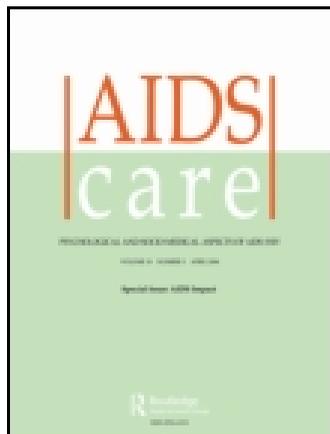


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Barriers to antiretroviral adherence in HIV-positive patients receiving free medication in Kayunga, Uganda

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Global and local efforts have been devoted to increase the supply of antiretroviral therapy (ART) in sub-Saharan Africa. Recent qualitative studies suggest that even with free ART, patients may fail to adhere to medication because of socioeconomic barriers such as transportation costs to clinics. The aim of this study was to measure adherence in a population of patients receiving free ART and to examine barriers to adherence. Adherence was measured using the pill count and self-report methods among 140 HIV-positive patients at four PEPFAR-facilitated ART clinics in Kayunga, a rural district in Uganda. Self-report was also used to examine reasons for non-adherence. Pill count adherence estimates revealed that 86.4% of the patients were adherent ($\geq 95\%$) in the past six months. Self-report estimates showed that all the patients were adherent in the past six months with average adherence of $99.7\% \pm 0.6$. The main reasons for non-adherence were being away from medication at dose time (29.4%) and forgetting to take pills (27.5%). Lack of access to food and transportation costs accounted for 11.7% and 7.8% of non-adherence, respectively. Patients with 100% adherence reported lack of access to food as the main challenge they had to overcome to stay adherent. Patients attending the rural clinic were significantly less adherent to ART than patients at the Kayunga district capital [OR 0.046 (0.008–0.269)]. The study revealed that the greatest patient-perceived challenge to adherence in this population is the lack of access to food; however, the immediate reasons for non-adherence were found to be forgetfulness and being away from medication at dose's time. These results suggest that interventions tackling lack of access to food are necessary, but interventions addressing forgetfulness and being away from medication at dose's time would be the most effective in enhancing adherence inpatients receiving free ART.

Keywords: HIV/AIDS; adherence; free ART; Uganda

Introduction

Approximately 33.2 million people worldwide are infected with HIV and 63% of the cases are in sub-Saharan Africa (UNAIDS, 2007). Uganda had one of the highest prevalence rates in Africa in the early 1990's (approximately 15%), but this has dramatically been reduced to 5.4% (UNAIDS, 2008). Even if the spread of HIV/AIDS in the country has decreased, the enormous challenge of managing the disease in approximately one million HIV-positive individuals still exists (WHO, 2005). Growing global and local efforts have been devoted to increase the supply of antiretroviral therapy (ART) for HIV-positive individuals; roughly 46% of HIV-positive patients in need of medication receive free ART in Uganda (UNAIDS, 2008). However, results from qualitative studies suggest that even when ART is provided free of charge to the patients, they may fail to adhere to the medication because of socioeconomic barriers such as lack of access to food and

transportation costs to clinics (Hardon et al., 2007; Murray et al., 2009; Tuller et al., 2009; Weiser et al., 2010).

Adherence to ART is vital for survival and control of the emergence of drug resistant strains in HIV infected individuals. An adherence rate of at least 95% is recommended for virologic suppression (Bangsberg, 2006). A meta-analysis examining adherence in sub-Saharan Africa found that financial constraints were the main reason for non-adherence (Mills et al., 2006). Whereas several studies on adherence to ART have been done including patients paying for ART, a limited number of studies have examined adherence solely inpatients receiving free ART. Quantitative studies among patients who receive free ART have focused on estimating numeric values for adherence with different measures, but rarely explain reasons for non-adherence. These studies have found adherence inpatients receiving free ART to range from 85% to 99%. (Bajunirwe

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et al., 2009; Bell et al., 2007; Vriesendorp et al., 2007; Watt et al., 2010). On the other hand, qualitative studies examining adherence inpatients receiving free ART describe barriers to adherence such as transportation costs and food insecurity, but do not estimate the extent to which each of these barriers is responsible for non-adherence (Gusdal et al., 2009; Hardon et al., 2007; Murray et al., 2009; Tuller et al., 2009; Weiser et al., 2010). Quantifying the impact of various adherence barriers is important in determining interventions to enhance adherence inpatients receiving free ART.

Adherence measurements in resource-poor settings are most commonly done using the self-report method because it is easily implemented during routine clinic visits and allows for a discussion of reasons for non-adherence. However, self-report measurements overestimate adherence and are vulnerable to social desirability bias (Berg & Arnsten, 2006). Pill-count adherence measurement eliminates recall bias, but is vulnerable to pill dumping by patients to mask non-adherence. A combination of these two methods of adherence measurement allows for qualitative data explaining reasons of non-adherence to be obtained by self-report and for objective quantitative data estimating adherence to be calculated using the pill-count method.

The aims of this cross-sectional study were to estimate adherence and to examine the extent to which various barriers explain non-adherence in HIV-infected adults receiving free medication in Kayunga District, Uganda. Kayunga is a rural district in central Uganda with a population of approximately 320,000 and an HIV-1 prevalence of 9.9% (Guwatudde et al., 2009). This study was conducted at four clinics in the district; Kayunga District Hospital (DH), Kangulumira Health Center, Bbaale Health Center, and Galiraaya Health Center that are supported by the US President's Emergency Plan for AIDS Relief (PEPFAR) through the Makerere University Walter Reed Program (MUWRP). The four clinics jointly provide free ART to approximately 2000 patients. The PEPFAR program was started at Kayunga DH in 2005 and has since been extended to the more rural health centers of Kangulumira, Bbaale, and most recently Galiraaya. There are differences in the provision of care at the clinics, particularly in the number of days that each of the clinics is open. The Kayunga DH, Kangulumira, Bbaale, and Galiraaya clinics are open on the fourth, third, second, and first day of the week, respectively. All four clinics were included in the study so as to obtain an estimate that is representative of the different clinics.

Methods

HIV-infected adults between the age of 18 and 65, who had received ART from the MUWRP/PEPFAR program at one of the four clinics for at least six consecutive months, were eligible to participate in this study. Data were collected between June and August 2008. Patients who had been hospitalized in the past six months were excluded from the study since adherence to ART is enforced at the hospitals. Also patients who had transferred between clinics in the past six months were excluded due to anticipated difficulty in tracing medical records.

Clinics were sampled on the highest volume day identified by the health professionals at each clinic. Each day was divided into time blocks (8–10 am, 10–12 pm, 12–2 pm, and 2–4 pm) and not more than four patients were interviewed during one block to ensure sampling of patients throughout the day. Every second patient in line to see a health professional was approached and asked to participate in the study. Patients were led to a private room where eligibility for the study was determined, the consent form was read to them, and interview was conducted if they agreed to participate. Interviews were conducted in either Luganda or English by one interviewer. Pill count adherence was abstracted from patient's charts after their medical visit and recorded on the patient's questionnaire.

Adherence measurements

Adherence to ART was measured using two methods, the pill count method and self-report method. Pill count information was obtained by abstracting monthly pill count adherence from patients' charts for past six months. Self-report adherence was measured by administering questionnaires asking for number of pills missed in the past three days, seven days, and every one month for the past six months. Unlike self-report, pill count adherence was not measured at day three and day seven since it is recorded on a monthly basis at routine monthly visits. The self-report questionnaire administered used pre-tested items (Liu et al., 2006; Munoz-Moreno et al., 2007). Patients were also asked to describe their dosage schedule in order to assess understanding of prescribed dosage schedule.

Self-reported adherence was calculated as the ratio of the number of pills taken by a patient to the number of pills the patient was supposed to take in a given period as stipulated by Uganda's HIV standard treatment guidelines (STGs). Self-report adherence values were calculated for three-day, seven-day, one-month, three-month, and six-month

time periods. Pill count adherence values were recorded during monthly visits by nurses. Patients carry medication bottles to each visit where nurses determine if there are any excess pills based on prescribed dosage. Tables relating different drug regimens, number of pills missed, and adherence values are provided in the examination rooms for nurses as they determine patients' adherence. The Kangulumira health center and Kayunga DH clinic recorded pill count adherence numerically where as the Bbaale and Galiraya health centers recorded pill count adherence categorically [Good ($\geq 95\%$), Fair (85–94%), and Poor ($< 85\%$)]. Adherence was analyzed as a binary variable; patients were categorized as adherent if adherence percentage was found to be $\geq 95\%$ and non-adherent if adherence percentage was $< 95\%$. For categorical pill count data from Bbaale and Galiraya health centers, patients were categorized as adherent if adherence was recorded as "Good" ($\geq 95\%$), and non-adherent if it was recorded as "Fair" or "Poor." Adherence percentages for individual time periods (three days, seven days, one, three, and six months) were used to generate an average adherence value for each patient for the past six months.

Barriers to adherence

Patients who reported missing any pills were asked to explain why from a list of possible reasons: (1) no transport to clinic, (2) lack of access to food, (3) lack of access to water, (4) forgot, (5) away from medication at dose's time, and (6) other reasons. Patients who did not report missing any medication (100% self-reported adherence) were asked to describe challenges faced in adhering to medication from the same list of reasons.

Statistical analysis

SAS (v. 9.3.1) was used for analysis. Logistic regression analysis was conducted to identify patient characteristics associated with the six month pill count adherence. The characteristics examined included: age, sex, clinic attended, employment, education, total number of family members, duration patients obtained ART from clinic, duration of known HIV-positive status, type of ART, and patients' attitude to medication (Table 1). Variables with p -values ≤ 0.1 in the univariate analysis were included in a multivariate model. Pill count values were used in regression analysis because they are a more objective measurement of adherence than self-report (Berg & Arnsten, 2006). Self-report measurement of adherence allowed for reasons for

Table 1. Characteristics of participants^a.

Characteristics	<i>N</i> (%) Total = 140
Age	
18–30 years	30 (21.43)
31–45 years	74 (52.86)
45–65 years	36 (25.71)
Sex	
Male	47 (33.57)
Female	93 (66.43)
Clinic attend	
Bbale	38 (27.14)
Galiraya	15 (10.71)
Kangulumira	35 (25.00)
Kayunga DH	52 (37.14)
Employment	
No	35 (25.00)
Yes	105 (75.00)
Education ^b	
No	33 (23.57)
Yes	104 (74.29)
Mean total number of family members ^c	4.61 (± 3.00)
Mean number of family members helping in daily activities ^c	1.53 (± 1.35)
Mean number of family members generating income ^c	1.24 (± 0.62)
Duration obtained ART from Clinic ^b	
3–24 months	63 (45.00)
> 24 months	74 (55.00)
Duration known HIV + status ^b	
3–24 months	52 (37.14)
> 24 months	85 (60.71)
Type of ART	
2 NRTIs + 1NNRTI	136 (97.14)
1 NtRTI + 1 NRTI + 1NNRTI	4 (2.86)
Mean attitudes to medication (on scale of 10)	
I will take medication for the rest of my life	9.90 (± 0.47)
HIV medication has positive effect on me	9.51 (± 1.21)

^aTable values are mean \pm standard deviation for continuous variables and *n* (column%) for categorical variables.

^bNumbers may not sum to 140 due to missing data, and percentages may not sum to 100% due to rounding.

^cFamily members defined as relatives living in the same household with patient for at least past six months.

non-adherence to be obtained. The frequencies for reasons for non-adherence and challenges patients faced in adherence were computed in SAS.

This study was approved by the Yale School of Medicine Human Investigation Committee, Makerere University School of Public Health Internal Review Board and the Uganda National Council on Science and Technology.

Results

Study population

A total of 143 eligible patients were approached; three (2.1%) declined to participate and 140 (97.9%) participated in the study. One hundred and thirty-eight (98.6%) interviews were conducted in Luganda, the main local language of the study population. Ninety-three (66.4%) of participants were female and 83 (59.3%) patients were part of large families of more than four family members. One hundred and thirty-six (97.1%) patients were on first-line medication consisting of two Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and one Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) (Table 1). An agreement of 96.4% was found between patients' description of their dosage schedule and the prescribed schedule.

Adherence

The number of adherent patients was found to be greater with self-report than with pill count estimates (Table 2). Using self-report, 133 (95.0%), 128 (91.4%), 134 (95.7%), 139 (99.2%), and 140 (100%) patients were found to be adherent (adherence \geq 95%) over the past three days, seven days, one month, three months, and six months, respectively. Pill count adherence measurements revealed that 81 (92.1%), 114 (95.0%), and 121 (86.4%) patients were adherent over the past one month, three months, and six months, respectively (Table 2). Agreement between pill count and self-report adherence measures for the one, three, and six month periods was found to be 88.6%, 94.2%, and 86.4%, respectively.

Barriers to adherence

Of the 140 patients, 51 were found to have missed at least one ART pill in the previous six-month period

(Table 3). The main reason for non-adherence was being away from medication at dose time (15 patients, 29.4%). Patients explained that they left their medication at home and were unable to return to take it on time. Thirteen (27.5%) patients sighted forgetfulness and six (11.7%) reported lack of access to food as the main reason for non-adherence. Patients explained that medication increased their appetite and that they didn't take pills if they knew that they wouldn't have any more food to eat. Other reasons for non-adherence included: running out of medication (five patients, 9.8%), no transport to clinic to refill medication (four patients, 7.8%), too busy (three patients, 5.9%), to avoid side effects (two patients, 3.92%), taking incompatible medication (one patient, 1.96%) and lack of access to water (one patient, 1.96%). A total of 89 patients showed 100% pill count adherence in the previous six months. These patients were asked to identify the main challenge that they had to overcome to maintain 100% adherence. Thirty-seven patients (41.6%) reported lack of access to food as the main challenge to adherence. Other challenges reported were: side effects (14 patients, 15.7%), lack of access to water (three patients, 3.4%), lack of social support (one patient, 1.1%), no transport to clinic (one patient, 1.1%), too sick to take medication (one patient, 1.1%), and avoiding others being aware (one patient, 1.1%) (Table 3).

Regression analysis

Logistic regression models were constructed to examine the association between patient characteristics and six month pill count adherence. The variables for the clinic and total number of family members had p -values \leq 0.1 in the univariate analysis and were included in a multivariate model (Table 4). Results showed that patients attending the Galiraaya and Bbaale clinics were significantly less adherent than those attending the Kayunga DH clinic [OR = 0.05 ($<$ 0.01–0.27) and OR = 0.16

Table 2. Number of patients found to be adherent to ART using different measures over different time periods.

Method	Time period	#Adherent patients (Adherence \geq 95%) (%) ^a	# Non-Adherent patients (Adherence $<$ 95%) (%) ^a
Self-report	Three days	133 (95.0)	4 (2.9)
	Seven days	128 (91.4)	12 (8.6)
	One month	134 (95.7)	6 (4.3)
	Three months	139 (99.3)	1 (0.7)
	Six months	140 (100.0)	0 (0.0)
Pill count	One month	81 (92.1)	7 (8.0)
	Three months	114 (95.0)	6 (5.0)
	Six months	121 (86.4)	19 (13.6)

^aNumbers may not sum to 140 due to missing data, and percentages may not sum to 100% due to rounding.

Table 3. Reasons reported for having missed ART medication.

Reasons	# Patients N = 51	%
Away from medication at dose time	15	29.41
Forgot to take medication	13	27.49
Lack of access to food	6	11.76
Run out of medication	5	9.80
No transport to clinic	4	7.84
No time to take medication	3	5.88
To avoid side effects	2	3.92
No answer/don't want to answer	1	1.96
Taking other incompatible medication	1	1.96
Lack of access to water	1	1.96

(0.03–0.79), respectively]. The total number of family members was not found to be significantly associated with adherence in the multivariate model.

Discussion

This study found very high adherence estimates; 100% of patients were adherent by self-report and 86% were adherent by pill count over the previous six months. The self-report estimates of adherence were greater than the pill-count estimates which may indicate an overestimation of adherence with the self-report method due to social desirability bias. Adherence estimates from this study are comparable to those from similar studies done in sub-Saharan Africa (Table 6). Bajunirwe et al. (2009) examined adherence inpatients receiving free ART at a government hospital in South-western Uganda and found that 85% of patients had 100% self-reported adherence. Similar studies conducted inpatients receiving free ART in Ethiopia, Tanzania, Malawi, and South Africa found self-reported adherence to be 94.3%, 96.5%, 98.6%, and 88%, respectively (Amberir,

Table 4. Challenges to adherence reported by patients with 100% self reported adherence.

Challenge	# Patients N = 89	%
Lack of access to food	37	41.57
No challenges	23	25.86
Resulting side effects	14	15.73
Declined to answer	8	8.99
Lack of access to water	3	3.37
Lack of social support	1	1.12
No transport to clinic	1	1.12
Too sick to take medication	1	1.12
Avoid others being aware	1	1.12

Woldemicheal, Getachew, Girma, & Deribe, 2008; Bell et al., 2007; Nachega et al., 2004; Watt et al., 2010). Abaasa et al. (2008) examined pill count adherence inpatients receiving free ART through The AIDS Support Organization (TASO) clinic in Kampala and found 78.2% of patients had adherence $\geq 95\%$. A recent ethnographic study suggests that one of the reasons for adherence success in sub-Saharan Africa, such as that observed in this study, is the patients' desire to promote good will with their family or friends supporting them as they receive treatment to ensure help in the future (Ware et al., 2009).

The main reasons for non-adherence were being away from medication at dose time and forgetting to take pills. These were also reported to be the main barriers to adherence in the Bajunirwe study conducted in South-western Uganda where they accounted for 35% and 25% of non-adherence, respectively (2009). Amberir et al. (2008) also found that forgetfulness was the main reason for non-adherence accounting for 19.5% of non-adherence in HIV patients receiving free medication in Ethiopia. Nachega et al. (2004) examined adherence in HIV patients receiving mainly free ART in Soweto, and found that being away from home accounted for 30% of non-adherence. The main reasons for non-adherence found in this study are comparable to those found in similar studies (Table 6). Socioeconomic barriers such as lack of access to food and transportation costs were found to account for smaller percentages of non-adherence in this population of HIV patients. However, lack of access to food was reported as the main challenge to adherence by patients with 100% self-reported adherence. More research is needed to explore the reasons for forgetfulness and being away from medication at dose time and how social factors may contribute to these adherence barriers.

The clinic variable was found to be significantly associated with adherence. Patients attending the semi-rural Bbaale clinic and rural Galiraaya clinic were found to have significantly lower adherence values in comparison to patients at the Kayunga DH clinic. The variability in adherence between the clinics may be explained by differences in the number of days the clinics are open. As mentioned in the introduction, the ART clinic at Kayunga DH is open four times a week, whereas the Bbaale and Galiraaya clinics are open twice and once a week, respectively. Having more time to see the patients may allow health professionals to take more time and care in encouraging patients to be adherent.

The main strengths of this study are that it included patients from both urban and rural settings

Table 5. Multivariate logistic regression examining the association between patient characteristics and six month pill count adherence (adherence $\geq 95\%$).

Variable	N (%) Total = 140	OR (95% CI)	p Value
Clinic			
Kayunga (district capital)	52 (37.14)	1.00	–
Bbale (semi-rural)	38 (27.14)	0.156 (0.031–0.791)	0.025
Kangulumira (semi-rural)	35 (25.00)	0.677 (0.090–5.080)	0.704
Galiraaya (rural)	15 (10.71)	0.046 (0.008–0.269)	<0.001
Total number of family members			
0–4 family members	57 (40.70)	1.00	–
>four family members	83 (59.30)	2.156 (0.739–6.288)	0.160

Table 6. Studies estimating adherence values in HIV patients receiving free ART in sub-Saharan Africa.

Source	Population	Adherence measure	Adherence estimate	Reasons for non-adherence
Amberir et al., 2008	N = 400 patients attending the Jimma Univeristy Specialized Hospital (JUSH) in Jimma, Ehtiopia.	Mean of one-day, three-day, and seven-day self-report adherence at baseline and at three months after follow-up.	96% of patients reported adherence > 95% at baseline and 94.3% reported adherence > 95% at follow-up.	Forgot Felt sick Run out of medication Busy
Abaasa et al., 2008	N = 897 patients at The Aids Support (TASO) clinic in Kampala, Uganda.	Highest measure of self-report or pill count measure was chosen. Adherence was measured over three days, two weeks, two months and six months.	78.2% of patients had a mean adherence > 95%.	Forgetfulness Lack of understanding of treatment benefits Severity of adverse events Level of complexity of drug regimen
Bajunirwe et al., 2009	N = 175 patients at a rural government hospital in South-western Uganda.	three-day self-report and six month pill count.	85% of patients reported 100% adherence with self-report adherence. 68% of patients were found to have > 95% adherence with pill count.	Missing scheduled visit Lack of disclosure of HIV status
Bell et al., 2007	N = 80 patients at a government hospital in Blantyre, Malawi.	one-day, two-week, and one-month self-report adherence, one month pill count and one month Medication Event Monitoring System (MEMS) cap adherence.	All patients were found to have self-report adherence > 95% over all time periods. Mean pill count adherence was 98.6% and mean adherence with MEMS cap was 88.1%.	None
Nachea et al., 2004	N = 66 patients receiving care at the Chris Hani HIV public clinic in Soweto, South Africa.	One month self-reported adherence.	88% of patients had self-reported adherence > 95%.	Being away from home Difficulty with dosing schedules Running out of medication
Peltzer et al., 2010	N = 519 patients attending three hospitals in Uthukela health district, KwaZulu Natal, South Africa.	four-day self-report adherence and 30-day adherence using Visual Analog Scale (VAS).	84.5% of patients were found to have 100% adherence with self-report. 82.9% of patients had adherence $\geq 95\%$ with VAS.	Rural location Higher levels of depression
Watt et al., 2010	N = 340 patients at an urban faith-based clinic in Tanzania.	four-day self-report and one month Visual Analog Scale (VAS)	96.5% of patients were found to have adherence of $\geq 95\%$ with self-report and 98.5% of patients were found to be adherent with VAS.	Being young (19–30) or older (51 +) Lower perceived quality of patient interaction Having ever missed a clinic visit

in Uganda and measured both pill count and self-report adherence values. The pill count method provided more objective measurements of adherence and the self-report questionnaire enabled reasons for non-adherence to be assessed. The main limitation of the study is the relatively small sample size that may have hampered regression analysis in determining predictors of adherence. However, it is important to note that similar studies conducted in Uganda with larger sample sizes did not find the patient characteristic variables such as education, duration on ART, employment, sex, or age to be associated with adherence (Bajunirwe et al., 2009; Byakika-Tusiime et al., 2005)

The study revealed that the greatest patient-perceived challenge to adherence in this population is the lack of access to food; however, the immediate reasons for non-adherence were found to be forgetfulness and being away from medication at dose's time. These results suggest that interventions tackling lack of access to food are necessary, but interventions addressing forgetfulness and being away from medication at dose's time would be the most effective in enhancing adherence inpatients receiving free ART. As free ART programs expand in sub-Saharan Africa, interventions to ensure adherence are a growing necessity.

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