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Changes in Body Mass Index Among Antiretroviral Therapy Naïve People Living with HIV in Southeastern Nigeria

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Abstract

The proportion of people living with HIV (PLHIV) who are overweight or obese is rising, leading to a double epidemic of HIV and obesity. The purpose of this retrospective longitudinal study was to examine changes in body mass index (BMI) among PLHIV who were new to antiretroviral therapy (ART) in two states in Southeastern Nigeria. The BMI at baseline and 12 months were compared and the difference in proportions in each BMI category was tested. The association between the BMI at 12 months and the demographic and/or clinical variables was examined using multiway analysis of covariance. The study included 2,146 participants. After 12 months on ART, the number of participants who were obese increased by 135% (81 to 190), while those who were underweight decreased by 130% (306 to 133). Overall, the BMI increased in 30.2% of the participants. Further analysis showed that age ($p=.009$; $\eta^2=.005$), baseline BMI ($p<.001$; $\eta^2=.435$), baseline regimen ($p<.001$; $\eta^2=.031$), HIV stage ($p=.039$; $\eta^2=.007$) and CD4 category ($p<.001$; $\eta^2=.012$) were all associated with increased BMI after 12 months of ART. Healthcare providers should be mindful of the likelihood of excess weight gain among PLHIV who are on ART and develop a plan to proactively address it.

Keywords: antiretroviral therapy, body mass index, HIV, obesity, people living with HIV

1. Introduction

People living with HIV (PLHIV) are living longer and this longevity is increasingly associated with the diagnosis of other chronic health conditions like obesity, cardiovascular diseases, and cancer (Lerner et al., 2019; Marcus et al., 2020; Tate et al., 2012). Early initiation of antiretroviral therapy (ART) among PLHIV has reduced the incidence of HIV related morbidities such as opportunistic infections, wasting, and death. However, considerable weight gain while on ART has been documented among some PLHIV (Dillon et al., 2013; Olawepo et al., 2020; Tate et al., 2012), leading to these PLHIV being classified as overweight or obese (Achokwa et al., 2020; Tate et al., 2012).

Excessive weight gain is closely associated with other clinical conditions such as hypertension, dyslipidemia, Type-2 diabetes mellitus (T2DM), coronary heart disease, stroke, sleep apnea, and certain cancers (National Heart, Lung, and Blood Institute [NHLBI], 1998). Globally, the prevalence of obesity among the general population of adults has tripled to 13% since 1975 while the prevalence of overweight is estimated at 39% (World Health Organization [WHO], 2020). In Nigeria, Africa's most populated nation, a systematic review reported an overweight prevalence of 20-35%, and obesity prevalence of 8-22% among adults (Chukwuonye et al., 2013). Additionally, the 2018 Nigeria Demographic and Health Survey (DHS) reported the prevalence of overweight among women in the southeastern region to be 23.4% and the prevalence of obesity to be 16.1% (National Population Commission [NPC] and ICF, 2019).

During the early stages of the HIV epidemic, severe weight loss or wasting was common among PLHIV. The

diagnosis of HIV wasting is a very strong predictor of mortality among PLHIV (Tang et al., 2005; Wanke et al., 2000). Wasting has been attributed to several causes including alterations in metabolism, malabsorption, chronic inflammatory processes, decreased food intake, and energy deficiency (Maas et al., 1998; Smit et al., 2002), and nutritional therapy alone was not able to address the HIV wasting syndrome (Kotler et al., 1985; Nahlen et al., 1993). Several treatments were used to manage HIV wasting including appetite stimulants (e.g. marijuana), anabolic agent (e.g. growth hormones), steroids (e.g. testosterone, oxandrolone), and cytokine modulators (e.g. thalidomide) (Pernerstorfer-Schoen et al., 1994; Hoy & Flanigan, 1994; Von Roenn et al., 1994; Waters et al., 1996). Some of these treatments, on their own, were not very effective in increasing body weight among wasted patients, and the optimal treatment to combat wasting was in commencing ART among these patients (Silva et al., 1998).

Weight gain among PLHIV has been encouraged and applauded by health care providers as a clinical indicator of treatment success and many PLHIV also desire to escape the stigma associated with wasting and HIV. Several authors have reported increases in BMI (among PLHIV who are on treatment) that is equal to or surpasses that in the general population. One of the earliest studies was by Amorosa and colleagues who reported a 31% prevalence of overweight and a 14% prevalence of obesity among PLHIV in Philadelphia (Amorosa et al., 2005). Crum-Cianflone et al. (2008) also reported a combined prevalence of 63% for overweight and obesity in a cohort attending two large naval clinics in the US. In Nigeria, this emergent phenomenon has also been described. Mustapha et al. (2011) reported a prevalence of 19% and 8.9% for overweight and obesity, respectively, among PLHIV in a cross-sectional study in one clinic in Abuja, Nigeria's capital city. Other studies from Nigeria have also reported significant increases in BMI among PLHIV who are on ART (Akinboro et al., 2013; Alo et al., 2014; Denue et al., 2013; Ezechi et al., 2016; Olowookere et al., 2015).

It is important to note, however, that there are major limitations to the previous studies from Nigeria, including that they were conducted in stand-alone clinics/sites and many of them had small sample sizes. Therefore, there is a need to further investigate this emergent phenomenon of rising obesity among PLHIV on treatment in Nigeria because of the country's high HIV burden. Hence, the objectives of this study were to determine (a) the difference in BMI at baseline and at 12 months of treatment among ART-naïve PLHIV and (b) if the BMI after 12 months of treatment was associated with demographic and/or clinical factors after accounting for age and baseline BMI.

2. Method

2.1 Study Setting and Sample

Using a retrospective longitudinal design, de-identified data for this study were retrieved from the archives of a recently concluded free HIV care and treatment program in two states in southeastern Nigeria - Enugu State and Ebonyi State. The data were collected between 2012 and 2015.

We included adult ART-naïve PLHIV who commenced treatment between January 2012 and September 2014 and remained on treatment for 12 months. Participants were excluded if (1) they were <18 years old, (2) they were not on a 3-drug regimen, (3) their height and weight measurements were not documented at baseline, (4) their weight were not documented at 12 months after ART start, or (5) they were pregnant during the period covered by this study. The dataset for this study included 2146 ART-naïve PLHIV who remained on treatment for 12 months. Ethical approval was obtained from the Institutional Review Board (IRB) of the University of Nevada Las Vegas.

2.2 Study Variables

The independent variables included both demographic and clinical variables. Demographic variables were age at baseline, sex (male and female), marital status (married, single, widowed, divorced, and unknown), and level of education (none, primary, secondary, post-secondary, and unknown). Clinical variables were retrieved at baseline and at 12 months, except the participant's height and stage of HIV infection, that were collected at baseline only. Clinical variables included the date of ART commencement, drug regimen, weight and height, stage of HIV infection, the CD4 count, and the blood pressure. The drug regimen covered all the different HIV medications that the participants were on at baseline, while the HIV stage was captured using the WHO stages (1=Asymptomatic, 2=mildly symptomatic, 3=moderately symptomatic, and 4=severely symptomatic). Two variables were chosen as covariates – participant's age and BMI at baseline. The outcome variable was the BMI at 12 months.

2.3 Data Analyses

Initial data screening included examination of frequency counts for categorical variables, and normality testing for continuous variables using the Kolmogorov-Smirnov test of normality. The variables did not meet the assumption of normality, and hence rank-based procedures were utilized in the analyses. Height and weight data were computed as BMI for each year. The BMI was also re-coded into four categories- underweight (BMI<18.5 kg/m^2); normal weight (BMI 18.5-24.9 kg/m^2); overweight (BMI 25.0-29.9 kg/m^2); and obese (BMI≥30 kg/m^2). The proportions in the different BMI categories were calculated at the start of ART and at 12 months.

The median BMI at baseline was compared with the median BMI at 12 months using a Wilcoxon signed-rank test. The difference in proportions in each BMI category at baseline versus 12 months was examined with the McNemar-Bowker test. Though the assumptions of normality and homogeneity of variance were not met, a multiway-ANCOVA (analysis of covariance) test was used because it is robust enough to accommodate departures from normality when there are adequate degrees of freedom (Pallant, 2016). Additionally, the ranked data produced similar statistical results as the parametric procedure, further strengthening the argument for the use of ANCOVA. ANCOVA was used to test if the BMI after 12 months of treatment was associated with demographic and/or clinical variables after accounting for age and baseline BMI. A parsimonious second model was then fitted with only the independent variables that met a significance level of $p<0.05$ and the two covariates. All analyses were done in SPSS (v. 26.0; Armonk, NY: IBM Corp.).

3. Results

3.1 Demographic and Clinical Characteristics of the Sample Population

The demographic and clinical characteristics are presented in Table 1 and Table 2 below. Approximately 69% of the sample population were female (n=1489) and the median age was 34 years (IQR: 28,41). Females commenced ART at a younger age (median age = 32 years, IQR: 28,38) than the males (median age = 39 years. IQR: 33,45). About half of the participants were married (51.5%, n=1105). At baseline, 62.4% (n=1340) of the participants were of normal weight, while 14.3% (n=306) were underweight, 19.5% (n=419) were overweight, and 3.8% (n=81) were obese. The median BMI at baseline was 22.2 kg/m^2 (IQR: 19.8, 24.8). A Mann-Whitney U Test revealed no difference in the baseline BMI for females (median = 22.1 kg/m^2, IQR: 19.5, 24.8, n = 1489) versus males (median = 22.3 kg/m^2, IQR: 20.2, 24.8, n = 657), [U = 514230.5, z = 1.897, p = .058, r = 0.04].

Table 1. Baseline demographic characteristics of the study participants

Gender	**Frequency**	**Percent (%)**
Female	1489	69.4
Male	657	30.6
Age at ART Start (years)		
18-29	623	29.0
30-39	875	40.8
40-49	426	19.9
50-59	190	8.9
≥60	14	0.7
Unknown	18	0.8
Level of Education		
Primary	367	17.1
Secondary	569	26.5
Post-Secondary	359	16.7
None	89	4.1
Unknown	762	35.5
Marital Status		
Married	1105	51.5
Single	484	22.6
Widowed	244	11.4
Divorced	53	2.5
Unknown	260	12.1

Baseline clinical variables showed that most (70.2%) of the participants were categorized as WHO HIV stage 1. About 34% of the participants also had baseline CD4 count of <200 cells/mm^3. Most of the participants (61.9%) in

this sample commenced Tenofovir-based regimen. As a third drug in the combination therapy, Nevirapine (54.1%) and Efavirenz (43.8%) were the most common, while the protease inhibitors made up only 2.9% (Table 2).

Table 2. Baseline clinical characteristics of study participants

BMI Category at Baseline	**Frequency**	**Percent (%)**
Underweight (BMI<18.5 kg/m^2)	306	14.3
Normal Weight (BMI 18.5-24.9 kg/m^2)	1340	62.4
Overweight (BMI 25.0-29.9 kg/m^2)	419	19.5
Obese (BMI≥30 kg/m^2)	81	3.8
WHO Stage at Baseline		
I	1507	70.2
II	203	9.5
III	121	5.6
IV	28	1.3
Unknown	287	13.4
CD4 Category at Baseline (cells/mm^3)		
<200	738	34.4
200 - <350	527	24.6
350 - <500	251	11.7
≥500	102	4.8
Unknown	528	24.6
ART Regimen at Baseline* (by backbone)		
Tenofovir-based	1329	61.9
Zidovudine-based	802	37.4
Abacavir-based	14	0.7
Stavudine-based	1	<0.1
ART Regimen at Baseline* (by third drug)		
Efavirenz	941	43.8
Nevirapine	1161	54.1
Lopinavir (boosted with ritonavir)	42	2.0
Atazanavir (boosted with ritonavir)	2	0.9

**Note*. Emtricitabine or Lamivudine were constant in all the regimens.

3.2 Changes in Mean and Median BMI at 12 Months

The Wilcoxon Signed Rank Test revealed a significant increase in the median BMI following the commencement of ART ($z = -21.864$, $p<.001$), with a moderate effect size ($r = .334$). The median BMI increased from 22.2 kg/m^2 (IQR: 19.8, 24.8) at baseline to 23.4 kg/m^2 (IQR: 21.0, 26.4) at 12 months.

3.3 Changes in the Proportion of Participants in the BMI Categories

The McNemar-Bowker Test showed that after 12 months on ART, the number of participants who were obese and overweight increased by 135% (81 to 190) and 36.3% (419 to 571), respectively. Additionally, the number of participants who were underweight or normal weight decreased by 130% (306 to 133) and 6.5% (1340 to 1252), respectively (McNemar-Bowker Test statistic = 301.857, $p<.001$) (Table 3).

Table 3. A crosstabulation of BMI categories at baseline versus at 12 months of ART

		BMI category at 12 months				
		Underweight	Normal Weight	Overweight	Obese	Total
BMI Category at Baseline	Underweight	85 (27.8%)	207 (67.6%)	8 (2.6%)	6 (2.0%)	306 (100%)
	Normal Weight	44 (3.3%)	953 (71.1%)	298 (22.2%)	45 (3.4%)	1340 (100%)
	Overweight	3 (0.7%)	84 (20.0%)	248 (59.2%)	84 (20.0%)	419 (100%)
	Obese	1 (1.2%)	8 (9.9%)	17 (21.0%)	55 (67.9%)	81 (100%)
	Total	133 (6.2%)	1252 (58.3%)	571 (26.6%)	190 (8.9%)	2146 (100%)

In total, 30.2% (n=648) of the participants moved to a higher BMI category, 7.3% (n=157) moved to a lower BMI category, while the remaining 62.5% (n=1341) stayed in the same BMI category. Among all the participants who were overweight at the beginning, one-fifth had an increase in BMI and moved to the obese category while another one-fifth had a decrease in BMI falling to the normal weight category. About one-fifth (21%) of all participants who were obese at baseline became overweight at the end of this study.

3.4 Factors Associated with BMI at 12 Months

The results of the preliminary checks for linearity, homogeneity of regression slopes, and reliability of covariates were all satisfactory. After adjusting for covariates, BMI at 12 months varied significantly by baseline regimen, HIV stage at baseline, and CD4 category at baseline (see Table 4). The parsimonious second model (Table 5) showed that after adjusting for covariates, there was significant interaction effect for baseline regimen, HIV stage at baseline, and CD4 category at baseline, [F (29, 1495) = 4.230, p<.001], with a small effect size (η^2=.076). The three variables were also independently significant though with small effect sizes (baseline regimen, p<.001, η^2=.031; HIV stage at baseline, p=.039, η^2=.007; and CD4 category at baseline, p<.001, η^2=.012).

Finally, the outcome of the model indicated that the two covariates (BMI at baseline and age) were significantly associated with BMI at 12 months. However, only the BMI at baseline uniquely adjusted the BMI at 12 months [F (1, 1495) = 1152.176, p <.001, η^2=.435] after it was adjusted for the other covariates, main effects, and interaction. The large effect size (η^2=.435) suggested that the strength of the relationship between adjusted BMI at 12 months and baseline BMI was very strong.

Table 4. Analysis of Covariance for BMI at 12 months on ART (Initial Model)

Tests of Between-Subjects Effects			
Dependent Variable: BMI at 12 months			
Source	F	Sig.	Partial Eta Squared
Corrected Model	28.239	.000	.436
Intercept	7.742	.005	.005
Age	10.385	.001	.007
BMI at baseline	987.174	.000	.403
Gender	2.739	.098	.002
Marital status	1.736	.123	.006
Education	1.041	.392	.004
Baseline regimen	1.748	.046	.015
Stage at baseline	5.003	.001	.014
CD4 category	5.934	.001	.012
SBP category	2.190	.112	.003
DBP category	.077	.781	.000
R Squared = .436 (Adjusted R Squared = .420)			

*SBP = Systolic blood pressure; DBP = Diastolic blood pressure.

Table 5. Analysis of Covariance for BMI at 12 months on ART (final model)

Tests of Between-Subjects Effects			
Dependent Variable: BMI at 12 months			
Source	F	Sig.	Partial Eta Squared
Corrected Model	13.970	.000	.502
Intercept	48.901	.000	.032
Age	6.875	.009	.005
BMI at baseline	1152.176	.000	.435
Baseline regimen	3.432	.000	.031
Stage at baseline	2.530	.039	.007
CD4 category	6.280	.000	.012
Baseline regimen * Stage at baseline	3.742	.000	.050
Baseline regimen * CD4 category	3.273	.000	.048
Stage at baseline * CD4 category	5.033	.000	.039
Baseline regimen * Stage at baseline * CD4 category	4.230	.000	.076
R Squared = .502 (Adjusted R Squared = .466)			

4. Discussion

The rapid expansion of HIV testing services in Nigeria (Avert, 2019) has led to increased access to care and treatment services. This study examined changes in BMI from baseline to 12 months in 2,146 ART naïve PLHIV who participated in a free HIV care and treatment program in southeastern Nigeria between 2012 and 2015. We found an increase in BMI among nearly a third of the participants, which is less than the increase documented by other studies conducted in Nigeria in which 83.1-85.3% of participants gained weight (Akinboro et al., 2013; Denue et al., 2013). A study in South Africa also found that 74% of the 230 PLHIV on treatment gained weight over a 12-month period (Hurley et al., 2011). A larger proportion of the participants in this study were in the normal weight category at treatment initiation (62.4%) and after 12 months on ART (58.3%). However, a significant drop in the proportion of those underweight (from 14.3% to 6.2%) shows that many of the PLHIV displayed a "return to health" pattern (Jones et al., 2013; Kumar & Samaras, 2018). In another study in Nigeria, Denue et al. (2013) had documented a drop in the proportion of underweight participants from 27% to 11.4% after 30 months on ART. With earlier commencement of therapy in the current era of 'treat all', more normal weight PLHIV are beginning treatment and there is a decrease in the number of people who are initiating treatment as underweight or wasted PLHIV.

The increase in the proportion of overweight (19.5% to 26.6%) and obese (3.8% to 8.9%) participants is a cause for concern, especially in the light of the chronic diseases associated with excess weight gain (NHLBI, 1998). Other studies from Nigeria show similar trends. Ezechi et al. (2016) had documented that the prevalence of obesity among PLHIV on treatment in a large metropolitan clinic increased from 7.4% to 13.9% and then to 26.5%, after two and five years on ART, respectively. The same study also reported that the overweight participants increased from 19.6% to 35.7% at the end of five years (Ezechi at al., 2016).

Globally, this same trend has been recorded. Erlandson and colleagues studied PLHIV in nine countries and showed that after three years on ART, about one-fifth to one-quarter of participants who were normal weight or underweight at baseline became overweight or obese. Overall, the proportion of overweight or obese clients increased from about 25% to 40% in three years in this sample (Erlandson at al., 2015). Other studies have also documented this increase in obesity among PLHIV across countries like the USA (Lakey et al., 2013; Tate et al., 2012), USA and Canada (Koethe et al., 2016), Cuba (Gil et al., 2011), and France (Bonnet et al., 2013). Some of these studies also show that the BMI rises steeply in the first 12 months of treatment and begins to plateau after 24 months (Koethe et al., 2016; Lakey et al., 2013; Olawepo et al, 2020; Tate et al., 2012).

It is well documented that obesity has several harmful effects on human health, including increased risk for type 2 diabetes (T2DM), cardiovascular disease (CVD), hypertension, dyslipidemia, stroke, sleep apnea, and certain cancers (Flegal et al., 2013; NHLBI, 1998; Ogden et al., 2007; Reaven, 2011). But these effects are more

concerning among PLHIV on ART. Several researchers have also documented increased rates of T2DM and CVD among PLHIV on ART (Freiberg et al., 2013; Herrin et al., 2016; Willig & Overton, 2016). Since HIV is now considered a chronic disease and PLHIV who are on ART live longer lives, excessive weight gain and obesity put them at risk for multiple chronic diseases and conditions.

4.1 Limitations to the Study

This study is not without its limitations. The data was collected for other purposes, hence, data on regimen changes, viral load, treatment adherence, and comorbidities were poorly documented in this database. Furthermore, a prospective cohort study would have yielded better results as data on diet, physical activity levels, and adverse events could have been collected from the participants. These data would have provided additional information and shed light on the influence of physical activity and diet on weight gain among PLHIV who commence ART. However, we interpret the results of this secondary data analysis as hypothesis-generating and necessary for planning future, prospective studies. We also note that there is a discrepancy in the proportion of participants in the WHO HIV stages versus the proportions in the different CD4 categories. We are not able to explain this difference. However, it is to be noted that those with missing data for staging were 13.4% and for baseline CD4 were 24.6% of the total participants. This level of missingness makes it difficult to draw any conclusion on this discrepancy. Additionally, the HIV staging is usually done at the first consultation with a physician, even before the lab results are complete. This may further explain this discrepancy.

4.2 Conclusion

Our results suggest that most PLHIV commencing ART experience an increase in BMI, particularly in the first year. PLHIV need to be educated about excess weight gain, and the possible health implications. Given the likelihood of excess weight gain among PLHIV who initiate ART, healthcare providers should ensure that they perform regular weight and BMI monitoring and have in place obesity prevention and management guidelines at the commencement of treatment.

Competing Interests Statement

The authors declare that there are no competing or potential conflicts of interest.

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