African Journal of Pharmacology and Therapeutics Vol. 6 No. 3 Pages 142-148, 2017
Open Access to full text available at http://www.uonbi.ac.ke/journals/kesobap/

Research Article

Socio-demographic and treatment-related variables associated with CD4 cell counts in Kenyan HIV patients on second-line regimens

Richard Kagia [a,b,*], Margaret Oluka [a], Faith Okalebo [a], and Anne Njoroge [c]

[a] *Department of Pharmacology and Pharmacognosy, School of Pharmacy, University of Nairobi, Kenya*
[b] *Department of Pharmacology, Mount Kenya University, Thika, Kenya*
[c] *Kenyatta National Hospital, Nairobi, Kenya*

* **Corresponding author**: Department of Pharmacology and Pharmacognosy, School of Pharmacy, University of Nairobi, P.O. Box 19676-00202 , Nairobi, Kenya; **Tel:** +254-70-4407405; **Email**: richkagz@gmail.com

Background: CD4 cell response in patients on second-line therapy has not been evaluated in Kenya. Patients failing second-line are changed to third-line, however, the drugs used for third-line are expensive and unavailable. Therefore, early identification of potential poor responders to treatment would lead to early intervention and thus improve therapy of patients on second-line.

Objectives: To identify socio-demographic and treatment related variables that affect CD4 response of HIV-positive patients on second-line regimens in Kenyatta National Hospital (KNH).

Methods: A historical cohort study carried out at KNH between January and April 2016 and entailed collection of patient data from the files. The main outcome variable was CD4 cell count. The predictor variables of interest were sex, age, education level, and ART regimens.

Results: All the study participants were on a lopinavir-based regimen. The study involved 84 study participants, 59.5% female study participants and 40.5% male. Male patients had significantly lower baseline CD4 cell counts and lower CD4 cell counts at ART (antiretroviral therapy) switch to second line compared to female patients. Efavirenz-based regimens were significantly associated with low CD4 cell count at ART switch to second-line.

Conclusion: Patients should be started on nevirapine-based regimens unless contraindicated.

Keywords: CD4 cell count, ART switch, second-line

Received: April, 2017
Published: August, 2017

1. Introduction

In sub-Saharan Africa, 24.7 million people were living with HIV in 2013 and there were 1.2 million AIDS-related deaths in 2012 (UNAIDS, 2013). In Kenya, 1.6 million people were estimated to be living with HIV in 2013 and 1.5 million in 2015. The HIV prevalence in Kenya among people aged 15-49 was 6% in 2013 and 5.9% in 2015. Prevalence was higher in women compared to men; in women the prevalence was 7.6% while in men it was 5.6% (NASCOP, 2014b).

The Kenyan Guidelines on Management of HIV in 2016 recommend that all individuals with confirmed HIV infection are eligible for ART provided that they are willing and ready to take and adhere to ART. Patients on ART are routinely followed up. CD4 cell count determination is done during initiation and every six months especially where viral load testing is not available. Viral load determination is done after 6 and 12 months of initiating therapy and thereafter annually (NASCOP, 2014). According to the Kenya ART Guidelines 2016, patients who experienced treatment failure were to be changed to second line regimen.

The recommended second-line ART regimens for adults are tenofovir (TDF) or zidovudine (AZT) + lamivudine (3TC) + atazanavir/ritonavir (ATV/r) or lopinavir/ritonavir (LPV/r). In cases of second-line ART regimen failure, the options for third-line are limited but include integrase inhibitors like raltegravir, new-generation NNRTIs like etravirine, protease inhibitors like darunavir and recycling of drugs that confer benefit like lamivudine and tenofovir (NASCOP, 2011). Initiation of third line regimen is based on HIV drug resistance patterns (NASCOP, 2014a).

Adherence to ART is critical in determining the immunological response. Patients who adhere to ART are more likely to have higher CD4 cell count compared to those who do not (Abrogoua et al., 2012). In a study done in Ethiopia, advanced clinical stage, anemia, low body weight, and lack of co-trimoxazole prophylaxis were predictors of mortality in HIV patients. In the same study, sex was not a predictor of mortality (Alemu and Sebastián, 2010).

Another study in Ethiopia indicated that WHO Stage III/IV of HIV disease or a higher CD4 cell count at baseline were risks for immunological failure (Yirdaw and Hattingh, 2015). In a study in South Africa, variables that significantly affected immunological response were older age and CD4 cell count at initiation of ART while body mass index, baseline haemoglobin, sex, concurrent TB co-infection and ART regimen did not affect immunological response significantly (Julg et al., 2012). A study in Ethiopia concluded that low baseline CD4 cell count, old age and higher educational status were associated with reduced CD4 cell count leading to immunological treatment failure (Teshome and Assefa, 2014). A study done in Western Kenya also found out that baseline CD4 cell count, age and use of stavudine were important predictors at change to second-line therapy (Inzaule et al., 2014).

Nutritional supplements taken with ART improve immune response in HIV –positive patients (Evans et al., 2013). Alcohol abuse leads to lower CD4 cell counts (Iralu et al., 2010). Patient's age, smoking, use of illicit drugs, hospital treatment, changing doctors and the use of ART affects the CD4 cell count (Montarroyos et al., 2014). Low CD4 cell counts were associated with high incidence of anaemia, lymphopenia and thrombocytopenia (Parinitha and Kulkarni, 2012). Psychosocial variables like depression and singlehood can affect adherence and hence affect CD4 cell count and eventually treatment response (Langford et al., 2007). Genetic variables may also affect immunological response(Coloccini et al., 2014; Zhu et al., 2013).

CD4 cell count is a key indicator of HIV disease progression (Langford et al., 2007). Patients with a low CD4 cell count normally have a greater risk of diseases (Pinzone, Di Rosa, Cacopardo, and Nunnari, 2012). CD4 cell response is also important in monitoring the success of antiretroviral therapy (Montarroyos et al., 2014). Low CD4 cell count is associated with mortality in patients on ART (Odafe et al., 2012). Therefore, CD4 cell count is a key predictor of treatment failure.

CD4 cell response in patients on second-line therapy has not been evaluated in Kenya. This study sought to identify socio-demographic and treatment related variables that affect CD4 response of HIV-positive patients on lopinavir-based regimens in Kenyatta National Hospital. It is hoped that identification of these variables will lead to early identification of potential poor responders to treatment leading to early intervention to improve therapy.

2. Methods

2.1 Study design, site and population

The design was a retrospective cohort study and entailed collection of patient data recorded in patient files from the time of initiation of therapy. The study was conducted at the Comprehensive Care Centre (CCC) of the Kenyatta National Hospital, which is the largest teaching and referral hospital in Kenya and East and Central Africa, with a diverse inter-ethnic population of patients. The study population consisted of HIV patients on any lopinavir-based second-line ART regimen who were seen at the KNH CCC between January 2016 and April 2016.

2.2 Inclusion and Exclusion criteria

The patients included in the study were HIV infected patients on any lopinavir-based second-line ART, at least 6 months of second-line ART, aged above 18 years, of either sex and gave informed consent to participate in the study. The patients excluded from the study were those who declined to give consent, were on second-line ART for less than 6 months and aged below 18 years.

2.3 Sample size

The expected main outcome of interest is change of CD4 levels. Consequently the Twisk (2003) formula for estimation of sample size of a continuous outcome variable in a cohort study was used.

The sample size needed to make a 0.3 difference in a continuous outcome variable statistically significant on a 5% level with a power of 80% with different within-subject association coefficients (ρ) of 0.5 and four repeated measurements was 59. To accommodate for expected missing files or incomplete data entries, the calculated sample size was inflated by 20%. Therefore, a minimum sample size of 71 participants was targeted.

2.4 Data collection

Data was abstracted from the patient files using a data collection tool. Demographic data collected included sex, age, body mass index, marital status, occupation, education and ethnicity. Clinical data collected included first line ART regimen and duration, second line ART regimen and duration, WHO staging, CD4 cell count at different time points, viral load, adherence, haemoglobin, ALT (Alanine transaminase) and creatinine levels.

2.5 Variables and outcomes

The main outcome variable in this study was CD4 cell count. The predictor variables of interest were sex, ethnicity, age, education level, ART regimens, body mass index and duration of therapy.

2.6 Data analysis

All variables were subjected to descriptive data analysis. Shapiro-Wilk test was used to determine if the continuous variables were normally distributed. Mean and standard deviation were used to summarize variables that were normally distributed and those that were not normally distributed were expressed as the median and inter- quartile range.

Multi-linear regression was then conducted to identify variables associated with baseline CD4 count (CD4 cell count at initiation of ART), CD4 count at ART switch from first-line to second-line and CD4 cell count at recruitment to the study. Generalized linear modelling with adjustment for clustering within the patients was done to identify the variables associated with rate of change of CD4 cell count. Manual forward stepwise model building was then done in all regression analyses. Data analysis was conducted using STATA version 10 software. The level of significance was set at 0.05.

2.7 Ethical considerations

Permission to conduct the study was granted by the KNH/UoN Research and Ethics committee (Ref: **KNH-ERC/A/499**). The letter that granted ethical approval is attached in Appendix C. The nature of the study was fully disclosed to the participants. Patients provided informed consent to participate in the study and data collected was handled with confidentiality

Table 1: Baseline socio-demographic and clinical characteristics

Variables	n (%) or Median [IQR]
Sex	
Male	34 (40.5)
Female	50 (59.5)
Age At diagnosis in years	36 [32 – 44]
Weight at diagnosis (kg)	61 [54.2 – 71.2]
Height at diagnosis (cm)	165 [158 – 171]
BMI at HAART initiation	
< 18.5	5 (6.0)
18.5 - 24.9	34 (40.5)
> 24.9	18 (21.4)
Missing values	27 (32.1)
Ethnolinguistic Groups	
Bantu	53 (63.1)
Nilotes	30 (35.7)
Cushites	1 (1.2)
Education level	
Primary level and below	13 (19.7)
Secondary level	37 (56.1)
Above tertiary level	16 (24.2)
Regimens at initiation of HAART	
TDF + 3TC + NVP	19 (22.6)
AZT + 3TC + NVP	11 (13.1)
AZT + 3TC + EFV	20 (23.8)
d4T + 3TC + NVP	15 (17.9)
d4T + 3TC + EFV	8 (9.5)
TDF + 3TC + EFV	9 (10.7)
d4T + DDI + EFV	2 (2.4)
First-line Duration of therapy	2 [0 – 5]
Second-line Duration of therapy	4 [2 – 6]
ALT at HAART initiation	23 [16 – 44]
Normal (≤ 40U/L)	22 (26.2)
Elevated (> 40U/L)	11 (13.1)
Missing values	51 (60.7)
Creatinine Levels	79. 5 [64.5 – 93]
Normal (≤ 120µmol/l)	32 (38.1)
Elevated (>120µmol/l)	4 (4.8)
Missing values	48 (57.1)
CD4 Cell Counts X 10^9L at diagnosis	88 [19 – 284]
≤ 200	49 (58.3)
> 200	19 (22.6)
Missing values	16 (19.1)

3. Results

All the study participants were on a lopinavir-based regimen. The study involved 84 study participants, 52 (61.9%) were on TDF + 3TC + Lopinavir/ritonavir (LPV/r) while 25 (29.8%) were on AZT + 3TC + LPV/r and 7 (8.3%) were on Abacavir (ABC) + 3TC + LPV/r. They were on second-line antiretroviral therapy since they had experienced either immunological failure or virological failure on first line therapy. The first line regimens that the study participants had previously used are presented in **Table 1**.

There were 50 (59.5) female study participants and 34 (40.5) male. The median age was 36 years [interquartile range (IQR) 32 – 44]. The median baseline body weight was 61 [IQR 54.2 – 71.2]. There were 5 (6.0%) patients with a baseline body mass index (BMI) of less than 18.5 while 34 (40.5%) had normal BMI. Only 16 (24.2%) study participants had tertiary education and above.

The median of duration of therapy during first line ART treatment was 2 years [IQR 0 – 5] while that during second line was 4years [IQR 2 – 6]. The median creatinine levels at HAART initiation was 79. 5 [IQR 64.5 – 93] while the median ALT levels was 23 [IQR 16 – 44]. A summary of the baseline characteristics is presented in **Table 1**.

Longitudinal changes of CD4 cell counts

The baseline, CD4 cell counts at switch and at recruitment are presented in **Table 2**. The median CD4 cell counts increased from baseline to treatment switch and at recruitment. At all three time points, younger patients below 40 years and females had higher median CD4 cell counts compared to their counterparts. Patients who had been on TDF+3TC+EFV had the lowest median CD4 cell counts at ART switch while those on AZT+3TC+NVP and D4T+3TC+NVP had the highest median CD4 cell counts. Study participants on AZT + 3TC + LPV/r had the highest CD4 cell counts at recruitment followed by those on TDF + 3TC +LPV/r. The participants on ABC + 3TC + LPV/r had the lowest CD4 cell counts at recruitment.

Table 2: CD4 cell counts at Baseline, ART switch and at recruitment attained in the study population

Patient Characteristics	Baseline CD4 cell counts, median [IQR]	CD4 cell counts at ART switch, median [IQR]	Current CD4 levels attained, median [IQR]
Sex			
Male	57.5 [15 – 254]	173.5 [56 – 294.5]	340 [221-441]
Female	131 [33-445.5]	374 [179.5-491]	554 [334-722]
Age			
≤ 40	115 [30-288]	303 [173-473]	437 [485-608]
> 40	88 [11-254]	189.5 [85-414]	358 [244-619.5]
BMI at initiation			
Underweight(< 18.5)	4 [2-132]		340 [296-374]
Elevated (18.5 - 24.9)	69 [19-288]		470 [309-617]
Overweight or Obese (> 24.9)	94 [30-180]		419.5 [164-514]
First-line regimens			
TDF+3TC+NVP	-	329 [167.5-444]	366 [297-441]
AZT+3TC+NVP	-	464 [313-606]	514 [346-781]
AZT+3TC+EFV	-	134 [70-222]	689 [689-689]
D4T+3TC+NVP	-	473.5 [197-706]	150 [32-245]
D4T+3TC+EFV	-	270 [218-365]	597.5 [400-722]
TDF+3TC+EFV	-	9 [6-42]	440.5 [374.5-655.5]
D4T+DDI+EFV	-	254 [254-254]	420 [253.5-574]
Current Regimens			
ABC + 3TC + LPV/r	-	-	243 [150-554]
AZT + 3TC + LPV/r	-	-	497.5 [114.5-683.5]
TDF + 3TC + LPV/r	-	-	414 [305-617]

Variables associated with baseline CD4 cell counts

In order to transform the CD4 cell counts to be normally distributed, the log baseline CD4 cell counts were generated. On univariable analysis, the variables associated with baseline CD4 cell counts were baseline creatinine and weight. On multivariable analysis, baseline creatinine ($p<0.01$) was the most important predictor for CD4 response at baseline and it remained significant even after adjusting for confounding by weight, body mass index, age, ALT, sex and WHO staging. Increased creatinine levels by one unit led to decreased baseline log CD4 levels by 0.004 units (-0.006, -0.003).

Variables associated with CD4 cell counts at ART switch to second line

In order to transform the CD4 cell counts to be normally distributed, the square root of the CD4 cell counts were generated. When univariable analysis was done, the study participants with low baseline weight and lower education level were significantly associated with higher square root of CD4 cell count at ART switch.

Those on efavirenz-based regimens had lower square root of CD4 count at ART switch compared to those on nevirapine-based regimens. Female study participants had higher square root of CD4 cell counts compared to the male study participants.

On adjusting for confounding, TDF+3TC+EFV ($p<0.01$), sex ($p<0.03$), weight ($p<0.05$) and baseline CD4 cell count ($p<0.02$) had a significant association with square root of CD4 cell counts at ART switch to second-line. Patients who had been on TDF+3TC+EFV had lower square root of CD4 cell count compared to other regimens by 8.887 units. An increase of weight by one kilogram resulted to a decrease of square root of CD4 cell count by 0.145 units. On the other hand, an increase in baseline CD4 cell count by one unit led to an increase in square root of CD4 cell count at change of therapy by 0.012 units. Females had a significantly higher square root of CD4 cell count at ART switch compared to males by 4.201 units.

Variables associated with rate of change of the CD4 cell counts

The logarithm of the CD4 cell counts was obtained and regressed against covariates using generalized linear modelling. On univariate analysis, the variables that were significant were sex, education level above tertiary, baseline creatinine, CD4 count at ART switch and first-line regimen. On multivariable analysis, sex ($p<0.01$), education level above tertiary ($p<0.01$), TDF+3TC+EFV ($p<0.01$) and an interaction between duration and education level still had a significant association with rate of change of CD4 cell count ($p<0.01$).

In order to improve the interpretation of the findings of generalized linear regression analysis, predictive plots were generated for each of the variables that were significant.

Effect of Education on rate of change of CD4 cell count

From generalized linear modelling, education affected the rate of change because the interaction between duration and education above tertiary level was statistically significant. The study participants who had tertiary education had lower CD4 cell counts at time of treatment switch but a higher rate of change of log CD4 cell counts while the study participants who did not have tertiary education had a higher CD4 cell counts at ART switch but a lower rate of change of log CD4 cell counts. This is illustrated in **Figure 1**.

Effect of Sex on rate of change of CD4 cell count

Females had consistently higher log CD4 cell counts compared to males. However, males had a slightly higher rate of change of log CD4 cell count compared to females as illustrated in **Figure 2**.

Effect of first-line regimen on rate of change of CD4 cell count

In order to control for the effect of education, two different plots of the rate of change of CD4 cell counts vs first line regimen were generated; the first for participants without tertiary education and the second for those with tertiary education. Patients who had been on TDF+3TC+EFV had consistently lower CD4 cell counts after ART switch than those who had been on other regimens. However, they had a higher rate of change of CD4 compared to those who had been on other regimens as illustrated in **Figure 3**.

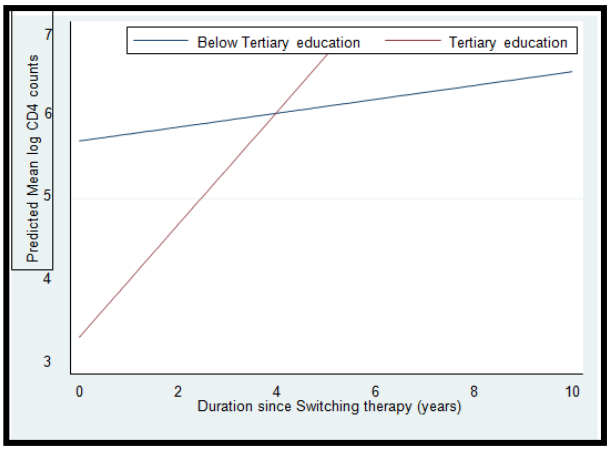

Figure 1: Effect of education on rate of change of CD4 cell count

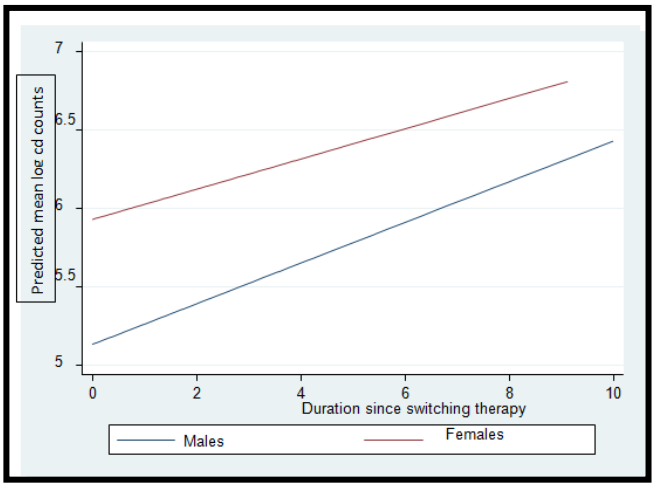

Figure 2: Effect of Sex on rate of change of CD4 cell count

Variables associated with CD4 cell counts at recruitment to the study

In order to transform the CD4 cell counts to be normally distributed, the square root of CD4 cell counts were generated. Square root of CD4 cell count at recruitment to the study was computed and regressed against various covariates. On univariate analysis, higher baseline weight, higher baseline creatinine levels, those with high education level and those on ABC+3TC+LPV/r were significantly associated with lower square root of CD4 cell counts at recruitment. Low CD4 cell counts at ART switch and low baseline WHO stage were significantly associated with low square roots of CD4 cell counts at recruitment. Females had a higher CD4 cell count at recruitment to the study compared to males.

On multivariable analysis, CD4 cell count at ART switch ($p<0.05$), education level ($p<0.03$) and baseline WHO stage ($p<0.03$) were important predictors of CD4 cell counts at recruitment. Participants with higher education level had lower CD4 cell count at recruitment while those who had a higher CD4 cell count at ART switch to second-line had a higher CD4 cell count at recruitment to the study. In addition, participants with a higher WHO stage at initiation of ART had a higher CD4 cell count at recruitment.

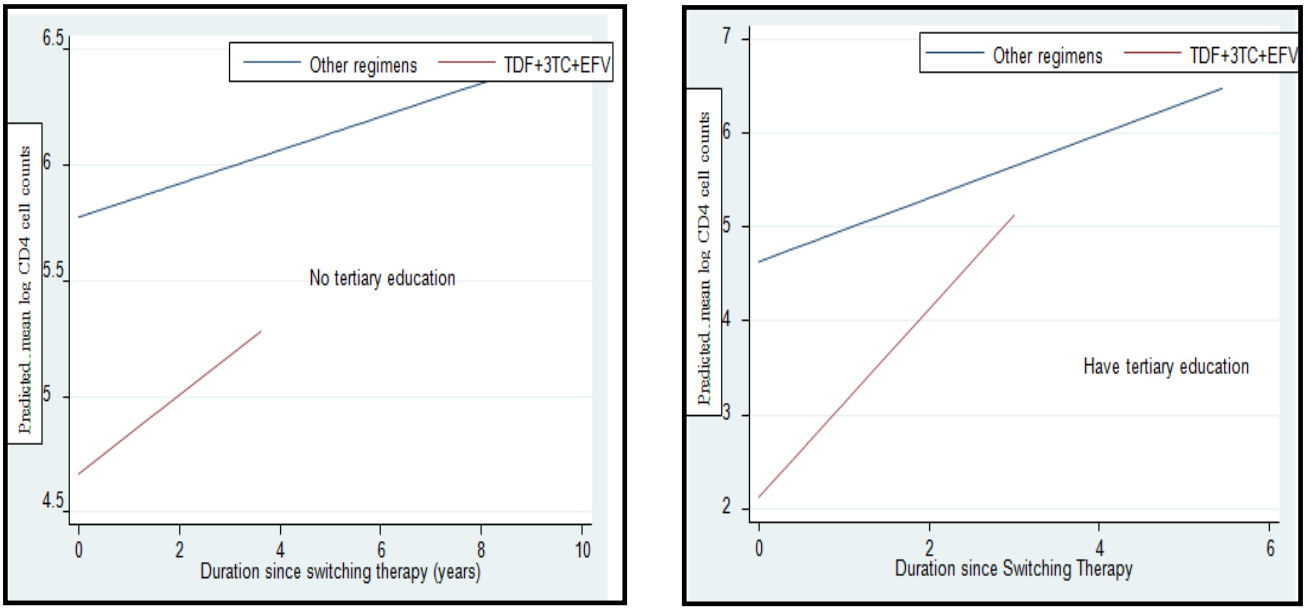

Figure 3: Difference in the rate of change in log CD4 counts of patients on TDF+3TC+EFV and other regimens

4.0 Discussion

Male study participants had lower baseline CD4 cell counts compared to female study participants. However, this was not statistically significant. A study done among Kenyan study participants found out that males had lower baseline CD4 cell counts and this was statistically significant, probably because the study had a larger sample size (Angima, 2015).

Female study participants had higher CD4 cell counts compared to male study participants at change to second-line antiretroviral therapy. A study done in Nigeria reported that males were more likely to be associated with loss to follow up (Odafe et al., 2012). This suggests that males are more likely to have poor adherence and this may lead to decline in CD4 cell response. Another study done in Burkina Faso indicated that men were strongly associated with virologic failure probably due to poor adherence (Penot et al., 2014). These studies were an indication that men were more likely to have poor adherence and this could explain their low CD4 cell count at ART switch.

Efavirenz-based regimens especially TDF+3TC+EFV were significantly associated with low CD4 cell count at ART switch compared to nevirapine-based regimens. Patients who had been on TDF+3TC+EFV still had significantly lower CD4 cell counts compared to those who had been on other regimens even after change of therapy from first-line to second-line. However, a study done in Uganda indicated that nevirapine was more likely to be associated with treatment failure than efavirenz (Sebunya et al., 2013). These findings suggest that current treatment guidelines need to be critically reviewed with regard to selection of NVP viz a viz EFV based regimens. The available scientific literature on the comparative effectiveness of these agents needs to be critically reviewed so as to guide treatment selection.

There was no statistically significant association between the second-line ART regimens and the Cd4 cell count at recruitment to the study in this study. This was in agreement with a study done in Ghana which did not find any significant association between CD4 cell count and type of ART regimen (Barry et al., 2013).

Baseline CD4 cell count significantly affected CD4 cell count at ART switch in this study. This was in agreement with a study done in Western Kenya which also found out that baseline CD4 cell count was an important predictor at change of therapy to second-line therapy (Inzaule et al., 2014). Another study done in South Africa also found out that baseline CD4 cell counts were determinants for recovery (Julg et al., 2012). A study in Ethiopia concluded that low baseline CD4 cell count was associated with immunological failure hence reduced CD4 cell count at ART switch (Teshome and Assefa, 2014).

Study participants with tertiary education and above had consistently lower CD4 cell counts than those without tertiary education. This is probably because they went to the hospital late as they tried to self-medicate or they were more likely to be in denial of their HIV status. A study in Ethiopia concluded that higher education was associated with reduced CD4 cell count leading to immunological treatment failure (Teshome and Assefa, 2014). However, study participants with tertiary education and above had a higher rate of change of CD4 cell count after ART switch compared to those without tertiary education. This is probably because they were more likely to understand the impact of treatment failure and hence they would

have improved adherence. This would have led to a higher rate of change of CD4 cell count.

In this study, there was no significant association between age and CD4 cell response. This is probably because this cohort was of patients who had already failed first-line regimen and thus younger patients were more likely to have still been using first-line regimens. This was unlike a study done in South Africa which reported a significant association between old age and severe CD4 cell count decline (Julg et al., 2012). A study in Ethiopia concluded that old age was associated with reduced CD4 cell count leading to immunological treatment failure (Teshome and Assefa, 2014). Other studies have also shown an association between age and rate of change of CD4 cell count (Montarroyos et al., 2014).

5.0 Conclusion

Male patients had significantly lower CD4 cell counts at baseline and at ART switch compared to female patients. Patients who had been on efavirenz-based regimens especially TDF+3TC+EFV were significantly associated with low CD4 cell count at ART switch compared to nevirapine-based regimens. In addition, Study participants with tertiary education and above had consistently lower CD4 cell counts compared to those without tertiary education. However, they had a higher rate of change of CD4 cell count after ART switch compared to those without tertiary education.

Patients should be started on nevirapine-based regimens unless contraindicated since participants on efavirenz-based regimens had systematically lower CD4 cell counts even after switching therapy to second-line. However, larger studies need to be done to compare the effectiveness of these two drugs. In addition, effort should be made to improve adherence among male patients.

Conflict of Interest declaration

The authors declare no conflict of interest.

References

Abrogoua DP, Brou JK, Boua ATK, Gilles A, Konan N, and Christian Z (2012). Assessment of the impact of adherence and other predictors during HAART on various CD4 cell responses in resource-limited settings. *Patient Prefer Adherence.* **6**:227–237.

Alemu AW, and Miguel SS (2010). Determinants of survival in adult HIV patients on antiretroviral therapy in Oromiyaa, Ethiopia. *Glob. Health Action.* **3**:1–10.

Barry O, Powell J, Renner L, Bonney EY, Prin M, Ampofo W, Kusah J, Goka B, Sagoe KWC, Shabanova V and Paintsil E (2013). Effectiveness of first-line antiretroviral therapy and correlates of longitudinal changes in CD4 and viral load among HIV-infected children in Ghana. *BMC Infect. Dis*. **13**:476

Coloccini RS , Dilernia D, Ghiglione Y, Turk G, Laufern N, Rubio A, SocíasME., Figueroa MI, Sued O, Cahn P, Salomón H, Mangano A and Pando MA (2014). Host Genetic Factors Associated with Symptomatic Primary HIV Infection and Disease Progression among Argentinean Seroconverters. *PLoS One.* **9**:e113146.

Evans D, McNamara L, Maskew M, Selibas K, van Amsterdam D, Baines N, Webster T and Sanne I (2013). Impact of nutritional supplementation on immune response, body mass index and bioelectrical impedance in HIV-positive patients starting antiretroviral therapy. *J. Nutr*. **12**:111.

Inzaule S, Otieno J, Kalyango J, Nafisa L, Kabugo C, Nalusiba J, Kwaro D, Zeh C and Karamagi C (2014). Incidence and Predictors of First Line Antiretroviral Regimen Modification in Western Kenya. *PLoS One*. **9**:e93106

Iralu J, Duran B, Pearson CR, Jiang Y, Foley K, and Harrison M (2010). Risk Factors for HIV Disease Progression in a Rural Southwest American Indian Population. *Public Health Reports*, **125**(Suppl 4):43–50.

Julg B, Poole D, Ghebremichael M, Castilla C, Altfeld M, Sunpath H, Murphy RA and Walker BD (2012). Factors predicting discordant virological and immunological responses to antiretroviral therapy in HIV-1 clade C infected zulu/xhosa in South Africa. *PLoS One*. **7**:7–11.

Langford SE, Ananworanich J, and Cooper DA (2007). Predictors of disease progression in HIV infection: a review. *AIDS Res. Ther.* **4**:11.

Montarroyos UR, Miranda-Filho DB, César CC, Souza WV, Lacerda HR, Albuquerque MDF, Aguiar MF and Ximenes RAD (2014). Factors related to changes in CD4+ T-cell counts over time in patients living with HIV/AIDS: A multilevel analysis. *PLoS One.* **9**:e84276.

NASCOP (2011). Guidelines for antiretroviral therapy in adults. Ministry of Medical Services, Kenya.

NASCOP (2014a). Guidelines on use of Antiretroviral Drugs. Ministry of Health, Kenya.

NASCOP (2014b). Kenya HIV Estimates 2014.

Odafe S, Idoko O, Badru T, Aiyenigba B, Suzuki C, Khamofu H, Onyekwena O, Okechukwu E, Torpey K and Chabikuli ON (2012). Patients' demographic and clinical characteristics and level of care associated with lost to follow-up and mortality in adult patients on first-line ART in Nigerian hospitals. *J. Int. AIDS Soc.* **15**:1–9.

Parinitha SS, and Kulkarni MH (2012). Haematological changes in HIV infection with correlation to CD4 cell count. *Australas. Med. J.* **5**:157–162.

Pinzone MR, Di Rosa M, Cacopardo B, and Nunnari G (2012). HIV RNA suppression and immune restoration: Can we do better? *Clin. Dev. Immunol*. Article ID 515962.

Teshome W and Assefa A (2014). Predictors of Immunological Failure of Antiretroviral Therapy among HIV Infected Patients in Ethiopia: A Matched Case-Control Study. *PLoS One. 9*: e115125.

UNAIDS (2013). Global Report.

Yirdaw KD and Hattingh S (2015). Prevalence and Predictors of Immunological Failure among HIV Patients on HAART in Southern Ethiopia. *Plos One.* **10**:e0125826.

Zhu P, Zhu Q, Zhang Y, Ma X, Li Z, Li J , Chen J, Luo L, Ring HZ, Ring BZ and Su L (2013). ABCB1 Variation and Treatment Response in AIDS Patients: Initial Results of the Henan Cohort. *PLoS One*. **8**: e55197.