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Evaluation of CD4 Count Progression in HIV-Infected Patients on Different Classes of Antiretroviral Regimens

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article.

Abstract
Background: Understanding the expected effects of different antiretroviral regimens on CD4 count will guide therapeutic decision and monitoring treatment progress that will improve patients' outcomes.
Objective: To evaluate the effects of two first line and one second line antiretroviral regimens on annual changes in CD4 count of HIV-infected patients at Usmanu Danfodiyo University Teaching Hospital, Sokoto.
Method: A retrospective analysis of patients' records between 2011 and 2015 which were selected using systematic random sampling was conducted. A total of 423 records of patients that met the inclusion criteria were evaluated for changes in CD4 count. The data were analysed using descriptive, correlation and linear regression statistics, with $p<0.05$ considered statistically significant.
Results: Majority of the patients were females (75.4%) and their mean age was 37.1±9.1 years. Correlation analysis showed that increasing duration of the disease state ($p=0.001$) and treatment ($p=0.001$) were significantly associated with low annual percentage increase in CD4 count. Linear regression models showed that among patients with CD4 cell counts of ≤300 cells/mm^3, the annual percentage increase of those on Tenofovir (TDF) + Emtricitabine (or Lamivudine) (XTC) + Efavirenz (EFZ), Zidovudine (AZT) + Lamivudine (3TC) + Nevirapine (NVP)and TDF+XTC + Lopinavir/ritonavir (LPV/r) regimens were 41.1%, 16.9% and 4.9% respectively. Patients with CD4 counts >300 to 500 cells/mm^3 mostly had insignificant increase of 4.5%, 1.3% and 2.9% respectively. All patients with CD4 >500 cells/mm^3 had insignificant decrease.
Conclusion: Significant increase in annual percentage CD4 count is observed only when the CD4 count is low with patients on TDF+XTC+EFZ regimen showing the best increase. Increase in duration of the disease and treatment were associated with low annual increase.
Key Words: Antiretroviral regimen, CD4 count, HIV, Highly active antiretroviral therapy

INTRODUCTION

Human Immune Virus (HIV) is a retrovirus affecting human immune system. CD4 cells are particularly targeted by the virus thereby predisposing the host to opportunistic infections due to compromised immunity (CDC, 2018). The consequence of continuous immune compromise is that patient's condition could deteriorate from clinical Stage 1 (acute infection that is asymptomatic) to Stage 2 (mild infections and weight lost), Stage 3 (chronic infection with severe weight lost) and consequently Stage 4 where a patient is said to have Acquired Immune Deficiency Syndrome (AIDS) associated with severe wasting and opportunistic infections (WHO, 2005).

According to the United Nation Agency for International Development (UNAIDS), as at the year 2017, the global HIV prevalence is 36.9 million out of which 25.7 million are found in Africa alone. Also in the same year, there were 1.8 million new infections and about 0.94 million death from AIDS-

related illnesses (UNAIDS, 2018b). Globally, Nigeria has the second largest number of people leaving with HIV/AIDS (PLWHA) with 3.1 million as at 2017. However, the percentage prevalence (2.8 %) is much lower than that of many African countries like South Africa (18.8 %) and Zambia (11.5 %) (UNAIDS, 2018a).

Antiretroviral therapy (ART) remains the treatment of choice for the lifelong management of PLWHA. The World Health Organisations (WHO) has guidelines recommending the use of different antiretroviral (ARV) regimens. These recommendations are reviewed periodically based on studies demonstrating the advantage or disadvantage of one regimen compared to others.

Several studies that compare the outcomes of different ARV regimens reported different findings. A study in India reported that tenofovir-based regimens were associated with increased survival and cost effectiveness (Bender *et al.*, 2010). In a different study, higher mortality was reportedly associated with Tenofovir (TDF) + Emtricitabine (or Lamivudine) (XTC) + Nevirapine (NVP) regimen (Chi *et al.*, 2011) among Zambian population. Viral suppression was found to be better among patients on TDF + XTC + Efavirenz (EFZ) regimen compared to those on other first-line regimens (Amoroso *et al.*, 2012). Also on viral suppression, EFZ-based regimens were found to be better than NVP-based (Pillay *et al.*, 2013) while PI-based regimens were reported to be better than Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI)-based regimens (Martin *et al.*, 2014). Other studies reported better Quality of Life associated with TDF + XTC + EFZ regimen (Biambo *et al.*, 2018) and reduced adverse effects with EFZ-based regimens (Shubber *et al.*, 2013).

ART normally suppress the virus thereby spearing the CD4 cells. Therefore, consistent increase in CD4 count is an indication of improvement in treatment outcome. Thus, CD4 count is considered as one of the markers of treatment outcome, hence, its use as one of the major monitoring parameters among HIV-infected patients.

Most studies did not compare the effect of different ARV regimens on CD4 changes of the patients on treatment but rather the general effect of ART on CD4 changes especially among treatment naïve patients (Mocroft *et al.*, 2007; Trotta *et al.*, 2010; Haines *et al.*, 2014). However, a study in Ethiopia reported that TDF-based regimens were better than AZT-based in terms of CD4 count improvement (Awoke *et al.*, 2016). Conversely, a study reported that difference in ARV regimens has no effect on the CD4 count changes of patients (Smith *et al.*, 2004).

Previous study in Usmanu Danfodiyo University Teaching Hospital, Sokoto showed that more than 87 % of the patients are managed with TDF + XTC + EFZ, Zidovudine (AZT) + Lamivudine (3TC) + NVP and TDF + XTC + Lopinavir/ritonavir (LPV/r) ARV regimens (Biambo *et al.*, 2018). Hence this study evaluated the rate of changes in CD4 counts of the patients on the three regimens.

METHODOLOGY

Study Setting

This study was carried out at Usmanu Danfodiyo University Teaching Hospital (UDUTH), Sokoto in 2015. The hospital is a tertiary health facility located in Sokoto State, North-western Nigeria. It offers health services to residents of the State and serves as a referral centre for neighbouring states including Niger, Kebbi and Zamfara. Comprehensive HIV management and care services are offered in the hospital's HIV Clinic, including Highly Active Antiretroviral Therapy (HAART).

Study Design

A retrospective analysis of patients' records between 2011 and 2015 which were selected using systematic random sampling was conducted. A minimum of 351 patients' folders were estimated to be sufficient in representing the population of PLWHA in the facility (about 4000 patients) at 5% error margin and 95% confidence interval using Raosoft® sample size calculator (Raosoft, 2004).

Inclusion and Exclusion Criteria

Records of adult patients aged 18 years or older, diagnosed with HIV/AIDS and being managed with the most prescribed first line regimens in the facility (AZT+3TC+NVP or TDF+XTC+EFZ) or the most prescribed second line regimen (TDF+XTC+LPV/r) (Biambo *et al.*, 2018) for at least 2 years were used. Also, the patients must have done CD4 count tests at least twice a year for at least two consecutive years within the years reviewed. Patients that were lost to follow-up and those whose adherence to ART was documented to be <95% were excluded from the study.

Data Collection Instrument

A structured data collection form was designed to capture patients' sociodemographic and clinical characteristics. The form also captured ART and CD4 count records of patients over the years reviewed.

Data Collection

The data were collected between May and November 2015. Folders of patients that visited the clinic within each week were used. Every other folder that met the inclusion criteria was sampled and evaluated. A total of 423 patients' folders were used. For each folder, patient's sociodemographic and clinical characteristics were collected. Also, data of patients' ART and the corresponding CD4 counts over the succeeding year (if the ART regimen remains the same) were collected. Only ART and CD4 count data that were documented within 5-yerars (2011 to 2015) were used.

Data Analysis

The collected data were coded and entered into Statistical Product and Service Solutions (SPSS) version 20.0 for analysis. Descriptive statistics was used to analyse the sociodemographic and clinical characteristics of the patients.

For each patient's record, the average CD4 count in each year was computed. The CD4 count of the earliest year was considered as baseline. The difference between the mean baseline CD4 counts of patients on each ARV regimen were analysed using one-way ANOVA (Post Hoc) at $p<0.05$. For the subsequent years, the percentage change in the CD4 count with respect to the baseline was also computed.

Using the existing literatures, patients' CD4 count was classified for further analysis. Most literatures considered CD4 count as low when it is ≤200 cells/mm^3 (CDC, 2018) against ≤350 cells/mm^3 in other literatures (WHO, 2016). Normal CD4 count is mostly considered at ≥500cells/mm^3(CDC, 2018). Thus, the baseline CD4 count of patients evaluated in this study was classified into three categories: Low (≤300 cells/mm^3), Moderate (>300 to 500 cells/mm^3) and High (>500 cells/mm^3). Annual percentage changes in CD4 count of patients based on their ARV regimen and CD4 count category was predicted using linear regression models at $p<0.05$. Patients' clinical characteristics associated with or predicting annual percentage CD4 changes were analysed using Pearson bivariate correlation and linear regression at $p<0.05$.

RESULTS

Sociodemographic and clinical characteristics of the patients

The result of this study shows that majority of the 423 patients evaluated were married (56.7%), belongs to female gender (75.4%) and they predominantly had no formal education (32.2%). They mostly belong to WHO clinical stage 1 of the disease (60.3%). See Table 1. Their average age, body weight, numbers of years since HIV diagnosis were 37.1±9.1 years, 65.8±15.2 kg and 6.6±2.6 years respectively.

Frequency and baseline CD4 cell count of patients on each regimen

About 84.4% of the patients in the facility were managed with AZT + 3TC + NVP regimen (Table 2). The average baseline CD4 count of the patients was 491.5 ± 249.9 cells/mm^3. One-way ANOVA (Post Hoc) revealed that the average baseline CD4 count of the patients on AZT + 3TC + NVP and TDF+XTC+EFZ regimens were statistically the same (p = 0.570). However, patients on TDF + XTC + LPV/r had significantly lower reading compared to others (p = 0.009).

Annual percentage change in CD4 cell counts of the patients

Pearson bivariate correlation analysis shows that years of HIV diagnosis (- 0.165, p=0.001), number of years on ART (- 0.170, p=0.001), number of years on the current ARV regimen (- 0.159, p=0.001) and baseline CD4 count (- 0.358, p=0.000) were all negatively associated with annual percentage increase in CD4 count of the patients in the facility at $p<0.05$. A linear regression model at $p<0.01$ shows that for every year a patient spent on a particular ARV regimen, the expected percentage change in the CD4 count is significantly reduced by 5.3%.

The result also revealed that difference in ARV regimen along with baseline CD4 count also determines the prediction of annual percentage change in CD4 count (Table 3). Using linear regression analysis at $p<0.05$, patients with CD4 cell counts ≤300 cells/mm^3 had the best percentage annual change in CD4 count. Among these patients, the percentage CD4 count of patients on TDF + XTC + EFZ, AZT + 3TC + NVP and TDF + XTC + LPV/r regimens was found to significantly increase annually by 41.1%, 16.9% and 4.9% respectively. Varied levels of increase were observed with CD4 cell counts >300 to 500 cells/mm^{3}patients, while those with above 500 cells/mm^{3}had reduction in their CD4 counts.

Table 1: Sociodemographic and HIV-related clinical characteristics of the patients (n=423)

Variables	Frequency (%)
Gender	
Female	319 (75.4)
Male	104 (24.6)
Level of education	
No formal education	136 (32.2)
Primary education	83 (19.6)
Secondary education	94 (22.2)
Post-secondary education	110 (26.0)
**Marital status*	
Married	236 (56.7)
Widowed	83 (20.0)
Single	69 (16.6)
Separated	28 (6.7)
**Occupation*	
Self employed	174 (55.9)
Employee	79 (25.4)
Student	52 (16.7)
Retired	6 (1.9)
Current WHO clinical stage	
Stage 1	255 (60.3)
Stage 2	166 (39.2)
Stage 3	2 (0.5)
	Mean ± SD
Age of the patients (years)	37.1 ± 9.1
Current body weight (kg)	65.8 ± 15.2
Years of HIV Diagnosis	6.6 ± 2.6
Number of Years on ART	6.1 ± 2.5
Number of Years on the Current ART Regimen	5.3 ± 2.0

* Values do not sum up to the total because of missing values.

Table 2: Frequency and baseline CD4 count of patients on each regimen (n=423)

Regimen	n (%)	Baseline CD4 count ($\bar{x}$±SD)
AZT+3TC+NVP	357 (84.4)	501.1 ± 258.3*
TDF+XTC+EFZ	45 (10.6)	478.8 ± 199.7*
TDF+XTC+LPV/r	21 (5.0)	355.3 ± 143.6**
Overall	423 (100.0)	491.5 ± 249.9

*No significant difference between their means using one-way ANOVA at $p<0.05$; **Mean baseline CD4 of patients in this regimen was significantly lower than that of other regimens using one-way ANOVA at $p<0.05$; AZT=Zidovudine; 3TC=Lamivudine; NVP=Nevirapine; XTC=Emtricitabine or Lamivudine; LPV/r=Lopinavir/ritonavir

Table 3: Linear regression models predicting the annual percentage CD4 increase of patients on different antiretroviral regimens and belonging to different CD4 count category

Antiretroviral Regimens	*Patients with CD4 cell counts ≤300 cells/mm^3*		*Patients with CD4 cell counts >300-500 cells/mm^3*		*Patients with CD4 cell counts >500 cells/mm^3*	
	Constant	Annual CD4 Increase (%)	Constant	Annual CD4 Increase (%)	Constant	Annual CD4 Increase (%)
AZT+3TC+NVP	117.3	16.9*	106.0	4.5*	100.8	-0.9
TDF+XTC+EFZ	118.2	41.1*	103.0	1.3	99.5	-3.7
TDF+XTC+LPV/r	106.7	4.9	100.8	2.9	105.3	-1.2

*the predicted annual % CD4 counts increase (beta coefficient) is significant at $p<0.05$; AZT=Zidovudine; 3TC=Lamivudine; NVP=Nevirapine; XTC=Emtricitabine or Lamivudine; LPV/r=Lopinavir/ritonavir; Constant = predicted constant of linear regression equation.

DISCUSSION

This study showed that majority of the patients were married and had no formal education. This is a reflection of the prevalence of the disease among married couples and people with low level of education. This shows the need for special and intensive patients' education by caregivers in this facility in order to ensure health literacy despite their educational level and reduce the epidemic of the disease in the study area. Furthermore, it was observed that three out of four patients were female. This is consistent with the 2017 global HIV statistics of UNAIDS where in sub-Saharan Africa, three in four new infections were among girls aged 15–19 years (UNAIDS, 2018b). This finding could be because females are more prone to risk factors of being infected with HIV virus than their male counterparts. About sixty percent of the patients evaluated were in clinical stage 1 of the disease which is good. However, the fact that the remaining patients were at best in stage 2 could be a warning sign of progression of the disease in this population and the need for optimising ART.

The baseline CD4 counts of the patients was moderate. Since the study did not evaluate treatment naïve patients, exact effect of ART in improving the CD4 count of the patients to this level cannot be known. However, studies have shown that up to 100 cells/mm^3 improvement in CD4 count can be achieved within the first year of ART initiation (Mocroft *et al.*, 2007) and the lower the baseline, the higher the observable change in CD4 count (Smith *et al.*, 2004).

In this study, the baseline CD4 counts of patients on TDF + XTC + EFZ and AZT + 3TC + NVP regimens were found to be statistically the same. This finding allows comparison of the effect of each regimen on CD4 count change over the succeeding years. The baseline CD4 count of patients on TDF + XTC + LPV/r regimen was significantly lower than that of other regimens. This could be due to the fact that it is a second line regimen whereby only patients that failed the other regimens (virologic and/or immunologic failure) were initiated on this regimen.

Annual percentage CD4 count change of the patients was found to be negatively affected by years of HIV diagnosis, on ART, and on the current ARV regimen. This could be a reflection of the effect of chronic disease states like HIV infection on the patients. The longer a patient stays with a disease or on treatment especially in infectious disease like HIV, a lot of factors can significantly affect the outcome of the ongoing treatment negatively. Some of those factors include resistance development by the virus, addictive toxicity of the medications, tolerance of the body system to the treatment and psychological effect of living with the virus (Trotta *et al.*, 2010; Cortez & Maldarelli, 2011; Shubber *et al.*, 2013).

The findings of this study also showed that the higher the patients' baseline CD4 count, the lower their annual percentage increase would be. The predicted annual percentage increase in CD4 count was higher among patients with low CD4 count (≤300 cells/mm^3), low among patients with moderate CD4 count (>300 to 500 cells/mm^3) and negative among patients with high CD4 count (>500 cells/mm^3). Some studies reported similar findings (Smith *et al.*, 2004; Mocroft *et al.*, 2007). This suggests that patients' increase in CD4 count is targeted towards 500 cells/mm^3 which is the lower limit of the normal range. The rate of increase in the CD4 count is increased if patient's baseline is much lower than 500 cells/mm^3. This could explain why patients with baseline higher than 500 cells/mm^3 tend to experience negative percentage change which could be towards maintaining the CD4 count at 500 cells/mm^3 for most patients.

Patients on TDF + XTC + EFZ regimen had the best annual percentage increase in CD4 count compared to those on AZT + 3TC + NVP and TDF +XTC +LPV/r when the baseline is ≤300 cells/mm^3. The superiority of TDF + XTC + EFZ regimen in terms of clinical and humanistic outcomes has been demonstrated in many studies (Amoroso *et al.*, 2012; Awoke *et al.*, 2016; Biambo *et al.*, 2018). This could be part of the reason for its recommendation as the preferred regimen by WHO (WHO, 2016). This finding could be useful to clinicians in predicting patient's CD4 count and also for possible utilisation in reviewing existing policies.

Patients on AZT + 3TC + NVP appeared to have better percentage annual increase when the CD4 count is moderate and high (>300 cells/mm^3). However, the predicted percentage CD4 change was significant only at moderate CD4 count. Further evaluation of patients with moderate and high CD4 could give an additional information for comparing AZT + 3TC + NVP with TDF + XTC + EFZ regimens.

Patients managed with TDF+XTC+LPV/r regimen did not experience significant change in annual percentage CD4 count in all the categories of baselines CD4 count (low, moderate or high). This is despite the fact that the patients are expected to have an advantage over patients on other regimens in terms of CD4 increase. This this could be attributed to the fact that the patients had significantly lower baseline CD4 count which is associated with higher annual increase. The poor percentage increase in the CD4 count could be due to the fact that only patients that fail the first line regimens are initiated in second line regimen. Hence, the patients probably have some

resistant strains of the virus which made them respond poorly to treatment. However, the little percentage increase experienced by patients could be clinically significant, despite not being statistically significant (McGlothlin & Lewis, 2014).

The limitation of this study is that it is retrospective. Prospective study could give a better control of the study participants and improve the efficiency of data collection.

CONCLUSION

Patients with low CD4 counts experienced high annual percentage increase. At CD4 count >500 cells/mm^{3}patients experienced no annual increase. Among patients with CD4 count≤300 cells/mm^3, those on TDF + XTC + EFZ regimen had the highest annual percentage increase in CD4 count. Patients on AZT + 3TC + NVP had slightly higher increase when the CD4count is>300 cells/mm^3. Patients on TDF + XTC + LPV/r regimen did not show significant annual increase at any class of CD4 count. This finding should be utilised in therapeutic decision and monitoring as well as policy review which will ultimately improve patients' outcomes.

Ethical approval

The ethical approval for this study was obtained from the Hospitals' Ethics Committee (UDUTH/HREC/2014/No.279). All data collected were handled confidentially.

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