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ORIGINAL RESEARCH

Aerobic-exercise training effects on immunological markers in individuals on highly active antiretroviral therapy in Uganda

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Abstract

There is critical relevance in understanding the multidisciplinary management of HIV/AIDs among individuals obtaining health services in Uganda. The purpose of the study was therefore to assess the effects of aerobic exercise training on immunological markers as a clinical outcome of Human Immunodeficiency Virus positive clients attending a chronic HIV clinic at a General Military Hospital-Bombo. A pre-post experimental design was used to understand differences between the experimental and control groups. Participants were Human Immunodeficiency Virus positive clients who had been on treatment that is, Highly Active Antiretroviral Therapy for at least 12 months. They were randomly assigned to either a control group (Group 1): who did not participate in the aerobic exercise, or an experimental group (Group 2): where a 12-week moderate intensity aerobic exercise, for not less than 3 times a week, and for at least 45 minutes per session was administered. Both groups were assessed using a physical activity readiness questionnaire. Thereafter, assessment of the clinical outcomes that is, immunological measures using Clusters of differentiation 4 were assessed. While the experimental group participated in the exercise, the control group members were followed up during the 12 weeks to ensure that they remained in the study. After the 12 weeks post-test was done. The findings of this study revealed that aerobic exercises significantly increased Clusters of differentiation 4 count in both males and females by 29.7% on average ($p<0.001$). Aerobic exercise is therefore likely to increase quality of life, reduce mobility and mortality rates in Human Immunodeficiency Virus positive clients on Highly active antiretroviral therapy.

Introduction

The decline of infections of Human immunodeficiency virus (HIV) among people in many countries including Uganda would signal a success in mitigating and ending the Acquired Immune Deficiency Syndrome (AIDS). Notably, there have been significant changes in the quality of human life since AIDS was first declared in humans in 1981 in Uganda (UNAIDS, 2023). HIV causes the sickness by slowly affecting a human body and depriving it of its immunity as it destroys Clusters of Differentiation 4 (CD4) cells which are critical to the immune system (Vithalani & Herreros-Villanueva, 2018). In 2022, Uganda had the approximate of 1.6 million people living with HIV/AIDS compared to the 40 million people living with HIV/AIDS. Among Key priorities in the elimination of HIV/AIDS is the goal of reducing the burden, involves providing life-long person centered services among those at most risk of HIV (USSPEPFAR, 2022).

Key immunological markers in individuals living with HIV/AIDS include the CD4+ count and the T-lymphocytes. Recently, scientific breakthroughs leading to the Anti-Retroviral Therapy (ART) such as the Highly Active Antiretroviral Therapy (HAART) has reduced hospitalization rates, lowered mortality, and generally improved the quality of life of patients (Bopp et al., 2003). A number of negative side effects such as nausea, pain, anxiety, sadness, decreased job functional ability and low energy are, however, linked to this treatment (Lu et al., 2021). The treatment also involves regular hospital visits mainly when one has

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opportunistic infections characterized by low CD4 count and high viral load.

Aerobic exercise, which according to Okechukwu et al. (2022) a low- to moderate-intensity physical activity that uses oxygen in the metabolic processes that produce energy, is currently being explored as a means of dealing with symptoms, complications, and unwanted side effects that reduce the quality of life for chronic HIV infection (McIntyre et al., 2020). Based on studies from both healthy individuals and patients with various chronic illnesses, aerobic exercise may be a helpful treatment for a variety of ART side effects and symptoms O'Brien et al. (2016). The exercise therapy should start as soon as possible after an HIV infection diagnosis so as to delay the onset of symptoms, lessen the severity of symptoms, and delay the progression of the disease and the subsequent onset of Non-Communicable Diseases (NCDs) (O'Brien et al., 2016).

Other benefits according to Nystoriak & Bhatnagar (2018) include several health benefits, such as strengthening muscles, improving circulation efficiency by strengthening heart muscle, and reducing blood pressure. In a study on the use of aerobic exercise in Nigeria, the quality of life and CD4 in HIV sero-positives was established to have improved by 36.9% (Ezema et al., 2014). Research also revealed that exercise increased CD4 counts in HIV patients receiving ART by 107.5% (Maduagwu et al., 2017). People Living with HIV (PLHIV) on ART get a greater increase in CD4 cell counts with appropriate exercises compared to non-exercising counterparts (Dang et al., 2018). However, despite several recommendations, casual observation indicates that clinicians in Uganda have not emphasized the use of aerobic exercise for PLHIV. This is partly due to a scarcity of scientific evidence to guide the utilization of aerobic exercise therapy to improve the quality of life of PLHIV during the course of treatment. This study addressed this gap in knowledge by investigating the implications of aerobic exercise on clinical outcomes for HIV positive clients in Uganda.

In HIV management, the key clinical outcomes that show client improvement or deterioration include immunological measures, functional work capacity, psychosocial markers etc (Vajpayee & Mohan, 2011). Immunological markers of HIV disease include cellular concentration of CD4+ and CD8+ T-lymphocytes, total lymphocyte count and immune activation measures obtained using proliferation assays, cytokine measurement, surface antigen expression, and cytotoxicity (Lu et al., 2021). This study determined how a 12-week aerobic exercise programme affected the CD4+ of PLHIV on ART in Uganda.

Methods

A pre-post-test experimental design with a control group was employed. The participants were selected purposively and randomly allocated to the two groups experimental and control. This was used as is widely used in medical informatics field (Harris et al., 2006). While unlike the randomized experimental design has a high level of control over the variables, this design was considered appropriate in this case as one cannot assign participants randomly due to ethical or practical constraints such as HIV positive clients incurring costs to come to the facility daily for exercises.

The inclusion criteria required that study participants should have been on HIV chronic care treatment for 12 months or more, be adults, and volunteering to participate in the exercise. Clients who were newly enrolled in care, those who were symptomatic, and those with exercise intolerance were excluded from the study. This study design consists of studying the experimental and control samples at two different points in time in order to establish change in a phenomenon or variables in order to establish the impact of an intervention (Estrada & Pardo, 2019). This design provided an opportunity for the variables to be measured at the start of the study and after subjecting the experimental group to a 12-weeks' aerobic exercise.

All groups were subjected to a pre-assessment of their CD4. As much as the experimental group underwent the aerobic exercise and the control group did not, the latter were followed up periodically to ensure that they remained in the study. At the end of the study, each study group was reassessed to track the changes over the intervention period. This provided an opportunity to determine the clinical effects of aerobic exercise on immunological markers.

Target Population

HIV-positive patients receiving HIV care in Uganda, a case study of General Military Hospital was selected. These were adult men and women who had received care for a minimum of 12 months and formed the majority of the 4150 clients that were receiving ART treatment at GMH according to District Health Information System two (DHIS2) 2019.

Sampling Procedure

The participants were purposively sampled on the basis of their duration on treatment, and absence of signs and

symptoms that would not allow them to take part in exercise. According to Odiya (2009), purposive sampling is used when participants possess characteristics being sought for, or because they are the only ones in their respective categories. Considering the stigma associated with HIV infection, time, and associated travel costs, volunteerism approach was used to generate the sample size. In a related study Maduagwu et al. (2017) used the same method to evaluate the effects of aerobic exercise on CD4 cell counts and quality of life in HIV-positive individuals in Nigeria. After health education sessions that were conducted for about six months,135 volunteers expressed willingness to participate in this study. Subjecting this number to the Yemen's formula, the sample size was determined as follows:

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

N: Population size; n: Sample size; e: Margin of error.

Out of the 135 participants who were involved in the study, the sample size was computed to be 99 participants.

Research Instruments

The Point of Care (POC) CD4 analyser (Pima machine) was used to provide real time CD4 cells count that helped in determining the immunological measures for the study participants. This analyser was accredited by the WHO for such analyses in 2016 (Pham, et al., 2016). Quality assurance tests were conducted as per the MoH requirement during data collection and all the results were satisfactory. Alere PIMA, the CD4 machine that was utilized, had a repeatability of 175.6 cells/ml and a coefficient of variability of 10.3%. It was revealed to have a sensitivity of 89.6% and a specificity of 86.7% in individuals five years of age and older when compared to the FACS Calibur TM at a cut off of 350 cells/ml (Kw = 0.7566).

Data Collection Procedure

The intervention aerobic exercises included on sport brisk walking, jogging and aerobic dance at moderate intensity with a music tempo of 120 to 150 beats per minute. The participants chose time to attend the exercise session themselves, knowing that they would have time, determined how they were grouped. At least three times a week, each subject attended under supervision of the research team. All sessions included 5 minutes of warm up followed by stretching, not less than 25 minutes of exercising (aerobic dance), as well as 5 minutes of relaxation activities to cool down. All types of exercise training were done according to the ACSM guidelines (Colberg, et. al. 2016). A venous blood sample of three (3) milliliters was obtained in K3 EDTA vacutainers. Using a lancet finger stick, a capillary blood sample was taken from the fingertip. To obtain adequate capillary blood flow, a blade-style lancet punctured the skin at a depth of 1.8 mm. Using an Aleles PIMA CD4 analyser, the venous or finger prick samples were examined in the laboratory, and the centre retained the test results.

Data Analysis

Data were analyzed using two tailed sample t-test to compare the means for two different samples namely experimental and control group. A p-value ≤ 0.05 was considered statistically significant. All analysis was performed using the Statistical Package for Social Sciences (SPSS) version 20.0.

Results

Out of a total of 135 participants who had voluntarily accepted and qualified to take part in the study were randomly allocated in the experimental and control groups each taking 67 participants. A total of 18 participants dropped out from the experiment group and 18 were selected randomly from the control group and dropped for easy statistical comparison. This gave an attrition rate of 27% which was good enough for the experimental study Meyer et al., (2022). It is indicated that a response rate of 70% and above is acceptable.

Demographic Information of Participants

The background information in terms of sex, age, marital status, and education of the participants is as summarized in Table 1.

Table 1 shows that the majority (67.3%) of participants in the experimental group were males while the females constituted 32.7%. Similarly, for the control group the males constituted 71.4% and the females 28.6%. This is a fair reflection of the members of the study population (clients attending the ART Clinic at Bombo Military Hospital) where the males are slightly above 2,490 (>60%) and female are slightly below 1,660 (<40%).

Table 1
Demographic information of participants.

Variables	Parameters	Experimental Group		Control Group		Total	
		n	%	n	%	n	%
Gender	Male	33	33.7	35	35.7	68	69.4
	Female	16	16.3	14	14.3	30	30.6
	Total	49	50.0	49	50.0	98	100.0
Age (years)	20-27	3	3.1	1	1.0	4	4.1
	28-37	12	12.2	15	15.3	27	27.6
	38-47	33	33.7	25	25.5	58	59.2
	48-57	1	1.0	8	8.2	9	9.2
	Total	49	50.0	49	50.0	98	100.0
Marital status	Married	30	30.6	38	38.8	68	69.4
	Single	12	12.2	5	5.1	17	17.3
	Divorced	6	6.1	6	6.1	12	12.2
	Widowed	1	1.0	0	0.0	1	1.0
	Total	49	50.0	49	50.0	98	100.0
Education	Primary	17	17.3	13	13.3	30	30.6
	Secondary	22	22.4	28	28.6	50	51.0
	Tertiary	10	10.2	8	8.2	18	18.4
	Others	0	0.0	0	0.0	0	0.0
	Total	49	50.0	49	50.0	98	100.0

Table 2
Changes in CD4 count**.**

Groups	Parameters	Post-test CD4 count	Pre-test CD4 count	Change in CD4	% Change in CD4 count
Experimental Group	Female	679.2	490.1	189.1	38.6
	Male	658	500.6	157.4	21.4
	Mean	644.9	497.2	147.7	29.7%
	SD	177.381	185.921		
Control Group	Female	435.9	485.6	-49.7	-10.2
	Male	413.1	425	-11.9	-2.8
	Mean	438.35	468.27	-29.9	-6.4%
	SD	178.990	221.575		

The results also show that majority of the participants were between the age of 38-47 years although those in experimental group had a slightly higher number (67.3%) compared to 51% in the control group. The least number of participants (2%) who participated in the survey from the two categories were in different age groups, the experimental groups were in the age bracket of 48-57 years and control group were in the age bracket of 20-27 years. The majority of participants in the control group (77.6%) and experimental group (61.2%) were married. This is in line with Pettee et al. (2006) who established that, married men and women unlike those who were single reported higher median levels of exercise participation than singles.

Effect of Aerobic Exercises on Immunological Measures of HIV+ Clients on ART

For both groups, the CD4 cell counts were determined twice, at the beginning (pre-test) and at the end of the intervention (post-test). The pre- and post-test CD4 cell count differences as considered to be due to the aerobic exercise were as presented in Table 2.

On average there was an increase of the mean CD4 count of the experimental group by 147.7 points while that of the control group seems to have slightly dropped by 29.9 points.

In terms of the CD4 count, the results show that there is a general difference in the patterns of the experimental group compared to the control group. The variance graph (Figure 1) show that was established to be far lower in the case of the control group compared to the experimental group implying that there was a marked improvement of the CD4 levels of the experimental group the variation is shown in Figure 1.

The inferential analysis was conducted by testing the study hypothesis which stated that "There is no significant effect of aerobic exercises on immunological measures of HIV positive clients on ART". This was done by conduction a paired-samples t-test. The outputs of this test comprised of three tables as shown below. The first one is the Paired samples statistics; the second is the paired samples correlations; and the third is the Paired sample test results.

The results of the experimental group show a significant difference between the mean of the post-test to the pre-test of 167.78 (664.94 - 497.16) compared to that of the control group of only -35.59 (438.35 - 473.94). The standard deviations of the results of the two groups are not exactly the same but are relatively close to assuming equal variances. This large variation in standard deviation implies a big variation in the results given within a sample. The paired samples correlation results were as presented in Table 4.

Table 4 results on pre-test and post-test CD4 counts in both the experimental and control groups were found to be correlated. This indicates that there is linear relationship between the pre-test and post results in that, the post-test CD4 reading for any given subject was related to what the corresponding pre-test reading was. Next it was important to establish whether the calculated sample mean falls into the confidence interval. The results for this are as presented in Table 5.

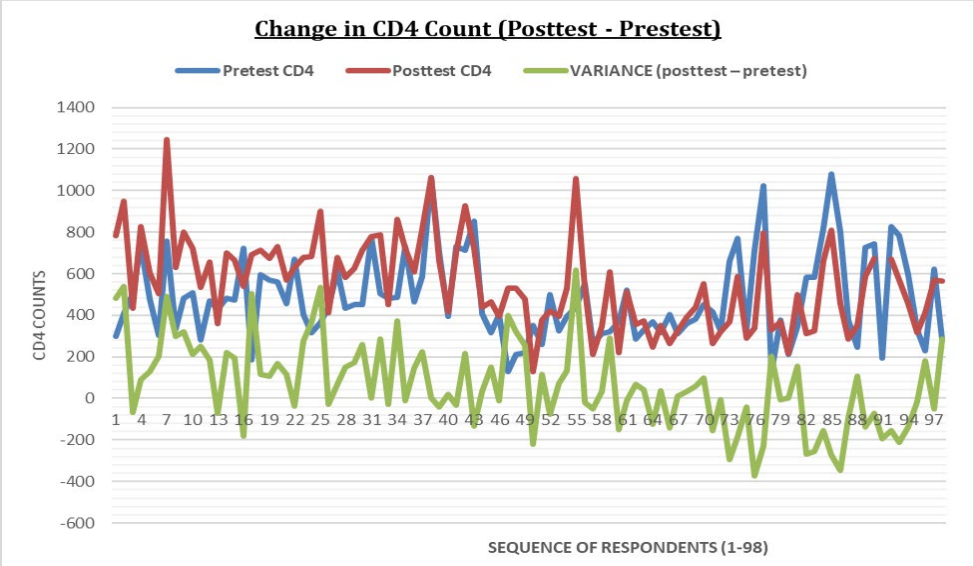

Figure 1. Changes in CD4 counts.

Table 3

CD4 counts according to the groups.

Groups	Tests	Mean	SD	SEM
Experimental Group	Pre-Test CD4 Count c/ml	497.16	185.921	26.560
	Post-Test CD4 Count c/ml	664.94	177.381	25.340
Control Group	Pre-Test CD4 Count c/ml	473.94	220.295	31.797
	Post-Test CD4 Count c/ml	438.35	178.990	25.835

Table 4
Correlation of the CD4 counts in the groups.

	Groups	Correlation	Sig.
Post-Test & Pre-Test CD4 Count	Experimental Group	.507	<0.0010
	Control Group	.595	<0.001

Table 5
Pretest - posttest comparison of CD4 counts.

Groups	Paired Differences		t	df	p
	Mean	SD			
Experimental Group	167.776	180.614	6.502	48	<0.001
Control Group	-35.583	183.444	-1.344	47	0.185

The calculated mean of the experimental group was 167.776 while the 95% confidence interval of the difference ranged from 115.897 to 219.654. This shows that the calculated mean indeed falls within the confidence interval. The calculated mean for the control group was equally within the 95% confidence interval considering that it was -35.583 and the interval ranged from -88.850 to 17.683.

The t-test of the experimental group was established to be statistically significant as the p-value of <0.001 is less than 0.05. The results are: $t(48) = 6.502$, $p < 0.001$. The t-test of the control group was, however, not statistically significant as the results were: $t(47) = 1.433$, $p = .185$ which is > 0.05. Considering that the p-value of the experimental group in this case was <.001 which was less than the alpha level (0.05) since a 5% level of significance was considered in this test, the null hypothesis that, "There is no significant effect of aerobic exercises on immunological measures of HIV positive clients on ART", is rejected. It was observed that the percentage change in CD4 count for the experimental group was 29.7% against -6.4% for the control group.

Discussions

In terms of percentages as shown in Table 2, the experimental group recorded a 29.7% increase in the CD4 count after the aerobic exercises while the control group reported a slight decline of 6.4%. Since the higher the level of CD4 count the higher is considered to be the level of immunity and good clinical outcomes, it follows that the aerobic exercises in this study had a positive effect on the immunity of the participants. This was supported by Maduagwu et al. (2017) who established that CD4 counts were 107.5% higher in HIV-positive individuals who self-reported exercising than in those who did exercise.

As highlighted by Asogwa et al. (2022), PLHIV on ART may be able to get a greater impact on their CD4 counts with appropriate exercise compared to those not taking ART. These results were consistent with a meta-analysis of primary studies that found a significant improvement in CD4 counts in the exercise group that were on ART. When the percentage change in CD4 count between the two groups was compared by gender, it was found that the female experimental participants' change was substantially higher (38.6%) than the female control group participants' change (-10.2%). Similarly, the males in the experimental group participants were substantially higher (21.4%) than those in the control groups (-2.8%).

The results imply that moderate intensity aerobic exercises have a positive implication on immunological markers for HIV positive clients on ART on both males and females. This was justified by the fact that there was an improvement in CD4 levels and that improves the quality of life of HIV positive clients on ART. These findings are consistent with a meta-analysis of primary studies that demonstrated improved CD4 counts after engaging in interval exercise for 41 to 50 minutes three times a week. The results imply that individuals living with HIV who are on ART might benefit more from appropriate exercise in terms of their CD4 counts than those who are not on ART (Asogwa et al., 2022).

The findings of this study were also consistent with those of Sujianto (2021) whose study revealed a statistically significant difference in the mean CD4 counts between the intervention group and the control group following the intervention, indicating that aerobic exercise is a useful strategy for raising CD4

counts in HIV patients. They concur with Heissel et al. (2019) findings as well, which show that a four-week aerobic exercise program can raise CD4 cell counts in HIV/AIDS patients. In a similar vein, the results of this investigation corroborate those of Heissel et al. (2019) study, which demonstrated that a four-week aerobic exercise regimen can raise an HV/AIDS patient's CD4 cell count. It was also mentioned that the results of this study are consistent with those of Stanley et al. (2017), who found that a significant increase in CD4 cell counts was observed in the experimental group after 12 weeks of moderate-intensity aerobic exercise. The study examined the effects of exercise on quality of life and CD4 cells in the HIV population. Further to the above, the results of this study agree with those of Dianatinasab et al. (2018) and of Nosrat et al. (2017) that there was a significant difference in CD4 cell count after the aerobic exercise.

On the contrary, the results of this study, were different from those of O'Brien et al. (2016) who as much as in their study acknowledged that exercise is a key strategy that may improve or sustain health for people living with HIV, instead found no significant differences in the change in the CD4 cell count and viral load of the HIV positive clients that were subjected to exercise. These results suggest that it is not any kind of exercise that is conducted anyhow that will have the positive results but that which is well organized, timed and well scheduled.

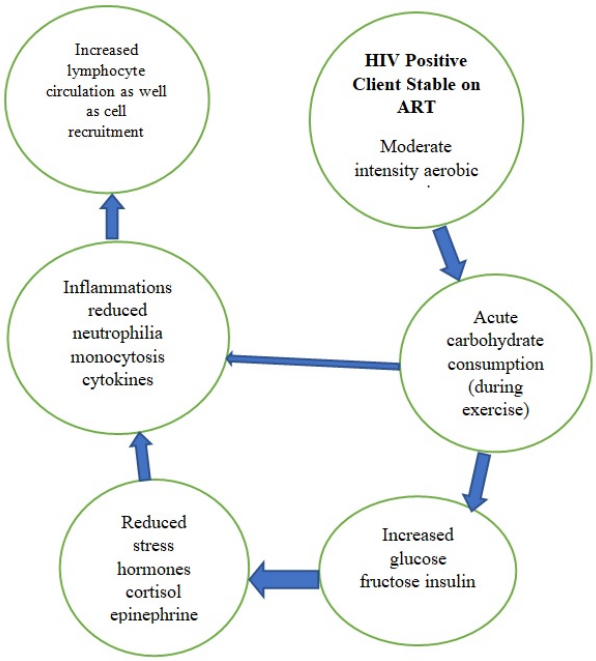

Figure 2. The link between aerobic exercise and body immunity.

Figure 2 showing the link between aerobic exercise and improving body immunity. Adopted with modification from, (Nieman & wentz 2019; da Silveira et al., 2021).

Conclusion

This study established that a well-structured supervised 12 weeks' moderate intensity aerobic exercises at a temple of 120-150 beats per minute improves CD4 cell in the body of HIV positive clients on ART. Such an exercise is very important to improve the clinical outcomes of PLHIV on ART.

Authors' Contribution

Study Design: MN, CANN, EO, MM; Data Collection: MN; Statistical Analysis: MM; Manuscript Preparation: MN, CANN, EO, MM.

Ethical Approval

The Study was approved by the Lacor Hospital Institutional Research and Ethical Committee (No 0183/07/2020) and was carried out in accordance with the Code of Ethics of the World Medical Association also known as a declaration of Helsinki. And thereafter it was approved by Uganda National Council for Science and Technology (Ref: HS 1276ES).

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Conflict of Interest

The authors hereby declare that there was no conflict of interest in conducting this study.

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