ORIGINAL RESEARCH

Adherence to antiretroviral therapy among HIV-positive adolescents attending the Korle Bu teaching Hospital

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Article Information

Abstract

Background: As a result of increased access to antiretroviral therapy, children with perinatal infections are surviving into adolescence. However, challenges during adolescence may result in poor adherence to treatment. Studies documenting poor adherence in adolescents have revealed that factors such as older adolescents, lack of HIV disclosure, and forgetfulness are some leading causes of non-adherence. Adherence is a key determinant in minimising the emergence of HIV drug resistance.

Aim: To determine the adherence rate to antiretroviral therapy among adolescents attending a tertiary hospital and the factors associated with adherence.

Methods: A cross-sectional study was done amongst adolescents (10-19 years) with HIV infection at Korle Bu Teaching Hospital, Ghana. The data was collected by face-to-face structured interviews and a medical record review. The tool used to determine adherence was the 3-day self-recall tool. The percentage of medication doses taken (≥95%) was used to define adherence, which translated as not missing any

dose in the 3 days prior to the study interview. The predictors of adherence were explored using univariate and multivariate logistic regression analyses.

***Results:** There were 210 adolescents enrolled, mostly younger adolescents (10-14years); 71.8%, and a slightly high male population of 52.4%. The adherence rate was 50.0%. Taking medication at the same time daily and having other people taking antiretroviral therapy in the same house were predictors of adherence.*

***Conclusion:** There was a low adherence rate of 50.0% among the adolescents. Interventions toward improving adherence among adolescents in this setting are needed. Taking antiretroviral therapy at the same time daily and having others in the home who take antiretroviral therapy can help to improve their adherence.*

Introduction

Increased access to Antiretroviral therapy (ART) in the past decade has ensured that children with perinatal HIV infections are now surviving into adolescence.[1] HIV has become a chronic illness among adolescents in light of the increased survival. During adolescence, specific challenges such as low self-esteem, cyber addiction, excessive alcohol intake, and use of tobacco and other illicit drugs occur.[2] In addition, adolescents deal with early sexual debut, teenage pregnancies, and sexually transmitted diseases, including HIV. Those with chronic illnesses such as HIV have an increased risk to their health from these behaviours and poor adherence to treatment. The transition of adolescents from paediatric to adult HIV care services might further disrupt adherence in the absence of transition services.[3]

In HIV, an adherence level of ≥95% has been considered the gold standard for ART[4], with a lower level of ≥90% set by the Pharmacy Quality Alliance.[5] In a Southern African cohort, the number of adolescents achieving 100% adherence was lower than adults at each time point; 20.7% at 6 months, 14.3% at 12 months, 6.6% at 24 months, compared to adults with 40.5% at 6 months, 27.9% at 12 months, and 20.6% at 24 months.[6] In a cross-sectional survey of HIV-infected children and adolescents in Port Harcourt, Nigeria, only 126 (59.2%) were completely (100%) adherent in the previous 1 month.[7]

Studies examining adherence in adolescents have revealed a range of diverse factors. Non-disclosure, prolonged duration on ART resulting in drug fatigue, especially among perinatally infected HIV adolescents, and complex regimens may poorly influence adherence.[8,9] Double orphans, especially those with a sibling as a caregiver, were at the highest risk of ART non-adherence among different orphan categories in Kigali, Rwanda.[10]School attendance with busy and varied schedules and other lifestyle barriers like forgetting and falling asleep before taking ART negatively impact ART adherence(9). To address these issues, simplified regimens, cognitive age-appropriate education that addresses adherence and HIV disclosure, and regimens with fixed-dose formulations that offer high barriers to resistance, such as dolutegravir (DTG) containing regimens, are among the solutions.

Antiretroviral therapy aims to reduce HIV-related mortality and morbidity with the initial goal of viral suppression. Viral suppression maintains the immune function and minimises the emergence of drug-resistant viruses.[11] Adherence is one of the critical determinants in minimising the emergence of drug resistance.[9,11]

Despite the importance of adherence in the clinical management of HIV infection, there is limited adherence data among adolescents in Sub-Saharan Africa, where most of those living with HIV are. In Ghana, no separate official guidelines exist for adolescent HIV care. This study sought to contribute to the knowledge about adherence among adolescents in sub-Saharan Africa.

This study aimed to determine the adherence rate among adolescents and the factors associated with non-adherence.

Methods

Study Design, setting and inclusion criteria

The study was a questionnaire-based cross-sectional study conducted at Korle Bu Teaching Hospital (KBTH), Accra, the largest tertiary hospital in Ghana. It has a paediatric HIV clinic at the Department of Child Health (DCH), which sees patients up to 14 years on Wednesdays and an adult HIV clinic under the Department of Adult Medicine, which runs an adolescent clinic on Thursdays. The study was done at these two sites. Patients at these clinics come mainly from southern Ghana, with the majority living in the Greater Accra Region. The category of patients seen is mostly perinatally infected HIV adolescents. The number of adolescents seen during the week usually depends on the school term. It ranges from an average of 3 during school to 10 during vacations. There are protocols in the clinic used to guide management. These protocols are always based on the most recent national guidelines in the country. During the study period, the first line treatment regimen was tenofovir+ lamivudine + efavirenz for adolescents ≥ 35kg. The alternative regimens were zidovudine + lamivudine + efavirenz or zidovudine + lamivudine + nevirapine. The most common regimen available was zidovudine + lamivudine + efavirenz. Disclosure is actively encouraged at the clinic from the age of 10 years if not already done. Trained paediatric ART counsellors counsel adolescents and their caregivers prior to initiation of treatment and during treatment. Three counselling sessions, each covering different aspects of the disease process, practical issues around treatment, and a formal demonstration of administering ART, are performed prior to and during ART initiation. After initiation of treatment, adherence is assessed by the attending physician and the pharmacist at each clinic visit using a self-report tool and announced pill count, respectively. Adolescents aged 10-19 years with HIV who received care in either clinic and had been on ART for at least 6 months were enrolled in the study.

Sample size estimation

Based on an average adherence rate of 60% among adolescents with HIV from the existing literature,[7,12] and with 95% confidence level and 10% allowable error, the minimum sample size was calculated as 200. Adolescents were enrolled by convenience sampling until a final sample size of 210 was achieved.

Adherence assessment

Adherence was calculated using the 3-day self-recall tool, that assesses adolescents' responses to medication taken yesterday, 2 days ago and 3 days ago. Self-report is a commonly used adherence measure in clinical and research settings. It requires a low staff and respondent burden, is inexpensive, flexible, and takes little time to administer. However, it is subject to recall bias and social desirability. Despite its limitation of overestimating adherence, self-report was used in this study due to its clinical value in predicting viral load and screening for poor adherence.

Moreover, the absence of electronic pharmacy records made the use of a pharmacy refill tool not possible and unannounced pills counts could not be done because some adolescents were in secondary school. Due to the inability to access viral load during the study period, adherence could not be corroborated with viral load. If any ART drug was missed in the past 3-days, the participant was classified as non-adherent. In addition, a structured questionnaire with a checklist of validated barriers to adherence adapted from the Reaching for Excellence in Adolescent Care and Health (REACH) project was explored for adolescents missing doses. Barriers inquired into included forgot, too tired, busy, and too many pills.

Data Collection

Face-to-face structured interviews were conducted by a trained interviewer and lasted about 20 minutes. The questionnaire was administered mainly in English, and to minimise the risk of underreporting non-adherence, interviewers were trained to initially acknowledge the known difficulty in taking medication daily. Information was collected on demographic characteristics such as age, residence, education, supervision of HIV medication, the timing of taking ART, and others taking the same medication at home.

Medical records were transcribed onto a data extraction form. They included the following information: the reported transmission route, family type (biologic parents, adoptive/foster, extended), type of caregiver, disease severity as determined by WHO clinical staging, current ART regimen, date at treatment initiation, co-morbidities such as opportunistic infections, tuberculosis, and other illnesses. In addition, the viral load measured 6 months to the interview date was recorded from the medical records. Those without a viral load within that period were to have one taken. Unfortunately, viral loads could not be done for all the adolescents due to the absence of reagents for the viral load at certain times during the study period and other technical challenges. HIV disclosure which is always recorded in the clinical notes after each clinic visit was extracted from the medical records to avoid inadvertent disclosure of a child's status.

Definitions

Disclosure of HIV status: If the adolescent knew explicitly, they had HIV.

Adherence: Not missing any antiretroviral drug dose in the 3 days prior to the study visit.

Non-adherence: Missing at least 1 antiretroviral drug in the 3 days prior to the study visit.

Adherence rate: The proportion of adolescents classified as adherent.

Primary caregiver: A person who lives with the adolescent, participates in the child's daily care and is the most knowledgeable about the adolescent's health. They were either biological parents or guardians acting as surrogate parents to the adolescent.

Single orphan: An adolescent who has lost one parent.[13]

Double orphan: An adolescent who has lost both parents (13).

HIV viral load suppression: HIV viral load copies less than 1000 copies/ml.[14]

Outcome

The primary outcome variables were adherence and non-adherence.

Data Analysis

The data was analysed using STATA Statistical software, release 11 (College Station, Texas, USA). Adherence was calculated as the proportion of adolescents classified as adherent, expressed as a percentage. Proportions were depicted as percentages. Chi-squared and Fisher's exact tests were used to compare categorical data. A two-sided significance level of $p < 0.05$ was considered statistically significant. Predictors of adherence were explored using univariable and multivariable logistic regression analyses. The logistic regression model was built by the stepwise backward selection, incorporating variables which, in the univariate analysis, had a p-value < 0.40. The logistic regression model results were expressed as adjusted odds ratio (aOR) and 95% confidence intervals (CIs).

Results

Between 1 January and 31 June 2017, 210 adolescents with HIV from the paediatric and adult HIV clinics at KBTH participated in the study. Most adolescents were from the paediatric HIV clinic, and sampling was unsuccessful in obtaining any horizontally acquired infections in adolescents. This was due primarily to very low numbers of behaviourally infected adolescents at the adult clinic and none at the paediatric clinic.

Characteristics of the study adolescents

There was a higher number of younger adolescents (10-14 years), 150 (71.8%) and a slightly higher male preponderance, 110(52.4%), enrolled in the study. Most adolescents were in primary education, 184 (87.6%). Among the primary caregivers, the majority, 86 (40%), were others. These others comprised grandparent(s) 42 (48.8%), aunt or uncles 21 (24.4%), other relatives 14 (16.3%) and caregivers from an institution where the adolescent lives, 9 (10.5%). Table 1 details the demographic characteristics of the study adolescents.

Table 1. Characteristics of study adolescents, N=210

Variable	Number (%)
Study site	
Paediatric HIV clinic	170 (80.9)
Adult HIV clinic	40 (19.1)
Age in years	
10-14 years	150 (71.8)
15-19 years	60 (28.2)
Gender	
Female	100 (47.6)
Male	110 (52.4)
Level of education	
None	8 (3.8)
Primary	184 (87.6)
Secondary	18 (8.6)
Primary Caregivers	
Self	5 (3.3)
Parents	63 (30.0)
Mother only	56 (26.7)
Others	86 (40.0)
Orphan status	
No	180 (85.7)
Single orphan	24 (11.4)
Double orphan	6 (2.9)
Body Mass Index	
Severe underweight	26 (12.5)
Underweight	48 (22.8)
Normal	124 (59.1)
Overweight	12 (5.6)

HIV clinical characteristics of study adolescents

The overall rate of adherence among the adolescents was 50.0%. The most common ART regimen was efavirenz with zidovudine and lamivudine, 160 (76.2%) and the majority, 157 (74.8%), had been on treatment for more than 2 years. Only 52 (24.8%) of the study adolescents took their ART at the same time daily in the three days before the study visit. There were 112 (53.3%) other persons taking ART in the home in addition to the study participant. This comprised mother only 70 (62.5%), father only 15 (13.3%), both parents 13 (11.6%), siblings 4 (3.6%), and other relatives or housemates 10 (8.9%). The 12 co-morbidities were tuberculosis 6/12 (50.0%), asthma 2/12 (16.7%) and sickle cell disease 4/12 (33.3%). Viral load results were available for 123 (58.6%) study adolescents due to the unavailability of test reagents.

Table 2. HIV clinical characteristics of study adolescents N=210

Variable	Number (%)
Adherence	
Yes	105 (50.0)
No	105 (50.0)
Duration on ART	
6 months - 2 years	53 (25.2)
>2 years	157 (74.8)
ART regimen	
Efavirenz based	160 (76.2)
Nevirapine based	35 (16.7)
Lopinavir-Ritonavir based	15 (7.1)
Medication supervision	
Self	83 (39.6)
Mother	53 (25.2)
Others	74 (35.2)
ART taken at the same time daily	
No	158 (75.2)
Yes	52 (24.8)
Disclosure of HIV status	
No	128 (61.0)
Yes	82 (39.0)
Others taking ART at home	
No	112 (53.3)
Yes	98 (46.7)
Use of Cotrimoxazole	
No	35 (16.7)
Yes	175 (83.3)
Other co-morbidities	
No	198 (94.3)
Yes	12 (5.7)
Recent hospitalisation[1]	
No	185 (88.1)
Yes	25 (11.9)
Viral load in past 6 months[2]	
<1000 copies/ml	59 (48.0)
≥1000 copies/ml	64 (52.0)
Viral suppression	
<50 copies/ml	36 (29.3)
≥ 50 copies/ml	87 (70.7)

[1]Hospitalisations within the past year; all had stage 3 and 4 diseases
[2]Missing data 87, viral load results = 123

Factors associated with adherence

The study found statistically significant associations in univariate analysis between adherence and medication taken at the same time daily, $p<0.0001$ and when others in the home took ART, $p < 0.03$. Virologic treatment failure was described almost equally among adherent and non-adherent adolescents, 31 (48.0%) and 33 (51.6%), respectively. This was not significantly associated with adherence, $p=0.94$. The factors associated with adherence are illustrated in Table 3

Table 3. Factors associated with adherence

Factor	Adherence N=105 (50%)	Non-adherence N=105 (50%)	Total N=210 (100%)	P value[1]
Age				0.4
10-14 years	72 (69.5)	78 (74.3)	150 (71.4)	
15-19 years	33 (30.5)	27 (25.7)	60 (28.6)	
Sex				0.9
Female	51 (50.5)	49 (49.1)	100 (47.6)	
Male	54 (49.5)	56 (50.9)	110 (52.4)	
Level of education				0.4
None	4 (3.8)	4 (3.8)	8 (3.8)	
Primary	87 (82.9)	97 (92.4)	184 (87.6)	
Secondary	14 (13.3)	4 (3.8)	18 (8.6)	
Orphan Status				0.7
No	89 (87.8)	91 (86.7)	180 (85.7)	
Orphan	11 (10.4)	13 (12.4)	24 (11.4)	
Double Orphan	5 (4.8)	1 (0.9)	6 (2.9)	
Disclosure				0.7
No	65 (61.9)	63 (60.0)	128 (61.0)	
Yes	40 (38.1)	42 (40.0)	82 (39.0)	
Medication supervision				0.7
Self	41 (39.1)	42 (40.0)	83 (39.6)	
Mother	29 (27.6)	24 (22.9)	53 (25.2)	
Other	35 (33.3)	39 (37.1)	74 (35.2)	
ART at the same time daily				<0.0001
No	64 (61.0)	94 (89.5)	158 (75.2)	
Yes	41 (39.0)	11 (10.5)	52 (24.8)	
Others take ART at home				0.03
No	49 (46.7)	63 (60.0)	112 (53.3)	
Yes	56 (53.3)	42 (40.0)	98 (46.7)	
Other co-morbidities				0.5
No	101 (96.2)	97 (92.4)	198 (94.3)	
Yes	4 (3.8)	8 (7.6)	12 (5.7)	
Recent hospitalisations				0.9
No	93 (88.6)	92 (87.6)	185 (88.1)	
Yes	12 (11.4)	13 (12.4)	25 (11.9)	
ART regimen				0.8
Efavirenz based	77 (74.3)	83 (79.0)	160 (76.2)	
Nevirapine based	19 (18.1)	16 (15.3)	35 (16.7)	
Lopinavir based	9 (8.8)	6 (5.7)	15 (7.1)	
Duration on ART				0.4
6 months to ≤ 2 years	25 (24.0)	28 (26.4)	53 (25.2)	
>2 years	79 (76.0)	78 (73.6)	157 (74.8)	
Viral load past 6 months				0.9
< 1000 copies/ml	29 (48.3)	30 (47.6)	59 (48.0)	

[1]Comparison of adherence and non-adherence groups; significant P value: < 0.05

Predictors of ART adherence

Multivariate analyses using logistic regression models were used to determine the demographic and clinical characteristics that could predict ART treatment adherence. All the factors associated with HIV

treatment adherence at the 0.40 level in the univariate analysis were included in the multivariate analysis. Age, gender, duration of ART, taking ART at the same time daily, and others taking ART at home were used. In the unadjusted models' adolescents who took their medication at the same time daily were 5 times more likely to adhere to ART, aOR 5.62 (CI 95% 2.57-12.33); and almost 2 times in an adjusted model, aOR 1.85 (CI 95% 2.88-14.29); p<0.0001. In univariate analysis, those who had others in the home taking ART were about 2 times more likely to adhere to their medication, aOR 1.83 (CI 95% 1.04-3.20); p =0.038 and in an adjusted model, 2.5 times more likely to adhere to their medication. aOR 2.47 (CI 95% 1.30-4.69); p= 0.045. The logistic regression model is summarised in Table 4.

Table 4. Predictors of antiretroviral treatment adherence

4a. Unadjusted analysis

	Unadjusted Odds ratio	**95% confidence interval**	**p-value**
Age ≥ 15yrs	0.78	0.42-1.43	0.4
Male gender	0.86	0.50-1.48	0.3
> 2 years on ART	0.82	1.01-3.89	0.3
ART taken at the same time daily	5.62	2.57-12.33	<0.0001
Others taking ART at home	1.83	1.04-3.20	0.04

4b. Adjusted analysis

	Adjusted Odds ratio	**95% confidence interval**	**p-value**
Age ≥ 15yrs	0.84	0.43-1.63	0.6
Male gender	0.76	0.53-1.69	0.9
> 2 years on ART	0.99	0.89-3.72	0.1
ART taken at the same time daily	1.82	2.88-14.29	<0.0001
Others taking ART at home	2.47	1.30-4.69	0.04

Reasons for missing ART
The most common reason for the adolescents' missing their drug doses was forgetfulness, 102 (97.1%). This was followed by "other" responses, 46 (43.8%). These were: watching TV, playing, and helping with housework. Only 3 of them complained of too many pills as a barrier. This was a multiple response answer, and all the reasons are expressed graphically in Figure 1.

Discussion
This study evaluated adherence to antiretroviral medication and its associated factors among HIV-positive adolescents attending KBTH. The overall rate of complete adherence (100%) to ART among adolescents (10-19) years, using the 3-day self-report, was 50.0%. In Ethiopia, Firdu et al. found an adherence rate of 71.8% among 273 HIV-infected adolescents receiving ART from three hospitals in Addis Ababa[15]. Among 519 HIV-positive adolescents attending two large HIV clinics in central and south-eastern Malawi, 153 (30%) reported having missed ART doses within the past week and 234 (45%) in the past month.[16] These low rates reflect the challenges adolescents living with HIV face, such as poor transitioning from children to adolescent services, behavioural problems, multiple schedules, treatment fatigue and medication burden, all previously reported.[8,9,17] In Ghana, there are no separate comprehensive adolescent health care services and a lack of formal transitioning from paediatric to adult care. As a result, healthcare providers (HCP) may be unaware of adolescents' poor adherence, and the clinic appointments may not address their specific needs. In contrast, Williams *et al.*[12] found a high

adherence rate of 84% among adolescents enrolled in the PACTG 219C study, which was attributed to the increased attention given to them at the clinic.
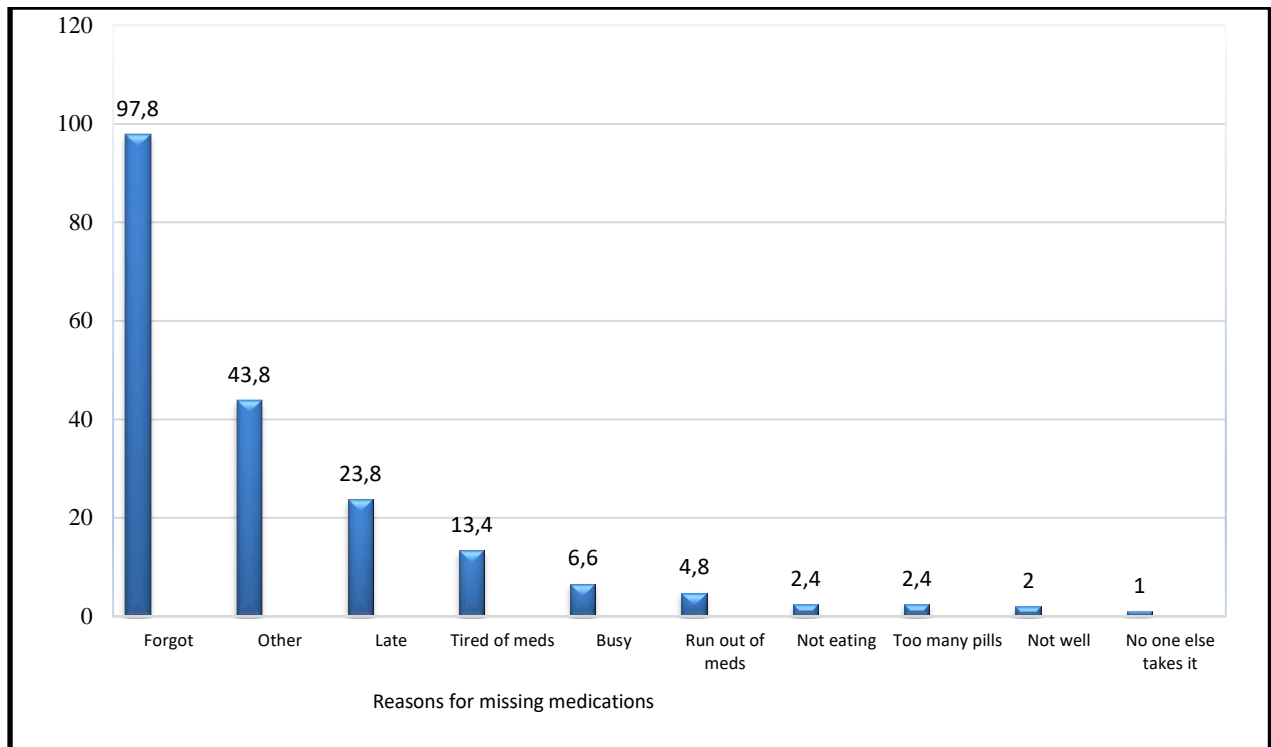

Figure 1. Reasons for missing ART presented as a proportion (%) of all adolescents

Newer ARTs such as dolutegravir, recommended by WHO in 2019 as the 1st line antiretroviral therapy, may allow a lower level of adherence while maintaining complete suppression of viral replication due to higher potency and longer half-life.[18] However, in a prospective cohort study to determine adherence among children and adolescents in Tanzania who were on a dolutegravir- based regimen, adherence, which was found to be a key predictor in viral load suppression, was 71%. Thus, even though Ghana has since 2020 made the switch to dolutegravir 50mg for adolescents and all those eligible, it is essential to assess adherence in adolescents continually.

In this study, taking the ART at the same time daily, which was seen in less than a third of the study adolescents, 52 (24.8%) was a strong predictor of adherence; aOR 1.82(CI 95% 2.88-14.29); p<0.0001. It has been suggested that patients may believe that taking ART off schedule is less likely to jeopardise the effectiveness of ART than missing actual doses.[19] This perception reflects the failure of the HCP to provide sufficient patient education and counselling. Dose timing is an essential aspect of ART, and inconsistent intervals may negatively affect the response to therapy due to viral replication, mutation, and treatment resistance(19). In a study conducted among HIV-positive adolescents in Tennessee, USA, Garvie et al. found that off-schedule dosing was a sensitive predictor of non-adherence. In that study, each per cent increase in interval dose increased the viral load by 2%.[20] Therefore, the HCP must include scheduled dosing as an essential component of the education on medication adherence throughout treatment.

For 112 (53.3%) adolescents, other people took ART in the house, and 85 (75.9%) were mothers. The study found that when other persons in the home took ART, they were 2.5 times more likely to adhere to it than when no one else took it, aOR 2.47 (CI 95% 1.30-4.69); p =0.04. Firstly, when others take their medication, they may remind the adolescents to take theirs, as the study found "forgetting" as the most common reason for missing medication. Secondly, this could help them take the medications at the same time daily, which will improve their adherence, according to existing literature and this study's

findings. Finally, the other person on ART, especially a treatment-experienced caregiver, may act as the unofficial treatment partner. Treatment partnering is an intervention developed in sub-Saharan Africa among HIV-positive adults to improve adherence to medication and keep hospital appointments. They may be family members or friends who assume a measure of responsibility for the adherence success of the patient they support.[21] Thus, peer motivators or adherence clubs may benefit this cohort.

Adolescents miss medications for several reasons. In this study, "forgetfulness" was the most common reason for missing medication. Research has commonly found 'forgetfulness' among the top reasons for poor adherence in youth living with HIV.[7,17,22] In a qualitative study to describe barriers and facilitators to ART among HIV-positive adolescents in Ghana, all the 19 adolescents interviewed mentioned forgetfulness as the primary reason for missing medications.[23] In Peru, it was the most common reason for missing ART among adolescents aged 13-15.[24] They may sometimes report that they ''forgot'' to take medications when they decided not to take them or have other reasons for not taking them. ''I forgot'' might sometimes be a dismissive or evasive answer for not taking medications rather than actual forgetting.[17] This may be particularly pertinent to adolescents with HIV, given their developmental challenges of asserting independence and desiring autonomy from caregivers and authority figures during their transition to adulthood.[22] Forgetting may also result from cognitive or behavioural issues, such as poor planning and lack of executive functioning.[25]

Other reasons for missing medications in this study were: late to school, 25 (23.8%), watching television, doing housework and being busy. These responses, which are part of the normal day-to-day activities, suggest that they have been unable to integrate their ART medication into their lifestyle. To optimise adherence amid life's daily demands, dose-time schedules linked to realistic daily activities and times of the day must be considered.[25] In addition, medication reminders must be incorporated into any intervention to address adherence.

Limitations
The single adherence self-report may have overestimated adherence prevalence because of both recall bias and the inability to capture intermittent non-adherence over extended periods. In addition, the cross-sectional design only evaluated the association between adherence and other factors at a point in time rather than the variability and consistency of adherence over time. Finally, we had challenges obtaining viral load results for all the study adolescents.

Conclusion
There was a low adherence rate (50.0%) to ART among the study adolescents, consistent with other HIV adherence studies in adolescents. Interventions aimed toward improving adherence among adolescents in this setting are needed. Taking ART on schedule and having others in the home who take ART can help to improve adherence. In addition, assessing and addressing the underlying causes of forgetting may facilitate adherence.

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