79, 3.86]	0.167
Most disadvantaged	1.50 [0.88, 2.55]	0.140	1.65 [0.93, 2.92]	0.086	2.27 [1.13, 4.58]	0.022	3.22 [1.46, 7.12]	0.004
Age at ART initiation								
0–2 years	Reference				Reference			
3–5 years	0.92 [0.51, 1.65]	0.770			0.60 [0.26, 1.39]	0.234		
6–14 years	1.98 [1.21, 3.25]	0.007			1.76 [0.95, 3.24]	0.072		

Adjusted models are adjusted for all covariates shown and for current antiretroviral therapy regimen

responsibility for adherence, and low to moderate concordance was observed across adherence items. Concordance between adolescent and caregiver report was generally higher among adolescents whose primary caregiver is a biological parent. Among older adolescents, both caregiver and adolescent report of adherence was significantly associated with elevated VL across most items assessed, but few significant associations were observed among younger adolescents.

Report of missed doses during the preceding 30 days by both adolescents and caregivers was common, and high levels of elevated VL were observed in this sample. This is of concern, especially given the long median duration of ART use in this sample, and the fact that all adolescents are engaged in routine HIV services. Older, male participants appear to be a high-risk group, with notable trends towards an increased proportion of elevated VL with increasing age in this group, independent of other characteristics. The association between older age and elevated VL observed here is well-documented [8–12], while the association with male gender has been previously inconsistently observed across studies [8, 13]. In this population, male adolescents should be identified as an important group that may require more intensive adherence monitoring and support, particularly as they age into older adolescence.

The relatively low levels of observed concordance between adolescent and caregiver report of adherence are consistent with those observed in prior studies [15, 20, 21, 24]. These low levels of concordance are concerning, and suggest that interventions to increase communication about adherence between caregivers and youth are needed, as has been discussed previously [12, 15]. Of additional concern is the fact that 36 adolescents were excluded from the present analysis because of incomplete adherence questionnaires. These participants were mostly of younger age, and were deemed unable to adequately complete these assessments, either because they had only very recently been disclosed to, displayed signs of cognitive impairment, or showed a lack of insight into their own adherence. Among younger adolescents included in this analysis, few significant associations were observed between reported adherence and elevated VL, again suggesting that younger adolescents may not yet have sufficient insight to report on and manage their adherence. In contrast, reported adherence among both older adolescents and their caregivers appeared to be valid measures of adherence across most items assessed.

A limitation of the present analysis is the fact that only adolescents who were engaged in routine ART services were enrolled into the cohort, although the inclusion of adolescents from multiple services across Cape Town means that the results observed are likely to be generalizable to other groups of adolescents accessing care in the region. In subanalyses, concordance between adolescent and caregiver report was examined across categories of caregivers, where categories were based on primary caregivers' relationships to participants. Although the vast majority of adolescents were accompanied to this study visit by their primary caregiver, in a few cases participants were accompanied by other caregivers and the report of these caregivers was used in analysis. Given the small numbers of participants whose primary caregivers are not biological parents, sub-analyses of the association between caregiver report of adherence and elevated VL stratified by caregiver category were not possible. As VL is influenced by a number of factors, including drug resistance, the low to moderate concordance between VL and report of adherence observed here may not indicate only that report of adherence is invalid. In addition, adherence was assessed in this study by research staff who are not involved in adolescents' routine care, thus it is likely that social desirability bias was minimized, and the adherence items assessed may perform differently in routine care settings.

Conclusions

Despite these limitations, the findings observed here add to the literature in important ways. Few data assessing the validity of reported adherence among perinatally-infected adolescents in sub-Saharan Africa exist, and these results suggest that further efforts are needed to refine adherence measures, particularly among younger adolescents. These data suggest that 30-day recall of missed doses may be a valid measure of adherence when administered to caregivers or older adolescents, but that this measure performs poorly among younger adolescents. Similarly, a simple rating scale assessing ART adherence may be valid when administered to caregivers and older, but not younger, adolescents. Further research including repeated measures over time may help to define at what age and under what circumstances adolescent report becomes acceptably valid, in the absence of caregiver report.

Given that elevated VL was observed in 1 in 4 adolescents in this sample, and the well-documented ceiling effect in adherence measurement, we suggest using any hint of suboptimal adherence from either caregivers or adolescents as a flag for further investigation, for example either caregivers or adolescents stating that taking ART is difficult. Finally, sustained adherence is needed in order to achieve optimal clinical outcomes, and these results suggest that older, male adolescents may constitute a particular high-risk group who require more intensive adherence monitoring and counselling interventions. Given the increasing number of perinatally-infected children who are surviving to adolescence and beyond, refined adherence assessments and tools to flag adolescents who require intervention and additional support are urgently needed in this context.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval This study was conducted in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments, and was approved by and conducted in accordance with the standards of the Faculty of Health Sciences Human Research Ethics Committee of the University of Cape Town. Written informed consent was obtained from the primary caregiver of each individual adolescent included in the study, and child assent was obtained.

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