

Full Length Research Paper

## Medication adherence and cluster of differentiation 4 (CD4) cells response in patients receiving antiretroviral therapy

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This study evaluated medication adherence following interventions and its association with cluster of differentiation 4 (CD4) cells response among patients receiving antiretroviral therapy (ART) in Specialist Hospital Sokoto, North Western Nigeria. Longitudinal study design was used. Interventions included training of health workers on adherence counseling; pre- and post-ART adherence counseling were provided to patients. Out of 1300 patients on ART who were provided interventions, 365 patients were selected using simple random technique. The CD4-cell measurements at months 0, 6, 12, 18 and 24 were extracted from the patients' hospital records; and announced pill counts were conducted. Chi square was used to test the association between groups of variables; and  $P < 0.05$  indicated statistical significance. Out of 365 participants sampled, data from 297 (81.4%) participants were valid for analysis. The mean age of participants was 34.7 (95%CI, 33.6 to 35.8) years; 60.9% were females and 76.4% received Zidovudine/Lamivudine/Nevirapine (AZT/3TC/NVP) regimen. The mean percent adherence was 83.4% (95%CI, 80.8% to 86.0%). The mean CD4-cells count (cells/mm<sub>3</sub>) at ART initiation increased from 198.9 (95%CI, 180.7 to 217.1) to 396.5 (95%CI, 368.3 to 424.7) at 6 months, 428.0 (95%CI, 400.4 to 455.6) at 12 months, 427.2 (95%CI, 405.6 to 448.8) at 18 months, and 501.4 (95%CI, 469.5 to 533.3) at 24 months. This increase was statistically significant ( $P < 0.05$ ). Participants' employment and educational status, age, sex and type of ART regimens received had no significant association with medication adherence ( $P > 0.05$ ). This study reported a mean adherence level that is below the required >95% necessary to achieve the goals of ART. The increase in CD4 cells count over the observation period was statistically significant at the estimated adherence level. Better immunologic outcomes may be achieved with higher adherence level.

**Key words:** Medication adherence, pill counts, human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), antiretroviral therapy (ART), Nigeria.

### INTRODUCTION

Life-long near-perfect adherence, >95%, is necessary to achieve the goals of antiretroviral therapy (ART) which

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include the suppression of human immunodeficiency virus (HIV) replication (HIV-RNA < 400 copies/ml) (Chalker et al., 2010; Arnsten et al., 2001; Paterson et al., 2000). It has also been suggested that 100% adherence rate is necessary to achieve even greater benefits (Lucas et al., 1999). Studies have shown that achieving medication adherence rates greater than 80% in chronic therapy has been problematic, even in resource-rich countries (DiMatteo, 2004; Osterberg and Blaschke, 2005). Non-adherence is the term used to describe a patient's inability to take his or her drugs in the collaboratively agreed manner. Non-adherence to ART poses a risk of HIV progression, a worsening of immunological and clinical states, development of drug resistance and consequently narrowing future treatment options.

A number of methods are employed, alone or in combination, to measure medication adherence. The common methods for measuring adherence to ART include patient self-reports, pill counts, pharmacy dispensing records and electronic medication monitors amongst others (Chalker et al., 2010); and each method has its strengths and limitations. Studies have also shown that the objective measures used in research, although impractical for most clinical settings, are more sensitive than patient self-report for detecting medication non-adherence (Chalker et al., 2010; Doung et al., 2001). Pill counts adherence rates have been shown to have reasonable correlations with electronic drug monitoring (EDM) and HIV viral load (Berg et al., 2006; Liu et al., 2001; Bangsberg et al., 2000). There are additional reports that data from pill count method agreed with data from viral load measurement; and pill counting was recommended as a reliable and economical tool for adherence measurement in a resource-limited setting (San Lio et al., 2008). Studies in Nigeria reported varying levels of adherence to ART ranging from 49.2% (Nwauche et al., 2006), 58.1% (Erah and Arute, 2008), 73.3% (Bello, 2011), 73.8% (Agu et al., 2010), and 44% (Afolabi et al., 2009) in Southern Nigeria, to 79.1% (Agu et al., 2011) and 80% (Mukhtar et al., 2006) in Northern Nigeria.

With effective ART, the cluster of differentiation 4 (CD4) cells count increases by >50 cells/ $\mu$ l within weeks after viral suppression, and increases by 50 to 100 cells/ $\mu$ l per year thereafter. The CD4 cells counts of some patients may not increase that steadily or quickly, even with durable viral load suppression. Additionally, patients who are older (age >50) and those with lower baseline CD4 cell counts are more likely to have reduced CD4 count responses (AETC, 2012). The mean CD4 counts of patients starting ART with baseline CD4 cell counts >350 cells/ $\mu$ l increased by over 500 cells/ $\mu$ l after one year of therapy (Wright et al., 2011). The median increases in CD4 cell counts after 6, 12, and 24 months of ART were 114, 181, and 248 cells/ $\text{mm}^3$ , respectively (Smith et al., 2004). In Nigeria, patients on ART reported a significant increase of baseline CD4-cell count (cells/ $\mu$ l) by over 100 cells/ $\mu$ l at 3, 6, 12 and 18 months of therapy (Agu et al.,

2010). However, studies that correlated the CD4 cells response of patients on ART with medication adherence are scanty in Nigeria. This study evaluated medication adherence following the interventions and its association with CD4 cells response among HIV-positive patients on ART in Specialist Hospital Sokoto, North Western Nigeria.

## METHODOLOGY

### Setting

This study was conducted in Specialist Hospital Sokoto, a secondary public health care facility in the North Western Nigeria. The hospital offers comprehensive HIV care services including ART for HIV-infected patients. It has a 540-bed capacity and serves the people living in the Sokoto metropolis and its environment including the bordering country, Niger Republic. The HIV-infected patients identified at the HIV counseling and testing service points were enrolled into a pre-ART register for follow-up and only those who meet the ART eligibility criteria are commenced on treatment. At the time of this study, there were 1300 HIV-infected patients currently receiving ART in this facility. The patients were required to come with their medication pill containers at every medication refill visit as a pre-condition for getting a refill. The pharmacist retrieves the patients' pill container during this visit, and counts the remaining medications before dispensing additional pills as an adherence quality improvement strategy instituted in this hospital. Medication adherence is reinforced through adherence counseling and education especially for those who were found to be non-adherent by pill counts; although these were poorly documented as a routine. HIV care and treatment services were supported by Global HIV/AIDS Initiative Nigeria (GHAIN) project and provided at no cost to the patients with funding from the United States (US) President's Emergency Plan for AIDS Relief (PEPFAR) through US Agency for International Development (USAID).

### Research design

This was a longitudinal study. The CD4 cells count (cells/ $\text{mm}^3$ ) of patients receiving ART was assessed at months 0, 6, 12, 18 and 24. An announced pill count was conducted to assess medication adherence of study participants following adherence intervention.

### Intervention

The intervention included training of health workers on patient adherence counseling and education. These trained adherence counselors provided group education and individual counseling to the patients on every clinic day. All HIV-infected patients who were eligible to commence ART in the facility went through at least three different sessions of adherence counseling and education before being placed on antiretroviral drugs. The patients' commitment to adhere to the medications was obtained in the last counseling session before ART commencement. Ongoing medication adherence counseling and pill counts were also provided at every medication refill visits. The copies of standard operating procedures (SOP) for patient adherence counseling and education were also provided to the adherence counsellors in the facility. There is a strong support group of People Living with HIV and AIDS (PLWHA) that serves as a self help group, and members also function as adherence counselors and treatment supporters.

## Outcome measures

The main variables of interest were measured as the percent adherence by pill counts and the CD4-cell counts (cells/mm<sup>3</sup>) from each patient's laboratory results obtained across multiple time points.

## Selection criteria

All adult HIV-infected patients who had received antiretroviral therapy for at least 6 months, benefited from the medication adherence interventions and refilled their medications between April 1, 2011 and July 18, 2011 were eligible to be included. Only patients that consented to participate were included in the study. Any patients who did not meet each of these criteria were excluded from the study.

## Study population

The study population included 1300 HIV-infected patients who were receiving ART and met the selection/inclusion criteria in the hospital.

## Sample size calculation and sampling

The sample size (n) was calculated as follows (Yamane, 1967):

$$n = \frac{N}{1 + N(e)^2}$$

where n = the sample size; N = the study population = 1300; e = the level of precision ( $\pm 5\%$ ). Therefore,

$$n = \frac{1300}{1 + 1300(0.05)^2} = 305.9 \approx 306 \text{ patients}$$

The calculated sample size (n) was a total of 306 ART patients; however, the sample included 365 HIV-infected patients to accommodate for losses due to incomplete or missing data on important variables of interest. Out of the study population, 365 HIV-infected patients were selected using simple random technique.

## Ethical consideration

Ethical approval for this study was obtained from National Health Research Ethics Committee (NHREC), Federal Ministry of Health Abuja Nigeria. Informed consent was obtained from the participants and confidentiality was assured by excluding identifiers during analysis.

## Data collection

Eight-item study-specific instrument was administered to the participants at the point of medications refill by trained research assistants. The items included patients' identity number (ID), sex, age, educational level, occupation, antiretroviral drug regimens, the expected number of pills remaining based on the last medications refill information and the actual number of pills remaining at this

refill visit. The last medications refill information included the number of pills dispensed at the last medication refill visits, taking into account the extra pills dispensed and missed coverage due to stock-outs. The research assistants retrieved the pill containers from the patients, counted and documented the number of pills in the container in the instrument. Using the patients' ID, the research assistants retrieved laboratory results from the patients' case folder and extracted their CD4 cells counts at months 0, 6, 12, 18 and 24.

## Data analysis

The data were analyzed using Predictive Analytics SoftWare (PASW) Statistics 18. Descriptive statistics such as frequency distribution were used to present sample characteristics. The percent adherence for each participant was calculated using the following formula: (no. of days of pills dispensed – no. of days of pills returned) / (no. of elapsed days between dispensed date and return date)  $\times$  100. The mean percent adherence of the participants was calculated by taking the average of percent adherence for all participants. Paired samples t-test was used to compare the CD4-cell counts at months 0, 6, 12, 18 and 24. Chi-square was used to test the association of the percent adherence and groups of variables. All reported P-values were 2-tailed and  $P < 0.05$  indicated statistical significance.

## RESULTS

### Characteristics of patients

Of the 365 ART patients sampled in this study, data from 297 (81.4%) participants were valid for analysis; while data from 68 (18.6%) participants were not used due to missing data on some core variables. The mean age of participants was 34.7 (95%CI, 33.6 to 35.8) years; 56.6% were 30 to 44 years old; and 60.9% were females. Of the participants, 42.4% had Islamic education, 38.4% were self-employed and 76.4% were receiving AZT/3TC/NVP regimen (Table 1).

### Medication adherence

The mean percent adherence level reported among the participants was 83.4% (95%CI, 80.8% to 86.0%). The mean percent adherence for male participants was higher as compared to female participants and the difference was not statistically significant ( $P > 0.05$ ). The participants' ART regimens, age, employment and educational status were not associated with adherence ( $P > 0.05$ ). Of the participants, 52.2% and 16.8% of them reported mean percent adherence of 100% and  $<60\%$ , respectively (Table 2). Of the 142 (47.8%) participants that reported  $<100\%$  adherence, the mean percent adherence rate was 65.3% (95%CI, 61.9% to 68.7%).

### Medication adherence and CD4 response

At the mean percent adherence level (83.4%) reported, the mean CD4-cell count (cells/mm<sup>3</sup>) at ART initiation increased

**Table 1.** Characteristics of the study participants segregated by reported adherence rates (n = 297).

Characteristic	Number of participants (%)	Mean percent adherence (95%CI)	P-value
<b>Sex</b>			
Male	116.0 (39.1)	84.4 (80.4 – 88.4)	0.279
Female	181.0 (60.9)	82.5 (79.1 – 85.9).	-
<b>Age (years)</b>			
15 – 29	81.0 (27.3)	85.1 (80.6 – 89.6)	0.889
30 – 44	168.0 (56.6)	81.6 (77.8 – 85.4)	0.911
45 – 59	42.0 (14.1)	86.2 (80.8 – 91.6)	0.668
> 59	6.0 (2.0)	82.1 (64.6 – 99.6)	-
<b>Educational status*</b>			
None	24.0 (8.1)	83.8 (75.5 – 92.1)	0.834
Primary	34.0 (11.4)	85.2 (79.0 – 91.4)	0.516
Secondary	60.0 (20.2)	85.8 (80.5 – 91.1)	0.178
Tertiary	43.0 (14.5)	84.5 (78.1 – 90.9)	0.896
Islamic	126.0 (42.4)	81.0 (76.5 – 85.5)	-
<b>Employment status**</b>			
Employed	41.0 (13.8)	78.9 (72.2 – 85.6)	0.719
Self-employed	114.0 (38.4)	85.2 (81.0 – 89.4)	0.934
Unemployed	98.0 (33.0)	80.4 (75.5 – 85.3)	0.785
Student	15.0 (5.1)	91.2 (82.2 – 100.0)	-
<b>ART regimen (irrespective of the type of formulation)§</b>			
Zidovudine/Lamivudine/Nevirapine (AZT/3TC/NVP)	227 (76.4)	84.5 (81.7 – 87.3)	0.100
Tenofovir/Lamivudine/Efavirenz (TDF/3TC/EFV)	8 (2.7)	90.0 (75.2 – 100.0)	0.098
Tenofovir/Lamivudine/Nevirapine (TDF/3TC/NVP)	15 (5.1)	83.4 (71.5 – 95.3)	0.667
Tenofovir/Emtricitabine/Efavirenz (TDF/FTC/EFV)	29 (9.8)	75.8 (65.9 – 85.7)	0.111
Tenofovir/Emtricitabine/Nevirapine (TDF/FTC/NVP)	10 (3.4)	72.4 (55.1 – 89.7)	0.306
Tenofovir/Emtricitabine/Lopinavir-boosted with Ritonavir (TDF/FTC/LPVr)	5 (1.7)	86.8 (69.8 – 100.0)	

CI, Confidence interval; \*Ten participants did not indicate their educational status; \*\*Twenty-nine did not indicate their employment status; §Three participants did not indicate the ART regimen received; and were excluded in the analysis. ART regimen presented.

**Table 2.** Mean percent adherence reported by the participants; n = 297.

Mean percent adherence	Frequency	Percentage
100	155.0	52.2
90 – 99	13.0	4.4
80 – 89	35.0	11.8
70 – 79	30.0	10.1
60 – 69	14.0	4.7
< 60	50.0	16.8
Total	297.0	100.0

from 198.9 (95%CI, 180.7 to 217.1) to 396.5 (95%CI, 368.3 to 424.7) among the 165 of 297 (55.6%) patients who had documented CD4 cells measurement at 6 months, 428.0 (95%CI, 400.4 to 455.6) among the 91 of 297 (30.6%) patients who had documented CD4 cells measurement at 12 months, 427.2 (95%CI, 405.6 to

448.8) among the 30 of 297 (10.1 %) patients who had documented CD4 cells measurement at 18 months, and 501.4 (95%CI, 469.5 to 533.3) among the 13 of 297 (4.4%) patients who had documented CD4 cells measurement at 24 months. The increase in CD4 cells count was statistically significant at 6, 12, 18 and 24 months (P<

**Table 3.** Adherence rates of the participants segregated by mean CD4-cell counts (cells/mm<sup>3</sup>) at different intervals; n = 297.

Mean percent adherence	Mean CD4-cell counts (cells/mm <sup>3</sup> ) at 95% Confidence Interval					P-value
	Month 0,	Month 6	Month 12	Month 18	Month 24	
100 Adherence	192.8 (166.3 – 219.3)	399.2 (353.9 – 444.5)	435.1 (391.1 – 479.1)	499.2 (470.9 – 527.5)	379.4 (347.9 – 410.9)	0.000
90 – 99 Adherence	243.0 (133.9 – 352.1)	604.0 (442.5 – 765.5)	622.5 (621.5 – 623.5)	360.5 (359.5 – 361.5)	953.5 (952.5 – 954.5)	0.000
80 – 89 Adherence	229.2 (178.1 – 280.3)	430.1 (344.5 – 515.7)	460.8 (350.0 – 571.6)	477.4 (324.8 – 630.0)	317.5 (251.8 – 383.2)	0.000
70 – 79 Adherence	213.6 (162.5 – 264.7)	374.1 (288.5 – 459.7)	335.8 (225.0 – 446.6)	330.4 (177.8 – 483.0)	615.5 (549.8 – 681.2)	0.000
60 – 69 Adherence	173.9 (105.1 – 242.7)	373.7 (234.9 – 512.5)	329.3 (227.7 – 430.9)	224.3 (117.3 – 331.3)	608.0	0.000
< 60 Adherence	182.2 (139.8 – 224.6)	367.7 (303.1 – 432.3)	447.6 (353.0 – 542.2)	469.5 (298.1 – 640.9)	370.5 (132.4 – 608.6)	0.000

0.001). Table 3 shows the participants' CD4 responses over time segregated by adherence level. The CD4 response over time increased significantly from the baseline value for both participants that reported 100% and <100% adherence levels in the first 12 months (Table 3).

## DISCUSSION

This study evaluated medication adherence and its association with CD4 cells response among HIV-positive patients receiving ART. The study reported mean adherence level (83.4%) that is below the required >95% necessary to achieve the goals of ART (Chalker et al., 2010; Arnsten et al., 2001; Paterson et al., 2000). This is similar to previous reports in Nigeria (Mukhtar et al., 2006; Olowookere et al., 2008; Agu et al., 2011). Over one-half of the participants reported 100% adherence level. This is highly desirable as 100% adherence rate is necessary to achieve even greater benefits of ART (Lucas et al., 1999). Participants' educational and employment status, age and sex were not found to have any association with medication adherence. This is contrary to previous reports that employment status (Kyser et al., 2011; Agu et al., 2010; Agu et

al., 2011) and age (Reda and Biadgilign, 2012; King et al., 2012; Sullivan et al., 2007) were associated with poor adherence but consistent with reports by Silva et al. (2009). These may be explained by previous reports that forgetfulness, being unemployed and looking for work were among the major causes of non-adherence among patients receiving ART (Kyser et al., 2011; Agu et al., 2011; Olowookere et al., 2008; Sullivan et al., 2007). However, further studies may be needed to investigate the differences in the various study findings.

The type of antiretroviral drugs regimens received by the participants had no association with medication adherence in this study. Toxicities/side effects and pill burden are known factors related to the type of antiretroviral regimens that adversely affect medication adherence (Olowookere et al., 2008; Agu et al., 2010). Drug toxicities/side effects were associated with poor medication adherence (Olowookere et al., 2008); whereas pill burden was not (Agu et al., 2010). This may be associated with the advent of fixed dose combinations and subsequently reduced number of pills in ART. The relationship between these specific factors and medication adherence was not assessed in this study; hence, we may not be able to make reasonable inference.

A comparison of adherence levels to CD4 cells count at 6 months intervals shows a steady increase in mean CD4 cells count from baseline in most adherence sub-levels. There are reports that the CD4 cells counts of some patients may not increase steadily or quickly, even with durable viral load suppression (AETC, 2012). Patients who are older (age >50) and those with lower baseline CD4 cell counts are more likely to have reduced CD4 count responses (AETC, 2012). However, the increase in CD4 cells count over the observation period was statistically significant. This is consistent with previous research findings (Smith et al, 2004; Wright et al, 2011; Agu et al, 2010); however, >95% adherence level is highly desirable for better immunologic and clinical outcomes.

There are some limitations which need to be acknowledged. As noted in previous studies, announced pill counts can be inaccurate if any of the following occurs: (a) patients empty pill containers without ingesting any pills ("pill dumping"), (b) the accurate start date for the pill supply cannot be determined, or (c) patients use multiple pill containers (Berg and Arnsten, 2006; Rudd et al., 1989; Pullar et al., 1989). These may cause overestimation of adherence rates by pill counts. The baseline adherence rates were not assessed before the study interventions. This limited the

comparison of adherence rates before and after the interventions. The small sample size in some subgroups may result in estimates with wide confidence intervals. This may have led to unreliable estimates in these subgroups.

## Conclusion

This study reported mean adherence level that is below the required >95% necessary to achieve the goals of ART. Participants' educational and employment status, age, sex and the type of antiretroviral drugs regimens had no association with medication adherence. The increase in CD4 cells count over the observation period was statistically significant at the reported adherence level. Better immunologic outcomes may be achieved with higher adherence level.

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