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Risk Factors for Suboptimal Antiretroviral Therapy Adherence in HIV-Infected Adolescents in Gaborone, Botswana: A Pilot Cross-Sectional Study

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Abstract

Objective: Little is known about factors associated with suboptimal antiretroviral treatment (ART) adherence among adolescents in Sub-Saharan Africa. Our objective was to determine the level of ART adherence and predictors of non-adherence among human immunodeficiency virus (HIV)-infected adolescents at the Botswana-Baylor Children's Clinical Centre of Excellence in Gaborone, Botswana.

Methods: In a cross-sectional study, 82 HIV-infected adolescents receiving ART and their caregivers were administered a structured questionnaire. The patient's clinical information was retrieved from medical records. Outcome measures included excellent pill count ART adherence (>95%) and virologic suppression (HIV viral load <400 copies/mL). Multivariate logistic regression analysis was performed to identify independent predictors of ART non-adherence.

Results: The overall median (interquartile range) ART adherence was 99% (96.5–100) (N = 82). Seventy-six percent of adolescents had excellent pill count ART adherence levels and 94% achieved virologic suppression. Male adolescents made up 65% of the non-adherent group ($P = 0.02$). Those who displayed suboptimal ART adherence were more likely to report having ever missed ART doses due to failure to pick up medication at the pharmacy (30.0% versus 9.7%, $P = 0.03$). In the multivariate logistic regression model, male sex (odds ratio [OR] 3.29, 95% confidence interval [CI] 1.13–9.54; $P = 0.03$) was the only factor which was independently associated with suboptimal ART adherence.

Conclusions: A high proportion of HIV-infected adolescents studied had excellent ART adherence and virologic suppression, with male adolescents at higher risk of suboptimal adherence than females. Further research to investigate how gender relates to suboptimal adherence may aid in the design of targeted intervention strategies.

Keywords

HIV/AIDS, ART adherence, adolescents, barriers, Botswana

Disciplines

Immune System Diseases

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Risk factors for suboptimal antiretroviral therapy adherence in HIV-infected adolescents in Gaborone, Botswana: a pilot cross-sectional study

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Conclusions: A high proportion of HIV-infected adolescents studied had excellent ART adherence and virologic suppression, with male adolescents at higher risk of suboptimal adherence than females. Further research to investigate how sex relates to suboptimal adherence may aid in the design of targeted intervention strategies.

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Introduction

In 2011, an estimated 330,000 children under the age of 15 years were newly infected with human immunodeficiency virus (HIV), contributing to an estimated 3.3 million children living with HIV worldwide. Over 90% of these children live in Sub-Saharan Africa and less than a third of them have access to antiretroviral treatment (ART).¹ In 2009 in Botswana, 19,125 children aged 0–14 years were living with HIV infection.^{2,3} Access to ART has significantly reduced mortality among children with HIV. However, children and adolescents experience unique challenges to sustained treatment adherence, including the need for support from caregivers and providers, issues surrounding the disclosure of HIV status, their rebellious nature, and management of adverse events.⁴⁻¹³

The few available data from sub-Saharan Africa have shown that, compared with adults, adolescents were less adherent to ART, had lower rates of virologic suppression,

and had a higher rate of virologic rebound after initial suppression.^{9–12} However, specific data on possible barriers for poor ART adherence were not reported. The objective of the present study, therefore, was to investigate ART adherence and the factors associated with suboptimal adherence among HIV-infected adolescents at the Botswana-Baylor Children's Clinical Centre of Excellence (BBCCOE).

Methods

We conducted a cross-sectional study of HIV-infected adolescents between August 2010 and March 2011 at the BBCCOE in Gaborone, Botswana. BBCCOE is a comprehensive HIV/AIDS treatment care center based at Princess Marina Hospital, the main referral hospital in Gaborone. At this clinical setting, informal one-on-one adherence education and counseling is provided to all patients during routine care. Patients and families found to have adherence challenges are given intensified counseling with the head nurse, clinical psychologist, or social worker. A support group is available for adolescents who are at least 13 years of age and who know their HIV status. Using purposive sampling, adolescents aged 13 to 18 years of age who had been on ART for a period longer than 6 months were eligible to participate in the study. The cut-off point of 6 months was chosen to allow us to use viral load as an endpoint, because it can take up to 6 months for individuals to achieve virologic suppression on ART.¹⁴ Because all study subjects were minors, consent from parents/guardians was required along with participant assent.¹⁵

A standardized self-administered questionnaire adapted from the AIDS Clinical Trials Group¹⁶ was used to collect socio-demographic information as well as other explanatory variables (HIV status of caregivers, the adolescent's relationship with caregivers, and the presence or absence of a family and friend network support, among others). In addition, electronic medical record system was used to retrieve clinical and laboratory data. Pill count data were used to assess adherence to ART over the previous month, as medication is dispensed on a monthly basis. The proportion of adherence was calculated as follows: the numerator was the total number of pills provided at the previous visit minus the number of pills remaining, and the denominator was the number of pills required per day times the number of days since the last visit; this ratio was multiplied by 100. Adherence to ART was considered excellent when the pill count was $\geq 95\%$ of prescribed doses.¹⁷

Sociodemographic and clinical characteristics of the participants as well as adherence rates were compared using

Chi-square or Fisher's exact test for categorical variables. Wilcoxon's rank-sum test was used for continuous variables. Logistic regression was performed to identify factors associated with adherence. Variables in the univariate analysis with a $P < 0.1$, as well as selected factors hypothesized to be confounding factors (a factor associated with the predictor and outcome but not in the causal path), such as age above the median, CD4+ T-cell count, and World Health Organisation (WHO) clinical stage, were included in the multivariate logistic regression model. All P -values reported are two-tailed. A P -value < 0.05 was considered significant. Data were entered in Epi Info 2003 (US Centers for Disease Control, Atlanta, GA, USA) and analyzed using Statistical Package STATA release 11.2 (STATA Corporation, College Station, TX, USA).

Ethical approvals were obtained from the following ethical review committees: the Health Research and Development Division, Ministry of Health, Botswana; the Human Research Ethics Committee, University of the Witwatersrand, Johannesburg, South Africa; and the Institutional Review Board for Human Subject Research, Baylor College of Medicine, Houston, TX, USA.

Results

Of 400 adolescents informed about the study, only 82 consented and enrolled. The most prevalent ($>90\%$) reasons for not enrolling in the study were nonavailability of a caregiver at the clinic and lack of interest. 40.2% of the adolescents were on a non-nucleoside reverse transcriptase (NNRTI, efavirenz or nevirapine)-based ART regimen and 58.5% were on a protease inhibitor (lopinavir-boosted ritonavir (LPV/r))-based ART regimen. But only 13 of 82 (16%) adolescents in this study were on a second-line ART regimen ([LPV/r-based ART: $n = 12$] or [raltegravir-based ART: $n = 1$]). The main demographics, clinical and laboratory data, as well as factors for nonadherence documented at enrollment, are shown in Table 1. Overall, 75.6% of adolescents had excellent ($>95\%$) pill count ART adherence levels, and all but 5 (94%) had virologic suppression to less than 400 copies/mL. Male adolescents made up 65% of the non-adherent group, but only 35.5% of the adherent group ($P = 0.02$). Study participants who self-reported suboptimal ART adherence were more likely to report having ever missed ART doses due to failure to pick up medication at the pharmacy (30.0% versus 9.7%, $P = 0.03$). In univariate analysis, male sex (odds ratio [OR] 3.38, 95% confidence interval [CI] 1.17–9.71; $P = 0.02$) and failure to refill ART medicine at the pharmacy (OR 4.31, 95% CI 1.19–15.53; $P = 0.03$) were significantly associated with suboptimal ART adherence. In the multivariate

Table 1 Clinical and socio-demographics at enrolment by pill count ART adherence threshold of 95%

Variables	Number (N = 82)	Adherent ($\geq 95\%$) (62, 75.6%)	Nonadherent ($< 95\%$) (20, 24.4%)	P-value
Age, median (IQR)	15 (14–16)	15 (14–16)	15 (14–16)	0.43
Male sex, n (%)	35 (42.7)	22 (35.5)	13 (65.0)	0.02
WHO Stage, n (%)				0.42
I	12 (14.6)	9 (14.5)	3 (15.0)	
II	11 (13.4)	9 (14.5)	2 (10.0)	
III	34 (41.5)	28 (45.2)	6 (30.0)	
IV	25 (30.5)	16 (25.8)	9 (45.0)	
CD4 T-cell count, median (IQR)	759 (575–946)	746 (528–1011)	779 (628–886)	0.70
Viral load < 400 copies/mL, n (%)	77 (93.9)	59 (95.2)	18 (90.0)	0.59
Duration on ART in years, median (IQR)	5 (3–6)	5 (3–6)	5 (3–6)	0.96
Duration on ART > 5 years, n (%)	37 (45.1)	27 (43.5)	10 (50.0)	0.80
ART regimen, n (%)				0.84
NNRTI-based	33 (40.2)	24 (38.7)	9 (45.0)	
PI-based	48 (58.5)	37 (59.7)	11 (55.0)	
Other	1 (1.3)	1 (1.6)	0 (0.0)	
Female caregiver, n (%)	73 (90.1)	55 (88.7)	18 (94.7)	0.67
Biologic relation with caregiver, n (%)	45 (55.6)	35 (56.4)	10 (52.6)	0.80
Caregiver HIV status known, n (%)	52 (64.2)	39 (62.9)	13 (68.4)	0.79
Caregiver with HIV+, n (%)	36 (73.5)	27 (71.0)	9 (81.8)	0.70
Family support network, n (%)				
Do you discuss with parents/caregiver about the importance of adherence to ART? (yes)	63 (76.8)	48 (77.4)	15 (75.0)	0.82
Perception (outcome expectancy), n (%)				
Do you believe the pills you are taking are going to make you a healthy person? (yes)	75 (91.5)	57 (91.9)	18 (90.0)	0.79
Drug toxicity, n (%)				
Do you feel fine after taking your pills? (yes)	75 (91.5)	57 (91.9)	18 (90.0)	0.79
Pharmacy no refill, n (%)				
Have you ever missed a dose because you, your parents or caregiver did not collect the pills at the pharmacy? (yes)	12 (14.8)	6 (9.7)	6 (30.0)	0.03

Abbreviations: IQR, interquartile range; ART, antiretroviral treatment; WHO, World Health Organisation; NNRTI, non-nucleoside reverse transcriptase; PI, protease inhibitor; HIV, human immunodeficiency virus.

analysis, male sex (OR 3.29, 95% CI 1.13–9.54; $P = 0.03$) was the only factor which was independently and significantly associated with suboptimal ART adherence (Table 2).

Discussion

This study found that 75.6% of adolescents with a median ART duration of 5 years had excellent ($> 95\%$) ART adherence, with an overall mean of 96.4%. These findings are important because there is emerging concern that there are specific challenges for adolescent patients, such as rebelliousness and potentially higher rates of mortality, when compared to other populations.¹⁸

Although some studies have shown similar high rates of ART adherence among HIV-infected adolescents,⁶ a lower rate of adherence among HIV-infected adolescents has been reported more often,^{5–7,9} and expectations have been that adherence will diminish over time. In 2009, a review of studies on ART adherence and intervention among HIV-infected youths

(13–24 years old) reported an overall rate of adherence ranging from 28.3% to 69.8%.⁶ The high proportion of HIV-infected adolescents with excellent pill count ART adherence and virologic suppression documented in our study is encouraging and demonstrates that excellent treatment outcomes can be achieved in HIV-infected adolescents in this setting. Interestingly, analysis of the barriers to adherence in this study revealed that male sex was an independent predictor of nonadherence to ART in our cohort. Our data are supported by a study of 804 children and adolescents between the ages of 3 and 16 years at initiation on NNRTI-based treatment at the same clinical site by Lowenthal et al,¹⁹ who reported that patients of both sexes were more likely to have had virologic failure on nevirapine-based treatment than on efavirenz-based treatment, but failure rates on both regimens were higher among males than among females, with males on nevirapine having the highest failure rates. The findings of our study suggest that the sex-specific differences in outcomes observed by Lowenthal et al may be

Table 2 Univariate and multivariate logistic regression model of factors associated with ART adherence <95%

	Univariate		Multivariate	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age above median	0.73 (0.24–2.15)	0.56	0.87 (0.27–2.77)	0.81
Male sex	3.38 (1.17–9.71)	0.02	3.29 (1.13–9.54)	0.03
WHO stage III and IV (versus I and II)	1.23 (0.39–3.88)	0.73	1.02 (0.30–3.47)	0.97
PI-based versus NNRTI-based regimen	0.79 (0.28–2.20)	0.65		
CD4 above median	1.30 (0.47–3.59)	0.61	1.18 (0.40–3.44)	0.76
VL <400 copies/mL	0.46 (0.07–2.95)	0.40		
Biologic relation with caregiver	0.86 (0.30–2.40)	0.77		
Caregiver who is HIV+	1.83 (0.34–9.88)	0.48		
Caregiver with HIV status known	1.28 (0.43–3.82)	0.66		
Having a support network	0.87 (0.27–2.83)	0.82		
Positive outcome expectancy	0.79 (0.14–4.42)	0.79		
Never experience ART side effects/toxicity	0.79 (0.14–4.42)	0.79		

Abbreviations: PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase; VL, viral load; ART, antiretroviral treatment; WHO, World Health Organisation; CI, confidence interval; OR, odds ratio; HIV, human immunodeficiency virus.

explained by worse adherence in males. Furthermore, there is a growing body of evidence indicating that adult men face important challenges in accessing HIV services as often as their female counterparts and also experience worse treatment outcomes, including mortality.^{18,20,21}

The fact that patients fail to pick up ART medications at the pharmacy at all suggests that structural barriers (eg, lack of transport money to access the clinic or other factors)^{22,23} may play a role in this study population. In addition, because even one incidence of not obtaining a refill on time is strongly associated with current pill count adherence suggests that there are long-term concerns (forgetfulness, not making their medicines a priority, chaotic households, and so forth) for those who ever miss a refill date. Essentially, if a patient has ever missed a refill, he or she is more likely to miss doses now, suggesting a long-term increased risk of suboptimal adherence even in the absence of ongoing refill problems. Although our results are informative and preliminary and need further confirmatory studies, they suggest that male adolescents, and those having a history of ever failing to refill ART at the pharmacy in this setting, may benefit from more intensive monitoring and adherence interventions.²⁴

Our study may be limited by selection bias and findings may not be generalizable to other settings in Africa. The BBC-CCOE site has better resources than many clinics in resource-limited settings, including a supportive environment that aims to equip teenagers with the appropriate skills to enable them to face the challenges of adolescence; this may in part explain the documented high ART adherence here. Furthermore, we recruited from among patients with an available caregiver at the clinic. Those who did not have an available caregiver, as

well as those not able to consent due to lack of interest or other reasons, were less likely to be included but may have been poorly adherent to their ART regimen.

Conclusions

This study found that a high proportion of HIV-infected adolescents aged 13 to 18 years who are attending the BBCCOE for HIV care are highly adherent to their ART medication regimens and achieved virologic suppression. Being male and having a history of failure to refill ART at a pharmacy were significant risk factors for suboptimal adherence among HIV/AIDS-infected adolescents in this study population. Our data call for a prospective evaluation in a larger study to confirm our findings and investigate further why males are more likely to have suboptimal adherence than females; this may improve the design of targeted intervention strategies in this setting.

Authors' contributions

MN conceived the study, collected as well as analyzed the data, and drafted the manuscript. PN contributed to the project in all stages: designing and drafting the article; critically reviewing and revising the manuscript; and data analysis and statistical interpretation. EJM, EDL, and RG critically reviewed and revised the manuscript for intellectual content; and contributed to the writing of the manuscript, data analysis, and interpretation. HN contributed to the writing of the manuscript, analysis and interpretation of the data, and critically reviewed the paper. JBN critically revised the paper for important intellectual content and contributed to the writing of the manuscript, analysis and interpretation of the data. All authors read and approved the final version of the manuscript.

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Disclosure

The authors report no conflicts of interest in this work

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