

# Treatment experienced persons living with HIV on atazanavir based second line regimens are not highly adherent to therapy: a report from a tertiary referral hospital in Kenya.

George Mugendi (✉ [george.mugendi@uonbi.ac.ke](mailto:george.mugendi@uonbi.ac.ke))

University of Nairobi College of Health Sciences <https://orcid.org/0000-0002-5385-3547>

Nasser Nyambane Nyamweya

University of Nairobi College of Health Sciences

Faith Apolot Okalebo

University of Nairobi College of Health Sciences

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## Research article

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# Abstract

## Background

Adherence to antiretroviral therapy is necessary for positive treatment outcomes. The objectives of this study were to determine adherence levels and their determinants in persons living with HIV on second line therapy.

## Methods

A cross-sectional study was undertaken at a HIV clinic within Kenyatta National Hospital in October, 2017. Data were collected through interviews and application of the Morisky Medication Adherence and then analyzed in R.

## Results

One hundred and ten patients were enrolled; 46 (41.8%) males and 64 (58.2%) females. The mean age was 39.8 years ( $\pm$  11.8). Most participants, 96 (87.3%), had moderate adherence while 14 (12.7%) had low adherence. None were highly adherent. Age (aOR = 1.10, 95% CI; 1.04, 1.19) and depression (aOR =0.17, 95% CI 0.04, 0.64) were independently associated with adherence.

## Conclusion

None of the treatment experienced patients on second line regimens were highly adherent to therapy. Younger patients and those with depression require additional adherence counselling.

# Introduction

Adherence to antiretroviral therapy (ART) is an important and overriding component towards the achievement of optimal treatment outcomes for persons living with HIV (PLHIV) on follow up. Adherence levels above 95% have been associated with better outcomes such as viral suppression, slowing of disease progression, decreased morbidity and mortality among others (1). Moreover, high initial adherence is reported to be crucial in determining long term optimal virological and immunological outcomes. High adherence initially and medium adherence in the maintenance phase are demonstrated to result in much favorable values of the aforementioned indices (2).

Maintaining high adherence levels is challenging. Reports from both high, low and middle countries in North America and sub Saharan Africa (sSA) indicate that the  $\geq$  95% adherence threshold is not usually attained (3). Though in this meta-analysis, countries in sSA were found to have higher adherence levels than the North American countries, it is of concern that adherence levels have been declining over time (4–6). This decline and the changes in adherence over time are not unique to these regions and have been reported by Carrieri et al. in a French cohort (7).

Failure to adhere to ART has been correlated with changing conditions over time (8). Some of the factors associated with poor adherence in sSA are patient characteristics such as depression (9), poor service provision (10) and structural factors like distance to the health facility (11). These risk factors for adherence differ between region and are context specific (12). Understanding them will enable healthcare workers to provide tailored care for those at risk of non-adherence.

Patients on second line ART may have be on these regimens for a number of reasons such as virological, immunological or clinical failure. These regimens tend to have a higher pill burden, require an increased dosing frequency and have more severe side effects (13). These reasons, among others yet to be identified in our context, could contribute to low adherence in this group of patients. Poor adherence in this subset of patients could have adverse effects beyond the individual rand impacting on the public HIV healthcare system. For instance, the cost of third line ART, should second line regimens fail due to non-adherence, is immense (14), and, coupled with risky sexual behavior, transmission of resistant strains to ART naïve patients would compound the problem (15).

Owing to the paucity of local data on adherence levels among PLHIV on second line ART regimens and the associated factors, we designed a cross sectional study with the aim of filling the gap. In addition, risk factors for poor adherence were identified.

# Methods

## Study design

A cross sectional study was conducted at the Comprehensive Care Clinic (CCC) of Kenyatta National Hospital (KNH), Nairobi, Kenya. The KNH is a teaching and referral hospital and is the largest healthcare facility in East Africa. The CCC offers care and treatment to patients of all age groups from all around the country and it runs from Mondays to Fridays.

Patients were eligible if they had a documented HIV infection, were 18 years or older, were enrolled for care at the clinic, voluntarily provided written informed consent and had been on an atazanavir/ritonavir based second line regimen for more than one month. They were excluded if they were pregnant or lactating, had a World Health Organization (WHO) stage IV illness, had a documented creatinine clearance of less than 60 mL/min, had ever experienced hyperbilirubinemia or were on certain co-medications (proton pump inhibitors, histamine 2 receptor antagonists or rifampicin). The strict exclusion criteria helped to eliminate confounding by side effects from multiple drugs therapies and comorbidities.

Informed consent was obtained before enrollment. Patients on second line ART regimens consisting of atazanavir were identified from the records department and their upcoming clinic dates noted. A random number generator was used to identify the patients that would be recruited. They were then called by the counsellor as part of routine follow up and requested to avail themselves to the counsellor's office regarding possible study participation. Upon reporting, the patients were briefed about the study, taken through screening using an eligibility checklist and those who met the eligibility criteria were enrolled consecutively.

The calculated sample size was 109 using the Kelsey et al. (16) formula for sample size estimation. We enrolled an additional 10% to cater for non-completeness of data. Trained research staff, who were clinicians within the clinic, administered pre-designed standardized case report forms and carried out chart reviews while collecting demographic and clinical history data. The clinicians also administered the 8 item Morisky Medication Adherence Scale (MMAS 8).

The MMAS-8 is an interviewer administered questionnaire that assists in the assessment of adherence. It consists of eight questions, seven of which are answered in the affirmative or negative and one which is a Likert scale. The seven questions each attract a score of either zero or one depending on the response while the eighth question is scored from 0–4. The individual scores are then summed up and divided by four to finally classify patients as either having low, medium or high adherence (scores of < 6, 6 to < 8 and > 8 respectively) (17).

## Data analysis

Hard copy data was transferred to a database that was created in Epi Info (version 7, CDC, Atlanta, GA, USA). Statistical analysis was done on the resultant data set in R (version 3.5.2 (2018-12-20)). Categorical variables were summarized in frequency tables and continuous measures were summarized using means and standard deviations or medians and ranges, as appropriate. The Shapiro Wilk test and Q - Q plots were used to test for normality of the data, whereas the student t-test was used to check for differences in means of continuous variables and the Chi-square test for discrete variables.

In the covariate search, logistic regression modelling was performed, specifically, using backward stepwise selection to identify variables to fit in the model. The threshold for statistical significance was set at 0.05.

## Results

One hundred and ten participants were enrolled between October and November 2017, the majority of whom were women (64, 58.2%; Table 1). The mean age of the study population was 39.8 ( $\pm$  11.8) years. Approximately half the participants were married (59, 53.6%) and had attained secondary school education (56, 50.9%). Nearly a third were unemployed (30, 27.3%) and less than 10% had hypertension or diabetes (9.1% and 4.5%, respectively). The median CD4 count was 219 cells/mL (IQR = 272) and half the participants had achieved viral suppression.

Table 1  
Baseline characteristics of the study population

Variables	n	%
Sex	46	41.8
Male	64	58.2
Female		
Age in years; mean (SD)	39.8 (11.8)	
Marital status; n (%)	34	30.9
Single	59	53.6
Married	10	9.1
Separated	1	0.4
Divorced	6	5.5
Widowed		
Number of children; median (IQR)	2 (0–3)	
Level of education	24	21.8
Primary	56	50.9
Secondary	29	26.4
Tertiary	1	0.9
Informal education		
Occupation; n (%)	30	27.3
Unemployed	43	39.2
Self employed	37	33.6
In formal employment	2	1.8
Smoke cigarettes; n (%)	12	10.9
Alcohol consumption; n (%)		
Hypertension; n (%)	10	9.1
Diabetic; n (%)	5	4.5
CD4 count; median (IQR)	219 (272)	50
Viral load; n (%)	55	98.2
< 1000 copies/mL	9.4 (3.8)	95.5
Time since diagnosis of HIV; median (IQR) years	8.4 (3.3)	2.7
Duration on antiretroviral therapy; mean (SD) years	108	1.8
Regimen ever modified; n (%)	105	9.1
Reason for regimen modification; n (%)	3	
Regimen failure	2	
Toxicity	10	
Other		
Current opportunistic infections; n (%)		

Using the MMAS 8, 14 (12.7%) of the participants had low adherence while 96 (87.3%) were moderately adherent to ART (Fig. 1). None of the participants had high adherence. The median MMAS 8 score was 8 (IQR 7–8) and the scores on each item are listed in Table 2.

Table 2  
Itemized scores on the 8 item Morisky Medication Adherence Scale

Item description		No (n, %)	Yes (n, %)		
1	Do you sometimes forget to take your medicines?	90 (81.8)	20 (18.2)		
2	People sometimes miss taking their medicines for reasons other than forgetting. Over the past two weeks, were there any days when you did not take your medicines?	105 (95)	5 (4.5)		
3	Have you ever cut back or stopped taking your medicine without telling your doctor because you felt worse when you took it?	104 (94.5)	6 (5.5)		
4	When you travel or leave home, do you sometimes forget to bring your medicine?	101 (91.8)	9 (8.2)		
5	Did you take all your medicine yesterday?	0	110 (100)		
6	When you feel like your symptoms are under control, do you sometimes stop taking your medicine?	106 (96.4)	4 (3.6)		
7	Taking medicine every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?	94 (85.5)	16 (14.5)		
8	How often do you have difficulty remembering to take all your medicine?				
	Never (n (%)) 1 (0.9)	Once in a while (n (%)) 8 (7.3)	Sometimes (n (%)) 25 (22.7)	Usually (n (%)) 76 (69.1)	All the time (n (%)) 0

The most common reason for non-adherence to ART was forgetting to take the medications (20, 18.2%) (Table 2). A considerable number of patients also felt that their treatment plans were an inconvenience and this resulted in non-adherence as well (16, 14.5%). Interestingly, all participants reported that they had taken their dose the day prior to their clinic visit.

At univariate analysis, only occupation was found to have a significant association with the adherence status (Table 3).

Table 3

Univariate analysis of sociodemographic and clinical characteristics versus adherence status

Variable	Adherence status		P - value
	Low adherence (n, %)	Medium adherence (n, %)	
Age	10 (9.1)	50 (45.5)	0.708
18–42	4 (3.6)	46 (41.8)	
Gender	7 (6.4)	39 (35.5)	0.708
Male	7 (6.4)	57 (51.8)	
Female			
Marital status	9 (8.2)	25 (22.7)	0.013
Single	5 (4.5)	54 (49.1)	
Married	0	17 (15.5)	
Separated, Divorced, Widowed			
Education	1 (0.09)	24 (21.8)	0.339
Primary	9 (8.2)	47 (42.7)	
Secondary	4 (3.6)	25 (22.7)	
Tertiary			
Occupation;	9 (8.2)	21 (19.1)	0.002
Unemployed	5 (4.5)	75 (68.2)	
Employed			
Smoke cigarettes	14 (12.7)	94 (85.5)	1
No	0	2 (1.8)	
Yes			
Alcohol consumption	11 (10.0)	87 (79.1)	0.180
No	3 (2.7)	9 (8.2)	
Yes			
Hypertension	12 (10.9)	88 (80.0)	0.613
No	2 (1.8)	8 (7.3)	
Yes			
Diabetes	13 (11.8)	92 (83.6)	0.501
No	1 (0.09)	4 (3.6)	
Yes			
Depression status	5 (4.5)	61 (55.5)	0.090
No depression	9 (8.1)	35 (31.8)	
Possible depression			
Regimen modification	0	2 (1.8)	1
No	14 (12.7)	94 (85.5)	
Yes			
Reason for regimen modification	14 (13.0)	91 (84.3)	1
Regiment failure	0	3 (2.8)	
Toxicity			
Current opportunistic infection	11 (10.0)	89 (80.9)	0.115
No	3 (2.7)	7 (6.4)	
Yes			

On bivariable logistic regression analysis, age, marital status and occupation were found to be significantly associated with adherence level (Table 4). In this case, a one-year increase in age was associated with 6% higher adherence levels among the participants (cOR 1.06, 95% CI (1.01, 1.12),  $p = 0.023$ ). Married participants had 3.89 higher odds of being moderately adherent in comparison to those who were single (cOR 3.89, 95% CI 1.22, 13.79),  $p = 0.026$ ). Self-employed participants had 8.79 times higher odds of being moderately adherent to ART compared to unemployed individuals (cOR 8.79, 95% CI (2.04, 61.17),  $p = 0.09$ ). Similarly, participants who were formally employed had 4.86 times higher odds of being adherent to ART compared to the unemployed (cOR 4.86, 95% CI (1.29, 23.80),  $p = 0.029$ ).

Using backward logistic regression analysis, a multivariable model was identified and fitted (Table 4). Age and depression were found to be significantly associated with adherence. Participants older by one year were more likely to have a 10% higher adherence compared to younger participants holding all other variables constant (aOR 1.10, 95% CI (1.04, 1.19),  $p = 0.004$ ). A positive depression screen was associated with an 83% lower likelihood of adhering to ART compared to participants with a negative screen holding all other variables constant (aOR 0.17, 95% CI (0.04, 0.64),  $p = 0.013$ ).

Table 4  
Bivariable and multivariable logistic regression analysis for association between demographics, clinical characteristics and adherence level

Variables	cOR (95% CI)	P value	aOR (95% CI)	P value
Age	1.06 (1.01, 1.12)	0.023	1.10 (1.04, 1.19)	0.004
Gender	1.46 (0.47, 4.59)	0.508	-	-
Marital status	1	0.026	-	-
Single	3.89 (1.22, 13.79)	0.992	-	-
Married	-	-	-	-
Separated, Divorced, Widowed	-	-	-	-
Education	1	0.159	-	-
Primary	0.22 (0.01, 1.26)	0.244	-	-
Secondary	0.26 (0.01, 1.92)	-	-	-
Tertiary	-	-	-	-
Occupation	1	0.002	-	-
Unemployed	6.43 (2.01, 22.91)	-	-	-
Employed	-	-	-	-
Alcohol use	0.38 (0.10, 1.90)	0.19	0.18 (0.03, 1.21)	0.069
Hypertension	0.55 (0.12, 3.89)	0.475	0.12 (0.01, 1.39)	0.080
Diabetes	0.57 (0.08, 11.51)	0.622	-	-
Depression	0.32 (0.09, 1.00)	0.055	0.17 (0.04, 0.64)	0.013
Regimen modification	-	0.993	-	-
Current opportunistic infection	0.29 (0.07, 1.48)	0.102	-	-
Years on ART	0.87 (0.72, 1.03)	0.124	0.84 (0.67, 1.03)	0.106
cOR – crude odds ratio; aOR – adjusted odds ratio				

## Discussion

In this cross-sectional study involving ART experienced PLHIV on second line regimens, none of the participants were highly adherent to treatment. Most had moderate adherence (96, 87.3%) while a smaller number had low adherence (14, 12.7%). Age and possible depression were identified as being independently associated with adherence status.

In a French cohort of PLHIV who were also intravenous drug abusers (IVDU), 22.9% of the participants had low adherence which is much higher compared to our findings (8). Adherence was determined by self-report which is subjective, but nonetheless, the high non-adherence rate was also understandable since substance abuse has been identified as a determinant in a meta-analysis (18).

Across Asia, the levels of adherence vary greatly, not unexpectedly, as it has been noted that the facilitators and barriers of adherence are context specific. The rates of adherence in China and Indonesia are 72% and 54% respectively, both of which are lower than what we report (19,20). However, in Myanmar, the documented adherence level is congruent to ours at 84% (21). Differences in the tools used to assess adherence may also explain the variances in part, since Aye et al. and Kipsang et al. both used the 30-day Visual Analogue Scale (VAS) (20,21).

Regionally, adherence levels to ART are comparable to our findings. In Botswana and South Africa, the documented adherence levels are approximately 87% (22,23), though this was ascertained through pill counts. In West Africa, adherence levels to ART range between 78–90%; these were determined by pill counts and self-report (24,25). In East Africa, specifically Tanzania, Uganda and Ethiopia, adherence levels between 52 and 95% have been reported, measured by a number of methods including the VAS, pharmacy refills, appointment keeping and pills consumed in a week (10,26,27). A prospective study conducted in Kenya at the African Medical Research Foundation (AMREF) clinic in Kibera reported that close to 38% of the patients were non adherent (28). This is about three times of what we report as poor adherence, yet these two clinics and patients are drawn from the Nairobi metropolitan area. The differences could be attributed to the fact that Kibera is an area mostly inhabited by individuals of low social economic status and as such issues such as stigma and food scarcity compete for attention with adherence to ART.

Being married and either self-employed or formally employed were associated with better adherence levels at bivariable analysis. This is comparable to findings from other studies in diverse populations (27,29). Married persons offer additional support to each other to adhere to treatment, whereas having a steady source of income may also motivate one to adhere to ART and keep providing for their family. Being older was identified as being significantly associated with better adherence at multivariable analysis, and this has been reported in multiple studies (10,26,27,29–31). Older individuals are more likely to be stable – socially and economically, mature and with more responsibilities and may therefore take their treatment more seriously than young individuals (10).

We also identified depression as being significantly associated with adherence, which has also been reported across multiple studies in diverse settings (8,18,27,30). Depression is a known risk factor for non-adherence based on the premise that persons with mental illness are less likely to find motivation in keeping with the prescribed treatment regimens.

Alcohol use is a known determinant of non-adherence (24,26,30,32,33), though this was not identified in this study. Persons who use alcohol excessively are less likely to remember to take their medication on time or even to take them at all. Though not a risk factor in this population, duration on ART has been identified as a determinant for adherence in South African and Chinese cohorts (13,20). We hypothesize that patients who have been on ART longer are more likely aware of its benefits and become more adherent.

Nine percent of the study population had hypertension as a comorbidity, which was not unexpected as protease inhibitors are known to cause the metabolic syndrome (34). PLHIVs on ART can expect a near normal population life expectancy, but due to the metabolic syndrome, conditions such as hypertension and diabetes are highly prevalent. In an urban population of PLHIV on therapy, 31.7% were found to have hypertension, which was much higher than what we found (35). Many comorbidities are known to impede adherence, primarily due to the pill burden (36), but also due to competing interests and a lack of understanding of the conditions (35).

Forgetfulness is documented to be the most common cause of non-adherence, a finding that we replicated (20,27,29,37). To decrease the contribution of this factor, use of innovative methods such as setting alarms to remind patients to take their medications might work. Other documented reasons for non-adherence include side effects associated with ART and travelling.

Our study was the first in our country to investigate adherence among PLHIV on long term ART. This provides invaluable insights to healthcare providers on how best to improve outcomes in this patient category. The cross-sectional nature of the study design did not allow us to investigate causality or to determine the dynamic nature of adherence with time. There are also variables such as disclosure and adherence self-efficacy that were not investigated upon and could potentially influence adherence to ART. Data on these variables and many more could be collected in future studies that may be longitudinal in nature.

Optimum adherence to ART is key in ensuring treatment success and reducing adverse outcomes such as increased mortality (19). Treatment programs should ensure that measures such as frequent counselling (22), having family support (27), encouraging patients to have adherence partners (22) as well as diagnosis and treatment of mental illness are prioritized to enhance adherence.

## Abbreviations

<b>HIV</b>	<b>Human Immunodeficiency Virus</b>
PLHIV	Persons Living with HIV
ART	Antiretroviral Therapy
sSA	sub Saharan Africa
WHO	World Health Organization
MMAS – 8	8 item Morisky Medication Adherence Scale
CCC	Comprehensive Care Clinic
IVDU	Intra-Venous Drug Users
VAS	Visual Analogue Scale
AMREF	African Medical Research Foundation

## Declarations

**Ethical approval and consent to participate:** All procedures performed in this study involving human participants were in accordance with the ethical standards of the Kenyatta National Hospital and University of Nairobi Ethics and Research Review Committee (Approval reference: KNH/ERC/R/114) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Participants provided written informed consent prior to taking part in this study.

### Consent for publication

Not applicable

### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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### Competing interests

The authors declare that there they have no competing interests.

### Authors' contributions

GM conceptualized the study, developed the proposal, supervised data collection, analyzed the data, and wrote the draft manuscript. NN and FO were supervisors/advisors on the research process and contributed invaluable in conceptualization, data collection, analysis and manuscript preparation.

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## Figures

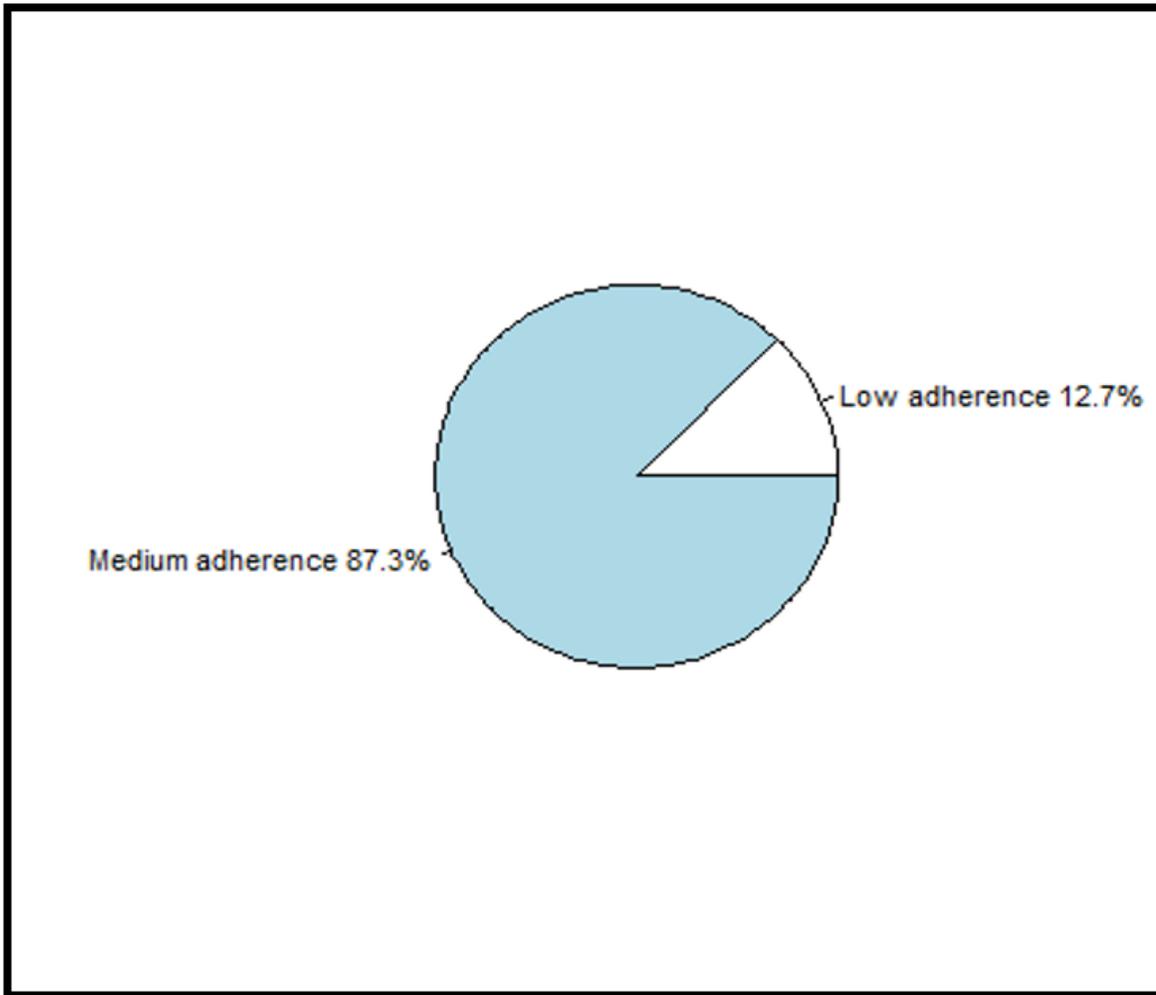


Figure 1

Distribution of adherence levels among the study participants