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Difference in Adherence to Anti-Retroviral Therapy in Resource - Constrained Setting: Adolescents and Young Adults in Rural and Urban Residents in Nigeria

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Abstract: Adherence to antiretroviral medicines is essential to halt human immunodeficiency virus progression, increase CD4 counts, decrease virologic impact, and improve quality of life for the infected people. However, sustaining good adherence among adolescents and young adults has been a challenge caused by various problems such as distance to clinic, improved CD4 count which lead to complacency in adherence, and the nature of the environment. Compare to the general population, there is low adherence to anti-retroviral therapy among adolescents and young adults. The study aims to assess the difference in adherence to anti-retroviral therapy between adolescents and young adults in rural and urban areas in resource-constrained settings. This was a retrospective cross-sectional study carried out between January 2011 – December 2014 with a sample size of 287 patients who accessed care for HIV in Federal Medical Center Makurdi, located in the Middle-Belt region of Nigeria. Univariate analysis was conducted using descriptive statistics. Pharmacy refill was used to measure adherence level while the data was analyzed using independent t-test and Chi-Square test. A *p* value < 0.05 was considered to be statistically significant in the study. In line with literature review, adherence level of at least 95% was considered optimal while anything less than that was deemed suboptimal**.** Adherence for patients in urban settings was 90.36% (182) while it was 95.12% (105) for those in rural settings (p = 0.001, 95% CI (-8.069, -1.450)). Among patients in rural settings, 57.14% (60) had adherence level of 100% compare to only 42.3% (77) from urban settings (p = 0.080, 95% CI (.052,.116)). Patients in rural settings in Federal Medical Center Makurdi in Benue State are more likely to have a comparative better health output than their counterparts in urban settings going by their adherence levels.

Keywords: Adherence, HIV, Young Adults, Adolescents, Urban and Rural

1. Introduction

Human Immunodeficiency Virus (|HIV) remains a pandemic that has claimed many lives and has impacted healthcare systems of many countries, especially those in developing nations [1]. The advent of effective Antiretroviral (ARV) medicines has changed the landscape of medical intervention in HIV, which is now considered a chronic illness [2, 3]. One useful strategy in the management of the HIV virus is ensuring patients' good adherence to antiretroviral therapy. The ARVs work better when there is adherence to treatment and this goes beyond the act of taking the ARV to include the individual's attitude towards treatment [4, 5]. From the population of adults living with HIV in 2015, 17.8 million representing 51% was 15 years while among the 1.8 million adults with new infections in the same year, 58% was in the age category 15 – 24 years [6]. In a world-wide systematic review and meta-analysis study of adherence in adolescents and young adults (AYAs) aged 15 – 24 years from 53 countries, only 62.3% was found to be

adherent. The highest adherence was from Africa and Asia [7] but suffice to say the adherence rate was below the generally acceptable minimum level of 85% [8, 9].

While it is a fact that how much antiretroviral regime could be effective is dependent on intrinsic properties of the cocktail regimen and adherence to the antiretroviral therapy, adherence to ART is impacted by many factors which could be broadly categorized into structural, psychosocial, economic and pharmaceutical factors. [8, 10]. Examples of structural factor would include transport cost and travel times to clinics which impacts more on people in rural areas [11]. Adolescent stage determines the trajectory of HIV management globally as the stage serves as the transition from pediatric to adulthood as such it is important to study adherence in this group as relate to their environment (urban and rural) [12]. In a systematic review of adherence among adolescents of ages 10 – 19 years of age in Africa, four important themes emerged as common barriers to adherence to ART. These include impact from family structure, nature of ARV regimen, urban versus rural location, and knowledge of HIV status and gender [13]. Poor adherence to ART has been found to be independently associated with location of health facility in rural area as urban dwellers are known to have a comparatively better adherence [14]. In a study of adherence to ART by people living in Calabar (a major city in Nigeria) and accessing care in University of Calabar Teaching Hospital and those coming from rural areas there was a difference between the two groups with the latter having a better adherence to ART [15]. In a study conducted in another part of Africa, the Republic of Togo, a cross-sectional study of 291 people living with HIV AIDS ages 10 – 19 years at the regional hospital of Sokode showed those residing in rural areas had a comparatively better adherence rate than those in the urban areas [13]. These studies were not focused on adolescents and young adults. Also, adherence measurement used in these studies was based on patient self-report is believed to the least reliable of all the methods of assessing adherence [16, 17]. What is however, unknown is difference in an objectively assessed adherence level to ART for patients who live in urban and rural areas but access treatment services in the same health facility. The dearth of studies on the differences in ART adherence rates among AYAs in Nigeria based on environment (urban or rural) made my research necessary to extend the body of knowledge in this area of HIV management with ART. This study seeks to assess impact of environment on adherence among AYA on antiretroviral medicines.

2. Materials and Methods

2.1. Study Design, Settings and Population

This was a retrospective study where secondary data was used from Federal Medical Center Makurdi in Benue State, Nigeria. The state had a population of 4.2 million in the most recent 2006 census by National Population Commission. The land mass is 33, 955 square kilometers and lies between Latitudes 6.5° and 8.5° N and Longitudes 7.47° E and 10^0 E, and is accessible by road [18]. There are 23 local government areas in the state and the surrounding states include Cross River, Ebonyi and Enugu States to the south; Kogi State to the west; Nasarawa State to the north; and Taraba State to the east. The state also shares an international boundary with the Federal Republic of Cameroon on the southeast flank. It is an agrarian state made up of two major tribes namely Tiv and Idoma, with Igede and Etulo as minority tribes. Most of the inhabitants are farmers and are mainly Christians with a few idol worshippers [19]. Because the health facility is a tertiary health institution and a referral center, it serves populations from the surrounding states as well. The data was from patients who received ARVs from the treatment center between January 2011 – December 2014. The studied population was adolescents and young adults within the age bracket of 15 and 24 years. In the research, adherence level of at least 95% was considered optimal while anything less was deemed suboptimal. Adherence was further categorized into 'excellent adherence' [100%], 'good adherence' (95-99%), 'moderate adherence' (80 – 94%) and 'poor adherence' (less than 80%).

2.2. Sample Size Estimation

In order to estimate the minimum required sample size, alpha level was set at 5% with confidence level at 95%, with an assumed marginal error of 2.5% while the proportion of adherent adolescents was 90.5% based on current literature [20]. Using the formula n $= \frac{Z^2 \, p \, q}{\delta^2}$ [21], sample size was calculated to be 528. Because of the reported high level of missing or incomplete data from the health facility, 24% was added which gave a total required sample size of 656.

2.3. Sampling Method

Random integers were generated through excel and assigned to the patients list for those that met the inclusion criteria. The first 657 in ascending order were selected. Many patients did not have complete variables of interest. These variables of interest included the following data: CD4, age, contact address, 3261084 duration on ART, pharmacy refill, and gender. The selected patients were further categorised into urban and rural based on their contact address.

2.4. Ethical Consideration

Ethics approval was obtained from the custodian of the data, Ethics Committee of Federal Medical Center Makurdi.

2.5. Data Analysis

Based on contact addresses, patients were categorized into rural and urban. Rate of adherence to ART was estimated using pharmacy refill records. This was done by dividing the number of actual pharmacy refills over expected pharmacy refills and multiplying the ratio by 100%. Other demographic data were also extracted. The data obtained was first entered

into an excel spread sheet, cleaned and imported into SPSS v24.0 for data analysis. Descriptive and inferential statistics including t-test and Chi-Square tests were performed and results presented. Chi Square test was carried to test for the significance of the association between adherence level (optimal or suboptimal) and environment (urban or rural) where patients lived. p value < 0.05 was considered to be statistically significant. An independent an independent t-test analysis was performed to test for the hypothesis that there was statistically significantly difference in adherence rate to ART between the population in urban and rural settlements. The data was first tested to ensure the variable of interest has a discernible distribution that approximate normal and the grouping variable was categorical and dichotomous [22]. This was followed by t-$test$ analysis. Levene's test for equality of variance was examined. The key assumptions for the test were met [23]. Therefore, a test for equal variance assumed was performed. In order to understand and appreciate the effect size of the difference, Cohen's d was estimated. Effect size is the quantification of difference

between two groups [24]. Cohen's $d = (M_2 - M_1)/ SD_{pool.}$ All patients with missing values were excluded from data analysis.

3. Results

Only patients with complete valid data (N = 287) were included in the analysis. The mean adherence rate for the total population was 92.11% while the mean CD4 counts was 544.5 cells/mm3 with average age of 21.50 years (Table 1). The ratio of female to male in the study was 1:8. The mean adherence rate to ART for those who lived in urban settlements (N = 182) was M_1 = 90.36 (SD_1 = 15.66) while it was M_2 = 95.12 (SD_2 = 9.45) for those in rural settings (N = 105) (p = 0.001, 95% CI (.014, .056)). For the study population, the age range was between 15.02 to 24.40 years. Among those with CD4 counts greater than 500 cells/mm^3, the mean adherence was 93.99% whereas, those with CD4 counts less than 500 cells/mm^3 was 89.87% (p =.130, 95% CI (-.7328, -.909)).

Table 1. Analysis of data characteristics.

Characteristic	Mean	Minimum	Maximum
Adherence rate (%)	92.11	10.00	100
CD4 counts (cell/mm^3)	544.50	10.00	135.60
Age (years)	21.50	15.02	24.40

Since the t-test result showed statistically significant difference in mean adherence rate to ART between those who lived in urban and rural settings, the study failed to accept the null hypothesis that there is no significant difference in adherence rate to ART between the groups. The Cohen's d was .4. Comparisons for gender, age, and CD4 counts, and duration on treatment were also performed. There was no statistically significant difference in adherence rate between:

Male and female (p = 0.442, 95% CI (-6.173, 4.240)); Age 15-19 years and 20 - 24 years (p =.357, 95% CI (-2.825, 4.775)); Duration on therapy (< 5 years and ≥ 5 years) (p =.352, 95% CI (.343, 7.073)). There was however, a statistically significant difference in adherence between those with CD4 counts of at least 500 cell/mm^3 and less than 500 cells/mm^3 (p = 0.013, 95% CI (-7.328, -.909)). (Table 2) with a Cohen's d value of .3.

Table 2. T-test Analysis.

Characteristics	Total patients (n = 656)	Mean adherence	Standard Deviation	P value	Confidence Interval	
					Lower	Upper
Environment						
Urban	182 (63.41%)	90.36%	M_1 = 15.66	.001	-8.069	-1.450
Rural	105 (36.59%)	95.12%	M_2 = 9.45			
CD4 counts						
≥ 500 cells/mm^3	131 (45.64%)	89.87%	M_1 = 15.18	.013	-7.328	-.909
< 500 cells/mm^3	156 (54.36%)	93.99%	M_2 = 12.45			
Duration on ART						
(Years)	187 (65.16%)	93.40%	M_1 = 13.92	.352	.343	7.073
< 5	100 (34.84%)	89.69%	M_2 = 13.57			
≥ 5						
Age (Years)						
15 – 19	68 (23.69%)	92.85%	M_1 = 11.16	.357	-2.825	4.775
20 – 24	219 (76.31%)	91.87%	M_2 = 14.65			
Gender						
Male	31 (10.80%)	92.97%	M_1 = 11.06	.442	-6.173	4.240
Female	256 (89.20%)	92.00%	M_2 = 14.21			

A total of 81 (44.51%) patients from urban settings had suboptimal adherence compared to the 32 (30.48%) in rural settings. Whereas, 101 (55.49%) had optimal adherence in urban settings, 73 (69.52%) from rural settings had optimal adherence with p =.019 (Table 3).

Table 3. Comparison of suboptimal and optimal adherence.

Environment	Adherence category		Pearson Chi-Square (sig.)	Phi Value	Confidence Interval	
	Suboptimal	Optimal			Lower	Upper
Urban	81 (44.51%)	101 (55.49%)				
Rural	32 (30.48%)	73 (69.52%)	.012	.138	.014	.056
Total	113	174				

Also, the analysis shows 57.14% (60) of patients in rural settings had excellent adherence compare to 42.31% (77) of those in urban settings; good adherence, 12.38% (13) was from patients in rural settings compare to 13.19% (24) in urban settings; Moderate adherence was observed in 22.86% (24) of those from rural settings compared to 30.77% (56) of those from urban settings; Only 7.62% (8) had poor adherence among those from rural areas whereas, 13.74% (25) had poor adherence among patients in urban areas (p = 0.080, 95% CI (.052,.116). (Table 4).

Table 4. Comparison of adherence levels between patients in rural and urban settings.

Adherence Level	Urban: Number of patients	Rural: Number of patients	P value	Confidence interval	
				Lower	Upper
Excellent Adherence	77 (42.31%)	60 (57.14%)			
Good Adherence	24 (13.19%)	13 (12.38%)			
Moderate Adherence	56 (30.77%)	24 (22.86%)	.080	.052	.116
Poor Adherence	25 (13.74%)	8 (7.62%)			
Total	182	105			

4. Discussion

To our knowledge, this is the first study to explore the difference in adherence to ART between adolescents in rural and urban area in Nigeria who accessed care and treatment in a common treatment center. The mean adherence rate of 95.12% among patients in rural settings shows the group had optimal adherence and is likely to have a better health outcome compare to the 90.36% for the urban group because adherence has virologic, immunological, and clinical implications for HIV management outcomes. It is important for patients to attain the optimal level of adherence as it helps to sustain the level of drug needed to suppress viral replication thereby reducing the plasma viral load [25]. Adherence at rates below the optimal is a serious public health issue because it potentially causes resistance to the currently limited available ARV regimens [26]. For example, resistance to first-line ARVs means a patient would have only a second-line regimen and salvage regimen as the remaining options [27, 28].

Excellent adherence (100%) is desired in the management of HIV/AIDS with antiretroviral medicines for an excellent therapeutic outcome. From the study, a higher proportion of patients in the rural settings, 57.14% (60) meets this desired target compare to only 42.31% (77) for those in the urban settings. Though the difference was not statistically significant (p = 0.080, 95% CI [.052,.116]), it could be a call for an increase focus on urban patients during adherence counselling session at ART centers [29]. In a related study in the same Middle-Belt region, Nigeria in 2013, only 31.2% (78) participants had 100% adherence to ART in Federal Medical Center Keffi, Nasarawa State [30]. In the study, both groups had almost the same proportion of patients with good adherence, 13.19% (24) and 12.38% (13) respectively. In a related cross-sectional study of 876 patients in Cuba where

adherence level was categorized as in the study, 8% had 'good adherence' [31]. The objective of vision '90-90-90' by the Joint United Nations Programme on HIV/AIDS [UNAIDS] is to have an HIV-free generation and one way to achieved this is by ensuring 90% of those in care have their viral load suppressed through adherence to ART generation [32]. The low proportion of patients with good adherence in these studies implies implementing partners in the management of HIV need to step out strategies that would encourage patients to remain adherent if the objective of vision '90-90-90' is to be achieved. Sustained adherence counselling once someone is enrolled into care should be encouraged.

The higher proportion of poor adherence, 13.74% (25) found among the urban category compares to the 7.62% (8) among rural category shows it is more likely to have poor therapeutic outcome among patients from the urban settings. Poor adherence comes with an attendant increase total health cost as well because health outcome is impacted negatively, thereby increasing the frequency of clinic visits, hospitalization [8]. Also, it could lead to increase in transportation costs, pill burden, increase incidence of HIV-related morbidity and mortality with an additional cost implication [8] and likelihood for treatment failure [33]. The adolescent fertility rate in Nigeria is very high [34]. So, the likelihood of pregnancy during the study period is high. Poor adherence in pregnancy is known to increase disease progression and increase the risk of virus transmission to the child [35–39].

The difference in adherence levels between the two groups is not unique. According to Hudelson and Cluver [13] who carried out a systematic study on adherence, environment (urban versus rural) could have impact on adherence to ART. In a related study for patients suffering from diabetes, Kim et al. [40] also concluded in their research on adherence to antidiabetic medication that adherence was greater in rural

than in urban. The common understanding is that those in rural communities accessing care in urban areas have challenges including low health literacy level, transportation to treatment centers, missed appointments due to patient wait time at the clinic, accommodation crisis whenever they had to spend a night in such urban areas where they are accessing care [3, 41, 42]. As such, they are expected to have worse adherence to medications comparatively.

The average adherence rate for both patients in rural (95.12%) and urban (90.36%) areas was 92.11%. Suffice to say that while the mean adherence rate in the study is suboptimal, however, it is in line with the trend in increasing adherence rate to ART by patients accessing ART care and treatment in Nigeria. For example, adherence rate to ART for a study in the Middle-Belt region of Nigeria between 2009 – 2010 was 87.9% (8). In 2008, researchers found adherence rate of 86% in Nigeria [43]. In a more recent study between September – December 2013 in Federal Medical Center Owerri, Imo State, Nigeria, 91% (191) of patients had good adherence defined as adherence equal or greater 95% [44]. The continuous improved adherence level to ART could be connected to the improvement in adherence strategies employed by various non-governmental organisations saddled with the responsibility of implementation of HIV management in the country. These include patient education, routine adherence counsel during clinical appointments, home-based care services including visitation by peers, use of treatment supporters to serve as treatment models, and directly observed therapy [45]. Also, over the years, antiretroviral fixed-dose combinations formulations have reduced the frequency of dosing in a day which encourages adherence [46]. The drug distribution system in the country has also improved as the key actors in supply chain management for antiretroviral medicines have continued to master and improve on the system that ensures regular supply thereby reducing stock out of antiretroviral medicines which impact adherence [47]. Decentralization of treatment centers which has led to a surge in the number of HIV treatment centers in the last two decades in sub-Saharan Africa could also be a contributing factor to the continued improved adherence level among patients in Nigeria [48].

Study limitations: The scope of the study was about exploring adherence to ART among AYA with respect to where patient resided. Findings from the study cannot be generalized to the entire Nigeria because it is a cross sectional study. Also, because of the nature of the study, the role of other factors in influencing the study outcome (adherence to ART) could not be explored. These roles include stigma; presence or absence of social support; and ARV counseling prior to commencement of ART. Data composition was also a limitation as sample was only from the FMC Makurdi ART center and attitude of health care providers is known to influence adherence rate [49].

5. Conclusion

This study finding indicates that the AYAs in Benue State who reside in rural areas are better in adherence to ART than their counterpart in urban areas. More than half of the AYAs on ART in the FMC Makurdi in Nigeria who resided in rural areas while accessing care in a city had an excellent adherence whereas, less than half of their counterparts in urban settings had excellent adherence. Only those in rural areas meet the minimum required adherence of 95% and are likely to have a comparatively better health outcome. Current adherence strategies should be reviewed to target urban dwellers. Also, a more in-depth study among AYA using a qualitative approach like a focused group discussion where other factors such as the role of peer pressure, religion and social support in adherence rate to ART could shed light on the discrepancy in adherence levels between the two groups.

Conflict of Interest

The authors declare that they have no conflict of interest and no support was received from any funding agencies, public or private.

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