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Research Article

People living with HIV on atazanavir-based second line regimens are not highly adherent to therapy; a report from a tertiary referral hospital in Kenya

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Background: Adherence to antiretroviral therapy is a necessity for the attainment of favorable treatment outcomes. Several factors are known to influence adherence levels among different cohorts of patients. These factors are likely to be different for patients on second line therapies and knowing them might improve the quality of care provided and generally raise adherence levels.

Objective: To determine adherence levels and their determinants in people living with HIV on second line therapy.

Methods: A cross-sectional study was undertaken in a HIV clinic within Kenyatta National Hospital in October, 2017. Data were collected through interviews and adherence was assessed by oral interview of past medication use and then analyzed in R.

Results: One hundred and ten patients were enrolled; 46 (41.8%) of whom were males. The mean age was 39.8 years (± 11.8). Most participants, 96 (87.3%), were moderately adherent 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 patients on second line regimens were highly adherent to therapy. Younger patients and those with depression require additional adherence counselling.

Key words: People Living With HIV, Antiretroviral Therapy, Adherence

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1. Introduction

Adherence is defined as "the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" (World Health Organization, 2003). Adherence to antiretroviral therapy (ART) is an important and overriding component towards the achievement of optimal treatment outcomes for people living with HIV (PLHIV) on follow up. Adherence levels above 95%, otherwise referred to as high adherence, have been associated with better outcomes such as viral suppression, slowing of disease progression, decreased morbidity and mortality among others (Conway, 2007). 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 CD4 count and viral load (Maria Patrizia Carrieri et al, 2003).

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 ≥ 95% adherence threshold is not usually attained with pooled estimates of 55% and 77% respectively for the aforementioned continents (Mills et al, 2006). Though in this meta-analysis, patients in 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 (Byakika-Tusiime et al, 2009; Liu et al, 2006; Parruti et al, 2006). This decline and the changes in adherence over time are not unique to these regions and have also been reported in a French cohort (P. Carrieri et al, 2001).

Failure to adhere to ART has been correlated with changing circumstances over time (M. P. Carrieri et al, 2003). Some of the factors associated with adherence levels lower than 50% (defined as poor adherence) in sSA are patient characteristics such as depression (Mayston et al, 2012; World Health Organization, 2003), poor service provision (Watt et al, 2010) and structural factors like distance to the health facility (Lankowski et al, 2014). These risk factors for adherence differ between regions and are context specific (Ware et al, 2009). Understanding them will enable healthcare workers to provide tailored care for those at risk of non-adherence. Patients on second line ART may have been 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 (Moosa et al, 2019). 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 and impacting on the public HIV healthcare system. For instance, the costs of hospitalization are reported to rise from 29% to 51% due to decreased adherence (Nachega et al, 2010). Compounded with risky sexual behavior, transmission of resistant strains to ART naïve patients would worsen the problem (Cambiano et al, 2013).

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 evaluated.

2. Methods

2.1 Study design and site

A cross sectional study was conducted at the Comprehensive Care Clinic (CCC) of Kenyatta National Hospital (KNH), Nairobi, Kenya.

2.2 Study population and eligibility criteria

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 (*vulnerability and ethical concerns*), had a World Health Organization (WHO) stage IV illness (*concomitant interacting medications, frailty*), had a documented creatinine clearance of less than 60 mL/min (*alteration to pharmacokinetic parameters*), had ever experienced hyperbilirubinemia (*confounding variable*) or were on certain co-medications (*proton pump inhibitors, histamine 2 receptor antagonists or rifampicin*).

2.3 Sampling and 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. Informed consent was obtained before enrollment.

The calculated sample size was 109 using the Kelsey *et al.* (1996) (Kelsey, 1996) formula for sample size estimation. We enrolled an additional 10 % to cater for non-completeness of data.

2.4 Data collection

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. Adherence was assessed by asking patients whether they sometimes forgot to take their medication. This question required a simple 'yes' or 'no' response. Patients were asked additional questions to identify reasons for non-compliance. They were also asked whether they reported non-adherence to the clinician.

2.5 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 using backward stepwise selection to identify variables to fit the model. The threshold for statistical significance was set at 0.05.

2.6 Ethical considerations

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/A/110**) 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.

3. Results

A total of 236 patients were screened between October and November 2017 with the subsequent enrollment of 110 individuals, majority of whom were women (64, 58.2%; **Table 1**). The mean age of the study population was 39.8 (± 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		
Male	46	41.8
Female	64	58.2
Age in years; mean (SD)	39.8 (11.8)	
Marital status: n (%)		
Single	34	30.9
Married	59	53.6
Separated	10	9.1
Divorced	1	0.4
Widowed	6	5.5
Number of children; median (Range)	2 (0-3)	
Level of education		
Primary	24	21.8
Secondary	56	50.9
Tertiary	29	26.4
Informal education	1	0.9
Occupation; n (%)		
Unemployed	30	27.3
Self employed	43	39.2
In formal employment	37	33.6
Smoke cigarettes; n (%)	2	1.8
Alcohol consumption; n (%)	12	10.9
Hypertension; n (%)	10	9.1
Diabetic; n (%)	5	4.5
CD4 count; median (IQR)	219 (272)	
Viral load; n (%)		
< 1000 copies/mL	55	50
Time since diagnosis of HIV; median (IQR) years	9.4 (3.8)	
Duration on antiretroviral therapy; mean (SD) years	8.4 (3.3)	
Regimen ever modified; n (%)	108	98.2
Reason for regimen modification; n (%)		
Regimen failure	105	95.5
Toxicity	3	2.7
Other	2	1.8
Current opportunistic infections; n (%)	10	9.1

Table 2: Participant responses to questions on adherence

	Item description	No (n, %)	Yes (n, %)
1	Do you on occasions forget to take your medicines?	90 (81.8)	20 (18.2)
2	In the last 14 days, were there any days when you did not take your medicines for reasons other than forgetting?	105 (95)	5 (4.5)
	Reasons for non-adherence		
3	Have you ever reduced the frequency/ quantity or stopped taking your medicine without telling your doctor because you felt worse when you took it?	104 (94.5)	6 (5.5)
4	Do you sometimes forget to carry your medicine when you travel?	101 (91.8)	9 (8.2)
6	Do you sometimes stop taking your medicine when your symptoms have gone away?	106 (96.4)	4 (3.6)
7	Have you felt inconvenienced by strictly following your treatment plan?	94 (85.5)	16 (14.5)
8	How often do you have difficulty remembering to take all your medicine?		

Never (n (%))	Once in a while (n (%))	Sometimes (n (%))	Usually (n (%))	All the time (n (%))
1 (0.9)	8 (7.3)	25 (22.7)	76 (69.1)	0

Fourteen (12.7%) of the participants had low adherence while 96 (87.3%) were moderately adherent to ART. None of the participants had high adherence. The reasons for non-adherence are listed in **Table 2**.

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.

On bivariable logistic regression analysis, age, marital status and occupation were found to be significantly associated with adherence level (**Table 3**). 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% (1.29, 23.80), p= 0.029).

On logistic regression analysis with backward stepwise model building, age and depression were found to be significantly associated with adherence (**Table 3**). 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).

4.0 Discussion

In this cross-sectional study involving 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 (M. P. Carrieri et al, 2003). 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 (Langebeek et al, 2014).

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 (Kipsang et al, 2018; Rai et al, 2013). However, in Myanmar, the documented adherence level is congruent to ours at 84% (Aye et al, 2017). Differences in the tools used to assess adherence may also explain the variances in part.

Table 3: Bivariable and multivariable logistic regression analysis for association between demographics, clinical characteristics and adherence levels in patients on second line regimens

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			-	-
Single	1			
Married	3.89 (1.22, 13.79)	**0.026**		
Separated, Divorced, Widowed	-	0.992		
Education			-	-
Primary	1			
Secondary	0.22 (0.01, 1.26)	0.159		
Tertiary	0.26 (0.01, 1.92)	0.244		
Occupation			-	-
Unemployed	1			
Employed	6.43 (2.01, 22.91)	**0.002**		
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

Regionally, adherence levels to ART are comparable to our findings. In Botswana and South Africa, the documented adherence levels are approximately 87% (Ehlers & Tshisuyi, 2015; Mabunda et al, 2019), 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 (Potchoo et al, 2010; Yaya et al, 2014). 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 visual analogue scale, pharmacy refills, appointment keeping and pills consumed in a week (Letta et al, 2015; Sangeda et al, 2018; Watt et al, 2010). 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 (Unge et al, 2010). 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.

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 (Watt et al, 2010). We also identified probable depression as being significantly associated with adherence, which has also been reported across multiple studies in diverse settings (M. P. Carrieri et al, 2003; Langebeek et al, 2014; Letta et al, 2015; Protopopescu et al, 2009). Depression, where definitively diagnosed, 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 has previously been reported as a determinant of non-adherence (Bukenya et al, 2019; Denison et al, 2015; Protopopescu et al, 2009; Sangeda et al, 2018; Yaya et al, 2014), 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 (Kipsang et al, 2018; Moosa et al, 2019). 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 associated with an increased risk of metabolic syndrome (Barbaro, 2006). 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 (Monroe et al, 2013). Many comorbidities are known to impede adherence, primarily due to the pill burden (Krentz et al, 2012), but also due to competing interests and a lack of understanding of the conditions (Monroe et al, 2013).

Forgetfulness is documented to be the most common cause of non-adherence, a finding that we replicated (Croome et al, 2017; Kipsang et al, 2018; Letta et al, 2015; Semvua et al, 2017). 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 provides insights to healthcare providers on how best to improve adherence among PLHIV by being more attentive to the young and those likely to be depressed. 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 others 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 (Rai et al, 2013). Treatment programs should ensure that measures such as frequent counselling (Ehlers & Tshisuyi, 2015), having family support (Letta et al, 2015), encouraging patients to have adherence partners (Ehlers & Tshisuyi, 2015) as well as diagnosis and treatment of mental illness are prioritized to enhance adherence.

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Conflict of Interest declaration

The authors declare no conflict of interest.

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