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Full Length Research Paper

Short-term combined exercise training improves the health of HIV-infected patients

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This study tested the benefits of combined aerobic and resistance exercise training (CARET) in HIV-infected individuals receiving antiretroviral therapy. Twenty-three human immunodeficiency virus (HIV)-infected men and women, predominantly of lower socioeconomic status (SES), were randomly assigned and completed 12 weeks of: (a) standard medical treatment plus CARET or (b) standard medical treatment only. At baseline and follow-up, immune functioning, metabolic variables, quality of life (QoL), physical characteristics, and physical fitness were measured. The control group showed a significant decrease in CD4+ T cell count (-16%, p<0.05), whereas the exercise group maintained a more stable count after the intervention (-3%, p=0.39). Furthermore, exercise participants showed significant improvements in waist circumference (-2%, p<0.05), fasting glucose (-16%, p<0.05), physical (+11%, p<0.03) and mental (+10%, p<0.02) QoL, estimated VO_{2max} (+21%, p<0.01), upper body strength (+15%, p<0.05), and lower body strength (+22%, p<0.05). Our 12-week, supervised, moderate-intensity CARET program resulted in more stable CD4 count and significant health improvements in HIV-infected individuals of lower SES.

Key words: Antiretroviral therapy, aerobic and resistance exercise training, immune functioning, quality of life.

INTRODUCTION

Each year, close to 50,000 Americans acquire human immunodeficiency virus (HIV), and recent reports indicate that Miami-Dade County, Florida has one of the highest number of new HIV cases in the country (Bureau of HIV/AIDS, 2011). Furthermore, women constitute the fastest growing group of new HIV/Acquired Immune Deficiency Syndrome (AIDS) diagnoses (Bokazhanova and Rutherford, 2006), and all groups that have a disproportionate lack of accessibility to health care, such as African Americans and Hispanics, have also been disproportionately affected by HIV/Acquired Immune Deficiency Syndrome (AIDS) (Fernandez et al., 2002). Today's standard of care of HIV-infected individuals is focused more on long-term adverse effects related to both infection and pharmacological treatment. However, despite the clear benefits, the previously unknown adverse effects of antiretroviral therapy (ART) have been

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emerging, representing a major health concern for this patient population.

Common but often mild undesirable effects of ART include disorders of the gastrointestinal tract (bloating, nausea, and diarrhea), nervous system (headache, pain/neuropathy, and fatigue), and integumentary system (rash and dry skin). Lipodystrophy, a visible condition characterized by abnormalities in the body's production, utilization, and distribution of fat can lead to increased risk for cardiovascular disease (CVD) and diabetes mellitus. Other serious but less prevalent adverse effects may include anemia, renal, liver, and mitochondrial toxicity, lactic acidosis, and osteopenia/osteoporosis (Calmy et al., 2007). In addition to adverse physical effects, patients receiving ART may also experience negative psychological responses such as agitation, confusion, anxiety, nightmares, mania, and depression (Horwath, 2011). Finally, these physical and psychological adverse reactions to ART may result in poor adherence to the treatment, which requires daily dosing at the appropriate times for the remainder of the patient's life. Ultimately, low adherence rates can cause drug resistance and consequently compromise a patient's immunity (Dieffenbach and Fauci, 2011).

Previous research has examined the impact of different forms of therapeutic exercise in HIV-infected individuals with aerobic exercise training representing the most widely used type of intervention. The research suggests that this patient population can achieve significant physical and psychological benefits from aerobic exercise after 12 weeks of moderate intensity training performed three times a week (Terry et al., 2006). More specifically, the benefits of any type of exercise in HIV-infected individuals may include improvements in body composition, functional capacity, muscular strength, lipid profile, cognitive function, depression, anxiety, and quality of life (QoL) (Bopp et al., 2003; Thoni et al., 2002; Yarasheski et al., 2011; Souza et al., 2008).

Given the rising prevalence and cost of lipodystrophy and metabolic consequences of ART and HIV itself, additional investigation of exercise training is justified. We examined the effect of a 12-week program of combined aerobic and resistance exercise training (CARET) on immune functioning, metabolic variables, QoL, physical characteristics, and physical fitness in a sample of persons with HIV on stable ART. The results of the study are intended to promote the use of CARET and its effects on our outcome variables of interest, leading to additional lines of research to address the multi-faceted problems of persons living with HIV.

MATERIALS AND METHODS

This study was a two-group, randomized controlled trial with assessments at two time points: (a) baseline or week 0 (±2 days; PRE) and (b) at the end of or during week 12 (±2 days; POST). Eligibility criteria included: (a) confirmed HIV infection with CD4+ T cell count ≥350 cells/mm^3, (b) men or women ≥18 years of age, (c) stable ART treatment in which therapy changes were not planned during the intervention, (d) a sedentary lifestyle, that is, failing to complete 30 min of exercise at least three times a week, as defined by American College of Sports Medicine (ACSM, 2006), and (e) a commitment to three weekly supervised exercise sessions for 12 weeks. Exclusion criteria included: (a) current opportunistic infection(s), (b) pregnancy, (c) use of lipid-lowering, insulin sensitizing, or hypoglycemic drugs, anabolic steroids, and/or growth hormone, or (d) any other medical condition or situation precluding adherence to and completion of the protocol.

The Institutional Review Board for human subjects at the University of Miami approved the study and its procedures. Potential participants (n=62) were recruited from the HIV Adult Outpatient Clinic at the University of Miami/Jackson Memorial Medical Center (UM/JMMC) and other local infectious disease clinics in Miami-Dade County between December, 2010 and August, 2011. Twenty-five participants failed the screening inclusion/exclusion criteria or they were eligible but never enrolled. Finally, 37 participants signed informed consent and Health Insurance Portability and Accountability Act (HIPAA) forms and enrolled in the study at baseline.

Subjects in the exercise (EX) group participated in a 12-week CARET intervention, consisting of three individual exercise sessions per week (Monday, Wednesday, and Friday) for a total of 36 sessions (Table 1). All sessions were 45 to 60 min long and contained different elements on various days: (1) endurance sessions utilizing a stationary treadmill or bicycle ergometer, (2) core exercises (back extension and abdominal crunches), and (3) ten strengthening exercises (leg press, leg extension, leg curl, chest press, lat pull, shoulder press, seated row, triceps press, biceps curl, and chest fly) consisting of one to three sets of 10 to 20 repetitions, performed on stacked-weight machines. All sessions were supervised by the study investigators. The control (CON) group did not participate in any supervised exercise as part of their 12 weeks in the study. CON participants were telephoned bi-weekly to maintain contact and promote their interest in the study.

The assessment protocol conducted at PRE and POST included: (a) immune functioning (CD4+ T cell count, CD4+/CD8+ ratio, HIV-RNA viral load), (b) metabolic variables (fasting glucose [FG] and lipids), (c) QoL (SF-36 Health Survey), (d) physical characteristics (body weight, body mass index [BMI], waist circumference [WAIST], and blood pressure), and (e) physical fitness (estimated VO_{2max} and one-repetition maximum [1RM] for upper and lower body strength).

Immune functioning

The number of CD4+ T lymphocytes was measured by flow cytometry (BD FACSCount, Bergen, NJ) using monoclonal antibodies, and plasma HIV-RNA was measured by the NASBA Nuclisens method (COBAS AmpliScreen, Roche, Quebec, Canada) with the lower limit of detection at 20 copies per milliliter.

Metabolic variables

Ten milliliters of venous blood were taken from the antecubital vein following an overnight fast of 10 to 12 h. Plasma glucose was measured by the glucose hexokinase method, and plasma levels of total cholesterol (T-Chol) and triglycerides (TG) were measured by enzymatic procedures. High-density lipoprotein cholesterol (HDL-C) was measured by selective inhibition and low-density lipoprotein cholesterol (LDL-C) was calculated by the Friedwald equation:

$$\text{LDL-C} = \text{T-Chol} - (\text{HDL-C} - 0.20 \times \text{TG}).$$

Table 1. Timeline for the combined aerobic and resistance exercise training (CARET) program.

Stage	Week	Session (week)	Type of exercise	Duration (min)	Intensity
Phase-in	0-2	3	Aerobic/Core/ Resistance	15-20/5-10 15-20	60% of HR_{max}/1RM
Step 1	3-6	1	Aerobic/Resistance	20-25/20-25	65% of HR_{max}/1RM
		1	Aerobic/Core	40-45/5-10	
		1	Aerobic/Resistance	5-10/40-45	
Step 2	7-9	1	Aerobic/Resistance	25-30/25-30	70% of HR_{max}/1RM
		1	Aerobic/Core	45-50/5-10	
		1	Aerobic/Resistance	5-10/45-50	
Step 3	10-12	1	Aerobic/Resistance	25-30/25-30	75% of HR_{max}/1RM
		1	Aerobic/Core	45-50/5-10	
		1	Aerobic/Resistance	5-10/45-50	

Very low-density lipoprotein cholesterol (VLDL-C) levels were calculated as the TG level divided by five, unless TG exceeded 400 mg/dl in which case VLDL-C was measured by enzymatic methods (Vitros 750 Analyzer, Johnson & Johnson, New York, NY).

QoL

QoL was assessed by the SF-36 Health Survey, which consists of 36 questions and evaluates eight scales: (a) physical functioning, (b) social functioning, (c) bodily pain, (d) general health perception, (e) vitality, (f) limitations due to emotional problems, (g) limitations due to physical health problems and (h) mental health. Each scale is scored 1 to 100, where a low score indicates perceived poor health and a high score represents perceived good health. Furthermore, the SF-36 is a generic measure that does not target a specific age, disease, or treatment group.

Physical characteristics

Weight and height were recorded to the nearest 0.1 kg and 0.1 cm, respectively, to calculate BMI. WAIST was measured in inches at the narrowest circumference halfway between the lowest rib and the iliac crest. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured to the nearest even digit by use of a random-zero sphygmomanometer (Mabis, IL, USA). Three readings were made with the subjects seated after they had rested for 5 min. The average of the second and third readings was used in the analysis.

Physical fitness

Submaximal testing for cardiorespiratory fitness was performed on a treadmill (Lifestyle Fitness 95T, Chicago, IL) using the Asymptomatic Cardiac Ischemia Pilot protocol. The subjects warmed up at 2 mph after which time of speed and/or incline were gradually increased until they reached 85% of age-predicted maximum heart rate. Heart rate was monitored with a chest-band transmitter and wristwatch display (Polar FT2, New York, NY). Each subject's treadmill time, speed, and incline were recorded, and estimated VO_{2max} was predicted from the following formula (Tamesis et al., 1993):

Estimated VO_{2max} (ml/kg/min) = (mph × 2.68) + (1.8 × 26.82 × mph × grade/100) + 3.5.

The protocol for 1RM testing followed the same American College of Sports Medicine (ACSM) guidelines (Hagerstwon, 2005) to determine maximum strength progress from a resistance training program from PRE to POST. More specifically, upper and lower body strength was assessed by chest press and leg press, respectively (Lifestyle Fitness, Chicago, IL). The subjects warmed up by completing a maximum of four trials of 10, 8, 6, and 3 repetitions with a rest period up to 4 min between trials. The initial weight was selected within the subject's perceived capacity (50 to 70% capacity), and resistance was progressively increased until the subject reached his/her maximum. The final maximum weight lifted successfully one time was recorded as the 1RM. Furthermore, all repetitions were performed at the same range of motion to ensure consistency between trials.

Statistical analysis

Data were analyzed using Statistical Package for Social Science (SPSS) 18 (IBM, Inc., Chicago, IL). Frequency and descriptive statistics were calculated on all variables. Independent sample t-tests were used to identify baseline differences for all variables between the CON and EX group. Repeated measures analyses of variance (ANOVA; 2 [group] × 2 [time]) were used to evaluate the effects for group, time, and the interaction between group and time for all outcome variables. An alpha level of 0.05 was used for all analyses.

RESULTS

At baseline, 18 EX and 19 CON subjects were enrolled in the study with 12 EX and 11 CON participants completing

Table 2. Socio-demographic characteristics of control and exercise participants.

Variable	Category	Control participants n (%)	Intervention participants n (%)
Years	Age	47.8 ± 4.5 (44, 59)	43.2 ± 9.5 (25, 57)
Gender	Female	4 (36.4)	5 (41.7)
	Male	7 (63.6)	7 (58.3)
Race	Non-Hispanic White	-	3 (25)
	African-American	11 (100)	6 (50)*
	Hispanic White	-	3 (25)
Marital status	Never Married	5 (45.5)	8 (66.7)
	Married	3 (27.3)	-
	Divorced	1 (9.1)	3 (25)
	Separated	1 (9.1)	1 (8.3)
Highest level of education	Up to high school	6 (54.5)	3 (24.9)
	Some Post High School Training	-	1 (8.3)
	College/Associate Degree	5 (45.5)	6 (50.0)
	College Graduate	-	2 (16.6)
Household Income ($)	Less than 5,000	6 (54.6)	2 (16.6)
	5,000-15,000	4 (36.4)	4 (33.3)
	15,000-30,000	1 (9.1)	4 (33.4)
	30,000-45,000	-	1 (8.3)
	45,000 or more	-	1 (8.3)
Other	Cups of Coffee/Day	1.3 ± 1.0	1.8 ± 1.9
	Days/Week Drinking Alcohol	1±1.4	0.08 ± 0.3*
	Nightly hours of sleep	7±2.5	7.7 ± 1.3

Values are mean ± standard deviation (minimum, maximum). *Significant difference between control and intervention subjects ($p<0.01$, unpaired t-test).

both PRE and POST evaluations (Table 2). Fourteen subjects (6 EX and 8 CON) dropped out of the study due to lack of interest or financial/family problems. Participants in the EX group attended an average of 29.4 (81%) supervised exercise sessions. The EX group (n=12) consisted of six African Americans, three non-Hispanic whites, and three Hispanic whites, while the CON group (n=11) consisted of all African Americans. The difference in proportion of African Americans between groups was significant (Table 1). Both groups were predominantly represented by individuals of lower socioeconomic status (SES), earning less than $15,000 per year. Finally, participants in both groups had been diagnosed with HIV for an average of more than 10 years (standard deviation (SD)±8.4, range 3 to 28), and all subjects were on stable ART for at least the prior 6 months.

Immune functioning

A significant main effects of time and the time × group interaction were found for CD4+ T cell count ($p=0.002$ and $p=0.03$, respectively; Figure 1) with the EX participants' values remaining stable and the CON participants' values decreasing from baseline (from 693.8 to 672.9 cells/mm^3 versus from 612.8 to 511.8 cells/mm^3). No significant main effect of time and time × group interactions were observed for CD4+/CD8+ ratio ($p=0.60$ and $p=0.49$) and HIV-RNA ($p=0.67$ and $p=0.29$; Figure 1).

Metabolic variables

A significant time × group interaction was found for FG ($p=0.048$) with the EX participants' values decreasing and

Table 3. Metabolic variables and physical characteristics of control and exercise participants at baseline and follow-up.

Variable	Control participants (CON)		Intervention participants (EX)	
	Pre	Post	Pre	Post
T-Chol (mg/dl)	191.9 ±43.0	184.9± 49.6	201.7 ± 48.5	195.5 ± 48.0
LDL-C (mg/dl)	107.4 ±32.1	101.9± 35.8	118.2 ± 37.3	111.5 ± 35.2
HDL-C (mg/dl)	58.4 ± 16.5	59.2 ± 14.7	49.9 ± 16.8	50.7± 18.7
VLDL-C (mg/dl)	26.0 ± 13.1	23.8 ± 17.4	33.6 ± 19.3	32.4± 24.5
T-Chol/HDL	3.5 ± 1.1	3.3 ± 1.3	4.3 ± 1.8	4.2± 1.6
TG (mg/dl)	129.1 ±66.8	119.6± 87.1	170.8± 105.0	157.9 ± 93.7
FG (mg/dl)	79.7 ± 10.3	83.1± 7.4	92.7 ± 16.4	80.7 ± 10.0†
BW (lbs)	195.5 ±41.3	196.5± 46.5	209.9 ± 64.6	209.9 ± 63.9
BMI	30.8 ±6.6	31.1± 7.5	33.6 ± 10.2	33.6± 10.1
WAIST (in)	39.1 ±7.1	39.5± 7.5	41.2 ± 8.0	40.4 ± 7.7†
SBP (mmHg)	132 ±16	124 ± 17*	119 ± 9†	120±6
DBP (mmHg)	80± 10	81± 9	81 ± 5	77± 11

Values are mean ± standard deviation (minimum, maximum). T-Chol: Total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; VLDL-C: very-low density lipoprotein cholesterol; TG: triglycerides; FG: fasting glucose; BW: body weight; BMI: body mass index; WAIST: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; PRE: baseline evaluation; POST: 12-week follow-up evaluation. *Significantly different from PRE within the same group ($p<0.05$, ANOVA). †Significantly different from CON at the same time point ($p<0.05$, ANOVA)

Table 4. The SF-36 of control and exercise participants at baseline and follow-up.

Variable	Control participants (CON)		Intervention participants (EX)	
	Pre	Post	Pre	Post
Physical functioning	77.2 ± 30.1	63.3 ± 41.6	78.3 ± 31.4	87.1 ± 16.8*
Role - Physical	67.0 ± 25.7	60.8 ± 34.5	73.9 ± 40.7	77.6 ± 23.3
General health	62.5 ± 24.7	60.3 ± 20.6	75.0 ± 28.1	76.4 ± 24.7
Vitality	56.3 ± 25.5	54.5 ± 28.1	69.8 ± 27.5	74.5 ± 18.6
Social functioning	84.7 ± 24.0	86.1 ± 26.1	71.9 ± 39.2	81.3 ± 20.9
Role - Emotional	70.5 ± 29.7	65.1 ± 30.5	84.7 ± 26.8.2	91.7 ± 13.3
Mental health	75.0 ± 22.7	65.5 ± 23.5	79.2 ± 23.7	87.1 ± 10.3*
Bodily pain	62.5 ± 29.5	61.5 ± 30.6	88.8 ± 11.8	77.9 ± 16.7

Values are mean ± standard deviation (minimum, maximum). PRE: Baseline evaluation; POST: 12-week follow-up evaluation. *Significantly different from CON at the same time point ($p<0.05$, ANOVA).

the CON group's values increasing from baseline (from 92.7 to 80.7 versus from 79.7 to 83.1, respectively; Table 3). Repeated measures ANOVAs for the serum lipid profile indicated no main effects for either time or time × group interactions for T-Chol ($p=0.17$ and $p=0.93$), LDL-C ($p=0.14$ and $p=0.89$), HDL-C ($p=0.64$ and $p=0.99$), T-Chol/HDL-C ratio ($p=0.20$ and $p=0.96$), and TG ($p=0.40$ and $p=0.90$; Table 2).

QoL

Significant time × group interactions were observed for the physical functioning ($p=0.03$) and mental health ($p=0.02$) scales on the SF-36 with the EX participants' values improving (+8.8 and +7.5 points, respectively) and the CON participants' values worsening (-14 and -9.5 points, respectively) from baseline (Table 4).

Physical fitness

Significant main effects of time and time × group interactions were found for VO_{2max} ($p=0.001$ and $p=0.002$, respectively; Figure 2) with the EX participants' values increasing (+4.7 ml/kg/min) and the CON participant's

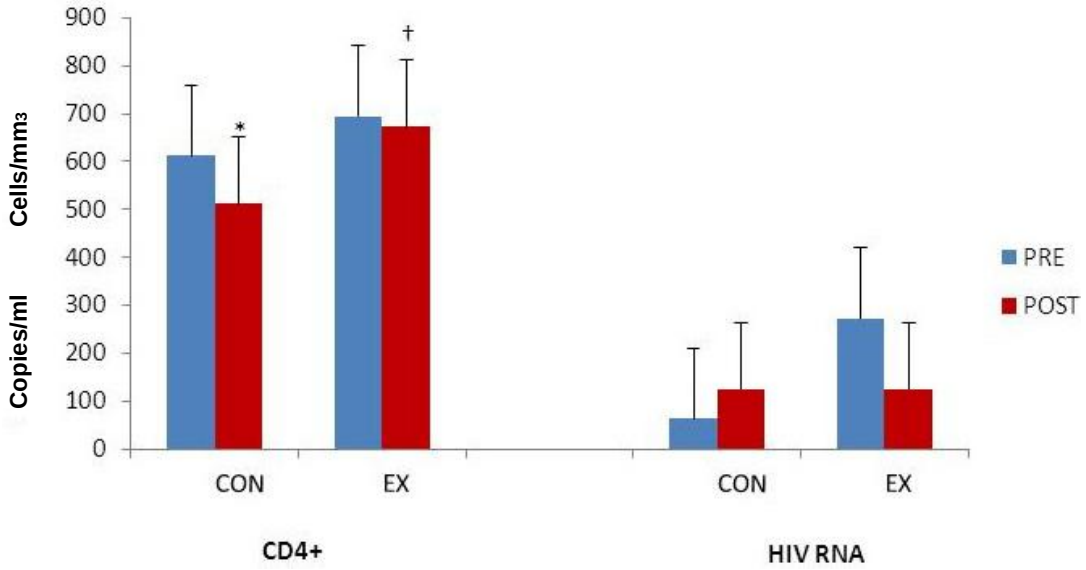

Figure 1. Changes in CD4+ cell count and HIV-RNA viral load in control and exercise participants at baseline and follow-up. CD4+: CD4+ T cell count; HIV RNA: HIV-RNA viral load; CON: control participants; EX: exercise participants; PRE: baseline evaluation; POST: 12-week follow-up evaluation. *Significantly different from PRE within the same group ($p<0.05$, ANOVA). †Significantly different from CON at the same time point ($p<0.01$, ANOVA).

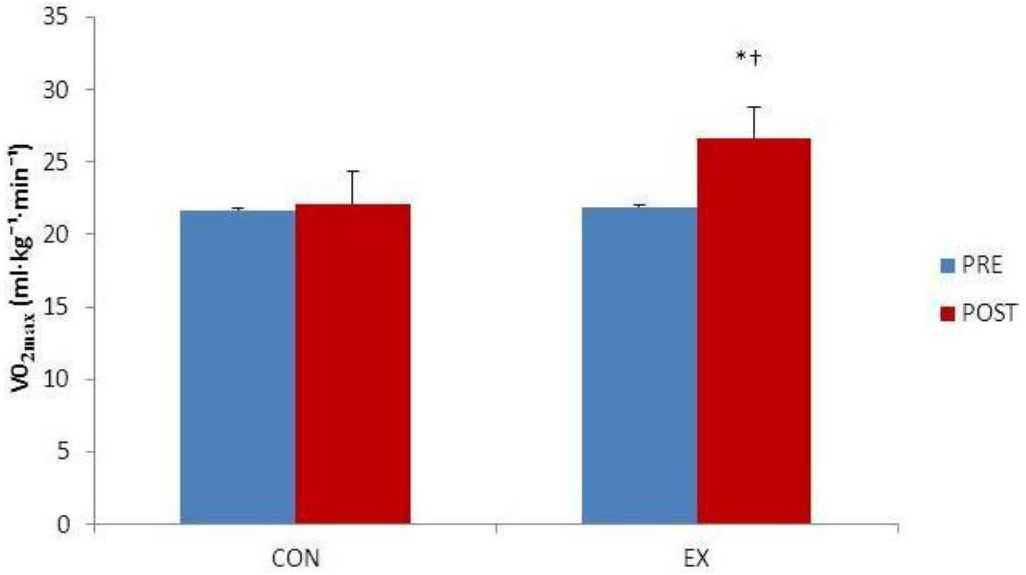

Figure 2. Changes in estimated maximum oxygen consumption (VO_{2max}) in control and exercise participants at baseline and follow-up. Estimated VO_{2max}: Estimated maximal oxygen consumption; CON: Control participants; EX: exercise participants; PRE: baseline evaluation; POST: 12-week follow-up evaluation. *Significantly different from PRE within the same group ($p<0.01$, ANOVA). †Significantly different from CON at the same time point ($p<0.01$, ANOVA).

values remaining the same (+0.4 ml/kg/min). Furthermore, significant main effects of time and time × group interactions were found for 1RM bench press for upper body strength ($p=0.003$ and $p=0.018$, respectively) and 1RM leg press for lower body strength ($p=0.01$ and $p=0.03$, respectively) with the EX participants' values

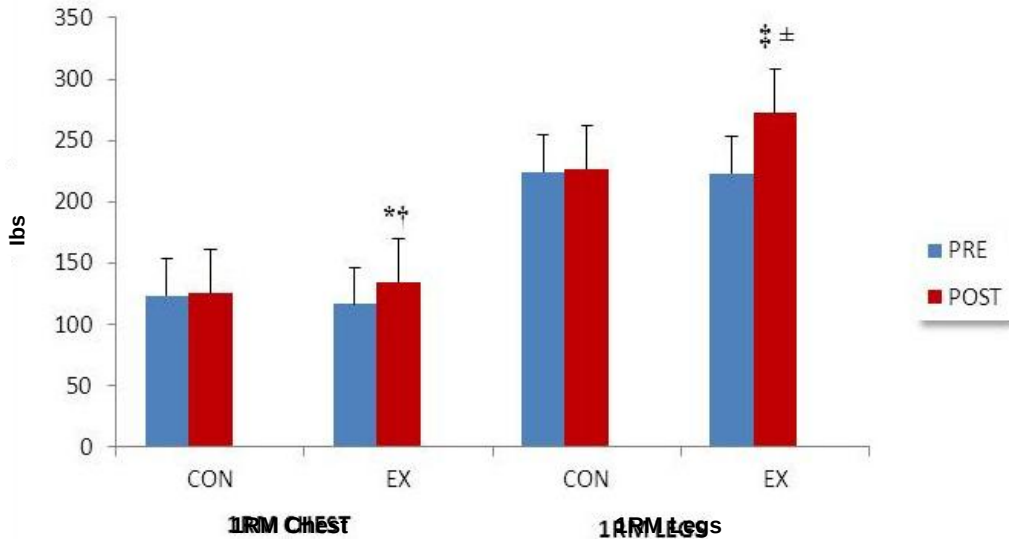

Figure 3. Changes in one-repetition maximum (1RM) for chest and legs in control and exercise participants at baseline and follow-up. LBS: pounds; 1RM CHEST: 1 repetition maximum for chest press; 1RM LEGS: 1 repetition maximum for leg press; CON: control participants; EX: exercise participants; PRE: baseline evaluation; POST: 12-week follow-up evaluation. *Significantly different from PRE within the same group ($p<0.05$, ANOVA). †Significantly different from CON at the same time point ($p<0.01$, ANOVA). ‡Significantly different from PRE within the same group ($p<0.05$, ANOVA). ±Significantly different from CON at the same time point ($p<0.05$, ANOVA).

improving (+17.9 and +49.1 lbs, respectively) and the CON participant's values remaining the same from baseline (+2.3 lbs and +1.9, respectively; Figure 3).

DISCUSSION

Thirty-eight percent of our subjects withdrew from the study, which is similar to the findings of a meta-analysis on aerobic exercise and HIV/AIDS in which six studies reported drop-out rates higher than 20% and two higher than 50% (Nixon et al., 2002). Furthermore, our EX participants achieved a higher completion rate (81%), compared to similar exercise intervention trials for this patient population (70 and 78%, respectively) (Fairfield et al., 2001; Hand et al., 2008).

Immunological markers not only give prognostic information on HIV, but they are also linked to HIV-related illness and mortality. Recent clinical trials have consistently shown no significant improvements in CD4+ T cell count and/or HIV-RNA levels after moderate-intensity training (Terry et al., 2006; Smith et al., 2001). Our result shows that the EX participants demonstrated a more stable CD4+ T cell count from baseline of -3%, while the CON group experienced a significant reduction of -16% after 12 weeks. Furthermore, the drop in CD4+ T cell count was observed in eight (73%) CON individuals compared to only four (33%) EX participants. Although EX participants had no significant increase in CD4+ T cell count, the fact that the group mean level remained stable is a positive finding. Favorable results were also found in viral load with only one EX participant (8%) having higher HIV-RNA viral load at 12 weeks follow-up, compared to four CON participants (36%) demonstrating a higher viral load. Finally, decreased HIV-RNA viral load, together with stable CD4+ count in the EX participants, represent more favorable prognoses and can attenuate progression to symptomatic disease. Two possibilities may explain the immunological responses of our intervention. Our trial included people of lower SES facing greater life-stress, and thus the exercise intervention may have indirectly caused a normalization of stress-induced CD4+ T cell count depletion. A similar result was reported in a study performed before the ART era in which a 10-week aerobic exercise program showed an increase of CD4+ T cell count in individuals with lower SES levels (Laperriere et al., 1994). Another possible explanation is the social support that our exercise intervention provided, which may have caused better adherence to ART and subsequently improved the immunological profile of the EX group. Similar results in social support and enhanced adherence to ART have been previously demonstrated (Van et al., 2005).

Regarding metabolic changes, both groups had normal baseline FG levels, but demonstrated opposite trends at 12-week follow-up. While the EX participants experienced a 13% reduction, the CON individuals showed a 4% increase in FG levels. This finding contrasts with the

results of a previous study in which a 12-week exercise intervention, combined with a diet, did not improve high FG levels in HIV-infected individuals receiving ART (Terry et al., 2006). A similar prevalence of metabolic syndrome has been reported for both HIV-infected and the general populations (De et al., 2008). In our study, HIV-infected individuals did not present with fasting hyperglycemia. However, a recent study suggested that higher values of FG (90 to 94 mg/dl), similar to the values observed in our EX group and still considered in the normal range, are associated with a significantly increased risk of type 2 diabetes (Nichols et al., 2008). Our results suggest that a 12-week CARET intervention can improve FG in euglycemic HIV patients and thus reduce the future risk of hyperglycemia and diabetes.

Past research has shown favorable changes in serum lipids after 12 weeks of training in patients with dyslipidemia not receiving ART (Halbert et al., 1999). Despite a more adverse metabolic lipid profile observed in the EX group at baseline, CARET did not result in significant changes in plasma lipid levels. Overall, our findings are consistent with two other studies performed in HIV-infected individuals receiving ART. Terry et al. (2006) showed no significant improvements in TG, T-Chol, and HDL-C after 12 weeks of aerobic exercise, while other investigators failed to show significant reductions in serum TG after 12 months of aerobic exercise (Birk et al., 2002). In contrast, Thoni et al. (2002) did find significant improvements in T-Chol, TG, and HDL-C (-23, -43, and +6%, respectively) after a 16-week aerobic training program in 17 lipodystrophic and dyslipidemic HIV patients. The lack of changes in serum lipids in our subjects may be related to the fact that subjects did not present with dyslipidemia at baseline and/or that the intervention was not of sufficient length.

In addition to negative physical changes, HIV-infected patients receiving ART can also experience psychological symptoms, and fatigue, depression, and anxiety represent the most common ones in this population. Our EX participants reported significant improvements in both physical and mental QoL scales (16 and 9%, respectively), while the CON participants had lower scores on the same scales (-18 and -12%, respec-tively). This indicates that the EX participants reported improvements in performing daily activities such as bathing, dressing, walking, climbing stairs, and carrying groceries, which are captured in the physical QoL scale. Furthermore, higher mental QoL scores observed in the EX group indicate improved mental health with CARET and lower risk of depression (Stoll et al., 2001). Interestingly, our intervention resulted in a positive trend in seven of the eight scales, while the CON participants exhibited negative trends in the same SF-36 scales. Our survey results may also explain the more stable CD4+ T cell count found in EX subjects, as impaired mental health status has been linked with decreased CD4+ T cell values (Leserman et al., 1999).

All physical variables were similar between groups initially with the exception of SBP, which was higher in the CON group compared to the EX group. This difference may be explained by higher rates of hypertension in African Americans and the fact that the CON group was entirely African American. This group experienced a significant reduction in SBP at the end of 12 weeks. Since no alterations in antihypertensive medications were made during the trial, the reduction in SBP in the CON group could have been due to variance (or error) in measurement.

Despite no significant changes in body weight in either group, the EX group experienced a reduction and the CON group an increase in their WAIST. Since HIV-infected individuals receiving ART are at risk for greater visceral fat accumulation, they represent a population more likely to have metabolic abnormalities associated with CVD and diabetes (Brown et al., 2010). Therefore, significant reductions in WAIST in the EX group may be a marker for decreased risk of metabolic diseases associated with abdominal obesity.

The EX group also improved their estimated VO_{2max}, an important measure of aerobic capacity related to health and longevity. Generally, aerobic fitness declines at approximately 1% per year in healthy individuals beyond the age of 25 (Rosen et al., 1998) and even more in adults with chronic diseases (Palella et al., 1998). More specifically, conditioned HIV-infected individuals may have up to 9% lower VO_{2max} values compared to age-matched healthy individuals (Johnson et al., 1990). These decrements may subsequently translate into lower endurance, quicker fatigue, and reduced independence during daily life activities in sedentary individuals. Abnormalities specific to reduced aerobic capacity in the HIV-infected population include decreased lactate threshold and reduced peripheral muscle oxygen utilization during exercise. These problems are often related to mitochondrial toxicity (Cade et al., 2003) caused by nucleoside reverse transcriptase inhibitors (NRTI), the cornerstone of ART therapy. Low estimated VO_{2max} values were observed in both CON and EX groups at baseline, signifying low functional aerobic capacity in this sample. This impairment is consistent with the finding that sedentary HIV-infected individuals may have estimated VO_{2max} values below 30 ml/kg/min with values of 24 to 44% below age-predicted norms (Keyser et al., 2000). However, despite continued ART therapy in both groups, the EX group was able to achieve a significant 21% improvement in estimated VO_{2max}, while the CON group showed no change. In contrast to our results, others have found non-significant 9 to 10% increases in VO_{2max} following a similar combined training protocol after 12 and 16 weeks in HIV-infected individuals (Smith et al., 2001; Robinson et al., 2007). Our results are more closely related to an older study (Robinson et al., 1992)

conducted in 37 male HIV-infected individuals in which VO_{2max} improved 17% after 12 weeks of aerobic training. Since reduced aerobic capacity can be associated with lower CD4+ T Cell count and faster progression to AIDS, improved cardiorespiratory fitness from our CARET intervention may translate into more stable and favorable health outcomes in HIV-infected individuals.

Muscular strength is another component of physical fitness relevant to health and longevity. In our trial, the EX compared to CON group achieved significant improvements in upper (15%) and lower (21%) body strength. Increases in both upper and lower body strength are associated with improved functional capacity, reduced risk of falls, and a lower incidence of hip fractures in the elderly (Robinson et al., 1987). Thus, our findings of improved musculoskeletal strength may have significant implications for better independence later in life. Despite our shorter intervention length, the strength gains of this study were similar to those of a 16-week CARET intervention (Robinson et al., 2007) using participants similar in age to ours. Their trial also showed an 18% increase in 1RM for four upper and three lower body resistance exercises. Similar to our findings, Yarasheski et al. (2001) found larger improvements in lower body, compared to upper body, strength in 18 HIV-infected individuals. Smaller increases in upper body strength can be attributed to NRTI medications, which can cause peripheral neuropathy and limited ability to recruit motor nerves in the upper body musculature (Fichtenbaum et al., 1995). This physiological limitation, associated with the side effects of NRTI, signifies the importance of performing more upper body training for persons living with HIV.

LIMITATIONS

Several limitations of this study should be noted. The small sample size represents a major limitation. Despite high compliance with the exercise protocol, we did observe a high attrition rate. African Americans had a higher attrition rate in the EX group and non-Hispanic whites and Hispanics withdrew at a higher rate in CON group. Each control subject had an opportunity to undergo the same exercise protocol after completing the study. However, all non-African Americans assigned to CON group discontinued the study, which explains our randomization bias.

The subjects in this study used laboratory analyses from the clinic, where they received their usual care. Therefore, the study protocol schedule and the participants' blood draw appointments were not always perfectly matched for every participant. Specifically, the baseline blood draw appointments may have occurred a few days before or after the beginning of the exercise intervention, and the same problem may have occurred with the 12-week follow-up appointments for both groups.

Finally, we had no formal protocol to check medication compliance. Based upon regular communication with each participant, we could only speculate that adherence to the ART regimen occurred. However, several participants from both groups reported a single short gap (3 to 5 days) in obtaining their medications from the pharmacy, which may have affected their immunological response.

Conclusions

In this study, it was found out that a 12-week, supervised, moderate-intensity CARET program resulted in more favorable clinical findings in immunological markers in HIV-infected individuals of lower SES compared to their non-exercising counterparts. This is an important finding, recognizing that HIV patients of lower SES have greater susceptibility to disease progression and premature mortality (Cunningham et al., 2005). The results indicate that the same exercise protocol can result in other health improvements, such as reductions in FG and WAIST and improvements in physical and mental QoL, aerobic fitness, and muscular strength. Given the promising results of our study, future trials should continue to utilize combined aerobic and resistance exercise, as a more health-promoting form of training in this patient population (Lindegaard et al., 2008). Finally, longer exercise protocols (>3 months) are needed to more conclusively determine the link between increased physical fitness and the immunological functioning of HIV patients receiving stable ART.

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